Lewis Acid Activated Electrophilic Alcohols as Alkylating Agents for the Stereoselective Synthesis of Heterocycles

A thesis submitted to the Board of the Faculty of the

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Yuxiang Zhu

Wolfson College

and

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Glossary of Abbreviations and Acronyms

Ar	Argon/Aromatic group
CI	Chemical ionization
cm^{-1}	Wavenumbers
DMAP	4-Dimethylaminopyridine
DMP	Dess-Martin periodinane
dr	Diastereomeric ratio
EI	Electronic ionization
equiv.	Equivalents
ESI	Electrospray ionization
ee	Enantiomeric excess
FCC	Flash column chromatography
g	Gram
h	Hour
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HIR	Hypervalent iodine reagent
HITB	[Hydroxy(tosyloxy)iodo]benzene
HPLC	High performance liquid chromatography
Hz	Hertz
IBX	2-Iodoxybenzoic acid
IR	Infrared spectroscopy
^{i}Pr	*iso*-Propyl
J	Coupling constant
m	Multiplet
M	Molar (mol dm^{-3})
MALDI	Matrix-assisted laser desorption/ionization
Me	Methyl
mg	Milligram(s)
min	Minutes(s)
mL	Millilitre(s)
mmol	Milimoles(s)
mol%	Molar percent
m.p.	Melting point
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
NOESY-2D	Two dimensional Nuclear overhauser experiment
Ph	Phenyl
PIDA	(Diacetoxyiodo)benzene
PIFA	(Bis(trifluoroacetoxy)iodo)benzene
PMP	*para*-Methoxyphenyl
p-OMe	*para*-Methoxy
ppm	Parts per million

r.b.f.	Round bottom flask
RSM	Recovered starting material
rt	Room temperature
SM	Starting material
T	Triplet
TFE	Trifluoroethanol
THF	Tetrahydrofuran
TLC	Thin layer chromatography
ν_{max}	Infrared absorption maximum

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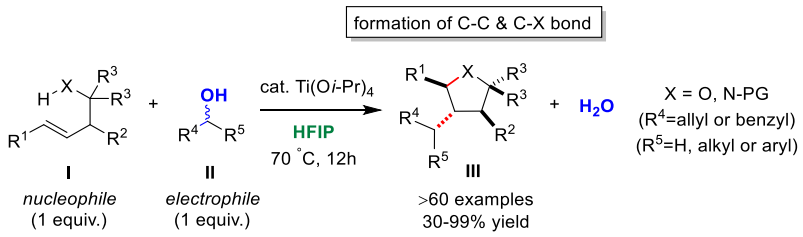
Wolfson College, Trinity Term 2020

Abstract

Oxygen- and nitrogen-containing heterocycles are precursors of many valuable synthons in both synthetic and medicinal chemistry, which facilitate the synthesis of a broad array of natural products with biological activities such as antitumor, anthelmintic, antimalarial, antimicrobial, and antiprotozoal. I have found that the polar and protic bonding solvent hexafluoroisopropanol (HFIP) plays an important role in the stereocontolled synthesis of complex oxygen- and nitrogen-containing heterocycles from simple linear precursors.

My novel method for the stereoselective functionalisation of homoallyl alcohols/amines uses readily available allylic or benzyl alcohols as alkylating agents (**Scheme 1**). Only one equivalent of the electrophilic partner is required for the cyclization process, and most of the products are obtained selectively as 2,3-*trans* diastereomers. Mechanistic studies reveal that $Ti(OiPr)_4$ in HFIP plays a unique role in this reaction, as the *in-situ* formation of the complex $Ti(Oi\text{-}Pr)_2(OHFIP)_2$, was found to initiate the cyclization, leading to a formal 5-*endo*-trig cyclization that involves the stereoselective formation of both a C-C

and a C-O/C-N bond in a single synthetic step. This method has been proven to be efficient and atom economic especially because only a catalytic amount of Ti(O*i*Pr)$_4$ is used and water is the only by product. Moreover, a wide range of the homoallyl alcohol or amine (**I**) and electrophilic initiators (**II**) show excellent compatibility with the system; finally, further functionalization of the products enables access to the synthetically useful heterocyclic molecules.



Scheme 1. Stereoselective homoallyl alcohols/amines (I) functionalization in HFIP

Chapter 1: Introduction

1.1. Background

Substituted tetrahydrofurans are widely found as structural motifs in a broad range of natural products and other biologically active molecules. A diverse range of useful bioactivities are found in these substances, including antitumor, anthelmintic, antimalarial, antimicrobial, and antiprotozoal.[1] For example, potent neurotrophic activities including neurite-outgrowth promotion and neuroprotection are found in THF-containing (–)-talaumidin.[2]

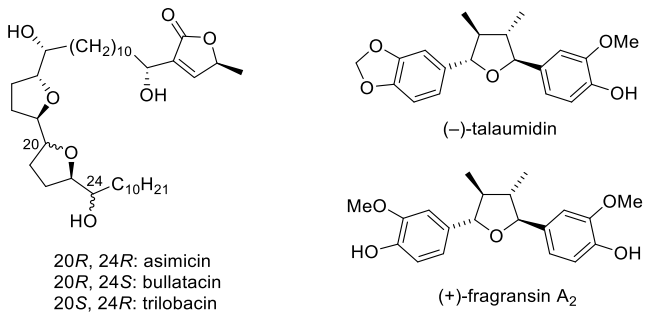


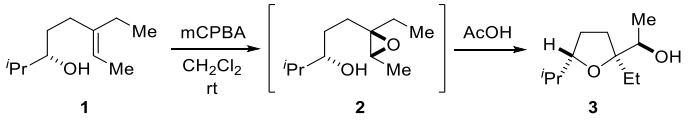
Figure 1.1 THF-containing natural products

Due to the important and useful biologically activities of these substances, people have made considerable efforts toward the development of stereocontrolled construction of substituted tetrahydrofurans, which will be discussed later on.

1.2. Established Methods for the Synthesis of Tetrahydrofuran derivatives *via* C-O Bond Formation

1.2.1. Synthesis of THF derivatives *via* epoxide ring opening

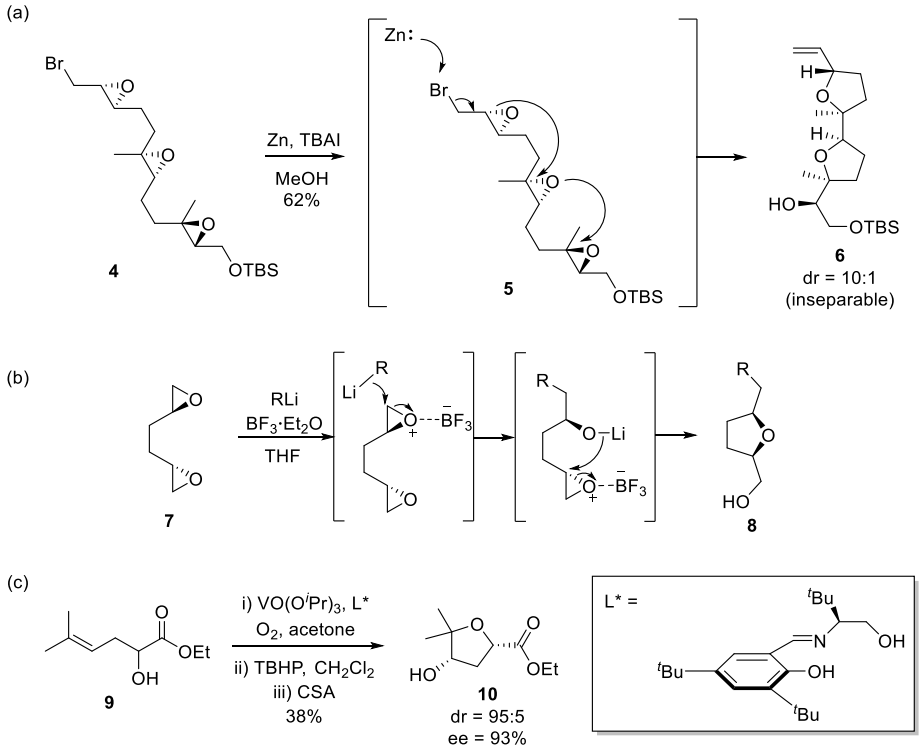
In 1978, Kishi and co-workers reported the first example of synthesizing THF derivatives *via* epoxide ring opening. THFs **3** was synthesized from the epoxidation of alkene **1** followed by the epoxide ring opening of **2** (**Scheme 1.1**).[4] This type of approach remained highly used in the preparation of THF derivatives as the epoxide can easily be prepared in enantioselective manner, such as through a Sharpless epoxidation,[5] Jacobsen epoxidation[6] or Shi epoxidation.[7]



Scheme 1.1 Synthesis of THFs **3** *via* epoxide opening.

Recent developments in this field are mainly focused on cascade epoxide opening, as it presents an elegant way to synthesize poly-THFs structures.[8] For instance, Marshall and co-workers developed a zinc-mediated cascade epoxide opening of **4**, which allows the generation of bis-THFs **6** with control at the previously set stereocentres of the epoxides (**Scheme 1.2**).[9] In addition, Florence and Cadou reported a Lewis acid catalyzed desymmetrization of the bis-epoxide **7**, which initiated by the addition of an organolithium and allowed the generation of 2,5-*cis* THFs **8**.[10] In 2006, Blanc and Toste developed a vanadium-catalyzed homoallylic alcohol resolution process, which proceeds through the epoxidation of the alkene **9** followed by a ring-opening cyclization. Later on,

this method was successfully applied to the first enantioselective synthesis of (−)-pantofuranoid E.[11]

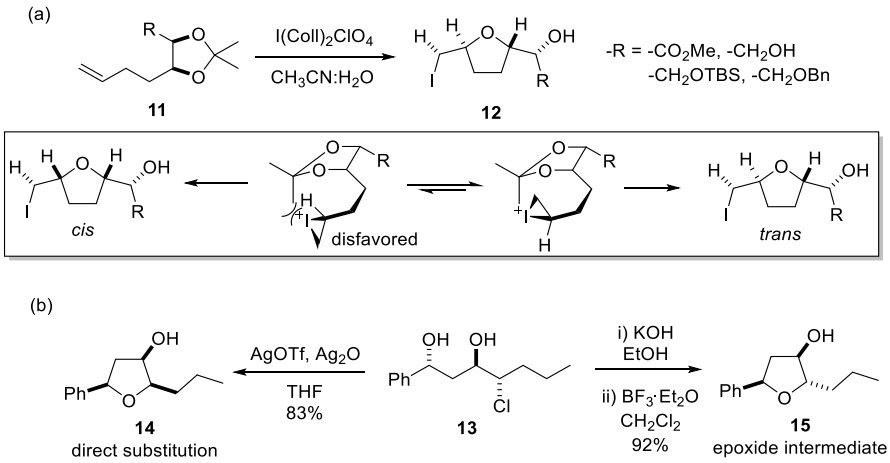


Scheme 1.2 (a) Synthesis of THFs **6** *via* Zn-mediated cascade epoxide opening; (b) Synthesis of THFs **8** *via* desymmetrization of bis-epoxide; (c) Vanadium-catalyzed resolution/oxidative cyclization

1.2.2. Synthesis of THF derivatives *via* Halo-etherifications and halogen substitutions

Halo-etherification provides a way to synthesize THF derivatives *via* olefin halogenation followed by the intramolecular cyclization of a pendant alcohol, which is interesting as post-functionalization is readily accessible. For example, the diastereoselective synthesis of pure *trans*-THFs **12** *via* iodonium dicollidine perchlorate (I(Coll)2ClO_4, IDCP) catalyzed iodocyclization of alkene **11** was recently reported by Ramos and co-workers (**Scheme 1.3a**). This diastereospecific outcome is attributed to the equilibration between two sets

of iodoniums.[12] Additionally, synthesis of THF derivatives *via* nucleophilic substitution of halide are one of the classic approaches and have been well developed. Recently, Britton and co-workers reported a way to access various diastereomers of THFs **14** and **15** through either direct substitution or epoxide formation followed by ring opening of **13** (**Scheme 1.3b**).[13]

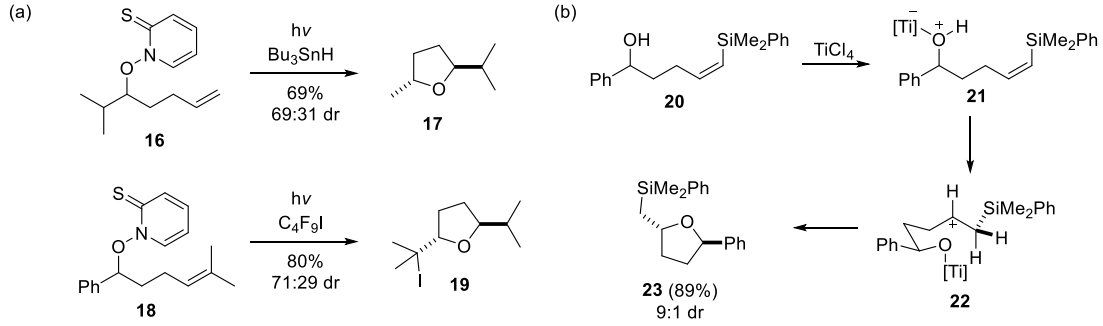


Scheme 1.3 (a) Synthesis of THFs **12** *via* haloetherification; (b) Synthesis of THFs **14** and **15** *via* halogen substitution.

1.2.3. Synthesis of THF derivatives *via* Hydroetherification

Alkene hydroetherification *via* oxygen radical cyclization or carbocation cyclization is a useful and straightforward approach for the synthesis of tetrahydrofuran subunits. Hartung and co-workers have developed the synthesis of THF derivatives from *N*-alkoxypiperidinethione with moderate diastereoselectivity. The reaction firstly goes through the homolysis of the weak N-O bond followed by a rapid 5-*exo*-trig cyclization. Additionally, it also enables the synthesis of 1'-halotetrahydrofuran **19** by addition of halogen source (**Scheme 1.4a**).[14] Hosomi and co-workers reported the synthesis of

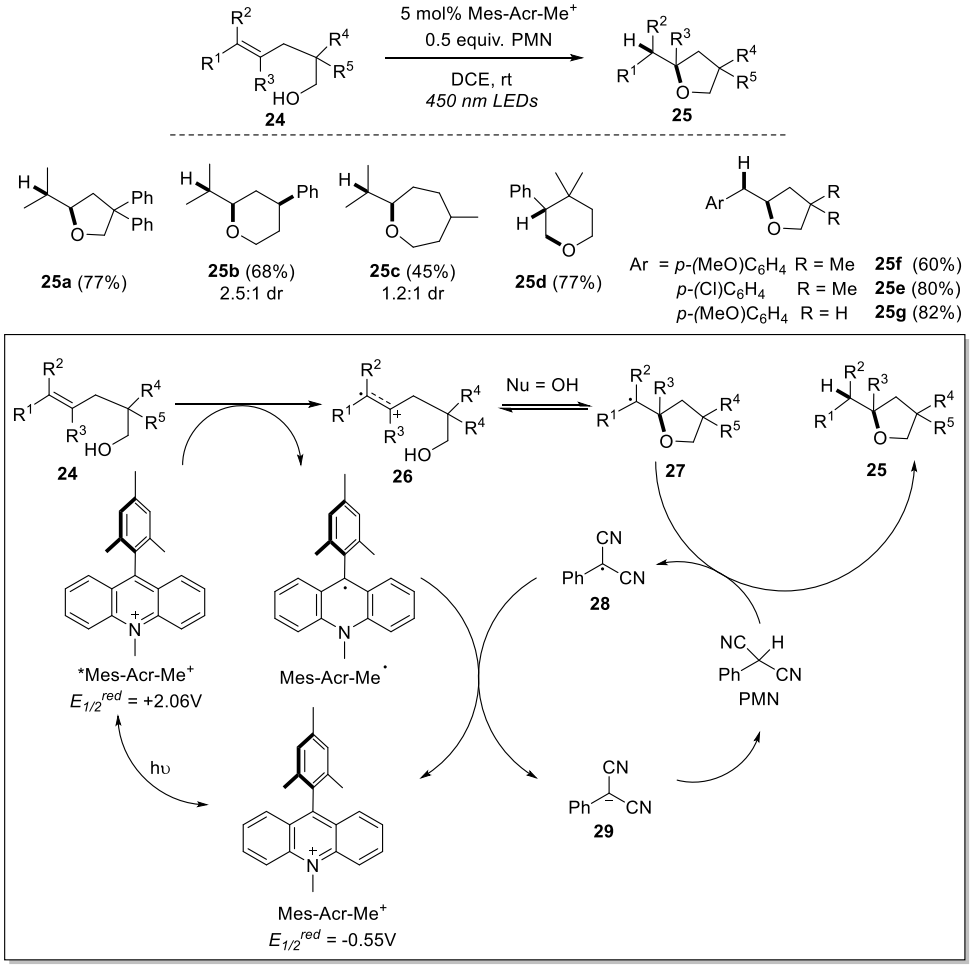
tetrahydrofuran *via* Brønsted or Lewis acid catalyzed cyclization of γ-hydroxyvinylsilanes **20**. The cyclization firstly undergoes Lewis acid activation of the alcohol, followed by the protonation of the vinylsilanes **21**. Its generated carbocation **22** is then captured by the nucleophilic oxygen to afford the final 2,5-*trans*-disubstituted tetrahydrofuran **23** (**Scheme 1.4b**).[15]



Scheme 1.4 (a) Alkene hydroetherification *via* radical cyclization; (b) Alkene hydroetherification *via* cyclization of carbocation

Recently, Nicewicz and co-workers developed an acridinium photocatalyzed anti-Markovnikov alkene hydroetherification (**Scheme 1.5**).[16] The anti-Markovnikov regioselectivity is enabled by the reverse of alkene polarity *via* single-electron oxidation of the alkene. The reaction utilizes *Mes-Acr-Me$^+$ as the photooxidant to facilitate single electron oxidation of the alkene **24** to generate the radical cation **26**, which undergoes oxygen nucleophilic addition and subsequent hydrogen atom transfer to afford the desired THFs products **25**. The reduced Mes-Acr-Me$^\cdot$ is then oxidised by the 2-phenylmalononitrile (PMN) radical **28** to regenerate *Mes-Acr-Me$^+$. A wide range of alkenes afford the desired anti-Markovnikov adducts such as trisubstituted aliphatic alkene which allows the formation of 5-7 membered rings (**25a-c**), and a challenging

6-*endo*-trig cyclization can be achieved to generate tetrahydropyran **25d**. Additionally, both electron-rich and deficient styrenes tolerates the system and gives products **25e-g** in good yields.

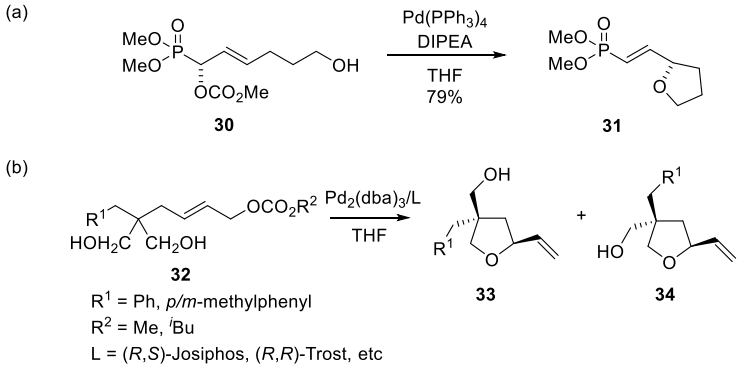


Scheme 1.5 Scope of acridinium photocatalyzed intramolecular alkene hydroetherification and its proposed mechanism

1.2.4. Synthesis of THF derivatives *via* allylic alkylations

Allylic alkylation was firstly discovered in 1977 by Trost and co-workers, [17] it remained as a powerful method in organic synthesis and has been applied in the synthesis of THFs. For example, Spilling and co-workers recently has developed a palladium catalyzed

synthesis of THF derivatives *via* the formation of oxolane intermediate from the phosphono-allylic carbonates (**Scheme 1.6a**).[18] This method is not limited to the synthesis of THF derivatives, it also allows the synthesis of large oxygen-heterocycles. In addition, Olszewska and co-workers reported a synthesis of THF derivatives *via* desymmetrization of bis(hydroxymethyl)allylic carbonates **32**, which gives products in good yields but moderate diastereomeric and enantiomeric outcome (**Scheme 1.6b**).[19]

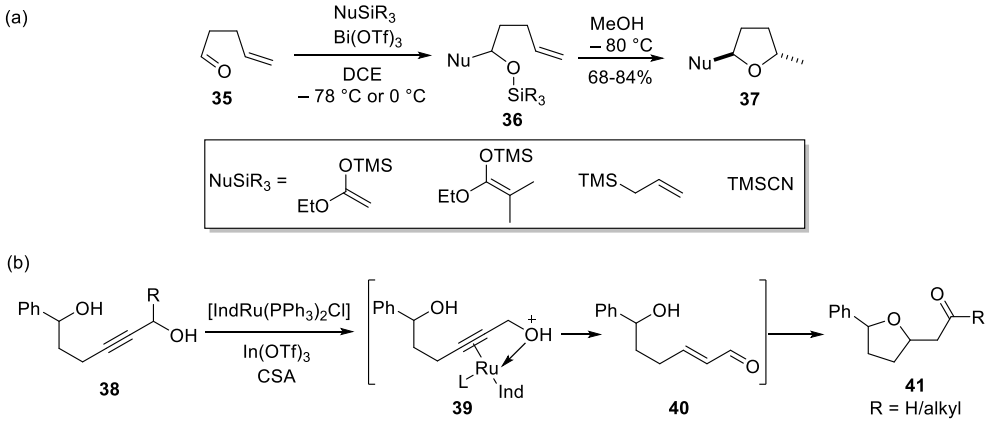


Scheme 1.6 Pd-catalyzed synthesis of THF derivatives *via* allylic alkylations

1.2.5. Synthesis of THF derivatives *via* hydroalkoxylations

Hydroalkoxylation is a straightforward and atom-economic way to synthesize THF rings, which usually goes through a 5-*exo*-*trig* cyclization. Recently, Lambert and co-workers reported a $Bi(OTf)_3$ catalyzed synthesis of THF derivatives from an addition to an aldehyde **35** followed by a hydroalkoxylation of **36**, and the resulting *trans*-THFs **37** were obtained in good yield and stereoselectivity (**Scheme 1.7a**).[20] Following his work, Trost and co-workers developed a Ru-catalyzed synthesis of THFs *via* the primary and secondary propargylic alcohol isomerization followed by intramolecular Michael addition of **40** (**Scheme 1.7b**).[21] This methodology tolerates enol ester and silyl groups,

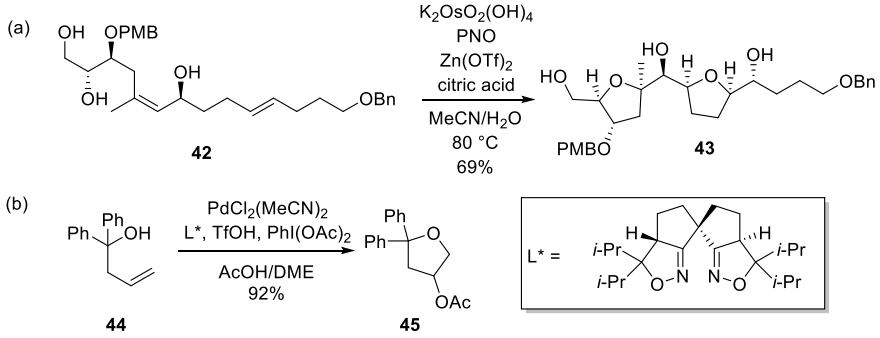
and affords good yields but poor diastereoselectivity.



Scheme 1.7 Synthesis of THF derivatives by hydroalkoxylation

1.2.6. Synthesis of THF derivatives *via* oxidative cyclizations

Oxidative cyclization was firstly discovered in 1965 by Klein and Rojahn[22] and became one of the popular methods to synthesize *cis*-2,5 THFs derivatives. For example, Donohoe and co-workers reported an Os-mediated oxidative cyclization and successfully applied the methodology for the total synthesis of (+)-Sylvaticin, (+)-*cis*-Sylvaticin and NeodysiherbaineA (**Scheme 1.8a**).[23] Additionally, Takenaka and co-workers achieved the synthesis of THFs with good enantiomeric excess by the asymmetric Pd-catalyzed oxidative cyclization of homoallylic alcohols **44**, where $PhI(OAc)_2$ is utilized as the oxidant. However, they did not identify the major enantiomer (**Scheme 1.8b**).[24]

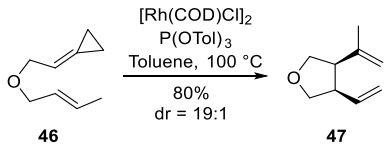


Scheme 1.8 (a) Os-catalyzed oxidative cyclization; (b) Pd-catalyzed oxidative cyclization

1.3. Established Methods for the Synthesis of Tetrahydrofuran derivatives *via* C-C Bond Formation

1.3.1. Synthesis of THF derivatives *via* cycloisomerization

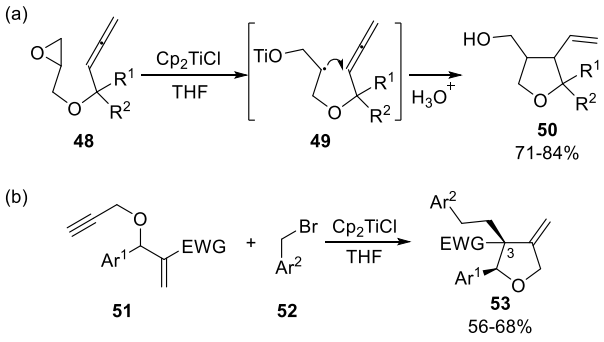
Cycloisomerization of acyclic ethers is well known to prepare 3,4-substituted THF derivatives.[25] Evans and co-workers recently reported a Rh-catalyzed cycloisomerization of alkenylidene cyclopropanes, allowing the formation of *cis*-3,4-substituted THF derivatives with good diastereoselectivity. Additionally, different from most of cycloisomerization reactions that affords 1,4-diene, it gives a 1,5-diene structure (**Scheme 1.9**).[26]



Scheme 1.8 Synthesis of 3,4-disubstituted THF derivatives *via* Rh-catalyzed cycloisomerization

1.3.2. Synthesis of THF derivatives *via* radical reactions

Radical cyclization has been well developed as an effective method for the synthesis of THF derivatives. For example, Huang and Roy has recently reported a titanium induced radical cyclization for the synthesis of THF derivatives.[27] Huang's method involves the reductive epoxide ring opening, followed by cyclization of the radical to an allene (**Scheme 1.10a**). Although it affords good yields, the drawback of this method is its poor diastereoselectivity. Roy and co-workers developed a method of synthesizing 2,3,4-trisubstituted THF derivatives which contains a homobenzylic substituent and an electron withdrawing substituent at C-3 position, with good yields and complete diastereoselectivity (**scheme 1.10b**).



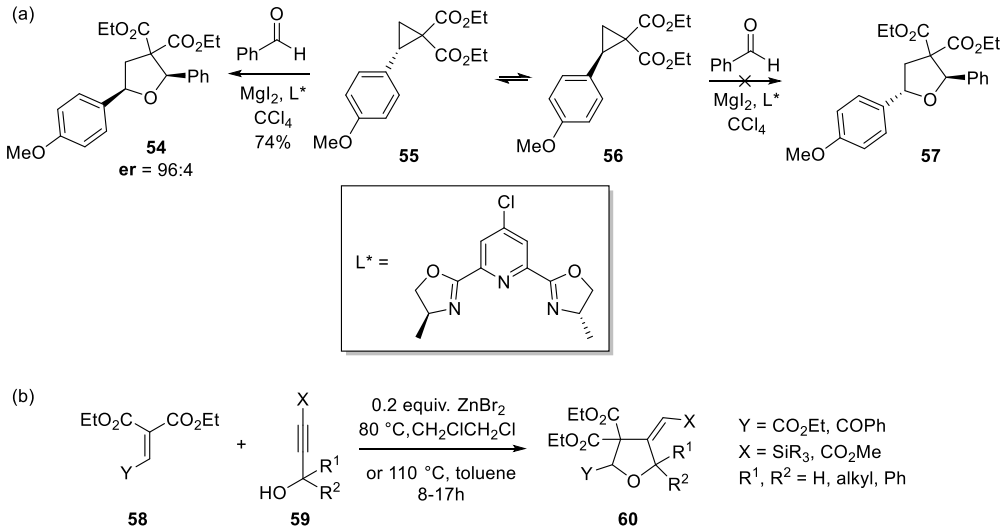
Scheme 1.10 Synthesis of 2,3,4-trisubstituted THF derivatives *via* Ti-triggered radical cyclization

1.4. Established Methods for the Synthesis of Tetrahydrofuran derivatives *via* Simultaneous C-C and C-O Bond Formation

1.4.1. Synthesis of THF derivatives *via* [3+2] cycloadditions

Diastereoselective synthesis of substituted THF derivatives can be achieved *via* [3+2]

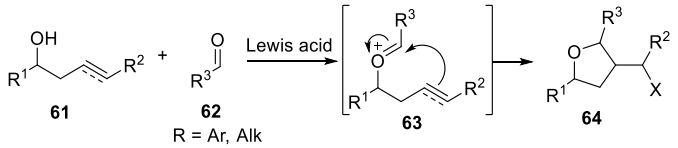
cycloaddition between an aldehyde and a 1,3-dipole.[28] Recently, developments have been made in utilizing a cyclopropane bearing electron-withdrawing group or electron-donating group as the 1,3-polar equivalent. For example, Johnson and co-workers reported an enantioselective synthesis of *cis*-2,5 THFs **54** *via* the deracemization of the cyclopropane starting materials **55/56**.[29] For this transformation, Lewis acid catalyst is used, along with the help of chiral ligand to promote [3+2] cycloaddition of one of the enantiomers (**Scheme 1.11a**). Additionally, [3+2] cycloaddition of an electron-deficient alkenes and allylic or propargylic alcohols using Lewis acid, Lewis base, Brønsted base or photocatalyst has been extensively developed in the past years.[30] For instance, Kiyomi and co-workers reported a $ZnBr_2$ catalyzed cycloaddition of olefins **58** and propargylic alcohols **59** for the synthesis of fully substituted THFs **60** (**Scheme 1.11b**).[31] However, the drawback of this reactivity is its moderate diastereoselectivities.



Scheme 1.11 (a) Enantioselective synthesis of THF derivatives by deracemization of cyclopropane; (b) [3+2] cycloaddition of propargylic alcohol with olefins.

1.4.2. Synthesis of THF derivatives *via* oxonium intermediate

Intermolecular cyclizations involving an oxonium intermediate, such as Prins reaction, can achieve the synthesis of 2,3,5-trisubstituted THF derivatives. This type of cyclization is catalyzed by Lewis acid and usually utilizes a homoallylic or homopropargylic alcohols and an aldehyde as starting materials to generate the key oxonium intermediate **63**, which is attacked by the alkene or alkyne to give the THF products (**Scheme 1.12**). Kim and co-workers described that the allylic stannane could attack the oxonium and gave desired product.[32] Additionally, Chavre and co-workers' method involves the attack of alkyne to the oxonium followed by the trapping of vinyl cation by a triflate anion.[33] Both methods tolerates secondary alcohol starting material and give good *cis*-2,5 diastereoselectivity.



Scheme 1.12 Synthesis of THF derivatives involving an oxonium intermediate

1.5. Rules for Cyclization Reactions

1.5.1. Baldwin's rules on cyclization process

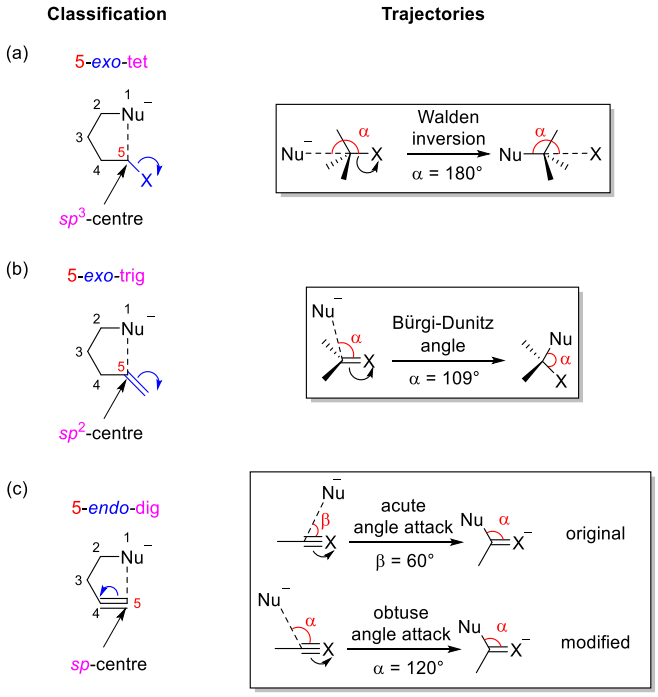
In 1976, a set of rules for cyclization processes was formulated by Professor Jack Baldwin. These rules have been widely used as a guideline for determining the relative favorability of ring closure processes (**Scheme 1.13**).[34] The type of ring closure is defined

in three ways: (i) the total number of atoms in the constructed ring; (ii) whether the position of bond broken is inside (*endo*) or outside (*exo*) to the ring that is being formed; (iii) the hybridization or geometry of the atom at the point of ring closure (sp^3-**tet**rahydral, sp^2-**tri**gonal, *sp*-**dig**onal). Additionally, Baldwin further expanded the rules to aldol cyclizations involving enolates, such as enol*exo*- and enol*endo*-cyclization.[35]

	3		4		5		6	
	exo	*endo*	*exo*	*endo*	*exo*	*endo*	*exo*	*endo*
tet	√		√		√	×	√	×
trig	√	×	√	×	√	×	√	√
dig	×	√	×	√	√	√	√	√

Scheme 1.13 Baldwin' s rules on favoured/disfavoured ring closure

The preferred angle of attack of the nucleophile component needs to be determined for application of the cyclization rules. For tet-cyclizations such as 5-*exo*-tet (**Scheme 1.14a**), a back-side attack is the preferred approaching pathway, where the angle of attack α is 180°; for *trig*-cyclizations such as 5-*exo*-trig (**Scheme 1.14b**), the preferred angle of attack is 109°, which was identified by the crystallographic study of Bürgi and Dunitz;[36] for dig-cyclization such as 5-*endo*-dig (**Scheme 1.14c**), it was more challenging to determine the correct trajectory due to the lack of experimental data. Initially, Baldwin suggested an acute angle of 60°, while later investigation showed the correct angle of attack α should be 120°. Note that for all of the cyclizations, the angle between the three interacting atoms (Nu-C-X) is unchanged before and after the reaction.



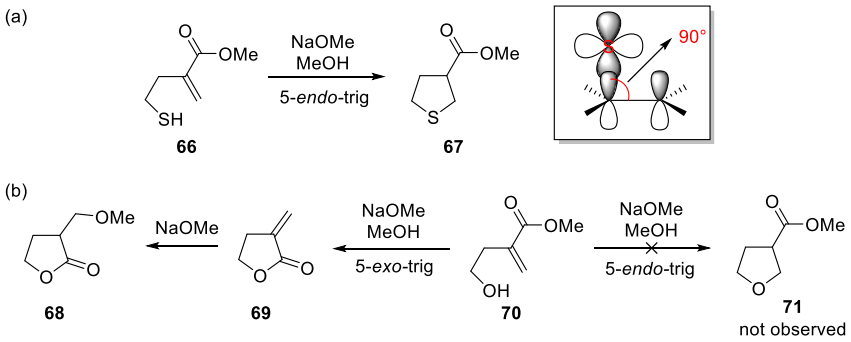
Scheme 1.14 Trajectories for intramolecular ring closure

1.5.2. Exceptions and violations of Baldwin's rules

Although Baldwin's rules have proven to be useful and effective in many ring closure reactions, several violations were discovered. Five main aspects of the origin of these violations and exceptions will be discussed.[37]

Although the rules apply well with period two elements, the heavier period three elements do not always obey the rules. This is attributed to their larger atomic radii and bond lengths, which allow them to access a suitable conformation to enable otherwise disfavored cyclizations. For example, a thiol **66** can undergo 5-*endo*-trig cyclization smoothly under basic reaction conditions to afford tetrahydrothiophene **67** (**Scheme 1.14a**). However, an alcohol prefers to attack the ester rather than the alkene *via* a

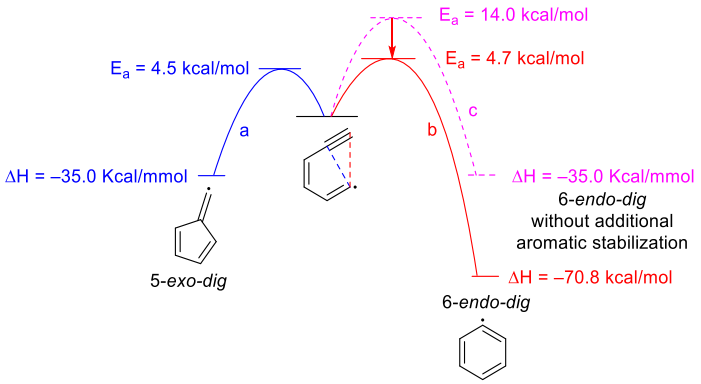
5-*exo*-trig cyclization, followed by a Michael addition of methoxide to the alkene **69** to afford a lactones **68** (**Scheme 1.14b**). This difference can be explained by the presence of unoccupied 3d-orbital of the sulfur atom which receives back donation from the occupied π-orbital of the alkene. This factor therefore reduces the angle of attack from 109° (for oxygen) to nearly 90°, leading to a less geometrically constrained 5-*endo*-trig cyclization.[38] Additionally, Baldwin's rules do not apply to cyclization involving much shorter atomic radii and bond length, such as radical 1,5-hydride shifts, which proceed in 6-*endo*-tet manner.[39]



Scheme 1.15 5-*endo-trig* cyclization of alcohol and thiol

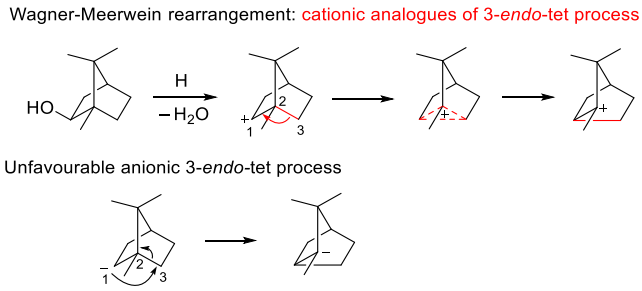
As Baldwin's rules describe the kinetic preference of cyclization reactions, cyclization that operates under thermodynamic control are another exception. A thermodynamic contribution can alter the reactivity of cyclization in two ways. For exothermic reactions, substrates possess a reactant-like, early transition state which requires less distortion to reach the ideal trajectory. Also, the activation energy can be lowered by thermodynamic contributions.[40] For example, the extra aromatic stabilization both lowers the activation barrier and increases the exothermicity of the 6-*endo*-dig cyclization shown (**Scheme 1.16**, pathway **b** vs **c**). With a similar activation energy (ΔE_a = 0.2 kcal/mol), the more

exothermic 6-*endo*-dig cyclization will be more preferred than the stereoelectronically favoured 5-*exo*-trig cyclization (**Scheme 1.16**, pathway **a** vs **b**).



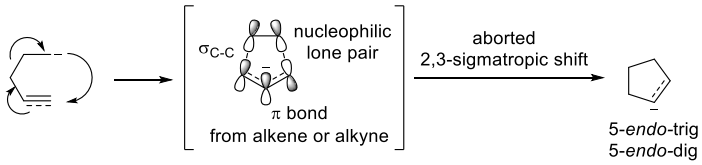
Scheme 1.16 Thermodynamic contributions of 6-*endo*-dig override the stereoelectronically preferred 5-*exo*-dig cyclization

Another controversial view of the Baldwin's rules is that they do not apply to cationic processes.[37] Anionic 3-*endo*-tet process, such as [1,2]-Wittig reactions, are generally unfavourable and non-concerted.[41] However, the Wagner-Meerwein rearrangement involves a fast and concerted 1,2-cationic shift, which is analogous to an unfavourable anionic 3-*endo*-tet process (**Scheme 1.17**). In addition, cyclizations that involve alkynes were considered to be different from those involving alkenes in Baldwin's prediction. However, in 1979, computational analysis carried out by Houk and co-workers suggested that the hydride addition to acetylene and ethylene possess similar energy barriers and nearly identical trajectories;[42] in 1990s, Bailey and co-workers discovered that carbanions can undergo regioselective 4-*exo*-dig cyclization, which is suggested as an unfavourable process by Baldwin's rules.[43]



Scheme 1.17 Wagner-Meerwein rearrangement: cationic analogues of 3-*endo*-tet process

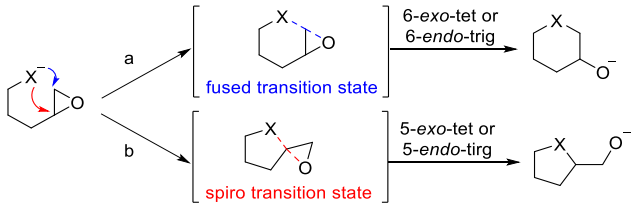
Although Baldwin suggested that the rules are not applicable to concerted electrocyclic reactions, connections between pericyclic reactions and Baldwin's rules have been discovered. In 2012, Alabugin and co-workers in a computational analysis suggested that the transition state of anionic 5-*endo*-dig and 5-*endo*-trig cyclizations are stabilized by a five-centre-six-electron intermediate, which consists of a nucleophilic lone pair, a π bond of an alkene or alkyne, and a C-C sigma bridge. These 5-*endo* cyclizations can be treated as an 'aborted' 2,3-sigmatropic shift, whose extra aromatic stabilization in the transition state allows the cyclizations to proceed (**Scheme 1.18**).[44]



Scheme 1.18 'Aborted' 2,3-sigmatropic shifts cyclization

Cyclizations involving intramolecular epoxide opening are difficult to classify and bring confusion to Baldwin's rules. Baldwin stated that this type of cyclization lies between tet- and trig-systems, and that *exo*-cyclization is generally preferred. However, for the epoxide ring opening, both route a and b can be considered *exo*-cyclization as the bond broken is outside the forming ring (**Scheme 1.19**). In an effort to avoid confusion,

Jamison and co-workers re-defined these cyclizations which classifies them into the 'fused transition state' mode (similar to 6-*exo*-tet or 6-*endo*-tirg) and 'spiro transition state' mode (similar to 5-*exo*-tet or 5-*endo*-tirg).[45]



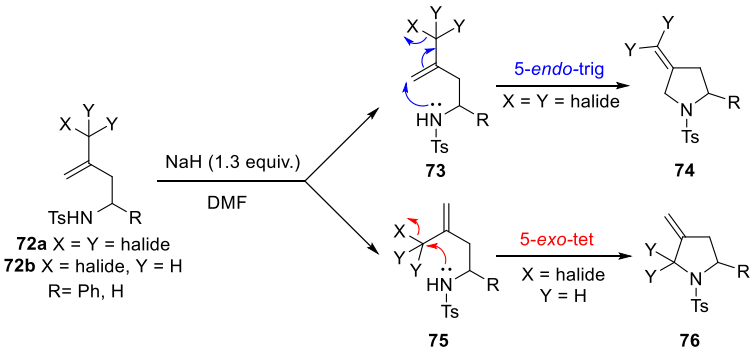
Scheme 1.19 'Fused' and 'spiro' modes of epoxide opening cyclizations

1.5.3. Reactions involving 5-*endo*-trig process

Although Baldwin's rules state that 5-*endo*-trig cyclization is a disfavored process, many examples have been reported, including those that are nucleophilic/electrophilic driven, and radical-initiated 5-*endo*-trig cyclizations.

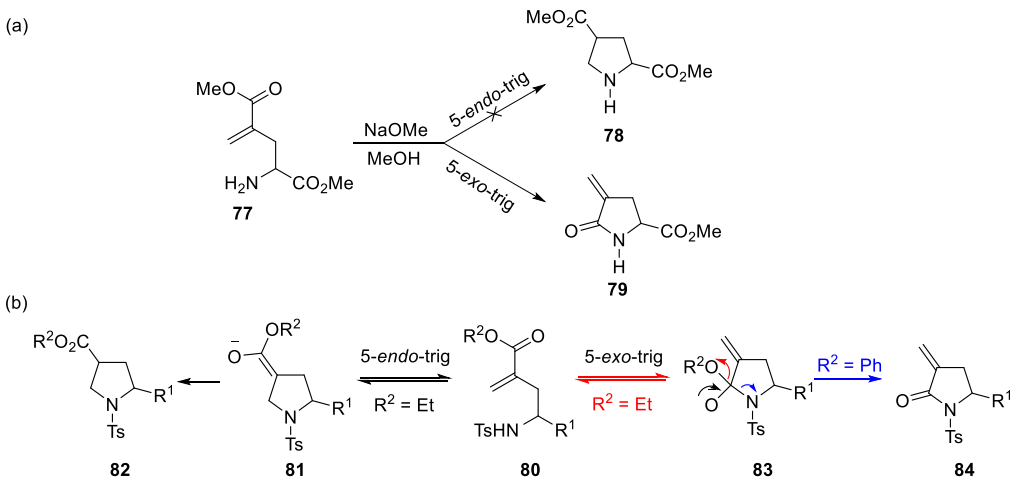
In 2007, Ichikawa and co-workers reported a nucleophilic 5-*endo*-trig cyclization of *N*-homoallylic sulfonamides.[46] The trihalide substituted sulfonamide **72a** (X = Y = halide) rapidly underwent a 5-*endo*-trig cyclization to afford pyrrolidines **74**; while mono-halide substituted sulfonamide **72b** (X = halide, Y = H) underwent preferential 5-*exo*-tet cyclization to afford pyrrolidines **76** (**Scheme 1.20**). For the trihalide substituted tosylamide, a 5-*exo*-tet approach is strongly disfavored by electrostatic and steric repulsion with the trihalo-substituents, which leads to the preference for *endo*-cyclization. With a weaker electrostatic and steric repulsion (as presented in the mono-halide substituted sulfonamide) the more geometrically favored 5-*exo*-tet

cyclization is preferred.



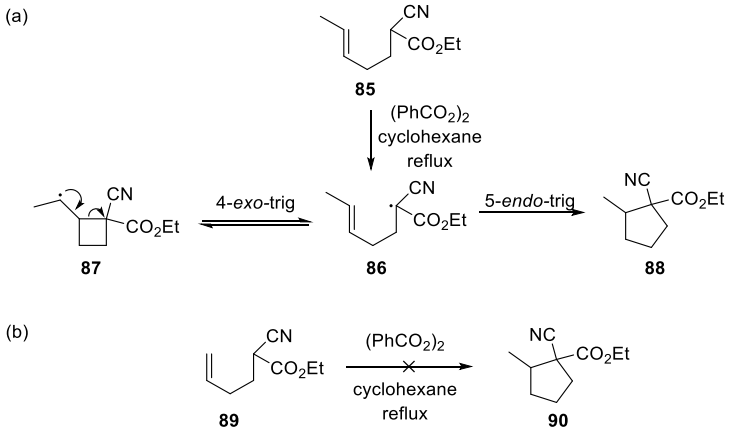
Scheme 1.20 Nucleophilic 5-*endo*-trig and 5-*exo*-tet cyclization of sulfonamides

Previous studies on cyclization of α,β-unsaturated esters **77** bearing an amine group by Baldwin and co-workers suggested that the 5-*exo*-trig cyclization was more favorable than 5-*endo*-trig cyclization (**Scheme 1.21a**).[34] However, Ichikawa and co-workers discovered that 5-*endo*-trig cyclization could be achieved by simply swapping the amine nucleophile with a sulfonamide moiety (**Scheme 1.21b**).[46] Under the reaction conditions, sulfonamide **80** proceeded to intermediate **83** *via* a nucleophilic attack on the ester group. As the ethoxy group (R^2 = Et) is a worse leaving group than the sulfonamide, it reverted to sulfonamide **80**, which underwent 5-*endo*-trig cyclization to afford product **82**. On the other hand, the phenoxy group (R^2 = Ph) is a better leaving group than the sulfonamide, which enabled 5-*exo*-trig cyclization to afford product **84**. Therefore, the disfavored 5-*endo*-trig process can be accessed by employing a suitable combination of nucleophile, electrophile and reaction conditions.



Scheme 1.21 Nucleophilic 5-*endo*/*exo*-trig cyclizations of α,β-unsaturated esters

In 2006, Masazumi and co-workers reported a radical 5-*endo*-trig cyclization.[47] Under the reaction conditions, 4-pentenyl radical **86** could either undergo 4-*exo*-trig or 5-*endo*-trig cyclization to give **87** and **88** respectively (**Scheme 1.21a**). However, due to the high strain presented in cyclobutane **87**, it rapidly underwent ring opening and 5-*endo*-trig cyclization to give cyclopentane **88**. Additionally, the combination of an electron-deficient radical with an electron rich olefin triggered cyclization, while for substate **89** with a less electron-rich olefin, the cyclopentane **90** was not observed under the reaction conditions (**Scheme 1.22a**).



Scheme 1.22 Radical initiated 5-*endo* -trig cyclizations

1.6. The Role of HFIP

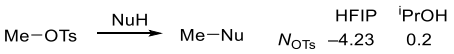
1,1,1,3,3,3,-Hexafluoroisopropanol (HFIP) has been widely used as an essential solvent to promote different and diverse chemical reactivities, including epoxidation, Friedel-Crafts reactions, and cyclization. This can be attributed to its unique physical and chemical properties.[49]

1.6.1. Physical and chemical properties of HFIP

HFIP is a thermally stable solvent with a relatively low boiling point of 59 °C (compared with ^{i}PrOH, which has a boiling point of 82.2 °C), which allows its recovery by distillation and reduces solvent waste.[50] An industrial procedure for recovering HFIP has been invented involving co-distillation with heptanes.[51] As a result of the inductive electron withdrawing effect of the two trifluoromethyl groups, water and common polar organic solvents are found to be miscible with HFIP.[52] It also displays significantly enhanced acidity in aqueous solution, with a pK_a value of 9.3 (compared with ^{i}PrOH, which has a pK_a value of 17.1),[53] and its achievable acidities are more similar to formic acid.[50]

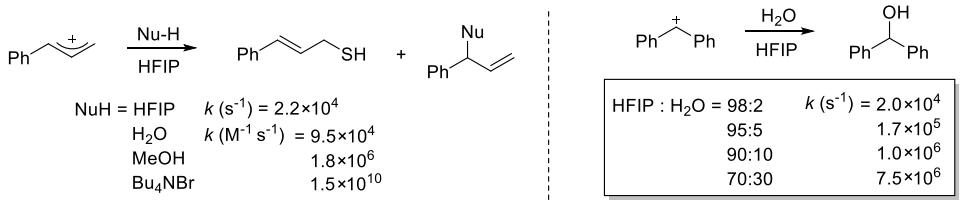
N_{OTs} is a measure of solvent nucleophilicity derived from the solvolysis of MeOTs.[54] HFIP is found to possess a reduced nucleophilicity compared with ^{i}PrOH (**Scheme 1.23**).[55] Only in the presence of highly reactive cationic electrophiles is HFIP able to act as a nucleophile.[56] HFIP is also known as excellent hydrogen-bond donor, which generates stable complexes with other hydrogen-bond acceptor solvents. For instance, a stable

complex is generated by mixing equimolar amount of HFIP with THFs, which possesses an increased boiling point of 100 °C.[57]



Scheme 1.23 Nucleophilicity parameter N_{OTs}

Other than thermal stability, HFIP also possess excellent oxidative stability, which makes it as an ideal solvent for redox chemistry involving highly oxidizing environments.[58] For instance, the epoxidation of olefins with hydrogen peroxide can be conducted in HFIP while other non-fluorinated alcohol solvents are incompatible. What is more, its low nucleophilicity and high dielectric constant (ε) of 15.7 allow it to be a suitable solvent for reactions involving generation of carbocations. The ability of HFIP to efficiently stabilize allylic and benzylic cations enables the rapid addition of nucleophile to these carbocations (**Scheme 1.24**).[59] Note that the rate of the reaction in neat HFIP was the slowest due to its low nucleophilicity.

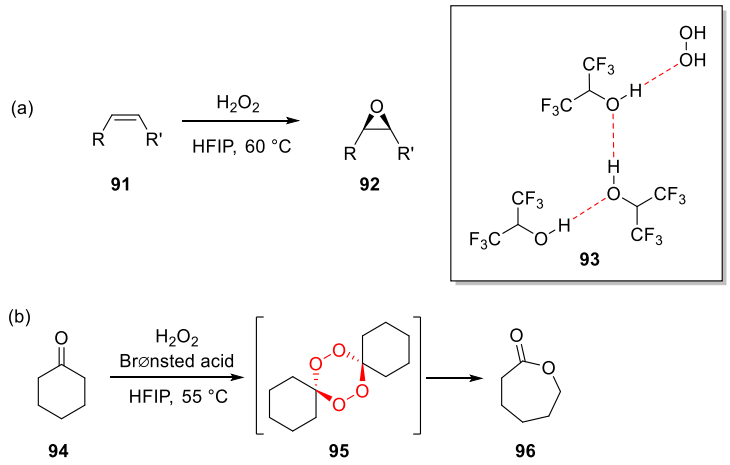


Scheme 1.24 Nucleophilic addition to carbocation in HFIP

1.6.2. HFIP enabled activation of hydrogen peroxide

Traditionally, HFIP has been widely used as a solvent for the transition metal catalyzed epoxidation of olefins with hydrogen peroxide. A recent discovery by Neumann and

co-workers has shown that HFIP can enable the metal free electrophilic activation of H_2O_2, allowing both epoxidation and Baeyer-Villiger oxidation.[60] Further investigation by Berkessel and co-workers discovered that a highly ordered transition state **93** consisting of H_2O_2 along with three HFIP molecules resulted in sufficient polarization of the O-O bond to enable the epoxidation of olefins (**Scheme 1.25a**).[61] Additionally, the use of HFIP in Baeyer-Villiger oxidation of cyclic ketone led to a different mechanism, where a unique spiro-bisperoxide intermediate **95** was generated (**Scheme 1.25b**).[62]

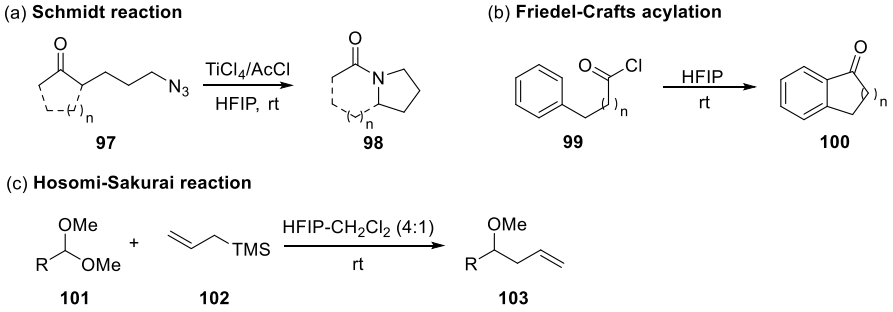


Scheme 1.25 (a) HFIP enabled epoxidation of olefins; (b) HFIP enabled Baeyer-Villiger oxidation of cyclic ketones

1.6.3. HFIP enabled activation of carbonyl and acetal functionalities

As an excellent hydrogen donor, HFIP has been commonly used in the activation of carbonyl functionalities. Recently, Aubé and co-workers developed a Lewis acid catalyzed intramolecular Schmidt reaction in HFIP, which allowed complete conversion of starting material with only a catalytic amount of Lewis acid employed (**Scheme 1.26a**).[63] In the absence of HFIP, the amine product would bind to the Lewis acid and thus inhibit the reaction, meaning that an excess amount of Lewis acid would be

required to achieve complete conversion. The same group has also discovered that it is possible to carry out Friedel-Crafts acylations in HFIP without the use of any Lewis acid catalyst. This is enabled by the strong hydrogen donating ability of the HFIP, which leads to activation of the acyl chloride (**Scheme 1.26b**).[64] Additionally, HFIP was found to polarize acetals *via* hydrogen bond donation, which enhanced the electrophilicity of the acetal and enabled a Hosomi-Sakural reaction with allyl silanes (**Scheme 1.26c**).[65]

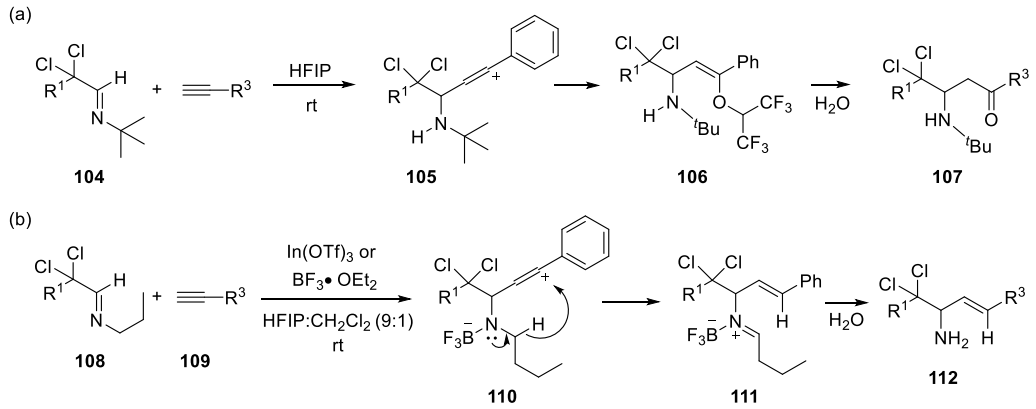


Scheme 1.26 (a) HFIP enabled Schmidt reaction; (b) HFIP enabled Friedel-Crafts acylation; (c) HFIP enabled Hosomi-Sakurai reaction

1.6.4. HFIP enabled activation of imine functionalities

Tehrani and co-workers have reported a nucleophilic addition of alkynes to *N*-alkyl-α, α-dichloroaldimines using HFIP as the solvent, which leads to the synthesis of β-amino-ketones or allylic amines depending on the protecting group (^{t}Bu or ^{n}Pr) of the imine.[66] For the synthesis of β-amino-ketones **107**, HFIP activates the imine **104** by protonation, followed by irreversible alkyne addition and trapping by HFIP. Rapid hydrolysis of the resulting enol ether **106** gives the desired product (**Scheme 1.27a**). For the synthesis of allyl amines **112**, HFIP plays a crucial role in stabilizing the allene carbocation intermediate **110**, which allows a key [1,5]-hydride shift to occur which is

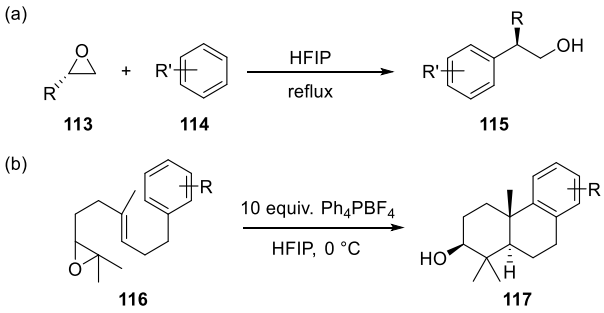
followed by hydrolysis (**Scheme 1.27b**).



Scheme 1.27 HFIP enabled synthesis of β-amino-ketones or allyl amines

1.6.5. HFIP enabled epoxide ring opening

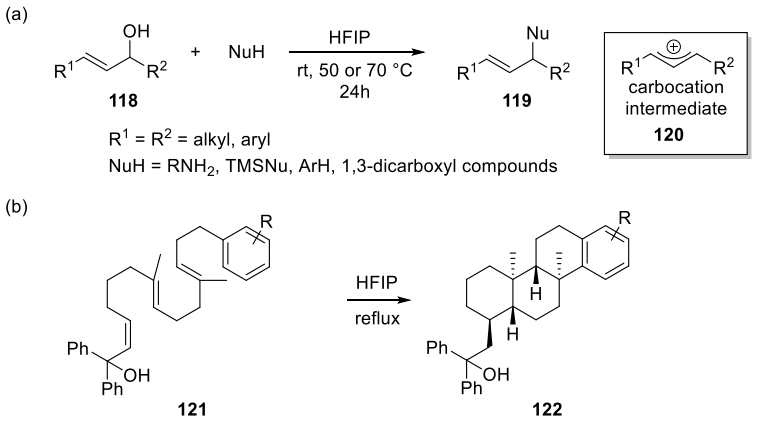
HFIP also provides an alternative approach to functionalize epoxide rings. Recently, Qu and co-workers reported an intramolecular Friedel-Crafts alkylation of electron-rich arenes *via* epoxide ring opening in HFIP. This process does not require any additional catalyst, and no related reactivity was observed with other solvents utilized, such as acetone, toluene and acetonitrile (**Scheme 1.28a**).[67] Further investigation by the same group has extended this methodology to intramolecular polycyclization reactions. The addition of ionic additive Ph_4PBF_4, which increases the ionic strength of HFIP, was used to increase the rate of these reactions. Interestingly, the use of alternative fluorinated solvents, including TFE and perfluoro-*tert*-butyl alcohol resulted in no formation of the cyclized product. It was suspected that the substrate adopted a more ordered chair conformation in HFIP, and the activation of the epoxide was achieved by a trace amount of HF generated from solvolysis of the BF_4^- anion (**Scheme 1.28b**).



Scheme 1.28 (a) Friedel-Crafts alkylation with epoxides; (b) HFIP enabled polyene cyclization

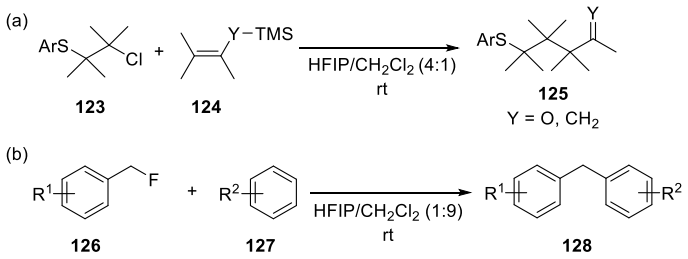
1.6.6. HFIP enabled alcohol, halide and sulfonate activation

In 2012, Nájera and co-workers reported the first example of alcohol activation by HFIP solvent, which enabled nucleophilic substitution of an allyl alcohol.[68] This process tolerated a range of nucleophiles including amines, allylic silanes, electron-rich arenes (Friedel–Crafts reaction) and 1,3-dicarbonyl compounds. During their investigation, the generation of allyl carbocation intermediates **120** was proposed, which was supported by the formation of identical product using alkenes with different geometries (**Scheme 1.29a**). Additionally, an intramolecular polycyclization of tertiary alcohols **121** in HFIP was developed by Qu and co-workers (**Scheme 1.29b**).[69]



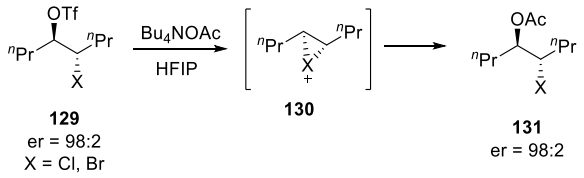
Scheme 1.29 (a) HFIP enabled S_N1 substitution of allyl alcohol; (b) HFIP enabled polyene cyclization

Previously reported activation of halides in HFIP required an extra neighboring group such as a β-thioether (**Scheme 1.30a**).[70] Paquin and co-workers have recently reported a HFIP enabled fluoride activation process, where the benzyl fluoride **126** was selectively activated by the HFIP and attacked by electron-rich arenes **127** in a Friedel-Crafts manner. The use of HFIP was crucial to activate the fluoride *via* hydrogen-bond donation (**Scheme 1.30b**).[71]



Scheme 1.30 (a) HFIP enabled alkylation of silicon-containing alkenes by a β-arylthioalkyl chlorides; (b) HFIP enabled Friedel-Crafts arylation with benzyl fluorides

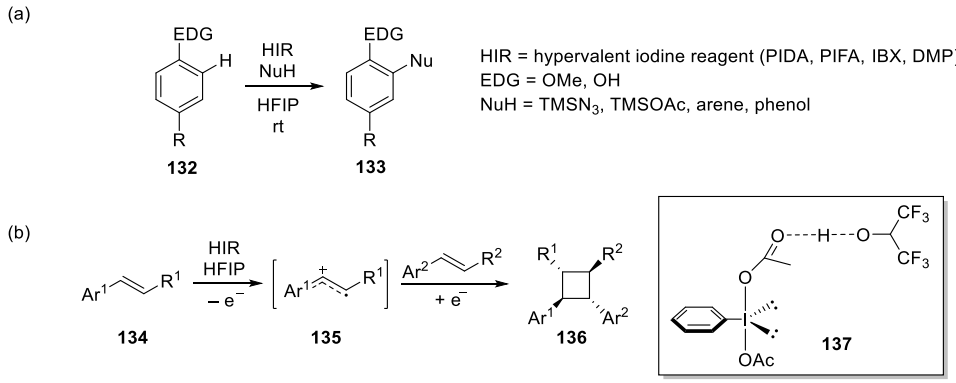
During an investigation into the configurational stability of enantiopure halonium ions, Denmark and co-workers found that β-halosulfonates **129** could be activated by HFIP through hydrogen-bond donation to form C2 chiral halonium ions **130**.[72] Addition of an external nucleophile, such as Bu_4NOAc then gave the final substituted product **131** (**Scheme 1.31**).



Scheme 1.31 HFIP enabled activation of sulfonates

1.6.7. HFIP enabled activation of hypervalent iodine reagents

Kita and coworkers reported the powerful oxidizing ability of a combination of hypervalent iodine reagents and HFIP in 1991. As an example, use of phenyliodine(III) bis(trifluoroacetate) (PIFA) in HFIP allows the functionalization of electron-rich anisoles, leading to a series of processes including anisole azidation, acetoxylation and aniline-arene cross-coupling (**Scheme 1.32a**).[73] Mechanistic studies suggested that a radical cation intermediate was generated by single-electron transfer (SET) in these reactions. Additionally, other common solvents such as THF, MeOH, CH_2Cl_2 and DMF do not facilitate this chemistry, and only HFIP is effective, which is likely a result of the polar, low nucleophilicity and radical-stabilizing ability of HFIP. Recently, Donohoe and co-workers reported the [2+2] intermolecular cycloaddition of styrenes initiated by hypervalent iodine reagents in HFIP enabling the highly diastereoselective synthesis of tetra-substituted cyclobutanes. Mechanistic studies, including electrochemical and NMR experiments, suggested the role of HFIP is to generate an adduct **137** *via* hydrogen-bonding with the iodine reagent, which enhances its oxidizing power (**Scheme 1.32b**).[74-75]



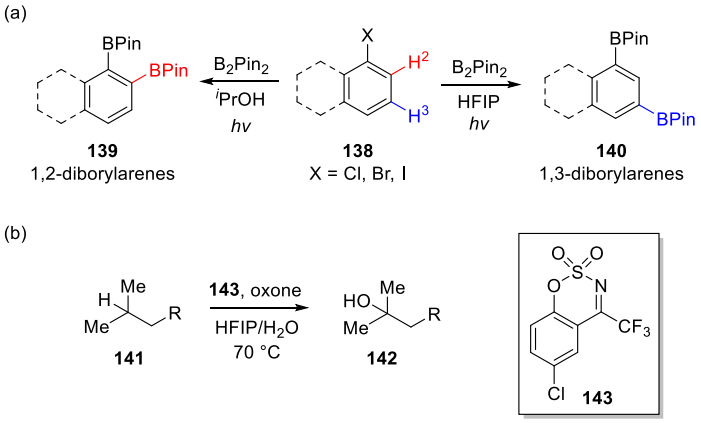
Scheme 1.32 (a) Nucleophilic functionalization of anisole derivative by hypervalent iodine reagent in HFIP; (b) [2+2] intermolecular cycloaddition of styrenes by HIR in HFIP

1.6.8. HFIP enabled metal-free C-H activation

Traditionally, the synthesis of aromatic diborylarenes not only needs an expensive catalyst or ligand, but also affords products in moderate yields and poor regioselectivity. In 2016, Larionov and co-workers developed a metal-free, scalable, photoinduced dual C-H and C-X borylation of aryl halides with high regioselectivity. 1,2-diborylarenes **139** and 1,3-diborylarenes **140** could be prepared selectively by treating an aryl halide with isopropanol or HFIP respectively. A mechanistic study showed that heterolysis of the C-X bond in polar HFIP solvent results in the favorable formation of 1,3-diborylarenes **140** (**Scheme 1.33a**).[76]

Recently, Du Bois and co-workers reported a HFIP enabled sp^3 C-H activation of tertiary and benzylic alkanes **141** for the synthesis of alcohols **142** in moderate to high yield. HFIP plays a crucial role in this process by increasing the lifetime of the *in situ* generated active oxaziridine catalyst (from **143**) *via* forming microdroplets of HFIP, which avoids

the reduction of catalyst by water (**Scheme 1.33b**).[77]

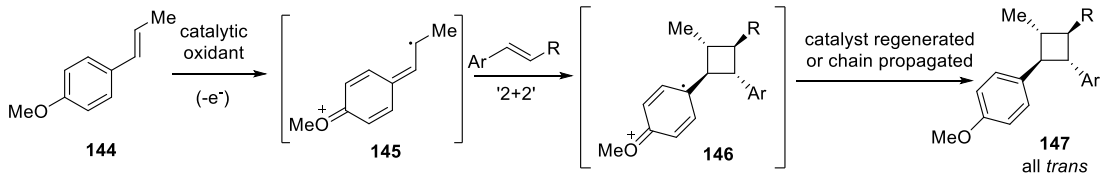


Scheme 1.33 (a) Photoinduced dual C-H and C-X borylation of aryl halide; (b) *sp*3 C–H hydroxylation reaction in HFIP

1.7. HFIP enabled stereoselective functionalization of alkenes

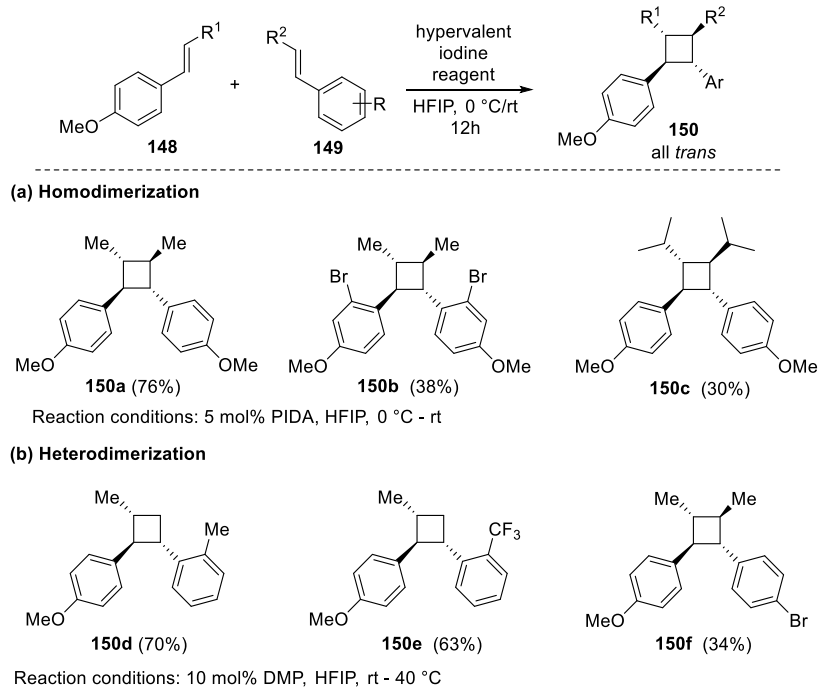
1.7.1. Hypervalent iodine reagent promoted [2+2] intermolecular cycloaddition of styrenes in HFIP

Donohoe and co-workers previously reported a hypervalent iodine reagent catalyzed dimerization of styrene for the synthesis of cyclobutanes, which generated two C-C bonds in a single step. This reaction is a regiospecific head to head coupling process which gives both symmetrical and unsymmetrical tetrasubstituted cyclobutanes **147** with high levels of diastereoselectivity (**Scheme 1.34**).[75] The role of HFIP is to stabilize the carbocation intermediate **145/146** and generate an adduct *via* hydrogen-bonding with the hypervalent iodine reagent, which enhances its oxidizing power (see **Chapter 1.6.7**).



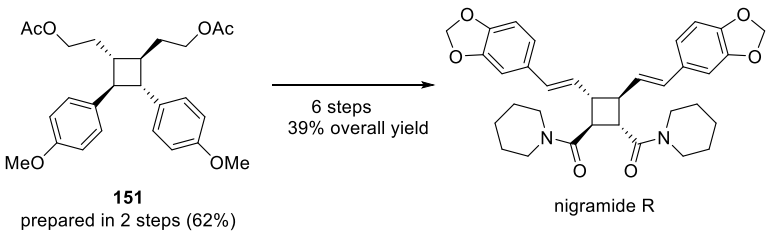
Scheme 1.34 Oxidation-promoted intermolecular styrene dimerization mechanism

The cycloaddition tolerated a wide range of alkenes, but it was essential that the aromatic substituent was electron-rich to promote the dimerization. For example, a significant drop in yield was observed in cyclobutane **150b** bearing a less electron-rich aromatic ring. In addition, bulky substituents such as an isopropyl group slowed the rate of cycloaddition, leading to a diminished yield of **150c** (**Scheme 1.35a**). Heterodimerization reactions were more challenging due to the competitive homodimerization pathway. This could be solved by re-optimizing the reaction conditions and using less reactive styrenes which did not dimerize under the reaction conditions (**Scheme 1.35b**).



Scheme 1.35 Homodimerization and heterodimerization of electron-rich styrenes

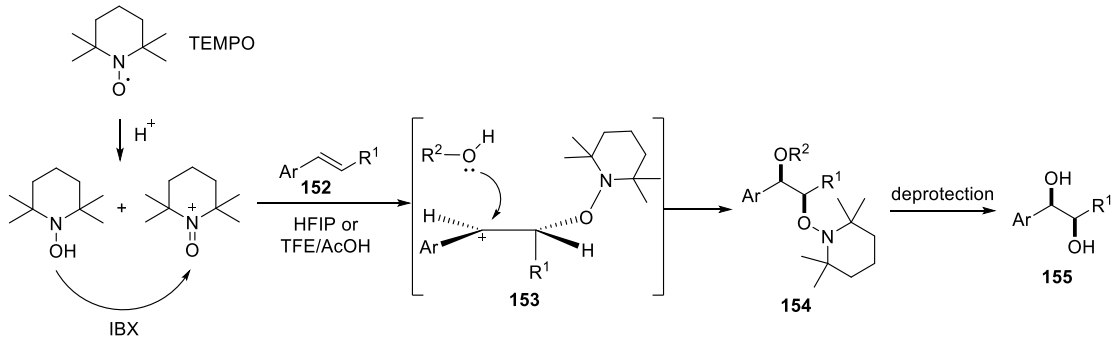
It was then decided to apply this methodology to the total synthesis of a natural product, nigramide R, which was successfully synthesized in 8 steps with an overall yield of 24% (**Scheme 1.36**). This natural product can be utilized to inhibit cytochrome P450 2D6 and possesses cytotoxicity against mouse lymphoma cell line L5178Y. [78]



Scheme 1.36 A eight-step total synthesis of nigramide R

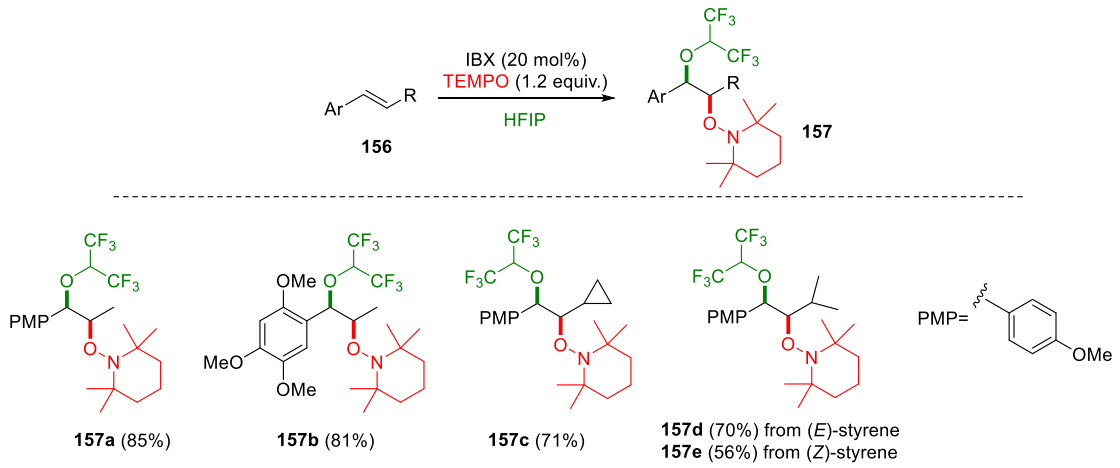
1.7.2. Metal free *syn*-dihydroxylation of alkene in HFIP

Intrigued by trapping the radical cation intermediate by a radical trapping agent, the Donohoe group further developed a novel metal-free *syn*-dihydroxylation of styrenes, which incorporates both TEMPO and an external nucleophilic alcohol or carboxylic acid (**Scheme 1.37**).[79] Under the acidic reaction conditions, it was proposed that TEMPO disproportionated into an oxoammonium cation and hydroxylamine, with the later being oxidized *in situ* by IBX. The electron-rich styrene **152** trapped the oxoammonium cation to generate a carbocation **153**, which was then attacked stereoselectively by a nucleophile which was opposite to the R^1 substituents to minimize the allylic strain, thus affording the product **155** as a *syn*-diol after deprotection.



Scheme 1.37 Metal-free *syn*-dihydroxylation of styrenes

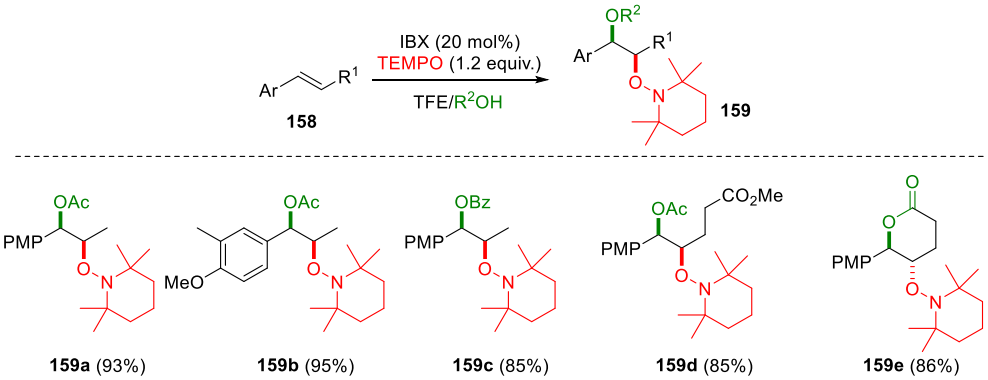
Moreover, HFIP (reaction solvent) could be utilized as the nucleophile for the addition to styrenes (**Scheme 1.38a**). A wide range of electron-rich styrenes were tolerated and the process was compatible with bulky allylic substituents R such as cyclopropyl (**157c**). Additionally, the use of both *E* and *Z* styrenes resulted in formation of the same product (**157d-e**), which supported the generation of a common carbocation intermediate.



Scheme 1.38 Metal-free *syn*-dioxygenation of styrenes using HFIP as the nucleophile

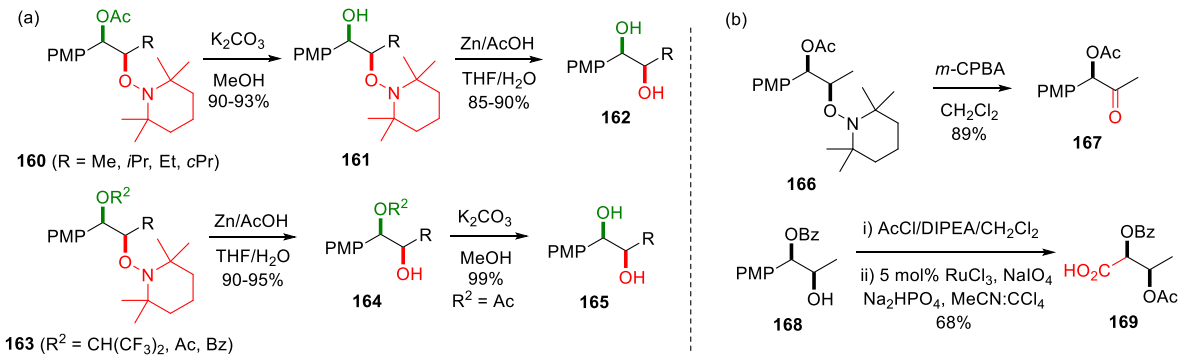
Next, attention moved to incorporation of carboxylic acids as the nucleophile including acetic acid and benzylic acid (**Scheme 1.39**). This process was successful, tolerating a wide range of electron-rich styrenes and allylic substituents R^1, including aliphatic

linear/branched, alicyclic groups, protected alcohols and esters, which led to good yields and high *syn*-diastereoselectivity. However, the related cyclization of a tethered carboxylic acid gave the product as a *trans* diastereomer **159e** which was attributed to the nature of the intramolecular reaction.



Scheme 1.39 Selected examples of the scope of *syn*-dioxygenation of styrenes

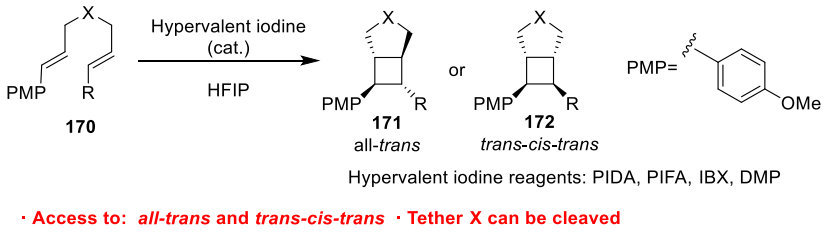
In order to access synthetically useful substrates, derivatization of the products was also attempted. The TEMPO and acetyl protecting groups could be selectively deprotected using Zn/AcOH and K_2CO_3/MeOH respectively (**Scheme 1.40a**). Additionally, ketones and carboxylic acids could be synthesized *via* oxidation of the OTEMP and PMP groups respectively (**Scheme 1.40b**).



Scheme 1.40 Selective functionalization of the products

1.7.3. Hypervalent iodine reagent promoted [2+2] intramolecular cycloaddition of tethered styrenes in HFIP

The Donohoe group further investigated the intramolecular variant of the hypervalent iodine initiated [2+2] cycloaddition by examining the scope of silicon and oxygen containing tethers (**Scheme 1.41**).[80]

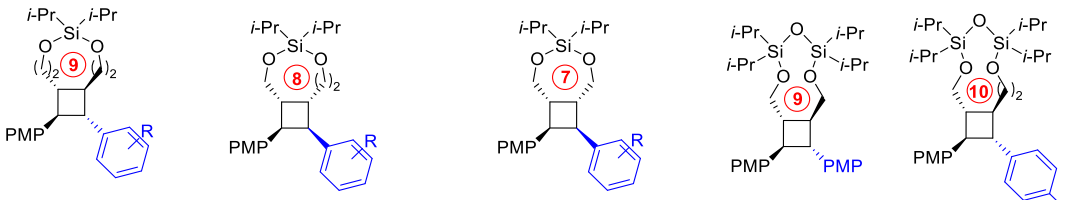


Scheme 1.41 Hypervalent iodine initiated intramolecular [2+2] cycloaddition

Firstly, the reaction to form cyclobutane **171a** was optimized. Then further substrates were prepared in order to expand the scope to more varied unsymmetrical substrates and different ring sizes. Replacing one of the PMP groups with a less electron rich *para*-methyl phenyl ring resulted in a slightly diminished yield while retaining the all-*trans* stereoselectivity (**Scheme 1.42**, **171a** and **171b**).

One of the limitations of previous intermolecular cycloaddition was an inability to cyclize allyl alcohols. However, this was overcome *via* the intramolecular approach. Incorporating both allylic and homoallylic alcohols led to a smaller fused [6.2.0] bicycles in good yields and modest diastereoselectivity, producing a mixture of all-*trans* and *trans-cis-trans* diasteromers (**Scheme 1.42**, **172c** and **172d**). Next, the synthesis of smaller fused rings was attempted. Both symmetrical and unsymmetrical fused [5.2.0]

bicycles were obtained in good yield and moderate diastereoselectivity (**Scheme 1.42**, **172e** and **172f**). Although a modest diastereoselectivity were observed with smaller fused bicycles, products with high or even full diastereocontrol in favour of all-*trans* cyclobutanes were observed with longer silicon tether (**Scheme 1.42**, **171g** and **171h**).



171a R=*p*-OMe (55%)
171b R=*p*-Me (40%)

172c R=*p*-Me (60%) dr 1.5:1
172d R=H (20%) dr 1.7:1

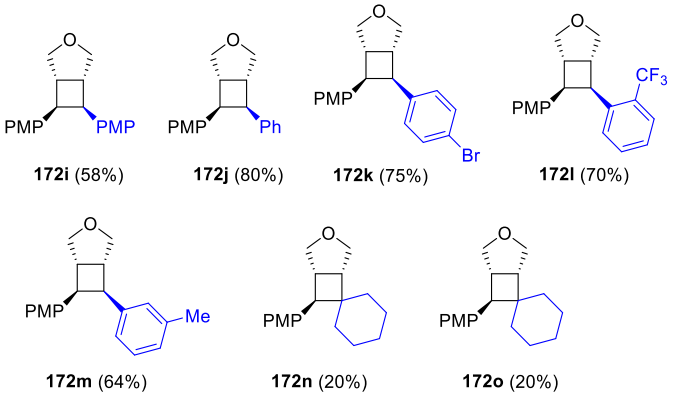
172e R = *p*-OMe (60%) dr 2:1
172f R = *p*-Me (40%) dr 2:1

171g (50%) dr 4:1

171h (53%)

Scheme 1.42 Scope of the intramolecular [2+2] cycloaddition-silicon tether

Encouraged by the trend that a smaller, constrained fused ring system led to the formation of *trans-cis-trans* configured products, the silicon tether was replaced with an oxygen tether. Both electron rich and electron deficient aromatic substituted systems gave high yields and led to a single *trans-cis-trans* diastereomer (**Scheme 1.43**, **172i**-**m**). Replacing the PMP groups with an aliphatic substituent resulted in slightly diminished yield (**Scheme 1.43**, **172n** and **172o**).

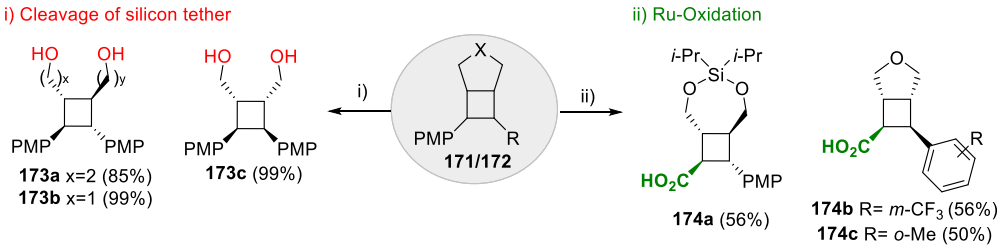


172i (58%)
172j (80%)
172k (75%)
172l (70%)
172m (64%)
172n (20%)
172o (20%)

Scheme 1.43 Scope of the intramolecular [2+2] cycloaddition-ether tether

Functionalization of the products was attempted after the scope of the reaction; one of

the advantages of the silicon tether is that it could be easily cleaved with TBAF, allowing quick access to corresponding diol with excellent yield (**Scheme 1.44**, **173a-c**). Additionally, Ru-catalyzed oxidation afforded synthetically useful carboxylic acids in good yield (**Scheme 1.44**, **174a-c**).

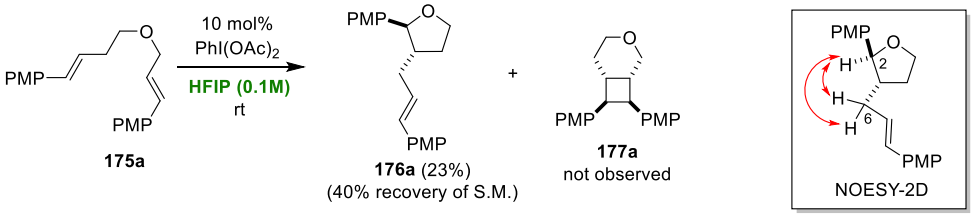


i) 3.0 equiv. of TBAF, THF; ii) 2.5-5 mol% $RuCl_3$, 20 equiv. $NaIO_4$, Na_2HPO_4 buffer: MeCN:CCl_4;

Scheme 1.44 Functionalizations of the tethered cyclobutane **171/172**

1.7.4. Hypervalent iodine reagents catalyzed stereoselective synthesis of heterocycles in HFIP

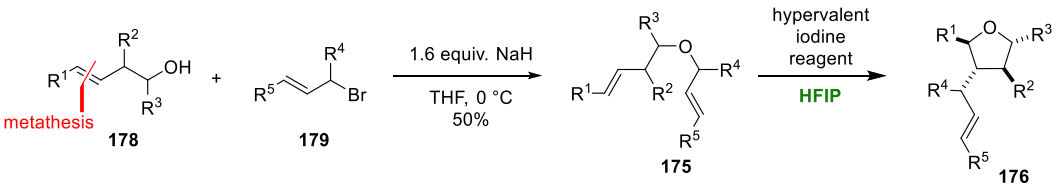
During the investigation of the hypervalent iodine initiated [2+2] cycloaddition of tethered ether substrates (undertaken by myself during my part II year), a unique and unexpected reactivity was discovered. Treating the diene starting material **175a** with 10 mol% of (diacetoxyiodo)benzene (PIDA) in HFIP afforded none of the desired cyclobutene **177** but instead, THFs **176a** was obtained in 23% yield as a single *trans*-diastereomer (**Scheme 1.45**).



Scheme 1.45 Unexpected synthesis of a THFs by cyclisation of tethered ether

It was decided to further investigate this unique reactivity to determine whether it can be applied to a wide range of this type of substrates. The aims of the project were threefold:

(i) As ether diene substrates **175** can be troublesome to synthesize from alcohols and bromides bearing R^3 and R^4 substituents, attention was focused on shortening the reaction sequence by using simpler starting materials (**Scheme 1.46**).



Scheme 1.46 Synthesis of starting material ether derivative **175** and THFs **176**

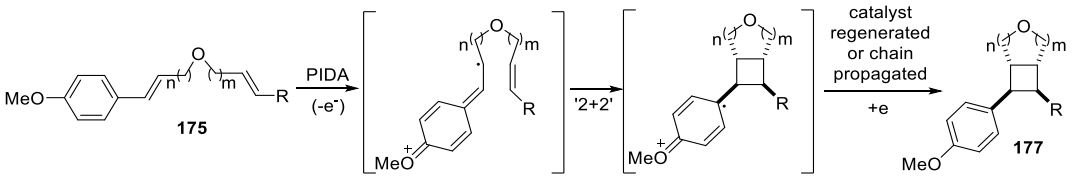
(ii) To expand the scope of the reaction to encompass tri- and tetra-substituted THF rings, and determine a way to synthesize enantiopure products using either enantiopure starting materials or chiral catalysts/auxiliaries.

(iii) Lastly, to further expand this methodology to the synthesis of other heterocycles such as tetrahydropyrans, lactones and pyrrolidines.

Chapter 2: Stereoselective Synthesis of Tetrahydrofurans

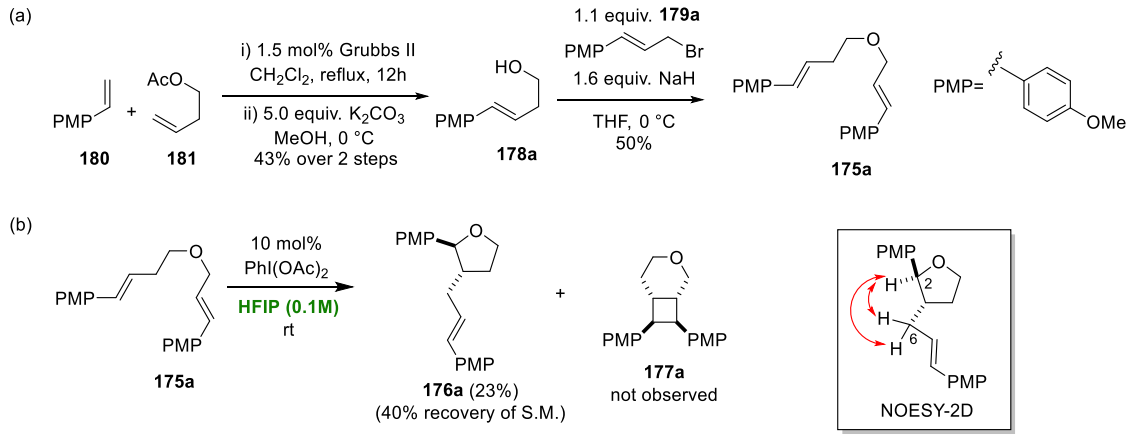
2.1. Discovery and Improvement of the Original Method

A stereoselective synthesis of cyclobutanes has been previously reported in the Donohoe group, where (diacetoxyiodo)benzene (PIDA) was utilized as a one-electron oxidant to promote intramolecular [2+2] cycloaddition of dienes. This process commenced with the one-electron oxidation of electron-rich alkene **175**, followed by [2+2] cycloaddition and catalyst regeneration, or chain propagation, to afford cyclobutane **177**. Additionally, hexafluoroisopropanol (HFIP) plays a critical role in this reactivity, because of its ability to stabilize charged intermediates and low nucleophilicity (**Scheme 2.1**).



Scheme 2.1 Hypervalent iodine promoted intramolecular [2+2] cycloaddition

During the investigation, a unique and unexpected reactivity was discovered. Subjecting diene **175a**, which was firstly prepared by the coupling of homoallylic alcohol **178a** with *para*-methoxycinnamyl bromide **179a**, with 10 mol% of PIDA in HFIP at room temperature led to no production of desired cyclobutane product **177a**. Surprisingly, the 2,3-*trans* tetrahydrofuran **176a** was obtained in 23% yield with 40% of diene **175a** being recovered. The 2,3-*trans* stereochemistry of the THFs **175a** was determined by a NOESY-2D experiment, as a clear nOe was seen between 2-H and 6-H_2 (**Scheme 2.2**).



Scheme 2.2 (a) Preparation of starting material ether **175a**; (b) Synthesis of THFs **176a** by cyclisation of ether **175a**

It was decided to start an investigation into the THFs formation by optimizing the reaction conditions using ether **175a** as a model. Using HFIP only at room temperature gave THFs **176a** in low yield with 90% of recovered S.M. (**Table 2.1, entry 1**). Extensive screening of different hypervalent iodine reagents revealed that Dess-Martin periodinane (DMP) was the best additive among them all, giving 30% yield with a loading of 10 mol% at room temperature (**Table 2.1, entries 2-6**). Another fluorinated solvent 2,2,2-trifluoroethanol (TFE) was also utilized, but it gave a much lower (4%) yield (**Table 2.1, entry 7**). Increasing the reaction temperature to 40 °C benefited the reaction with an encouraging 59% isolated yield (**Table 2.1, entry 8**). Increasing the loading of DMP to 15 mol% or continuing to increase the reaction temperature to 70 °C resulted in a lower yield. Increasing the reaction time to 36 hours also lowered the yield to 42% (**Table 2.1, entries 9-11**). Those results might indicate destruction of ether **175a** and THFs **176a** *via* increasing the temperature, loading of hypervalent iodine reagent or reaction time as lower recovery of ether **175a** and lower yield were observed. Thus, no

further optimization was carried out at this point.

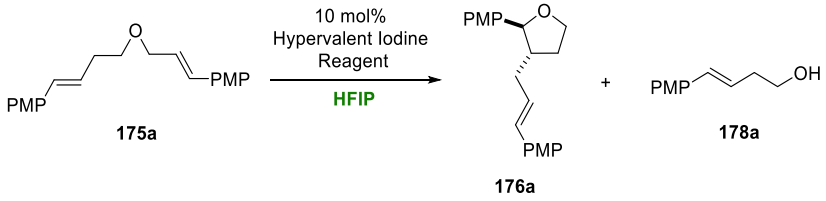
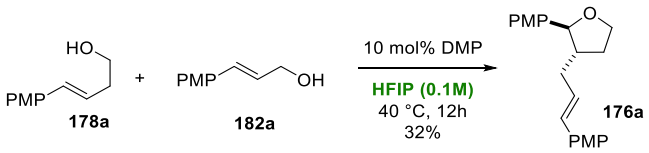


Table 2.1 Screening of different hypervalent iodine reagents and Lewis acids

Entry	Hypervalent Iodine Reagent	Temperature	Time	Yield **176a** (%)	Recovered ether **175a** (%)	Alcohol **178a** (%)
1	None	r.t.	12h	9	90	None
2	10 mol% PIDA	r.t.	12h	28	33	None
3	10 mol% DMP	r.t.	12h	30	28	None
4	10 mol% IBX	r.t.	12h	23	72	None
5	10 mol% HTIB	r.t.	12h	16	0	None
6	10 mol% PIFA	r.t.	12h	13	0	None
7 (TFE)	10 mol% DMP	r.t.	12h	4	91	None
8	10 mol% DMP	40 °C	12h	59	31	5%
9	15 mol% DMP	40 °C	12h	45	22	Trace
10	10 mol% DMP	70 °C	12h	45	8	10%
11	10 mol% DMP	40 °C	36h	42	6	Trace

* TFE was used as solvent

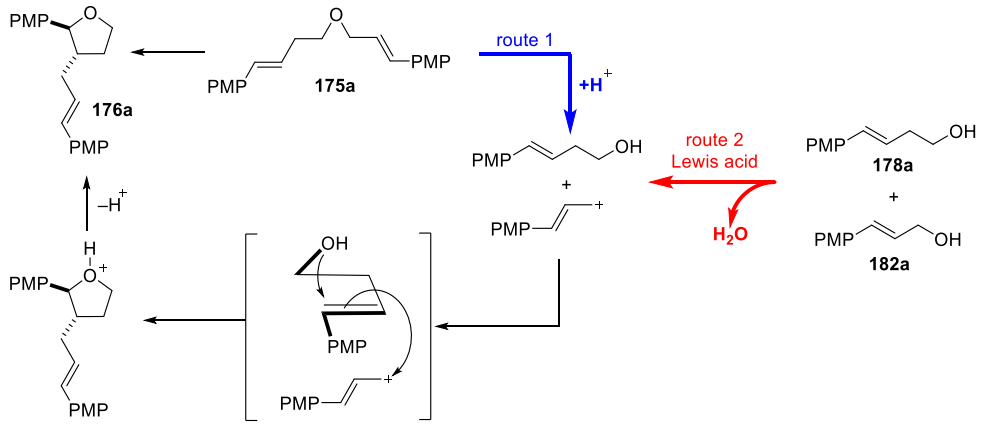
Interestingly, conducting the reaction at high temperature or using high catalyst loading led to recovery of alcohol **178a** in small amount, which might indicate that the cleavage of the C-O bond in ether **175a** was necessary for the construction of the THFs (**Table 2.1, entries 8-11**). Thus, a trial reaction was conducted to investigate whether the ether tether was actually necessary for the cyclisation. Pleasingly, mixing the two alcohols **178a** and **182a** under the optimized conditions successfully led to the formation of substituted THFs **176a**, which shortened the reaction sequence into a one-step process (**Scheme 2.3**).



Scheme 2.3 Synthesis of THFs **176a** by cyclisation of alcohols

2.2. Optimization of the Reaction Conditions

Based on the fact that alcohol **178a** was isolated from the ether cyclization process and the successful synthesis of THFs **176a** from two alcohols **178a** and **182a**, it was suggested that a carbocation was potentially one of the intermediates. Also, due to the fact that the reaction was able to produce a small amount of product with acidic HFIP in the absence of other reagents (**Table 2.1, entry 1**), it is highly possible that hypervalent iodine reagent acted as a Lewis acid rather than oxidant and the cyclization was in fact an acid-catalysed process: the carbocation could be generated from either ether **175a** (**Scheme 2.4, route 1**) or allyl alcohol **182a** (**Scheme 2.4, route 2**), which was then trapped by the nucleophilic alkene in alcohol **178a** to form the THFs **176a** in a 5-*endo*-trig process.



Scheme 2.4 Proposed mechanism for formation of the THFs **176a**

In order to find the best Lewis acid catalyst, a series of different hypervalent iodine reagents and Lewis acids were screened in the reaction of alcohols **178a** and **182a** in HFIP solvent. Two different hypervalent iodine reagents (DMP and PIDA) were used and both showed around 30% conversion (**Table 2.2, Entries 1 and 2**). Next, nine different Lewis acids were used to promote ionisation and titanium tetraisopropoxide showed the most promising results, giving a 41% yield with 58% of recovered alcohol **178a** (**Table 2.1, Entry 11**).

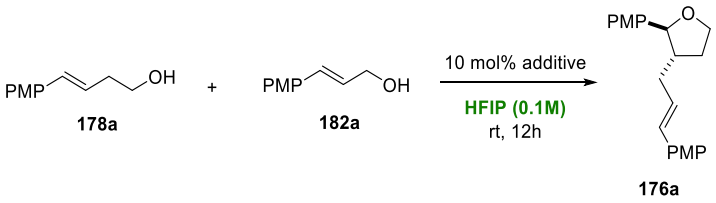


Table 2.2 Screening of different hypervalent iodine reagents and Lewis acids

Entry	Additive	Yield	Recovered	
		176a	Alcohol **178a**	Alcohol 18**2a**
		(%)	(%)	(%)
1	10 mol% PIDA	28	33	19
2	10 mol% DMP	30	28	10
3	10 mol% $Zn(OAc)_2$	33	49	28
4	10 mol% $MgCl_2$	29	32	0
5	10 mol% $Mg(OAc)_2$	10	49	30
6	10 mol% $Cu(OTf)_2$	11	17	0
7	10 mol% $ZnCl_2$	38	29	0
8	10 mol% $FeCl_3$	22	30	10
9	10 mol% $Sc(OTf)_3$	13	80	80
10	10 mol% $TiCl_4$	0	0	0
11	10 mol% $Ti(O^iPr)_4$	41	58	trace

Titanium tetraisopropoxide was selected as catalyst for further optimization because it performed the best among these Lewis acids (**Table 2.1)**. As the alcohol **182a** was only recovered in trace amounts, this might indicate the instability of alcohol **182a** in concentrated HFIP solution; therefore the addition of $Ti(O^iPr)_4$ *via* a syringe pump was

attempted, providing less harsh conditions by slowly raising the concentration of $Ti(O^iPr)_4$. However, the yield of THFs **176a** dropped, with much lower recovery of alcohol **178a** (**Table 2.3, Entry 2**). The addition of 2 equivalents of alcohol **182a** was also attempted, but a similar yield was obtained (**Table 2.3, Entry 3**). Finally, varying the concentration was also unfruitful, only 29% of THFs **176a** was obtained with reaction being run at a 1M concentration. (**Table 2.3, Entries 1 and 3**).

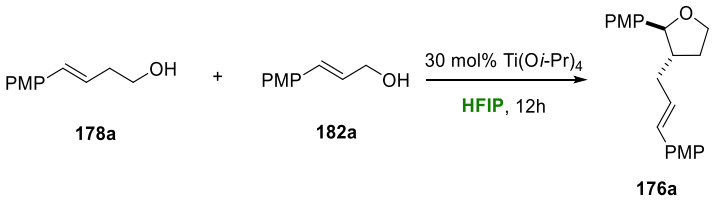
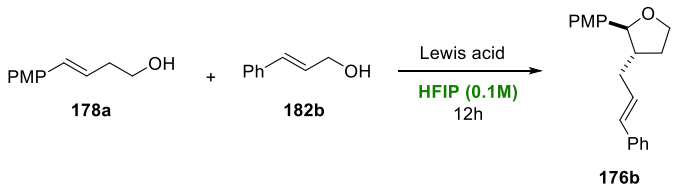


Table 2.3 Screening of $Ti(O^iPr)_4$ catalysed variables

Entry	$Ti(O^iPr)_4$ Loading	Concentration	Alcohol **178a** : **182a**	Yield **176a** (%)	SM recovered (%)	
					Alcohol **178a**	Alcohol **182a**
1	10 mol%	0.1 M	1:1	41	58	trace
2	10 mol% (addition *via* syringe pump)	0.1 M	1:1	28	28	trace
3	10 mol%	0.1 M	1:2	40	49	42
4	10 mol%	1 M	1:1	29	32	trace

The above results showed that the yield of reaction stopped at around 40%, which could be attributed to the instability of any carbocation intermediate generated by alcohol **182a** under the reaction conditions, possibly because the generated carbocation was either trapped by the HFIP molecule or destroyed under the reaction conditions. In order to improve the yields, alcohol **182b** bearing a phenyl ring was used instead and then a short optimization was carried out (**Table 2.4**)



Entry	Additive	Temperature	Yield **176b (%)**
1	10 mol% $Ti(O^iPr)_4$	r.t.	11
2	10 mol% $Ti(O^iPr)_4$	40 °C	18
3	30 mol% $Ti(O^iPr)_4$	40 °C	22
4	30 mol% $Ti(O^iPr)_4$	70 °C	52
5	30 mol% $Cu(OTf)_2$	70 °C	0
6	30 mol% $Sc(OTf)_3$	70 °C	0
7	30 mol% $Zn(OAc)_2$	70 °C	46
8*	0.025 mol% TfOH	70 °C	0
9	30 mol% Ph_4PBF_4	70 °C	47

*Mixture of HFIP/Perfluoro-2-butyltetrahydrofuran (1:1) were used as solvent

Table 2.4 Optimization of cyclisation using cinnamyl alcohol **182b**

Treating alcohol **178a** and less electron-rich cinnamyl alcohol **182b** with the previous best conditions only afforded 10% of the THFs **176b**. However, increases in temperature and $Ti(O^iPr)_4$ loading led to an increase in the yield (**Table 2.4, Entries 2 and 3**). Finally, performing the reaction at 70 °C with 30 mol% $Ti(O^iPr)_4$ loading gave the best result of 52% yield (**Table 2.4, Entry 4**).

Other Lewis acids; such as $Cu(OTf)_2$, $Sc(OTf)_2$ or $Zn(OAc)_2$ were also screened, but none of them performed better, giving 0%, 0% and 46% yield respectively (**Table 2.4, Entries 5-7**). Literature known conditions for related cyclization were also attempted; Brønsted acid TfOH with 1:1 mixture of HFIP/perfluoro-2-butyltetrahydrofuran gave only recovered starting materials (**Table 2.4, Entry 8**).[83] An ionic additive Ph_4PBF_4, which has been reported to strengthen the cation stabilizing ability of HFIP, gave a promising result

of 47% yield;[66] although all of the homoallylic alcohol **178a** was consumed, and this was not the case with Ti(O^iPr)$_4$ conditions (**Table 2.4, Entry 9**).

The screening study finished by examining a wide range of common solvents, such as $CHCl_3$, CH_2Cl_2, toluene, etc (**Table 2.5, Entries 2-12**). None were found to be compatible with the reaction and only starting material was recovered. Other fluorinated solvents, such as nonafluoro-*tert*-butyl alcohol, perfluoro-2-butyltetrahydrofuran and TFE were also screened, but none of them gave a better yield (**Table 2.5, Entries 13-15**).

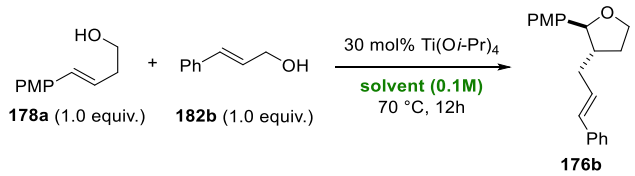


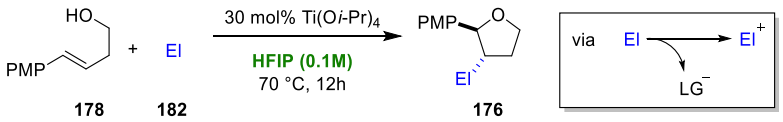
Table 2.5 Screening of different solvents

Entry	Solvent (0.1M of **178a**)	Yield **176b** (%)
1	HFIP	52%
2	$CHCl_3$	0
3	CH_2Cl_2	0
4	Toluene	0
5	Et_2O	0
6	EtOAc	0
7	MeCN	0
8	THF	0
9	IPA	0
10	MeOH	0
11	^{t}BuOH	0
12	DMF	0
13	Nonafluoro-tert-butyl alcohol	20%
14	Perfluoro-2-butyltetrahydrofuran	0%
15	TFE	Trace
16	CH_2Cl_2:HFIP 1:1	40%
17	CH_2Cl_2:HFIP 3:1	30%
18	CH_2Cl_2:HFIP 1:3	50%

Finally, mixtures of CH_2Cl_2 and HFIP were attempted, giving lower yields which were proportional to the percentage of HFIP used (**Table 2.5, Entries 16-18**). Thus, HFIP was determined to be the most suitable solvent for the cyclization. This can be explained by its high dielectric constant (ε=15.7) and low nucleophilicity, which is an ideal solvent for reaction involving generation of carbocations.

2.3. Scope of the Reaction-electrophiles

With the optimum conditions obtained, attention was then turned to explore the scope of the cation forming electrophiles **182** (**Scheme 2.5**). Suitable electrophiles should possess a group which could readily leave under the acidic conditions and should be able to generate a stabilized carbocation. Firstly, electrophilic alcohols needed to be explored, including acyclic allyl alcohols, cyclic allyl alcohols, benzylic alcohols, propargyl alcohols. Next, the use of other common non-alcoholic electrophiles were also planned, such as epoxides, orthoformates, halides, carbonyl substrates, etc.

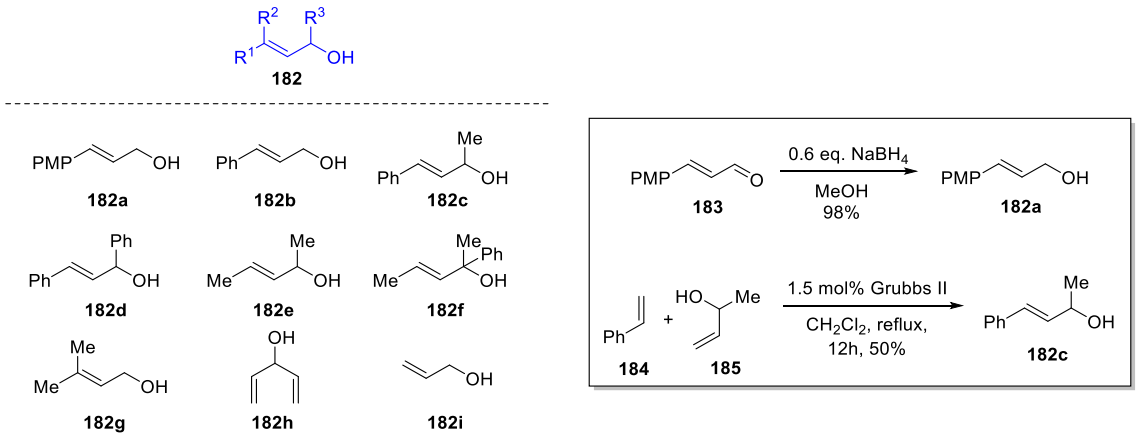


Scheme 2.5 scope of the electrophiles

2.3.1. Acyclic allyl alcohols acting as electrophiles

The exploration of the electrophiles started with varying the substituents R^1, R^2 and R^3 groups on the allyl alcohol component. Aromatic allyl alcohol **182a** was synthesized

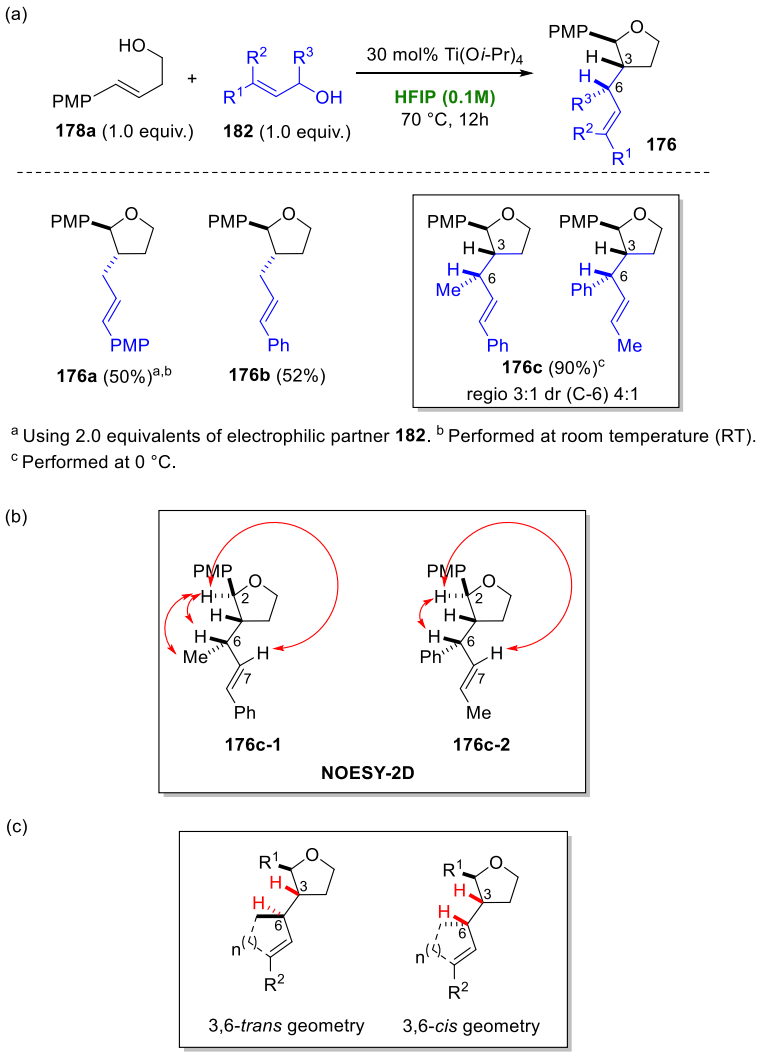
from the reduction of 4-methoxy cinnamyl aldehyde **183** and branched alcohol **182c** was synthesized from the Ru-catalyzed metathesis of styrene **184** and allyl acetate **185** followed by deprotection of the acetate. The other allyl alcohols were commercially available (**Scheme 2.6**).



Scheme 2.6 Synthesis of the acyclic allyl alcohols

THFs **176a** and **176b** were previously made during optimization process, affording 52% and 50% yield respectively (**Scheme 2.7a, 176a-176b**). Next, (*E*)-4-phenylbut-3-en-2-ol **182c** was subjected to the optimized reaction conditions in order to investigate the effect of an α-substituted allyl alcohol on the reactivity. Interestingly, two separable regioisomeric products **176c** were obtained in 90% yield and a 3:1 ratio, both were a mixture of 4:1 diastereoisomers (the 3,6-*cis* stereochemistry was determined by the crystal structure of compound **240b** which was prepared later on) (**Scheme 2.7a, 176c**). The stereochemistry of THFs **176c** was characterized by NOESY-2D experiments. Correlations could be seen between 2-H and 6-H, 2-H and Me, 2-H and 7-H for pyrrolidines **176c-1;** correlations could be seen between 2-H and 6-H, 2-H and 7-H for

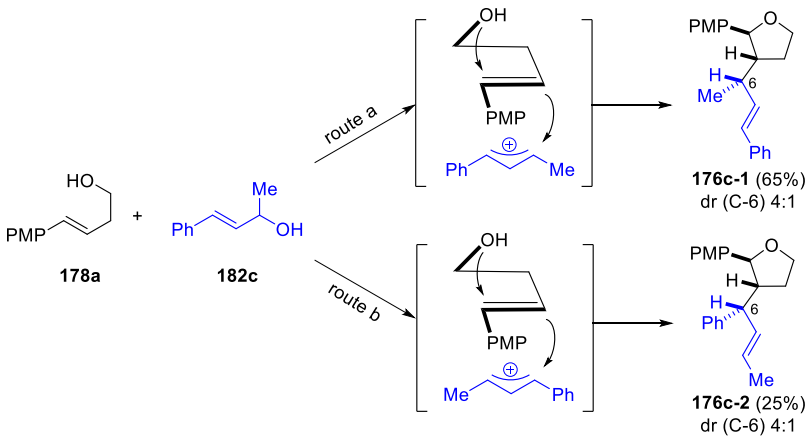
pyrrolidines **176c-2**, suggesting the 2,3-*trans* geometry (**Scheme 2.7b**). Additionally, it was decided that all THFs bearing an allylic substituent would be drawn in the conformation which locates the carbon double bond at the right-hand side. This allows easy comparison of the stereochemistry between the C-3 and C-6 positions for acyclic and cyclic substituents. When drawn in this way, the 3,6-*trans* geometry means the 3-H and 6-H are in a *trans* arrangement, vice versa (**Scheme 2.7c**).



[a] Using 2.0 equivalents of electrophilic partner **182**. [b] Performed at room temperature (RT). [c] Performed at 0 °C.

Scheme 2.7 (a) Scope of the electrophiles-acyclic allyl alcohols; (b) NOESY-2D experiments on THFs **176c;** (c) Definition of 3,6-*trans* and 3,6-*cis* geometry

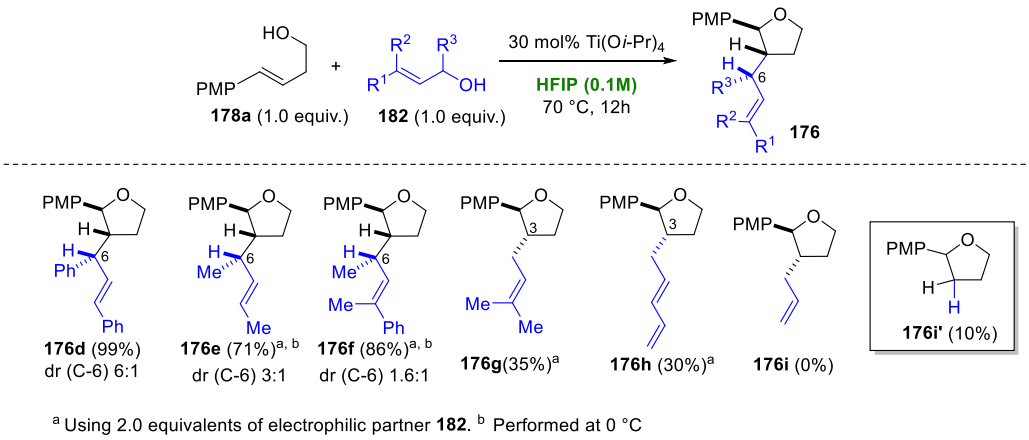
The regioisomeric selectivity problem was attributed to the formation of an unsymmetrical allylic carbocation from allyl alcohol **182c** (**Scheme 2.8**), which allowed alcohol **178a** to attack the carbocation at either end. Pleasingly, due to the larger steric bulk of the phenyl group, attack on the side of methyl group (route a) was more accessible and major regioisomer **176c-1** was obtained in 65% yield while the minor regioisomer **176c-2** was obtained in 25% yield.



Scheme 2.8 Synthesis of regioisomeric tetrahydrofuran **176c**

In order to avoid this regioisomeric selectivity problem, it was decided to use symmetrical α-substituted allyl alcohols (**Scheme 2.9, 176d-e**). Treating (*E*)-1,3-diphenylprop-2-en-1-ol **182d** with alcohol **178a** afforded one regioisomeric product **176d** in quantitative yield with 6:1 dr. To investigate whether the presence of aromatic groups on the allyl alcohol were necessary for cyclization, (*E*)-pent-3-en-2-ol **182e** was examined, and this afforded 71% of desired product **176e** with 2:1 dr; although this reaction needed two equivalents of the alcohol **182e**, it allowed the cyclization to occur at 0 °C. Another way to solve the regioisomeric selectivity problem was to install an additional substituent at the terminal end of the alkene of the allyl

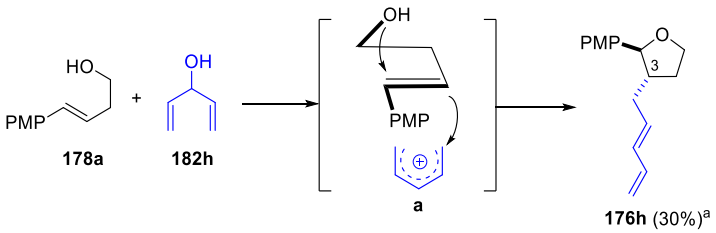
alcohol, such as alcohol **182f**, which formed a carbocation that was completely inhibited from attack at the more hindered side, giving 86% yield with 1.6:1 dr (**Scheme 2.9, 176e**). Next, less reactive aliphatic allyl alcohols **182g** and **182h** were subjected to the reaction conditions, allowing access to a nonaromatic substituent at the C-3 position in the tetrahydrofuran products (**Scheme 2.9, 176g-176h**); although with a decrease in yield, giving 35% and 30% respectively. Pleasingly, no regioisomeric selectivity problem was observed with only one product being obtained. The 2,3-*trans* stereochemistry of THFs **176d**-**176h** was assigned by analogy with THFs **176a** and **176c**.



[a] Using 2.0 equivalents of electrophilic partner **182**. [b] Performed at 0 °C

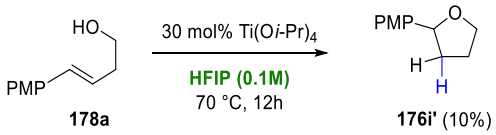
Scheme 2.9 Scope of the electrophiles-acyclic allyl alcohols

For the latter, diallyl alcohol **182h,** a THFs bearing a diene substituent at the C-3 position was obtained as a single regioisomer. This is because the primary positions of the generated conjugated diallylic carbocation **a** was less steric hindered and more accessible than secondary position, leading to the sole formation of THFs **176h** (**Scheme 2.10**).



Scheme 2.10 Synthesis of conjugated diene tetrahydrofuran **176h**

Finally, non-activated allyl alcohol **182i** produced no desired product **176i**, even when 5 equivalents of alcohol **182i** were used (**Scheme 2.10, 176i**). Interestingly, protonated product **176i'** was observed in 10% yield. Unlike the previous examples where alcohol **182** was fully consumed, alcohol **182i** were recovered in quantitative amounts, indicating that no desired carbocation was generated so that only a proton from the solvent could be trapped by the alcohol **178a** to form the protonated product **176i'**. In order to support this conclusion, a control experiment was carried out where alcohol **178a** alone was subjected to the reaction conditions, leading to the formation of **176i'** in the same yield (**Scheme 2.11)**.

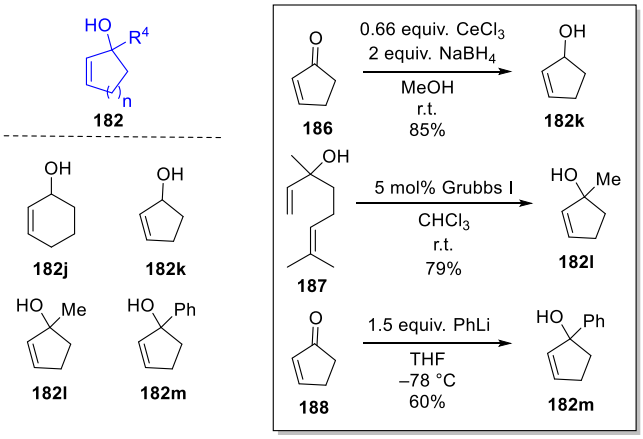


Scheme 2.11 Control experiments-formation of protonated product **176i'**

2.3.2. Cyclic allyl alcohols acting as electrophiles

Next, it was decided to focus on investigating the reactivity of the cyclic allyl alcohols by varying the ring size of the alcohol and the α-substituent R^4. Cyclopentenyl alcohol **182k** was synthesized by the reduction of cyclopent-2-en-1-one **186**; alcohol **182l** was made

from ring-closing metathesis of linalool **187** and alcohol **2m** was obtained from addition of phenyl lithium to cyclopent-2-en-1-one **188**. Note that cyclohexenyl alcohol **182j** was commercially available (**Scheme 2.12**).



Scheme 2.12 Synthesis of the cyclic allyl alcohols

Treating cyclohexenyl alcohol **182j** with alcohol **178a** afforded THFs **176j** in 65% yield and pleasingly there was diasterocontrol at the C-6 position, giving the products as a 2:1 mixture of diastereomers (the 3,6-*trans* stereochemistry at C-6 position was determined by the crystal structure of compound **176aad** which was made later on) (**Table 2.6**, **Entry 1**). However, 10% of the protonated product **176i'** was also found which was only partially separable from the THFs **176j**. To inhibit the formation of protonated product **176i'**, a short optimization study was conducted. Lowering the temperature to room temperature successfully avoided the formation of **176i'**, but the yield was compromised (**Table 2.6**, **Entry 2**). Next, the yield was improved to 65% by using two equivalent of alcohol **182j** (**Table 2.6**, **Entry 3**). Further decreasing the temperature to 0 °C with 2 equivalents of alcohol **182j** employed was not beneficial, giving THFs **176j** in a diminished 45% yield (**Table 2.6**, **Entry 4**). Unfortunately, attempts to improve the

diastereocontrol at the C-6 position were not successful, both conducting the reaction at 70 °C and 0 °C gave a 2:1 dr.

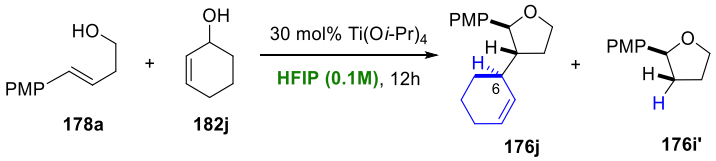
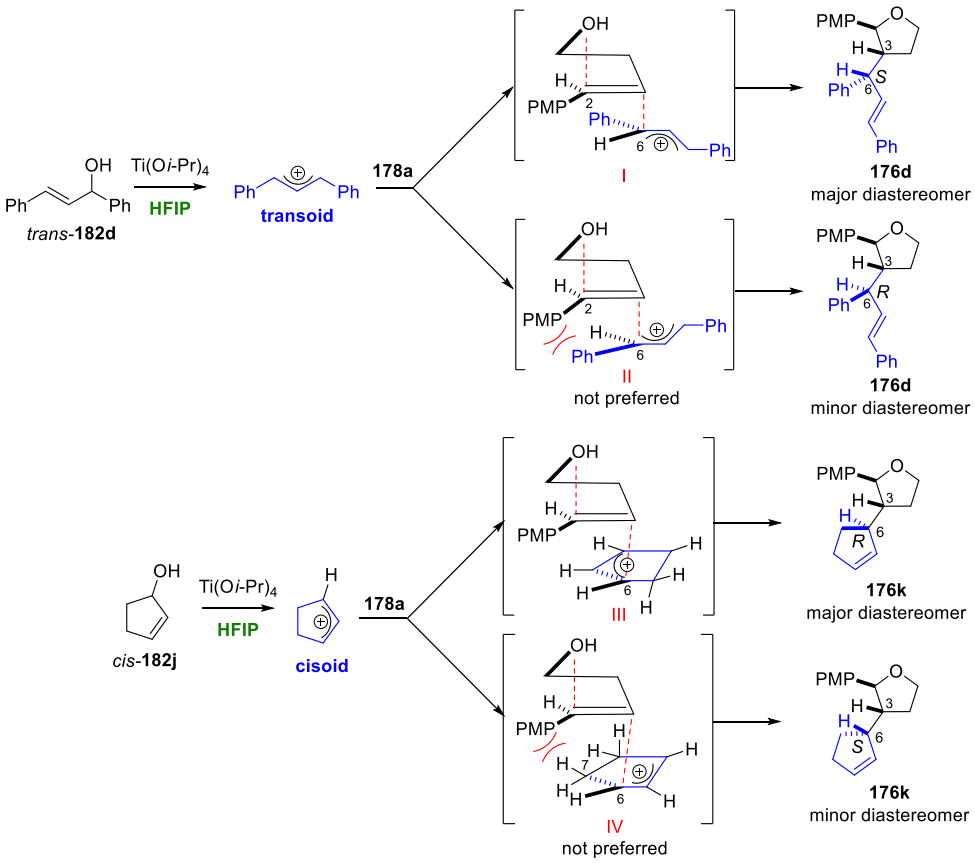


Table 2.6 Optimization of cyclization with alcohol **182j**

Entry	Temperature	Equivalent of **182j**	Yield (%) **176j**	**176i'**	dr (C-6)
1	70 °C	1.0	65	10	2:1
2	rt	1.0	50	0	2:1
3	rt	2.0	65	0	2:1
4	0 °C	2.0	45	0	2:1

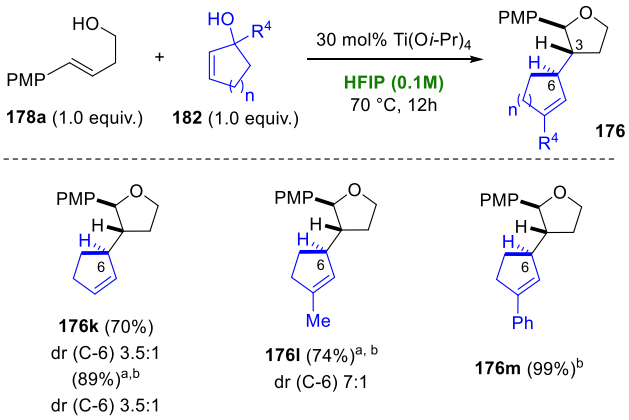
Interestingly, inspection of the X-Ray structures (**176aad** and **240b,** see **Scheme 2.33** and **2.46**) revealed that in the major isomers, the stereochemistry at the C-6 position of THFs bearing a cyclic substituent was opposite to the acyclic variant. This could be attributed to the rigid cyclic ring, resulting in completely opposite geometry of the generated carbocation intermediate from the acyclic and cyclic allyl alcohols (transoid verses cisoid). For cyclization involving an acyclic allyl carbocation, it may prefer to adopt conformation I to give the major diastereomer having a 3,6-*trans* geometry, where the phenyl and PMP groups are pointing directly toward the 2-H and 6-H atom to avoid a steric clash in the conformation II. For cyclization involving a cyclic allyl carbocation, it prefers to adopt the conformation III to give the major diastereomer as a 3,6-*cis* geometry, where the planar allylic carbocation is now placed directly under the alkene to a to avoid steric clash between the PMP group and 7-H_2 in the conformation II (**Scheme 2.13**).



Scheme 2.13 Proposed mechanism for the cyclization of homoallylic alcohol with acyclic and cyclic allyl alcohols

Next, employing cyclopentenyl alcohol **182k** as the electrophile under standard conditions gave THFs **176k** in 70% yield with 3.5:1 dr, which had slightly better diasteroselectivity than **176j**. Protonated product **176i'** was again obtained in 10% yield as an inseparable side-product from the THFs **176k**. Using re-optimized reaction conditions was also beneficial, improving the yield to 89% and inhibiting the production of side-product **176i'**, but the diastereomeric ratio remained unchanged as expected. (**Scheme 2.14, 176k**). In an effort to improve the modest stereoselectivity at the exocyclic C-6 stereocentre, it was decided to use tertiary cyclopentenyl allyl alcohols with aliphatic or aromatic substituents (**Scheme 2.14, 176l-176m**). Subjecting two

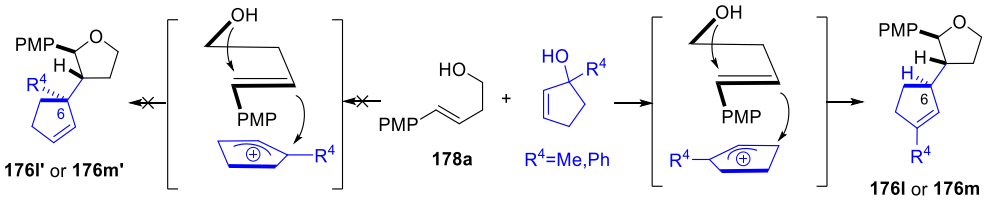
equivalents of methyl bearing tertiary alcohol **182l** at room temperature afforded 74% yield with much higher diasteroselectivity, giving THFs **176l** as a 7:1 mixture of diastereomers. Pleasingly, replacing the methyl substituent with a bulkier phenyl group led to complete diasterocontrol over the newly formed stereogenic center at the C-6 position, giving THFs **176m** in quantitative yield and as a single diastereomer.



[a] Using 2.0 equivalents of electrophilic partner **182**.
[b] Performed at room temperature (RT).

Scheme 2.14 Scope of the electrophiles-cyclic allyl alcohols

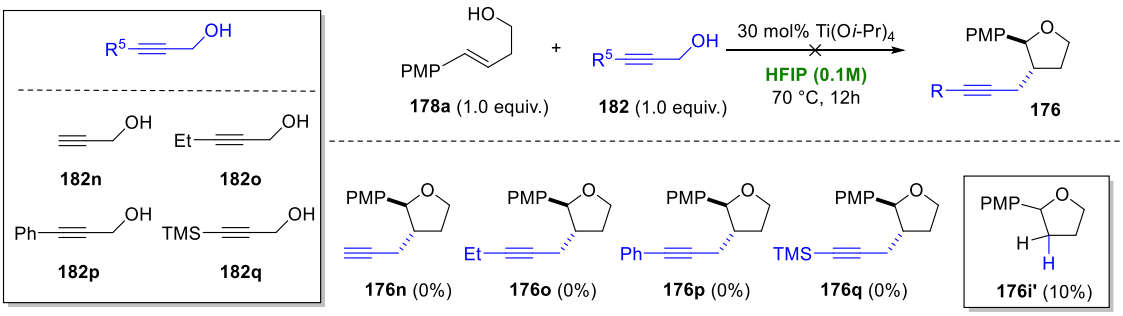
In addition, both THFs **176l** and **176m** were obtained with complete regioisomeric control, only one regioisomer was observed. This was attributed to attack at the less steric hindered position at the secondary carbocation, completely inhibiting access at the tertiary carbocation. (**Scheme 2.15**).



Scheme 2.15 Synthesis of THFs **176l** and **176m**

2.3.3. Propargyl alcohols acting as electrophiles

Inspired by the good yields and modest to high diastereoselectivity observed *via* using allyl alcohols, it was decided to utilize its propargylic variants to examine their reactivities. Aliphatic and aromatic propargyl alcohols **182n**, **182o 182p** and **182q**, which were all commercially available, were treated with alcohol **178a** under the optimized conditions. Unfortunately, none of them gave the desired THFs; only the protonated product **176i'** was obtained in 10% yield. (**Scheme 2.16)**.



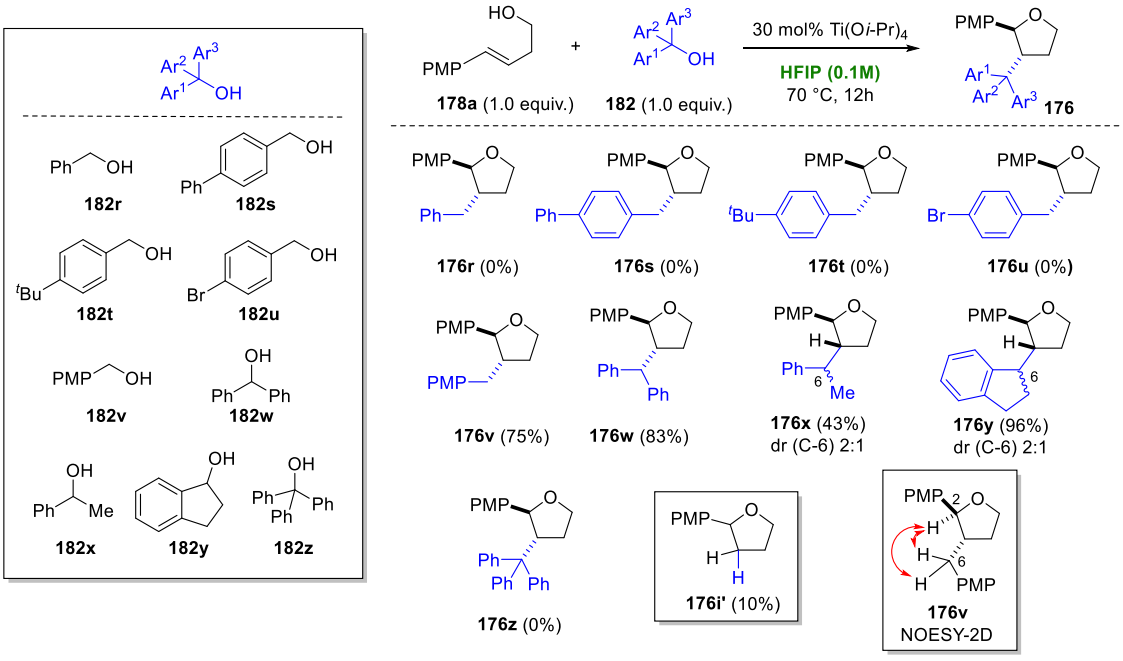
Scheme 2.16 Scope of the electrophiles- propargyl alcohols

2.3.4. Benzylic alcohols acting as electrophiles

Next, exploration of the reactivities of benzylic alcohols was undertaken, especially those which were able to generate more stabilized carbocation under the acidic conditions. Electron deficient, electron neutral and electron rich benzylic alcohols **182r**-**182z** were screened, all of them were commercially available (**Scheme 2.17)**.

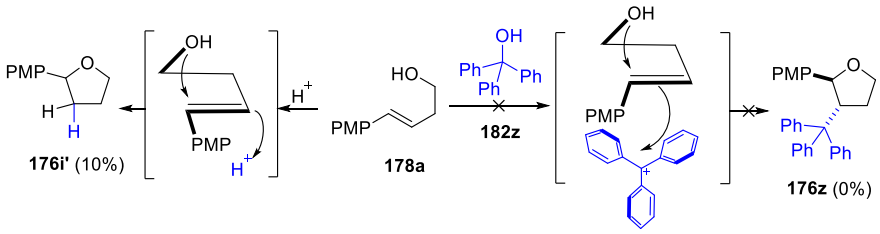
Using electron neutral or electron deficient primary benzylic alcohols **182r**-**182u** afforded none of desired THF product; all of them gave protonated product **176i'** in 10%

yield and recovered benzylic alcohol **182r**-**182u** in quantitative amounts. As electron-rich benzylic alcohols led to more stable carbocations, alcohol **2v** was treated with alcohol **178a** under standard conditions, leading to the successful formation of THFs **176v** in 75% yield. Inspired by this result, secondary benzylic alcohols **182w-182y** were subjected to the reaction conditions as they were able to generate stable carbocations, giving THFs **176w** and **176x** in 83% and 43% yield respectively. The yield of THFs **176x** was much lower yield than **176w** as alcohol **182x** generated a less stabilized carbocation; and it was a mixture of diastereomers in 2:1 ratio. Next, indanol **182y** gave same diastereocontrol at the C-6 position as **182x** but much higher yield, producing **176y** in 96% yield with 2:1 dr (the stereochemistry at C-6 position in THFs **176x** and **176y** were unassigned). The stereochemistry of THFs **176v** was determined by NOESY-2D experiment, where correlations could be seen between 2-H and 6-H_2, suggesting the 2,3-*trans* geometry.



Scheme 2.17 Scope of the electrophiles- benzylic alcohols

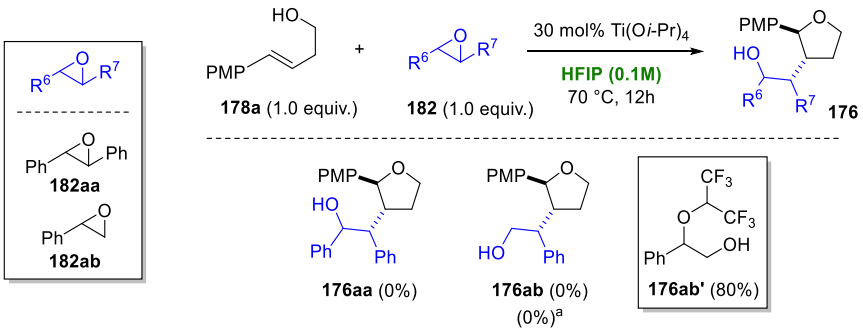
Finally, although tertiary benzylic alcohol **182z** could form a stabilized tertiary carbocation, exists as a propeller shape which prevented the attack from alcohol **178a** to generate the desired product **176z**. Alcohol **178a** therefore could only trap the proton from HFIP to afford 10% of protonated product **176i'** (**Scheme 2.18)**.



Scheme 2.18 Generation of protonated product **176i'**

2.3.5. Epoxides acting as electrophiles

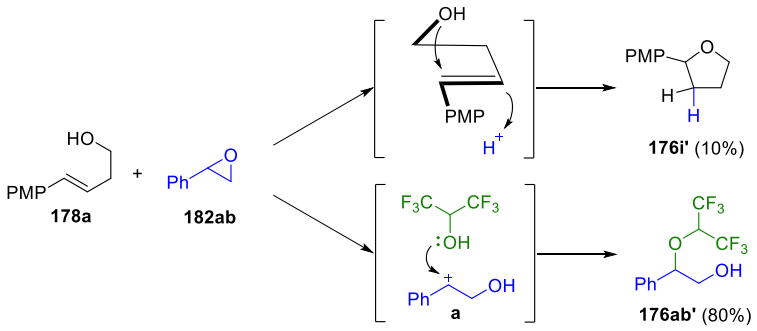
Epoxides are known to be able to generate carbocation upon ring opening, so commercially available epoxides **182aa** and **182ab** were treated with alcohol **178a** under the optimized conditions (**Scheme 2.19)**. Unfortunately, epoxide **182aa** gave no cyclized THFs **176aa**, producing only protonated product **176i'** and recovering most of the alcohol **178a** and epoxide **182aa**. This could be attributed to the steric bulk of the carbocation generated. To solve this problem, less bulky epoxide **182ab** was used. However, no desired product **176ab** was observed and a side-product **176ab'** was obtained in 80% yield.



[a] reaction was conducted in a solvent mixture of CH_2Cl_2:HFIP (1:1)

Scheme 2.19 Scope of the electrophiles- epoxides

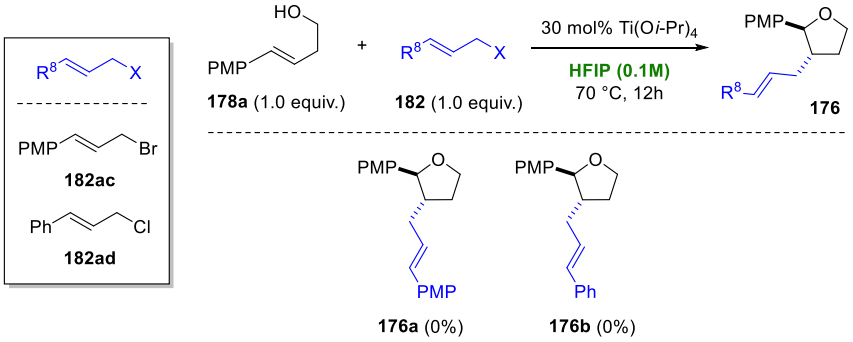
Although the generation of a carbocation intermediate from epoxide **182ab** was successful, the alcohol **178a** failed to trap it to form THFs **176ab**, which could be attributed to the competition between two sets of nucleophiles (alcohol **178a** versus HFIP solvent). After the formation of carbocation intermediate **a** from epoxide **182ab**, instead of alcohol **178a**, HFIP solvent attacked it to generate side-product **176ab'**. Without any carbocation available to be trapped, alcohol **178a** could only attack a proton to form the protonated product **176i'** (**Scheme 2.20)**. Next, mixed solvents of 1:1 HFIP: CH_2Cl_2 were used which aimed to shut down the formation of **176ab'** *via* decreasing the concentration of HFIP, but only **176i'** and **176ab'** were observed with diminished yield.



Scheme 2.20 Generation of protonated product **176i'** and side-product **176ab'**

2.3.6. Halides acting as electrophiles

Allylic halides were also screened as they are good electrophiles and are widely used as alkylating agents. Bromide **182ac** and chloride **182ad** were treated with alcohol **178a**, affording a complex mixture without any alcohol or halide being recovered and TLC study showed a multi-component mixture. This could be attributed to the destruction of starting materials under the reaction conditions, as the colour of substrates turned into black and produced lots of fumes as soon as a solution of $Ti(O^iPr)_4$ in HFIP was added, which might indicate the instability of halides in HFIP and production of hydrogen halide, leading to the compete destruction of the starting materials (**Scheme 2.21)**.

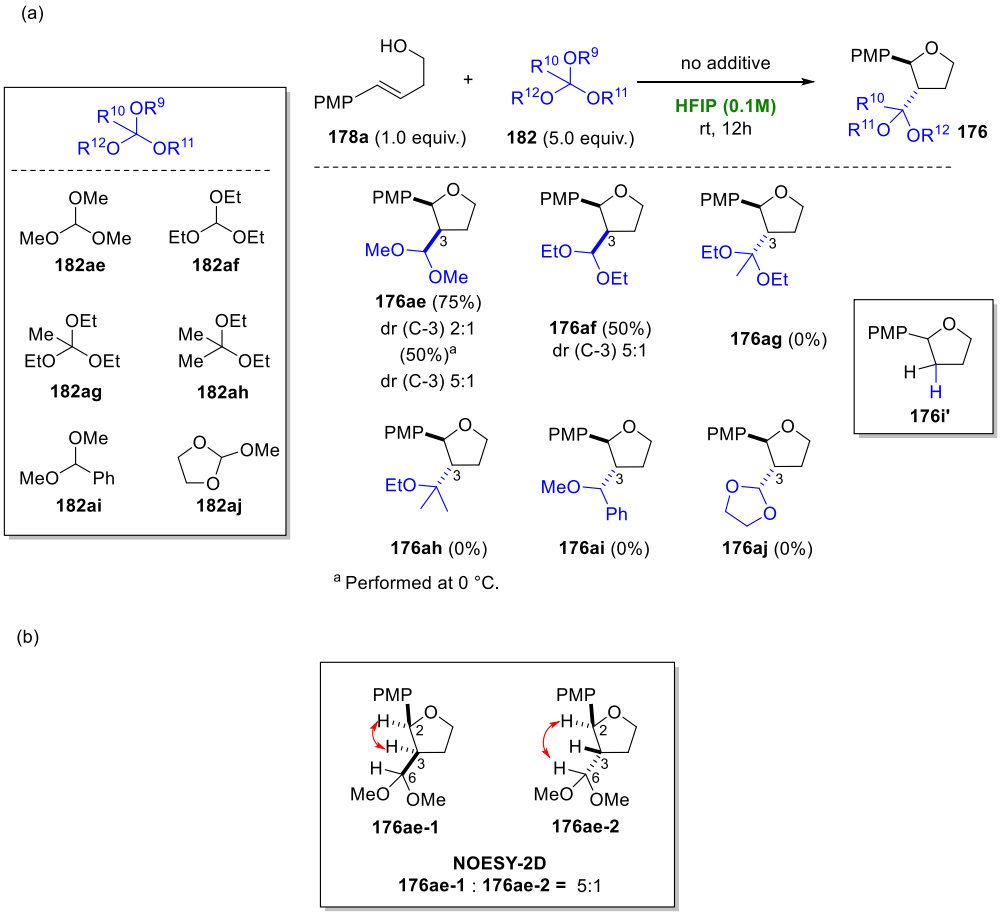


Scheme 2.21 Scope of the electrophiles - halides

2.3.7. Orthoformates and acetals acting as electrophiles

Attention was then moved to orthoformates and acetals, which could be used as good electrophiles and easily modified into useful functional groups by hydrolysis. Initial attempts using trimethyl orthoformate **182ae** were unsuccessful, leading to full consumption of **182ae** while all alcohol **178a** was recovered, which might indicate that the reaction conditions were too harsh for orthoformate **182ae**. It was therefore

decided to remove the $Ti(O^iPr)_4$ and lower the temperature to room temperature. Interestingly, treating trimethylorthoformate **182ae** with these mild conditions gave a separable mixture of 2:1 *cis* to *trans* diastereomers **176ae** in 75% yield. This was the first time that a 2,3-*cis* diastereomer was observed, which might indicate the cyclization proceeds through a different reaction pathway. Decreasing the temperature to 0 °C helped to improve the diastereocontrol to 5:1 dr, although with a slightly diminished yield. Subjecting orthoformate **182af** to the reaction conditions produced **176af** in the same yield and diastereomeric ratio as **176ae**. The stereochemistry of THFs **176ae** was determined by a NOESY-2D experiment. Clear nOe correlation could be seen between 2-H and 3-H for the major diastereomer, suggesting the 2,3-*cis* stereochemistry. Clear nOe correlation could be seen between 2-H and 6-H for the minor diastereomer, suggesting the 2,3-*cis* stereochemistry. (**Scheme 2.22b)**. The stereochemistry of THFs **176af** was assigned by analogy with THFs **176ae.** Next, the use of acetals **182ag**-**182aj** was not fruitful, none of them gave the cyclized product **176ag** to **176aj**, only large amount of alcohol **178a** and acetals were recovered and protonated product **176i'** was observed in a small amount (**Scheme 2.22a)**.

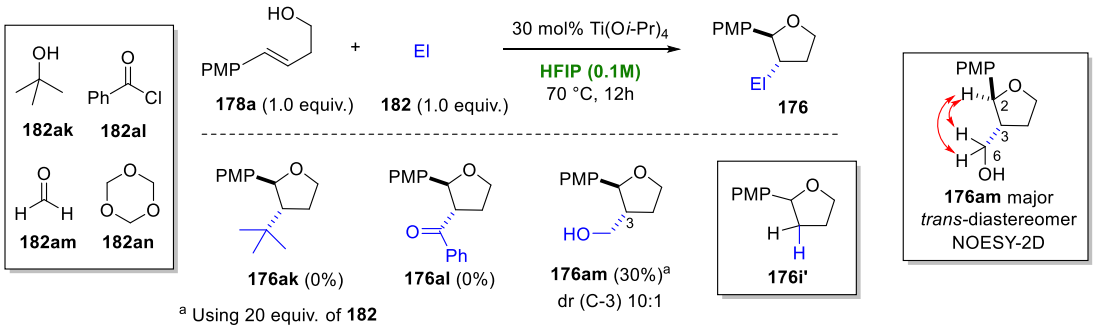


Scheme 2.22 (a) Scope of the electrophiles- orthoformate; (b) NOESY-2D experiments of THFs **176ae**

2.3.8. Miscellaneous

Finally, other miscellaneous electrophiles **182ak-182an** were screened to complete the scope of the electrophiles (**Scheme 2.23a)**. Using aliphatic tertiary alcohol **182ak** afforded no production of THFs **176ak**, while producing 10% of the protonated product **176i'**, which could be attributed to the steric hinderance of the formed tertiary carbocation. Similarly with allylic halides, acyl chloride **182al** gave a complex mixture where no starting materials were recovered and no THFs **176al** was obtained, which was probably due to the instability of acyl chloride in HFIP. Next, treating 20 equivalents of

paraformaldehyde **182am** with alcohol **178a** yielded 30% of THFs **176am** as a mixture of 10:1 *trans* to *cis* diastereomers. The 2,3-*trans* stereochemistry of the major diastereomer in THFs **176am** was determined by a NOESY-2D experiment, as a clear nOe was seen between 2-H and 6-H_2 for the major *trans* diastereomer.



Scheme 2.23 Scope of the electrophiles- miscellaneous and NOESY-2D experiments of THFs **176am**

In order to optimize the yield and obtain a better stereocontrol outcome, a short optimization study was carried out. Initial attempts at decreasing the temperature to room temperature or 0 °C completely shut down the reaction, giving only recovered starting material (**Table 2.7**, **Entries 2-3)**. It was then found that HFIP was not the optimal solvent for dissolving paraformaldehyde as a cloudy reaction solution was observed, a 1:1 mixture of methanol and HFIP was therefore used for the cyclization. Unfortunately, although the addition of methanol helped in dissolving the paraformaldehyde, it completely stopped the reaction at either 70 °C or room temperature, giving only recovered starting materials (**Table 2.7**, **Entries 4-5)**.

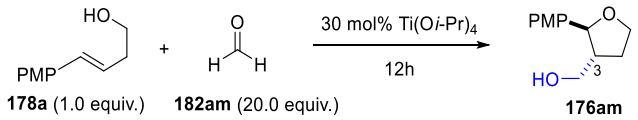


Table 2.7 Optimization of cyclization with paraformaldehyde **182am**

Entry	Temperature	Solvent	Yield **176am** (%)	dr (C-3)
1	70 °C	HFIP	30	10:1
2	rt	HFIP	0	
3	0 °C	HFIP	0	
4	70 °C	HFIP:MeOH 1:1	0	
5	rt	HFIP:MeOH 1:1	0	

As paraformaldehyde is generally cracked under basic conditions and 1,3,5-trioxane **182an** is known to be compatible with acidic conditions. It was then subjected to the cyclization under standard conditions. Although all trioxane was dissolved in HFIP, the reaction yielded neither recovered starting materials nor desired THFs **3am**, while producing protonated product **176i'** in quantitative yield (**Table 2.7**, **Entry 1)**. This interesting result might indicate rather than being trapped by alcohol **178a**, trioxane **182an** was destroyed and so gave only protonated product **176i'**. Further optimization of this cyclization was unfruitful, neither varying the temperature nor loading of $Ti(O^iPr)_4$ afford cyclized product **176am**, while no protonated product **176i'** was found (**Table 2.7**, **Entries 2-4)**.

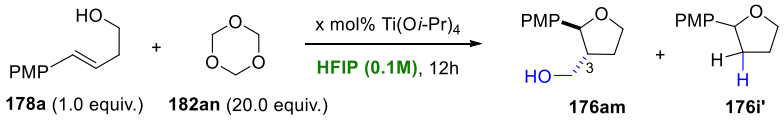
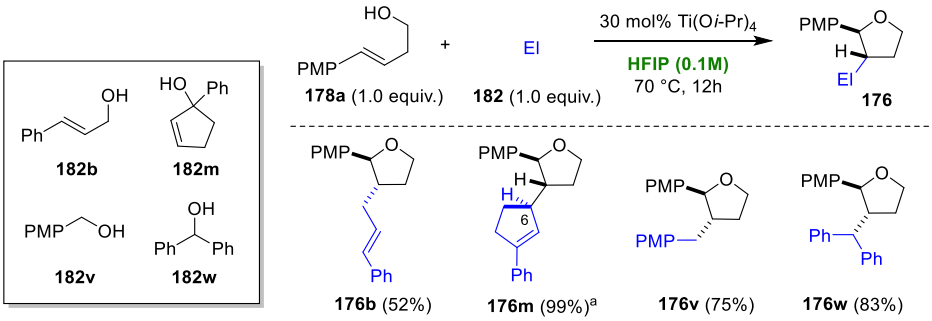


Table 2.8 Optimization of cyclization with 1,3,5-trioxane **182an**

Entry	Loading of $Ti(O^iPr)_4$	Temperature	Yield	
			176am (%)	**176i'** (%)
1	30 mol%	70 °C	0	99
2	30 mol%	rt	0	0
3	0 mol%	70 °C	0	0
4	0 mol%	rt	0	0

2.3.9. Summary of the electrophile scope

With a wide variety of electrophiles screened and satisfying results obtained, alcohols were found to be the most suitable electrophiles for the cyclization reaction. Alcohols **182b**, **182m**, **182v** and **182w** were chosen to be the best among them all, as they afforded THFs in high to quantitative yield. Additionally, they gained complete diastereocontrol at the newly generated stereogenic centres, giving products as a pure *trans* diastereomer. Finally, these THFs were easily modified to other useful functional groups *via* ozonolysis, hydrogenation or Ru-catalyzed oxidation of aromatic ring (**Scheme 2.24, 176b, 176m and 176v)**, and the bulky substituent could also be used to control the diastereoselectivity of other substituents on the THF ring (**Scheme 2.24, 176w**).



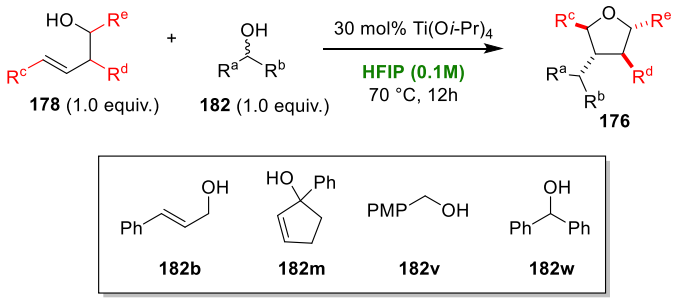
[a] Performed at room temperature (RT).

Scheme 2.24 Best electrophiles for the synthesis of THFs **176**

2.4. Scope of the Reaction-nucleophiles

With the optimum reaction conditions in hand and the best electrophiles identified, ie. allyl alcohols **182b**, **182m** and benzylic alcohols **182v**, **182w**, it was decided to further

explore the versatility of the nucleophilic homoallyl alcohol **178**. Evaluation of the nucleophile scope focused on three parts; firstly, the nature of the substituents R^c, R^d and R^e on the alcohol **178** component; next, the synthesis of enantiopure products; finally, the tolerance of other functional groups, such as carboxylic acids (**Scheme 2.25**).



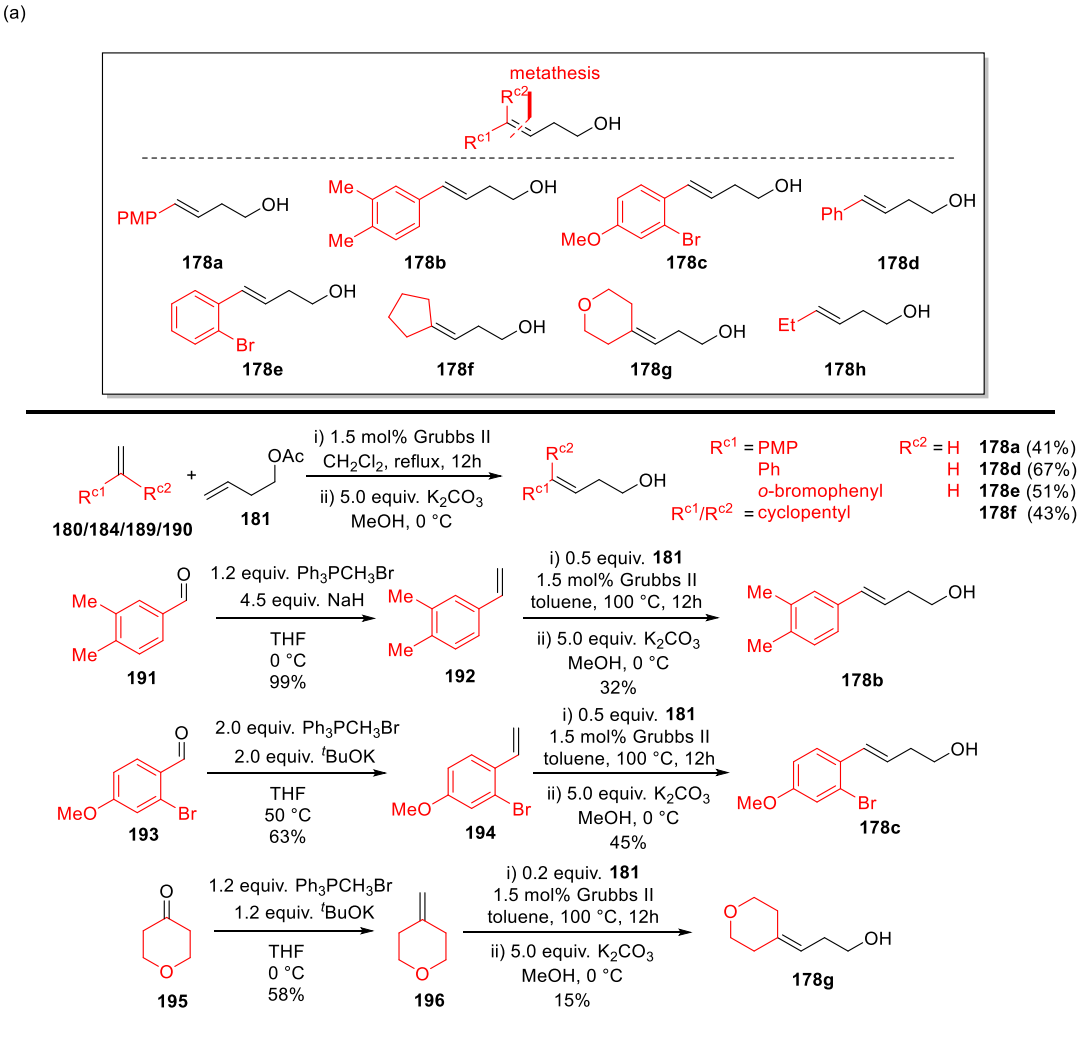
Scheme 2.25 Scope of the nucleophiles **178**

2.4.1. Scope of the nucleophiles: versatility of the substituent R^c

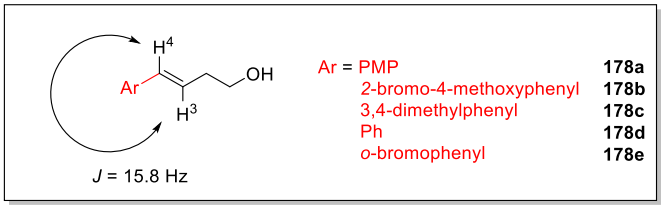
The scope of the nucleophiles was first evaluated by varying the nature of substituent R^c on the homoallylic alcohol **178**. Aromatic homoallylic alcohols **178a**, **178d**, **178e** and tri-substituted aliphatic homoallylic alcohol **178f** were synthesized by using Ru-catalyzed metathesis of the corresponding styrenes with the but-3-en-1-yl acetate **181**, which were all commercially available, followed by deprotection of the acetate group under basic conditions to afford the corresponding alcohols. Preparation of aromatic homoallylic alcohols **178b**, **178c** and tri-substituted aliphatic homoallylic alcohol **178g** followed the same synthetic route, except that the styrenes were firstly obtained from the Wittig reaction of the corresponding aldehydes (**Scheme 2.26a**). Note that only di-substituted aliphatic homoallylic alcohol **178h** was commercially available.

All alcohols **178a**-**178e** were obtained as single *E*-isomers (based on crude ^{1}H NMR spectroscopy), which were confirmed by the large *J* coupling constant between H^4 and H^3 of the alkenes (*J* = 15.8 Hz). The sole formation of the *E*-alkenes is attributed to the thermodynamic bias in cross-metathesis reactions as *E*-alkenes are generally more stable than Z-alkenes (**Scheme 2.26b**).

(a)

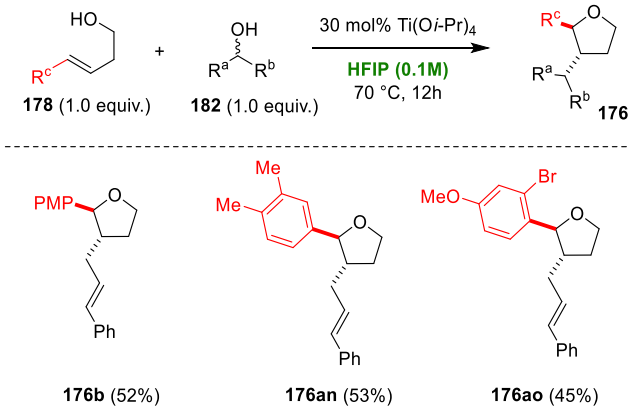


(b)



Scheme 2.26 (a) Synthesis of homoallylic alcohols **178a-178g**; (b) *J* coupling constants for alcohols **178a**-**178e**

In order to further investigate the effect of the electron-richness of aromatic groups on the reaction efficiency, it was decided to vary the aromatic ring in alcohols **178a-178e**. THFs **176b** was previously made in 52% yield with employing cinnamyl alcohol **182b** as the electrophile. The use of electron-rich 3,4-dimethylphenyl substituted alcohol **178b** tolerated the reaction, afforded **176an** in similar yield (**Scheme 2.27, 176a and 176an**), while using less electron-rich 2-bromo-4-methoxyphenyl substituted alcohol **178c** revealed a slight decrease in the yield, producing THFs **176ao** in 45% yield (**Scheme 2.27, 176ao**).

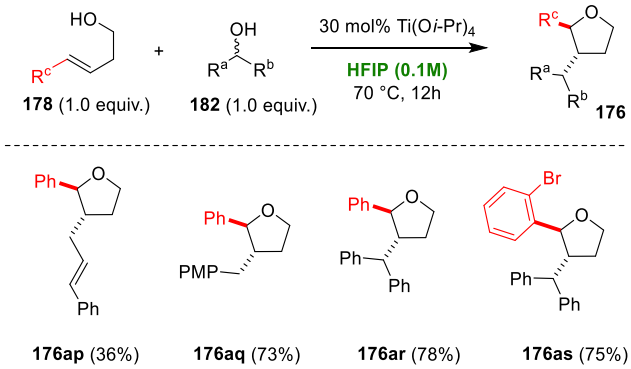


Scheme 2.27 Synthesis of THFs bearing electron-rich aromatic substituents

An obvious decrease in yield was observed when an electron-neutral phenyl ring was attached to the homoallylic alcohol **178d**, giving THFs **176ap** in 36% yield with cinnamyl alcohol **182b** as the electrophile. In an attempt to improve the yield, two of the best electrophiles: 4-methoxybenzylic alcohol **182v** and benzhydrol **182w** were then employed, which managed to bring the yield up to 73% and 78% respectively (**Scheme 2.28, 176aq-176ar**). It was therefore decided to employ benzhydrol **182w** as the electrophile with alcohol **178e** bearing an electron-deficient aromatic substituent,

affording THFs **176as** in 75% yield (**Scheme 2.28, 176as**). To sum up, as the electron-richness of the aromatic ring became lower, the nucleophilicity of the alkene in homoallylic alcohol **178** became weaker, possibly leading to a slower trapping of the electrophile and thus a diminished yield was observed. In this case, a better electrophilic partner was required to compensate for the weakened nucleophilicity of the homoallylic alcohols **178**, so that a higher yield could be obtained. Thus, benzhydrol **182w** was selected for the cyclization of remaining less reactive alcohols.

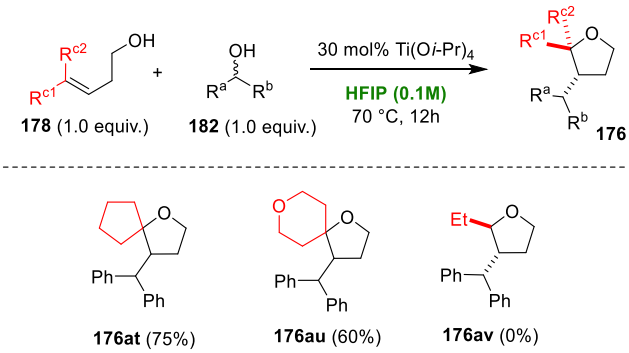
Note that all of the THFs listed above were obtained as a 2,3-*trans* single diastereomer. THFs **176b**, **176an** and **176ao** were assigned by analogy with the previously synthesized THFs **176a**. The stereochemistry of THFs **176aq** was assigned by analogy with the previously synthesized THFs **176v** (see **Scheme 2.17**). Additionally, diphenyl substituted THFs **176ar** and **176as** were assigned by analogy with the THFs **176aah** synthesized later on (see **Scheme 2.36**).



Scheme 2.28 Synthesis of THFs bearing electron-neutral/deficient aromatic substituents

Challenging aliphatic tri-substituted homoallylic alcohols **178f** and **178g** were then attempted, giving valuable five and six-membered spirocycle rings **176at** and **176au** in

75% and 60% yield respectively without any starting materials being recovered (**Scheme 2.29, 176at-176au**). Unfortunately, subjecting the less activated di-substituted homoallylic alcohols **178h** to the reaction conditions afforded no sign of THFs **176au**; only starting materials were recovered, which was attributed to the weakened nucleophilicity of the alkene in the alcohol **178h** (**Scheme 2.29, 176av**).

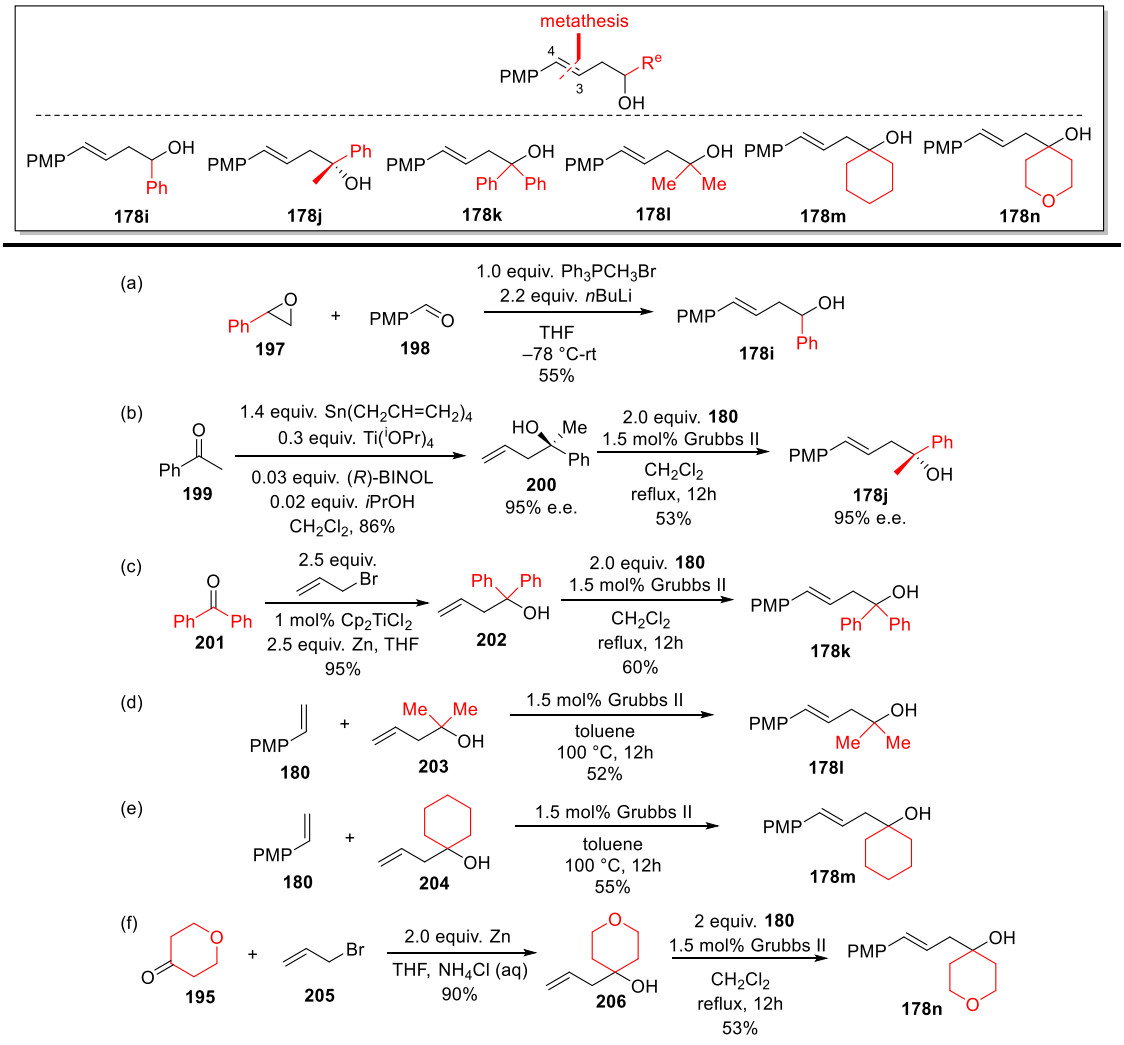


Scheme 2.29 Synthesis of THFs bearing aliphatic substituents

2.4.2. Scope of the nucleophiles: versatility of the substituent R^e

After evaluation of the substituent R^e on the homoallylic alcohol **178**, *para*-methoxyphenyl (PMP) group was determined as the most suitable substituent and would be fixed for further screening of the methodology scope. Next, the compatibility of substituent R^e was investigated. Alcohol **178i** was obtained through the formation of a Wittig salt from epoxide **197**, followed by addition of 4-methoxybenzyl aldehyde **198** under basic conditions (**Scheme 2.30a**). Alcohols **178j, 178k and 178n** were synthesized *via* the Ru-catalyzed metathesis of 4-methoxystryrene with terminal homoallylic alcohols **200**, **202** and **206**, which were all prepared from addition of an allyl group to the corresponding ketones (**Scheme 2.30b,c,f**). Alcohols **178l** and **178m** were

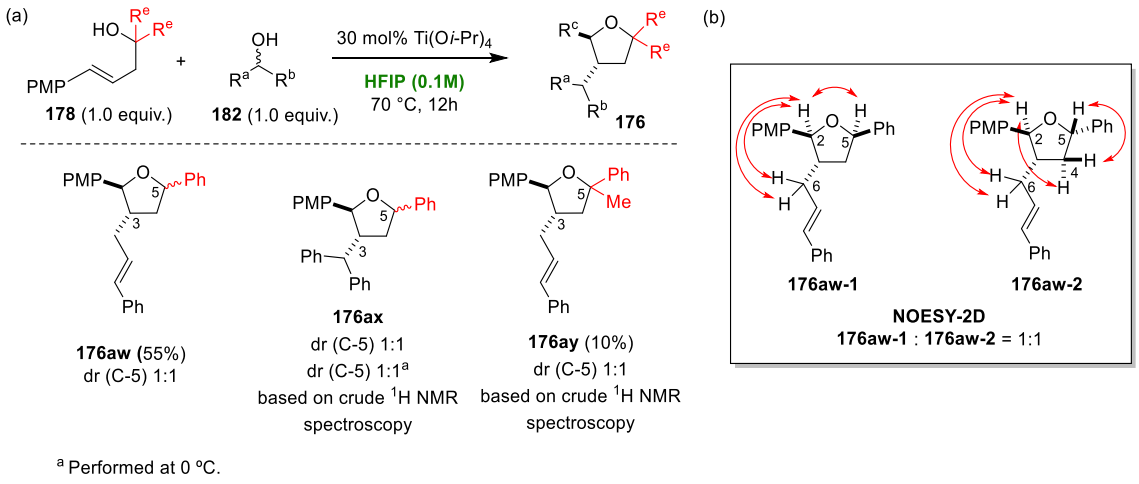
synthesized from the Ru-catalyzed metathesis of 4-methoxystryrene **180** with the corresponding commercially available alcohols **203** and **204** (**Scheme 2.30d,e**). All alcohols **178i**-**178n** were obtained as single *E*-isomers (again confirmed by a large *J* coupling constant of 15.8 Hz between 3-H and 4-H).



Scheme 2.30 Synthesis of homoallylic alcohols **178i-178n**

To begin with, installing a Ph group at the α-position of homoallylic alcohol **178i** gave THFs **176aw** in 55% yield as a 1:1 mixture of 3,5-*trans* and *cis* diastereomers. The loss of stereocontrol at the C-5 position could due to the fact that electrophile at C-3 was both

too small and too far from C-5 to affect the selectivity at that position (**Scheme 2.31a**, **176aw**). The stereochemistry was determined by NOESY-2D experiments, where correlations could be seen between 2-H and 6-H_2 for both **176aw-1** and **176aw-2**, suggesting the 2,3-*trans* geometry. While correlations observed between 2-H and 5-H in **176aw-1** but not in **176aw-2**, indicating the 2,5-*cis* and 2,5-*trans* geometry respectively (**Scheme 2.31b**).

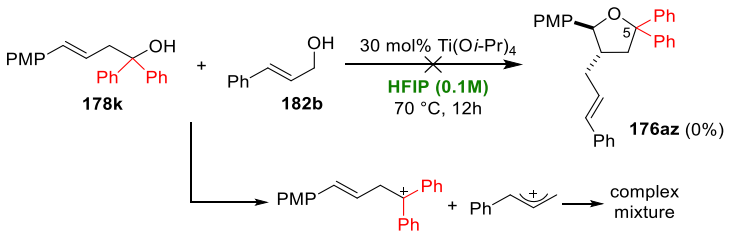


Scheme 2.31 (a) Cyclization of α-substituted homoallylic alcohols; (b) NOESY-2D experiment on THFs **176aw**

To improve the diastereocontrol at the C-5 position, a bulkier electrophile benzhydrol **182w** was attempted. However, neither conducting the reaction at 70 °C nor lowering the temperature to 0 °C gained any stereocontrol at C-5 position, a 1:1 diastereomeric ratio was observed based on crude ^{1}H NMR spectroscopy in both cases (**Scheme 2.31**, **176ax**). The poor stereocontrol at the C-5 position could be explained by the distance between the C-5 position and the electrophile at the C-3 position; therefore, even the bulkiest electrophile **182w** was unable to control its diastereoselectivity. Similarly,

homoallylic alcohol **178j** bearing a phenyl and methyl group at C-5 position afforded a 1:1 mixture of diastereomers **176ay** in 10% conversion based on the crude ^{1}H NMR spectroscopy (**Scheme 2.31, 176ay**).

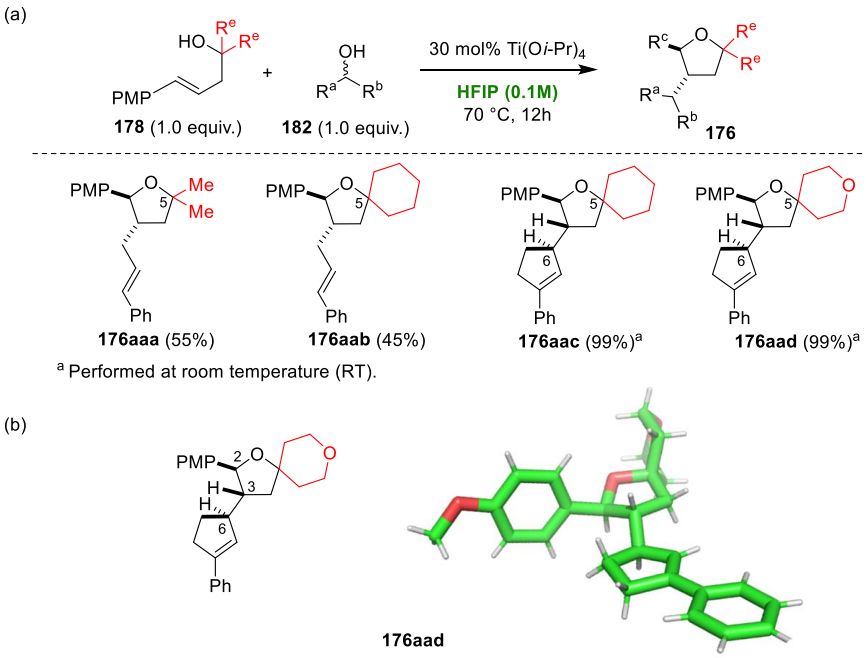
As there was no diastereocontrol at the C-5 position, it was decided to install two identical substituents at the α-position of homoallylic alcohol. Unfortunately, a complex mixture was obtained with no starting materials being recovered when treating alcohol **178k** with cinnamyl alcohol **182b** under standard reaction conditions. This could be attributed to the formation of stable carbocations from both electrophilic allyl alcohol **182b** and nucleophilic homoallylic alcohol **178k** under the acidic conditions. The generation of a carbocation from alcohol **178k** was attributed to the stabilization of both homoallylic and di-benzylic substituents, leading to a complex mixture (**Scheme 2.32**). Thus, the two substituents at the C-5 position should possess weak carbocation stabilizing power in order to avoid the formation of homoallylic carbocation.



Scheme 2.32 Attempted synthesis of 5,5-diphenyl substituted THFs **176az**

Using α-dimethyl substituted alcohol **178l** gave THFs **176aaa** in 55% yield, avoiding the problem described above. Next, valuable spirocycle-bearing THFs **176aab** was synthesized in 45% yield with cinnamyl alcohol **182b** as the electrophile. To improve the

yield, another electrophilic alcohol **182m** was utilized, affording THFs **176aac** in quantitative yield and the reaction proceeded at room temperature (**Scheme 2.33a**). Finally, using alcohol **182l** afforded spirocycle **176aad** in 99% yield as a yellow solid, which was then recrystallized to obtain an X-Ray crystallographic structure, confirming the 2,3-*trans* geometry and the stereochemistry at the newly formed stereogenic centers. (**Scheme 2.32b**).

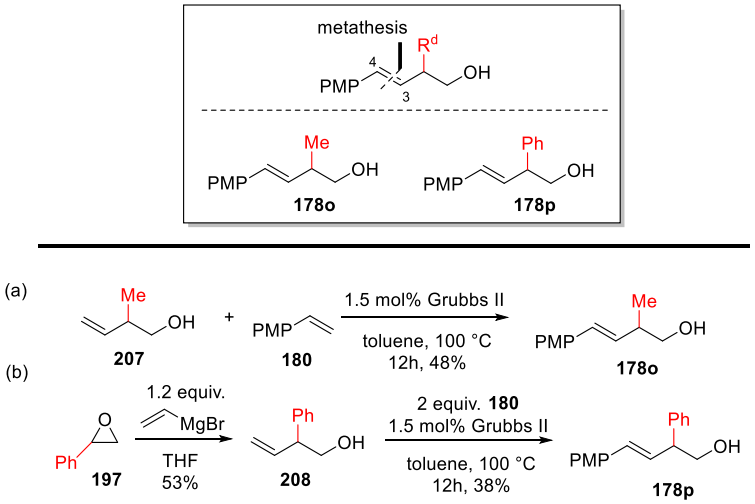


Scheme 2.33 (a) Cyclization of α-disubstituted homoallylic alcohols; (b) X-Ray crystallographic structure of THFs **176aad**

2.4.3. Scope of the nucleophiles: versatility of the substituent R^d

Retaining the PMP substituent on alcohol **178**, substitution at R^d was then investigated. Alcohols **178o** and **178p** bearing β-methyl and β-phenyl substitutents were synthesized from the Ru-catalyzed metathesis of 4-methoxystryrene with the corresponding

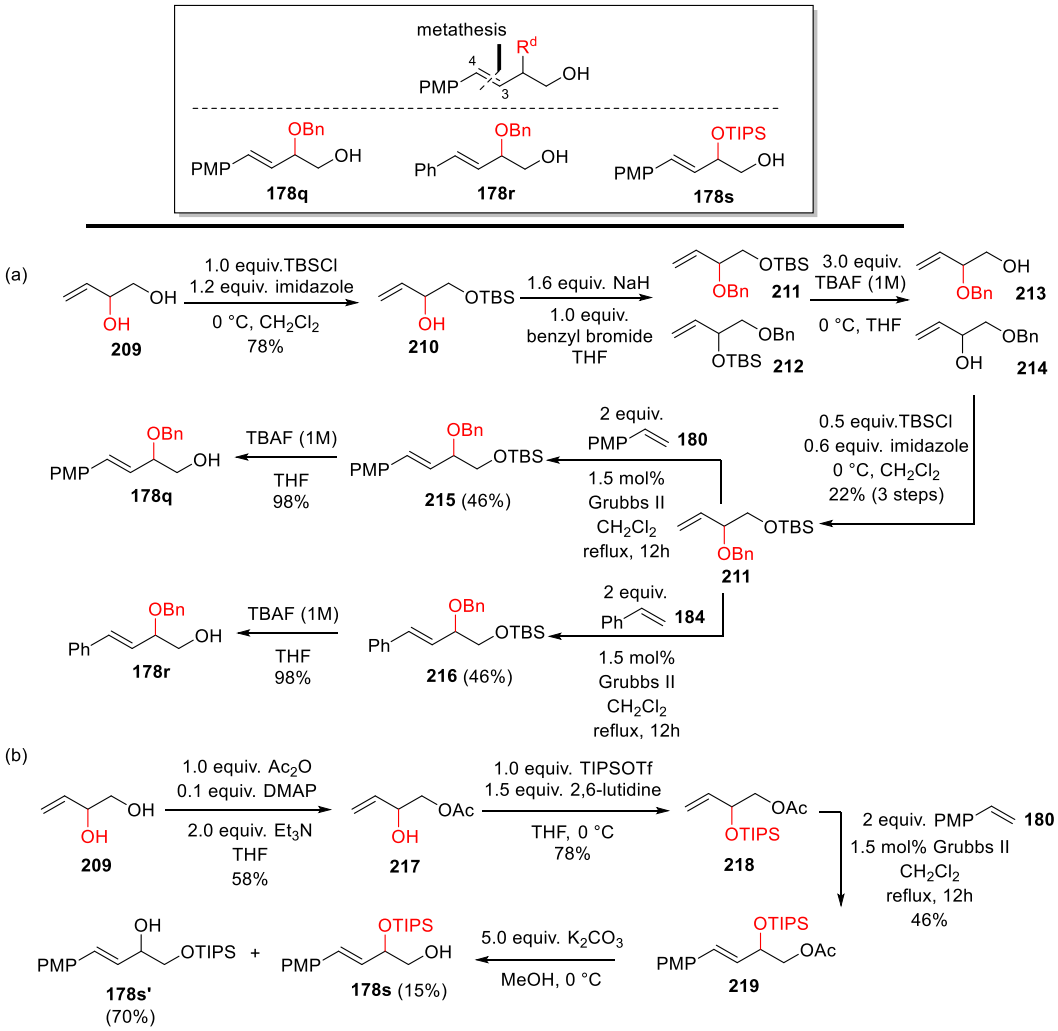
homoallylic alcohols **207** and **208**, which were either commercially available or prepared from addition of vinylmagnisum bromide to the epoxide **197** (**Scheme 2.34**). Alcohols **178o** and **178p** were obtained as single *E*-isomers (again confirmed by a large *J* coupling constant of 15.8 Hz between 3-H and 4-H).



Scheme 2.34 Synthesis of homoallylic alcohols **178o-178p**

Next, alcohols bearing an oxygen protected substituent at the β-position were prepared. The syntheses of alcohols **178q** and **178r** started with TBS protection on the primary alcohol of the diol **209** followed by benzyl protection. However, it was found the TBS group had migrated from the primary position to the secondary position under the alkylation conditions, giving an inseparable mixture of **211** and **212**. The TBS group was then removed, and was reinstalled on the primary alcohol of **213**, so that **214** could be separated from **211**. Alcohols **178q** and **178r** were then synthesized from Ru-catalyzed metathesis of **211** with the 4-methoxystyrene **180** and styrene **184** respectively (**Scheme 2.35a**). Synthesis of alcohol **178s** started with the protection of diol **209** to give acetate **217**, followed by TIPS protection on the secondary alcohol to form **218**. Acetate

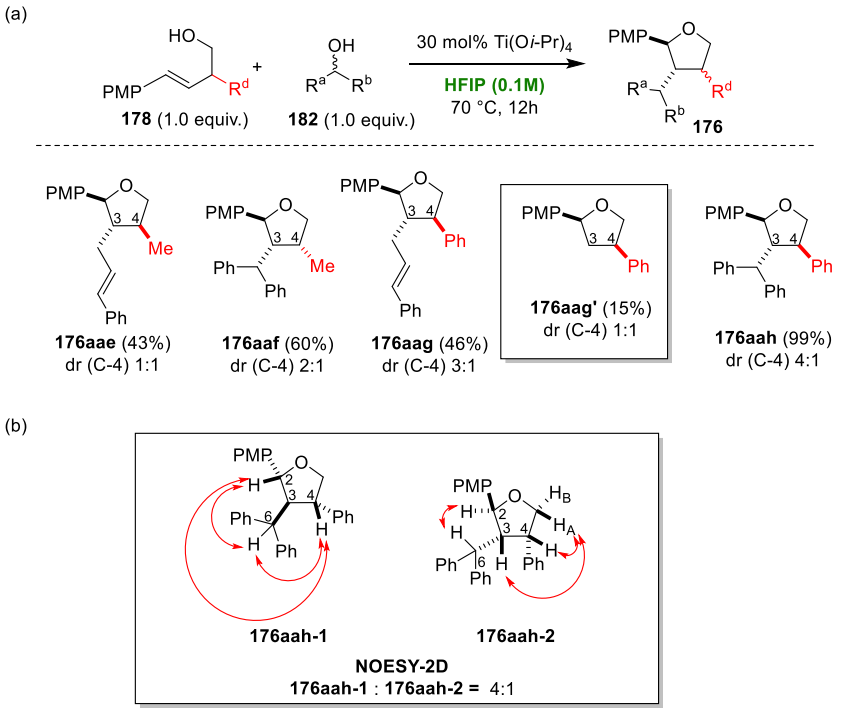
219 was then synthesized from the Ru-catalyzed metathesis of 4-methoxystryrene **180** and acetate **218**. Unfortunately, deprotection of acetate **219** resulted in migration of the TIPS group, giving desired alcohol **178s** in only 15% yield (**Scheme 2.35b**). Alcohols **178q**-**178s'** were obtained as single *E*-isomers (again confirmed by a large *J* coupling constant of 15.8 Hz between 3-H and 4-H).



Scheme 2.35 Synthesis of homoallylic alcohols **178q-178s**

Alcohol **178o** was firstly treated with cinnamyl alcohol **182b** under the reaction conditions to form THFs **176aae** in 43% yield as a 1:1 mixture of diastereomers. Using bulkier electrophilic alcohol **182w** was beneficial, giving THFs **176aaf** in 2:1 dr (**Scheme**

2.36a). Unlike those THFs bearing substituents at the C-5 position, stereoselectivity at C-4 position was under steric control improved by the electrophile. Using β-phenyl substituted alcohol **178p** led to an improved 3:1 dr with cinnamyl alcohol **182b** as the electrophile. Additionally, protonated product **176aag'** was observed in this case, producing a 1:1 mixture of diastereomers. The lower diastereomeric ratio of **176aag'** was attributed to the much smaller proton electrophile attached at the C-3 position. Those results suggested that the diastereoselctivity was controlled by the size of substituents on both C-3 and C-4 position. To gain better stereoselectivity at the C-4 position, a bulkier electrophile benzhydrol **182w** was employed, leading to the formation of **176aah** in quantitative yield with 4:1 dr (**Scheme 2.36a**). The stereochemistry of THFs **176aah** was characterized by NOESY-2D experiment (**Scheme 2.36b**). Correlations could be seen between 2-H and 6-H, 2-H and 4-H, 4-H and 6-H for the major diastereomer, suggesting the 2,3,4-all *trans* geometry. Correlations could be seen between 2-H and 6-H, 4-H and 5-H_A, 3-H and 5-H_A, for the minor diastereomer, suggesting the 2,3,4-*trans cis* geometry. The stereochemistry of the THFs **176aae**-**176aag'** were then all assigned by analogy with THFs **176aah**.



Scheme 2.36 (a) Cyclization of β-substituted homoallylic alcohols **178o**-**178p**;

(b) NOESY-2D experiment on compound **176aah**

A short optimization study was conducted for the synthesis of THFs **176aah**. Lowering the temperature to 40 °C improved the dr to 5:1 (**Table 2.9**, **Entry 2**). Further decreasing the temperature to rt afforded 6:1 dr with quantitative yield (**Table 2.9**, **Entry 3**). Next, conducting the reaction at 0 °C gave 8:1 dr without harming the yield (**Table 2.9**, **Entry 4**). As the HFIP solvent froze at –4 °C, a solvent mixture was required if lower temperature was attempted. Finally, the reaction was carried out at –10 °C in a mixture of 1:1 HFIP to CH_2Cl_2, giving THFs **176aah** in the same dr while the yield diminished to 40% with 60% of starting materials being recovered (**Table 2.9**, **Entry 5**).

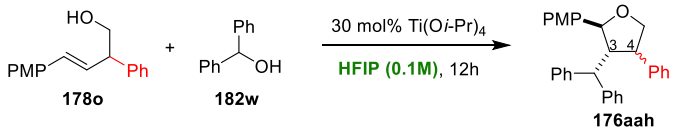
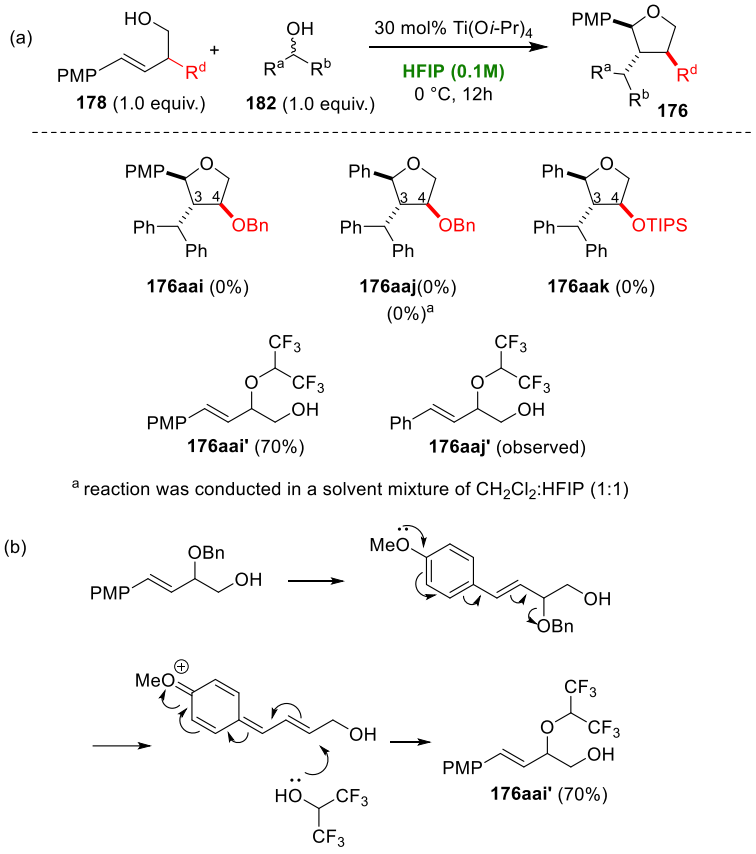


Table 2.9 Optimizations of synthesis of THFs **176aah**

Entry	Solvent	Temperature	Yield (%)	dr (C-4)
1	HFIP	70 °C	99	4:1
2	HFIP	40 °C	99	5:1
3	HFIP	rt	99	6:1
4	HFIP	0 °C	99	8:1
5	CH_2Cl_2 : HFIP (1:1)	–10 °C	40	8:1

With the best electrophile and optimized condition identified for the synthesis of C-4 substituted THFs, alcohols **178q**-**178s** were screened (**Scheme 2.37a**). Initial attempts with alcohol **178q** at 0 °C resulted in no formation of THFs **176aai** and recovery of benzhydrol **182w**, while side-product **176aai'** was obtained in 70% yield. Presumably, the formation of **176aai'** was initiated by the removal of the OBn group *via* conjugation, followed by addition of HFIP (**Scheme 2.37b**). As this process would be encouraged by the electron-rich aromatic ring attached to the alkene, use of alcohol **178r** bearing an electron-neutral phenyl group was attempted. Unfortunately, the same type of side-product **176aaj'** was obtained. Using a mixture of 1:1 HFIP to CH_2Cl_2 was also not helpful, leading to the same side-product. Finally, alcohol **178s** bearing a bulky OTIPS group was subjected to the reaction conditions, giving no trace of THFs **176aak** but only side-product **176aaj'**.



Scheme 2.37 Cyclization of β-substituted homoallylic alcohols **178q**-**178s**; (b) Proposed mechanism for the formation of side-product **176aai'**

2.4.4. Scope of the nucleophiles: synthesis of fully substituted THFs

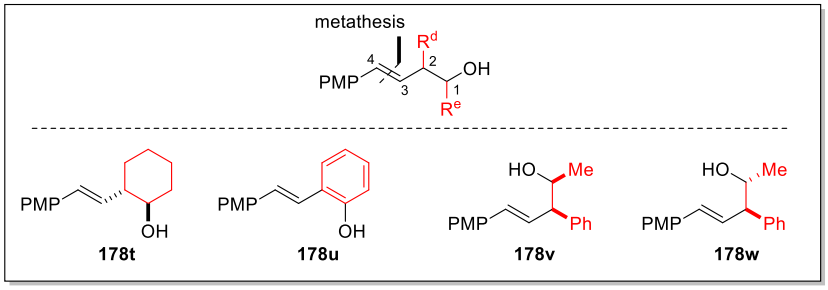
In order to synthesize fully substituted tetrahydrofurans, α,β-substituted homoallylic alcohols were then prepared, retaining the PMP substituent. Based on the previous scope, the stereoselectivity at R^e was not controllable while at R^d bulky electrophiles and low temperature should help in controlling the stereocontrol outcome. Thus, a bulky substituent was required on R^d and it should be a poor leaving group to avoid formation of side products *via* the addition of HFIP solvent to the homoallylic alcohol **178**. Additionally, an attached ring could possibly help control the stereocontrol outcome. Alcohols **178r**-**178w** were then synthesized based on the restrictions listed above

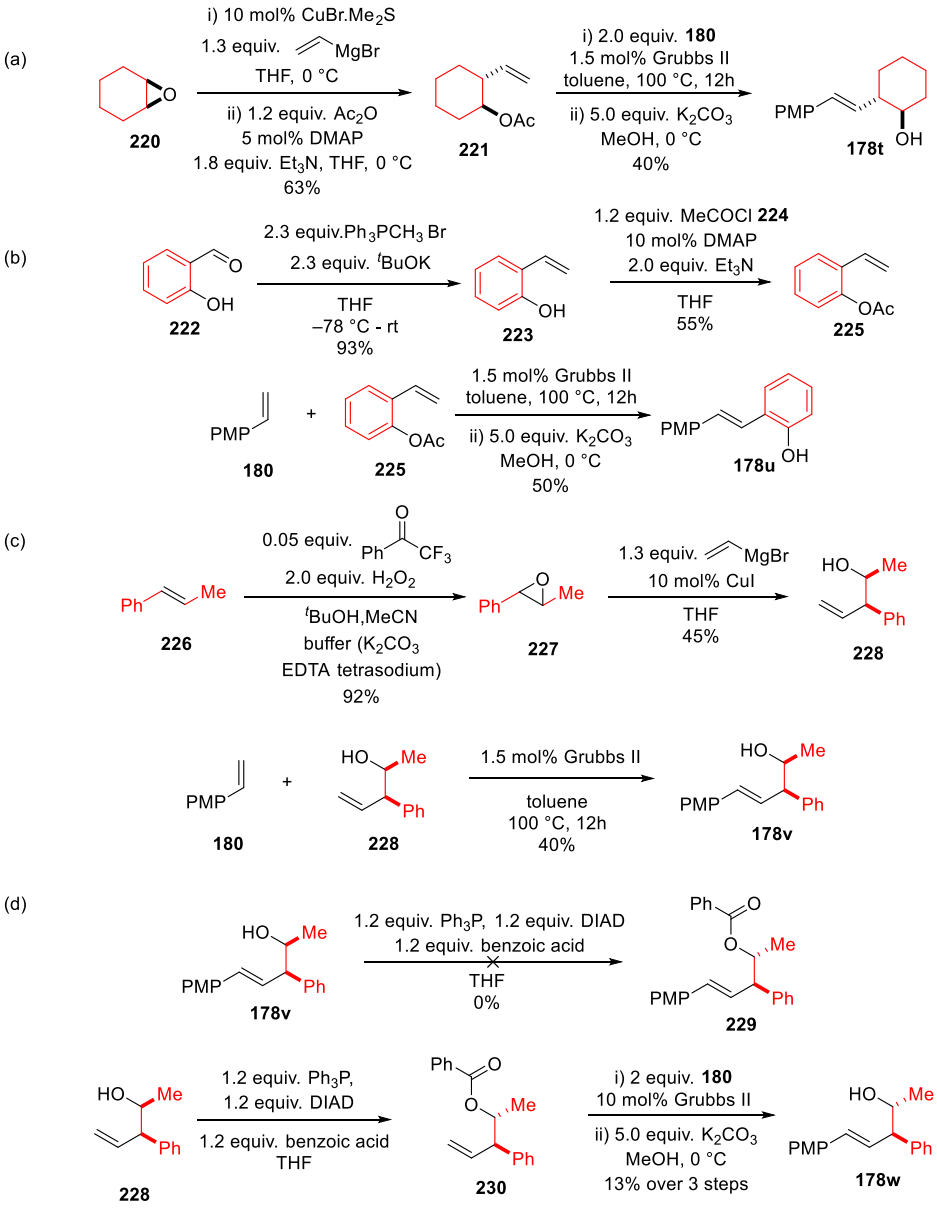
(**Scheme 2.38**).

Synthesis of alcohol **178t** started with addition of vinyl magnesium bromide to the epoxide **220**, followed by acetyl protection to afford the acetate **221**. This was then treated with 4-methoxystryrene **180** under the Ru-catalyzed metathesis conditions to produce alcohol **178t** (**Scheme 2.38a**). To make alcohol **178u**, styrene **223** was firstly prepared by the Wittig reaction of aldehyde **222** followed by acetyl protection of alcohol. Next, it was subjected with 4-methoxystryrene **180** under Ru-catalyzed metathesis conditions followed by deprotection of acetate to give alcohol **178u** (**Scheme 2.38b**).

The synthesis of alcohol **178v** started with the epoxidation of styrene **226**, which was then treated with vinyl magnesium bromide to afford homoallylic alcohol **228**. It was then treated with 4-methoxystryrene **180** under Ru-catalyzed metathesis conditions to afford alcohol **178v** (**Scheme 2.38c**). Alcohols **178v** and **178w** were only different in the stereochemistry between the phenyl and methyl groups. Initial attempts at the synthesis of **178w** was carried out *via* a Mitsunobu reaction to invert the *trans* geometry to *cis*. However, the reaction went to a complex mixture with no recovery of starting materials, which could be attributed to the instability of the activated alkene of the homoallylic alcohol **178v** under the Mitsunobu contidions. To overcome this problem, alcohols **228** with a non-activated alkene was used to generate ester **230** successfully, but in only 26% yield, which was attributed to the steric hinderance of the secondary alcohol. Following by the Ru-catalyzed metathesis and benzoyl deprotection,

alcohol **178w** was successfully prepared (**Scheme 2.38d**).

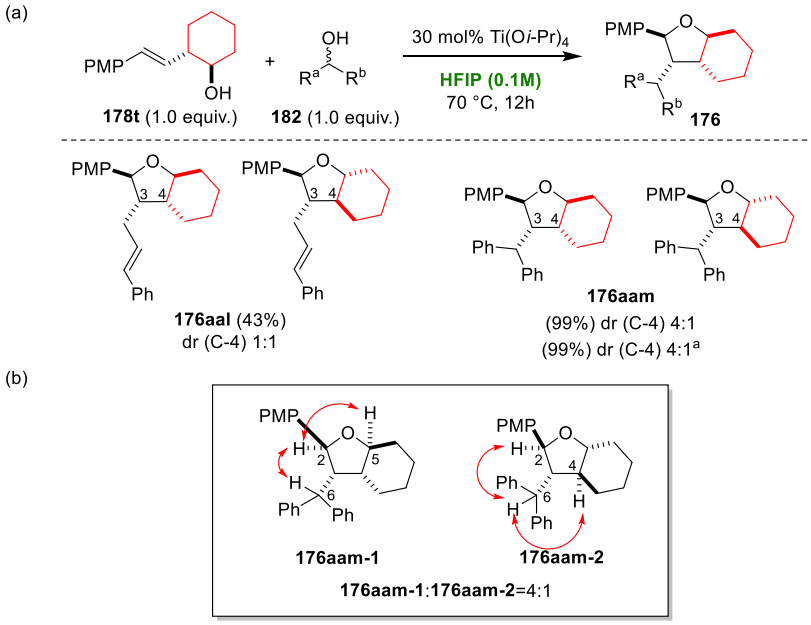




Scheme 2.38 Synthesis of α,β-substituted homoallylic alcohols **178t-178w**

All alcohols **178t**-**178w** were obtained as single *E*-isomers (again confirmed by a large *J* coupling constant of 15.8 Hz between 3-H and 4-H). The 1,2-*trans* geometry of the alcohol **178t** was confirmed by comparing its chemical shift and *J* coupling constant with the literature data. The *cis* and *trans* geometry between the methyl and phenyl substituents on alcohols **178v** and **178w** were determined by the NOESY-2D experiments of their cyclized products **176aaq** and **176aar** which were synthesized later on (see **Scheme 2.30b**).

Treating alcohol **178t** bearing cyclic substituents with cinnamyl alcohol **182b** as the electrophile gave THFs **176aal** in 43% yield as a 1:1 mixture of diastereomers (**Scheme 2.39a)**. Switching the electrophilic alcohol to benzhydrol **182w** raised the yield of **176aam** to 99% and improved the diastereomeric ratio to 4:1 at both 70 °C and 0 °C, with the major diastereomer having *trans*-*cis*-*trans* geometry. The stereochemistry of **176aam** was characterised by NOESY-2D experiments (**Scheme 2.39b**). Correlations could be seen between 2-H and 6-H for both **176aam-1** and **176aam-2**, suggesting the 2,3-*trans* geometry. Correlations were also observed between 2-H and 5-H in **176aam-1**, indicating the 2,5-*cis* geometry. While there was a correlation observed between 4-H and 6-H but not between 2-H and 5-H in **176aam-2**, suggesting the 2,5-*trans* geometry.

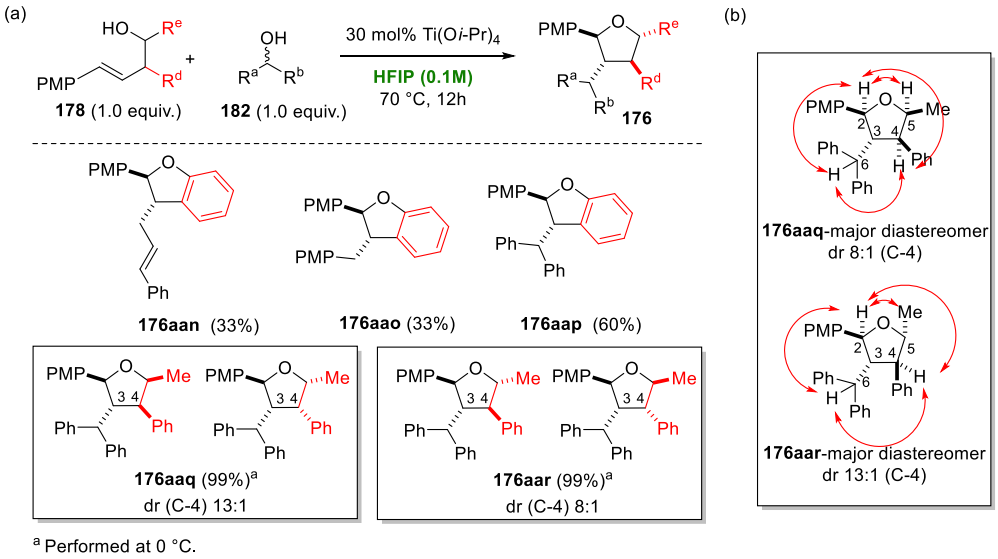


[a] Performed at 0 °C.

Scheme 2.39 (a) Cyclization of alcohol **178t** with alcohol **182b** and **182w** as the electrophile; (b) NOESY-2D experiment on compound **176aam**

Treating alcohol **178u** bearing a phenyl ring with cinnamyl alcohol 18**2b** as the electrophile afforded benzofuran motif **176aan** in 33% yield. Switching the electrophile to 4-methoxybenzylic alcohol **182v** was not beneficial, the same yield was obtained. While utilizing benzhydrol **182w** as the electrophile improved the yield to 60% (**Scheme 2.40a, 176aan-176aap)**. Next, acyclic α,β-substituted alcohols were examined with benzhydrol **182w** as the electrophile, and the reactions were conducted at 0 °C in order to maximize the yield and gain the best stereocontrol outcome. Using alcohol **178v** afforded THFs **176aaq** in quantitative yield with 13:1 dr, and the major diastereomer had a *trans-trans-cis* geometry. Treating alcohol **178w** with benzhydrol **182w** afforded THFs **176aar** in quantitative yield with 8:1 dr and the major diastereomer had an all-*trans* geometry (**Scheme 2.40a, 176aaq-176aar)**. The stereochemistry of **176aar** and **176aas** was characterized by NOESY-2D experiments (**Scheme 2.40b**). Correlations could

be seen between 2-H and 6-H for both **176aaq** and **176aar**, suggesting the 2,3-*trans* geometry. There were correlations observed between 2-H and 4-H, 2-H and 5-H, 2-H and 6-H, 4H and 6-H in **176aaq**, indicating the *trans-trans-cis* geometry. There were also correlations observed between 2-H and Me, 2-H and 4-H, 4H and 6-H in **176aar**, suggesting the all-*trans* geometry.



[a] Performed at 0 °C.

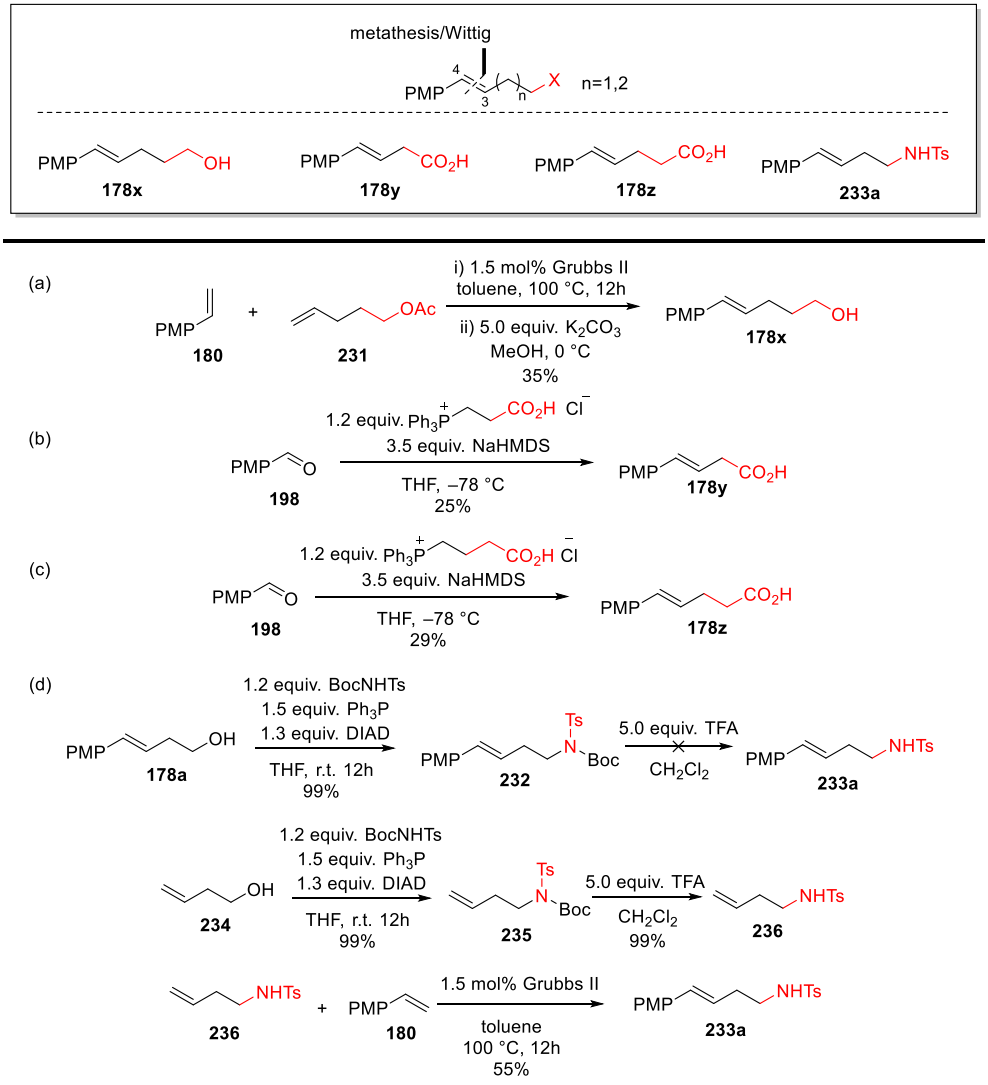
Scheme 2.40 (a) Scope of the nucleophiles- varying the substituent R^e and R^d;

(b) NOESY-2D experiments on compounds **176aaq** and **176aar**

2.4.5. Scope of the nucleophiles: cyclization of homoallylic variants

In order to expand this methodology to more diverse and useful heterocycles, other homoallylic variants were synthesized to examine their compatibility. Alcohol **178x** was synthesized from the Ru-catalyzed metathesis of 4-methoxystyrene **180** and acetate **231**, followed by deprotection of the acetate (**Scheme 2.41a**). Next, carboxylic acids **178y**-**178z** were obtained from Wittig reaction of the 4-methoxybenzylic aldehyde **198** with the corresponding Wittig salts (**Scheme 2.41b,c**).

A first attempt at synthesizing homoallylic amine **233a** was unsuccessful due to failure of the Boc deprotection on **232**, which could be explained by the instability of the electron-rich styrene under the acidic conditions. Thus, non-activated Boc protected amine **235** was prepared from homoallylic alcohol **234** under Mitsunobu conditions. Following by deprotection of the Boc group and Ru-catalyzed metathesis with 4-methoxystyrene **180**, amine **233a** was successfully prepared (**Scheme 2.41d**).

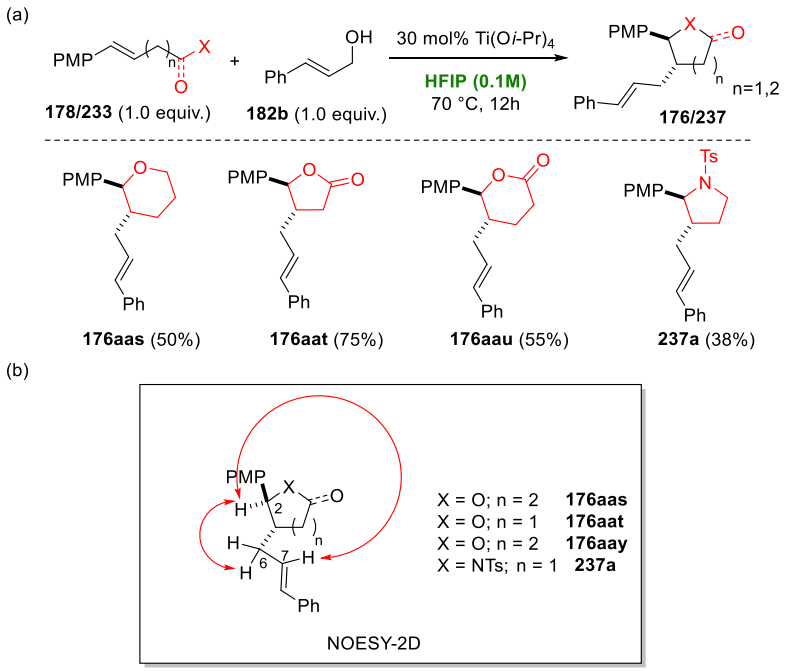


Scheme 2.41 Synthesis of alcohols **178x**, carboxylic acids **178y**-**178z** and amine **233a**

All homoallylic compounds **178x**-**233a** were obtained as single *E*-isomers (again

confirmed by a large *J* coupling constant of 15.8 Hz between 3-H and 4-H).

It was soon found that this methodology was not limited to the synthesis of tetrahydrofurans (**Scheme 2.42a**). Adding an extra carbon to the starting material led to the production of six-membered tetrahydropyrans **176aas** in 50% yield. Next, replacing the alcohol functional group with carboxylic acid afforded β-butyrolactone **176aat** in 75% yields. While using carboxylic acid **178z** gave δ-valerolactone **176aau** with slightly lower yield. Finally, treating homoallylic amine **233a** with cinnamyl alcohol **182b** as the electrophile afforded pyrrolidines **237a** in 38% yield. The stereochemistry of compounds **176aas**-**237a** was characterized by NOESY-2D experiments (**Scheme 2.42b**). Correlations could be seen between 2-H and one of proton 6-H, 2-H and 7-H, suggesting the 2,3-*trans* geometry.

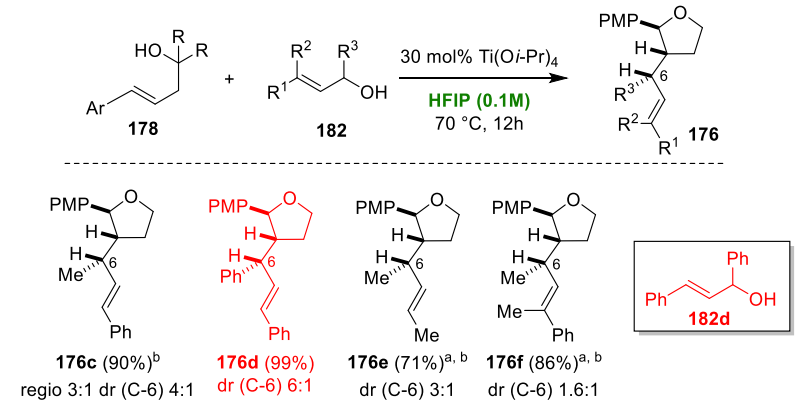


Scheme 2.42 (a) Scope of the nucleophiles- cyclization of homoallylic variants;

(b) NOESY-2D experiments on compounds **176aas**-**237a**

2.4.6. Scope of the nucleophiles: attempts to determine the stereochemistry in the THF derivatives bearing an α-branched acyclic allylic substituent.

In order to determine the stereochemistry at the C-6 position in THFs bearing an α-branched acyclic allylic substituent (**176c**-**176f)**, a solid product was required to obtain an X-Ray crystallographic structure. However, none of THFs **176c**-**176f** was a solid, so it was decided to synthesize a variant as a solid. Electrophilic alcohol **182d** was selected as the best electrophile as it produced the highest yield, the best diastereoselectivity at the C-6 position and produced only one regioisomeric product (**Scheme 2.43**).

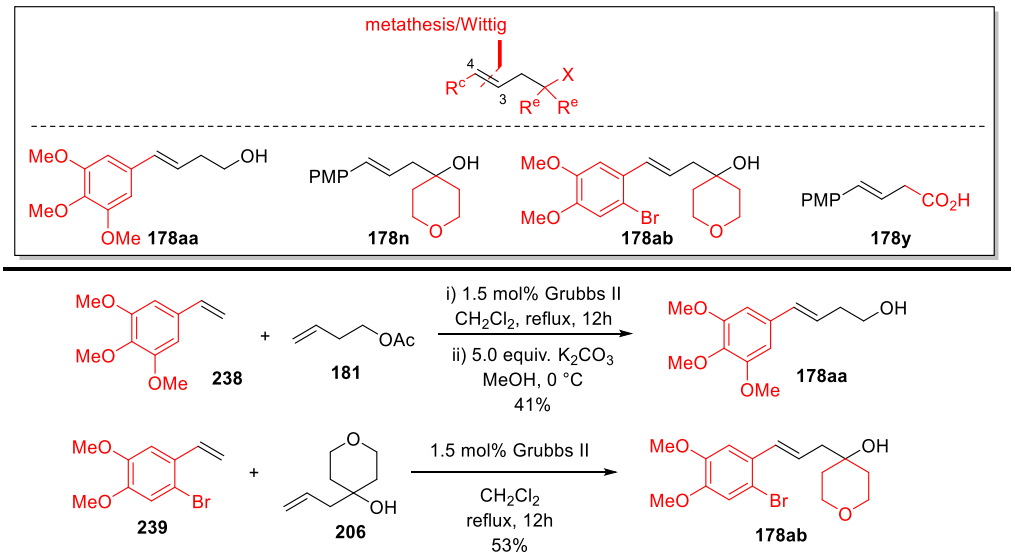


[a] Using 2.0 equiv. of **182**. [b] Performed at 0 °C.

Scheme 2.43 THFs bearing α-branched acyclic allylic substituent

Next, suitable homoallylic substrate **178** needed to be found as a partner. As a methoxy group was helpful in crystallizing products, alcohol **178aa** bearing a tri-substituted methoxy phenyl ring was prepared from the Ru-catalyzed metathesis of styrene **238** and acetate **231**, followed by acetyl deprotection. As a bromine group was also helpful in crystallizing products, alcohol **178ab** was prepared from the Ru-catalyzed metathesis of styrene **239** and commercially available alcohol **206**. Additionally, previously synthesized alcohol **178n** was selected as it previously gave product **176aad** as a solid; previously

synthesized carboxylic acid **178y** was also chosen as it enabled further derivatization *via* alkylation or acylation, which gave a better chance to obtain the product as a solid. All homoallylic substrates were obtained as single *E*-isomers (again confirmed by a large *J* coupling constant of 15.8 Hz between 3-H and 4-H).

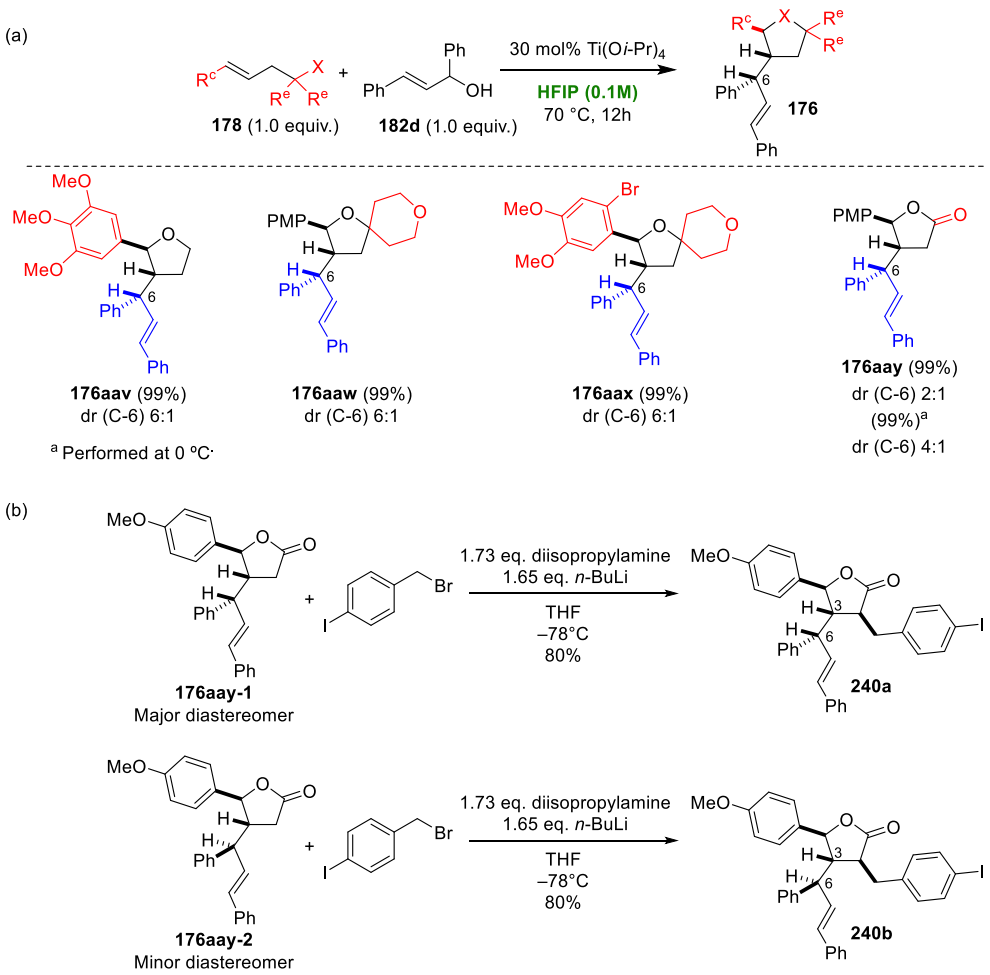


Scheme 2.44 Synthesis of homoallylic alcohols **178aa-178ab**

Alcohol **178aa** bearing a tri-substituted methoxy phenyl ring were treated with alcohol **182d**, affording **176aav** in 99% yield with 6:1 dr. However, it was a foam and could not be used to make a crystal. Next, treating alcohol **178n** with alcohol **178d** afforded THFs **176aaw** in identical yield and diastereomeric ratio, which unfortunately was an oil. Alcohol **178ab** bearing bromophenyl and tetrahydropyranyl substituents was then examined, giving THFs **176aax** as a foam. Finally, utilizing carboxylic acid **178y** afforded lactones **176aay** in 99% yield as a 2:1 separable mixture of diastereomers. Further optimization managed to improve the dr to 4:1 *via* reducing the temperature to 0 °C. The major diastereomer of **176aay** existed as an oil and its minor diastereomer existed

as a foam (**Scheme 2.45a**).

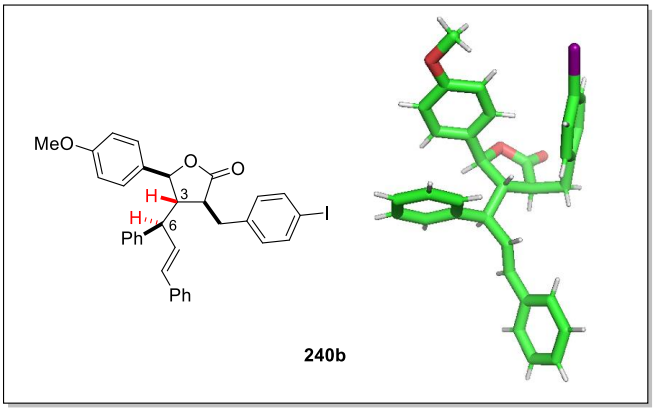
Although some of those products exist as foams, they were still unable to be crystalized. Thus, further functionalization of those products was required. Lactones **176aay** was selected as it was easier to modify and existed as a mixture of separable diastereomers.



Scheme 2.45 (a) Scope of the nucleophiles- synthesis of THFs **176aav**-**176aax** and lactones **176aay**; (b) Alkylation of lactones **176aay-1** and **176aay-2**;

Lactones **176aay-1** and **176aay-2** were then treated under alkylation conditions with 4-iodobenzylic bromide (**Scheme 2.45b**). Although **240a** was produced in 80% yield as a foam, product **240b** was successfully obtained as a solid in 80% yield, which was then

crystallized to obtain its X-Ray crystallographic structure. This confirmed the 4,6-*trans* geometry in minor diastereomer **176aay-2**, which indicated the 4,6-*cis*-geometry in major diastereomer **176aay-1** (**Scheme 2.46**).



Scheme 2.46 X-Ray crystallographic structure of lactones **240b**

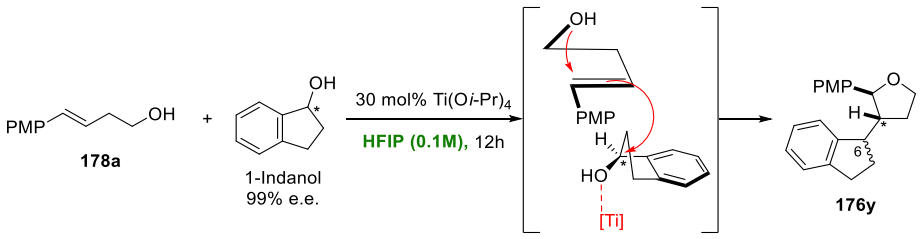
2.5. Synthesis of Enantiopure THF derivatives

Tetrahydrofuran rings are present in the core of many different natural products and are valuable synthons and building blocks, often used in medicinal chemistry. As high diastereoselectivity and broad scope was observed with this methodology, further exploration of this chemistry into the synthesis of enantiopure products was conducted.

2.5.1. Synthesis of enantiopure THF derivatives *via* using enantiopure electrophilic alcohols 182

An electrophilic enantiopure alcohol was utilized to investigate the transfer of chirality from the starting material to the product. If the reaction proceeds through a S_N2 trapping of the electrophile, the chiral information in the starting material should be

inverted and afford an enantiopure THFs (**Scheme 2.47**). However, if it generates a carbocation, a racemic product would be obtained.



Scheme 2.47 Proposed asymmetrical synthesis of THFs using enantiopure electrophilic alcohol

Treating racemic 1-indanol with alcohol **178a** afforded THFs **176y** as a racemic product (**Table 2.10**, **Entry 1**). Next, two different enantiopure alcohols (*R*)-(-)-1-indanol and (*S*)-(+)-1-indanol were subjected to the standard conditions; both of them led to a production of racemic THFs **176y** (**Table 2.10**, **Entries 2-3**). Lowering the temperature to 0 °C was not helpful again, only racemic product was observed (**Table 2.10**, **Entries 4-5**). The failure to synthesize enantiopure product could be attribute to the loss of chirality *via* the formation of a planar carbocation intermediate, which allowed the homoallylic alcohol **178a** to attack from either top or bottom face and led to the formation of racemic THFs **176y**.

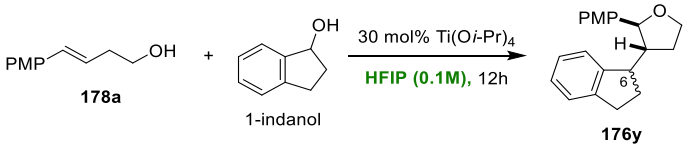


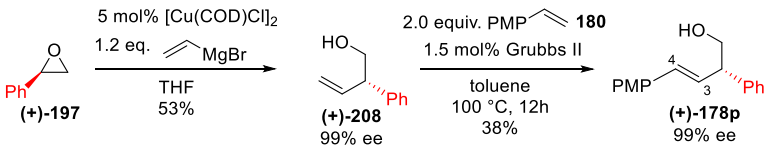
Table 2.10 Attempted synthesis of enantiopure product **176y**

Entry	Electrophilic partner	Temperature	Yield (%)	d.r. (C-6)	e.e. (%)
1	1-indanol	70 °C	96	2:1	0
2	(*R*)-(-)-1-indanol	70 °C	96	2:1	0
3	(*S*)-(+)-1-indanol	70 °C	96	2:1	0
4	(*R*)-(-)-1-indanol	0 °C	96	2:1	0
5	(*S*)-(+)-1-indanol	0 °C	96	2:1	0

(e.e. was determined by HPLC on Agilent 1200 series instrument)

2.5.2. Synthesis of enantiopure THF derivatives *via* using enantiopure nucleophilic alcohols 178

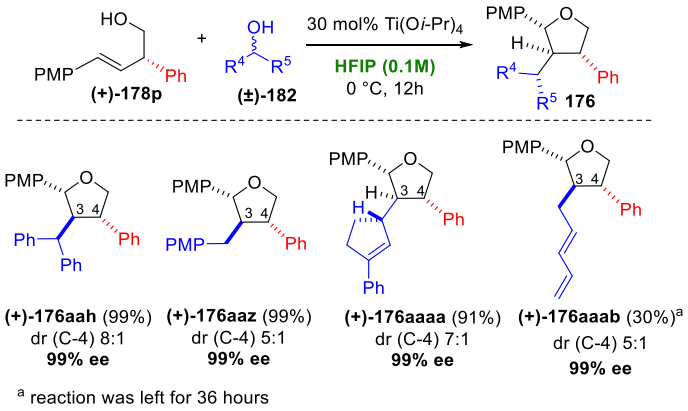
It was then decided to establish a stereogenic centre at the β position of the homoallylic alcohols as it could retain its chirality under the reaction conditions. Alcohol **178p** was then selected as it gave good diastereoseletivity and high yield. Synthesis of **(+)-178p** started with the addition of vinyl magnesium bromide to enantiopure epoxide **(+)-197**, followed by Ru-catalyzed metathesis of 4-methoxystyrene **180** and alcohol **(+)-208** to form enantiopure **(+)-178p**. Alcohol **(+)-178p** was obtained as a single *E*-isomer (again confirmed by a large *J* coupling constant of 15.8 Hz between 3-H and 4-H) (**Scheme 2.48**). The absolute stereochemistry of alcohol **(+)-208** was determined by comparing its $[\alpha]_D^{25}$ value with the literature data (see experimental chapter in detail).



Scheme 2.48 Synthesis of enantiopure homoallylic alcohol (+)-**178p**

Pleasingly, employing benzhydrol **182w** as the electrophile at 0 °C afforded enantiopure THFs **(+)-176aah** in 99% yield with 8:1 dr, indicating the successful transfer of chirality from the starting material to the product. Then, using 4-methoxybenzylic alcohol **182u** gave enantiopure THFs **(+)-176aaz** in 99% yield with 5:1 dr. Treating alcohol **182l** with (+)-**178p** led to formation of THFs **(+)-176aaaa** in 91% yield with 7:1 dr. Finally, utilizing diallyl alcohol **182g** gave THFs **(+)-176aaab** bearing diene substituent in 30% yield with 5:1 dr (this reaction required 36 hours). Therefore, utilizing an enantiopure homoallylic

alcohol could allow access to enantiopure THFs with up to three new stereogenic centers in a single step (**Scheme 2.49**). The stereochemistry of THFs **176aah** was previously characterized by NOESY-2D experiment (see **Scheme 2.36**). The stereochemistry of the THFs **(+)-176aaz-(+)-176aaab** were then all assigned by analogy with THFs **176aah**. The enantiomeric excess of THFs **(+)-176aah-(+)-176aaab** was determined by HPLC analysis (see experimental chapter in details).



Scheme 2.49 Synthesis of enantiopure products

(e.e. was determined by HPLC on Agilent 1200 series instrument)

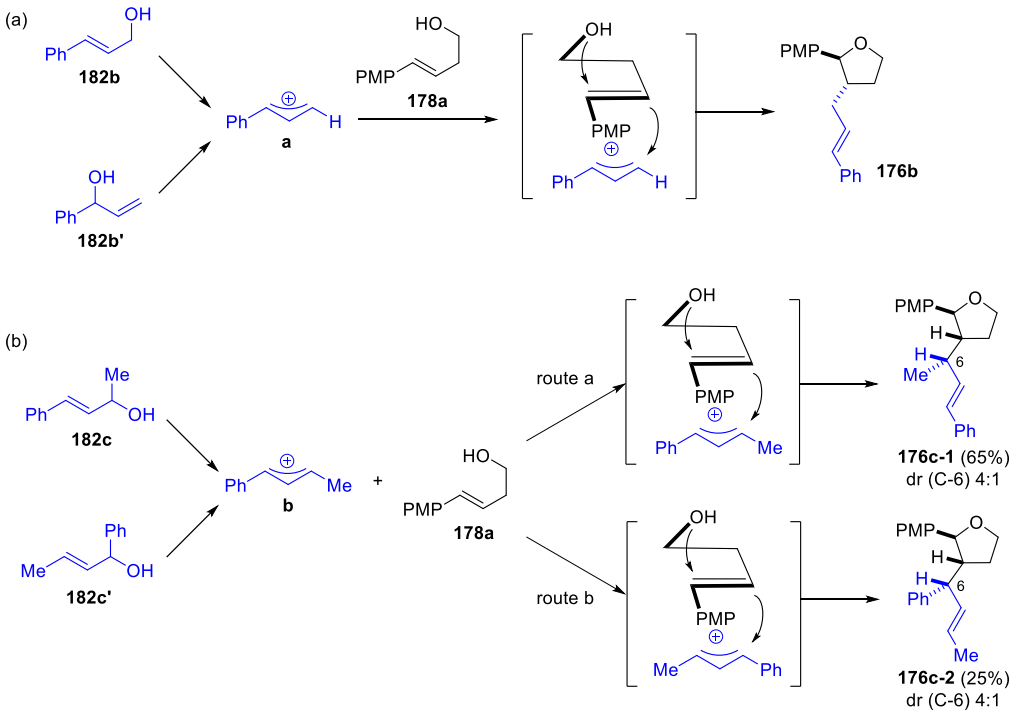
2.6. Mechanistic Study

With the completion of the electrophile and nucleophile scope, and successful synthesis of enantiopure products, attention was then moved to investigate the mechanism of this new transformation.

2.6.1. Evidence for an allyl cationic intermediate

Two major different type of electrophiles were used for the cyclizations: allyl alcohols

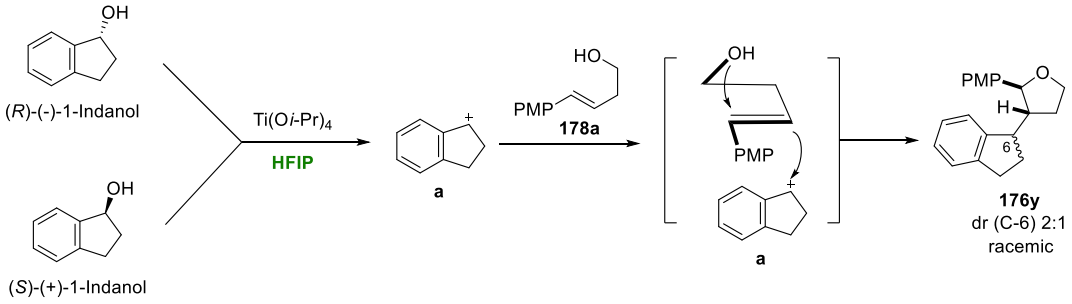
and benzylic alcohols. For the cyclization involving allyl alcohols, using two different regioisomeric allyl alcohol **182b** and **182b'** led to the formation of same THFs **176b** (**Scheme 2.50a**). Submitting another two different regioisomeric allyl alcohol **182c** and **182c'** to the cyclization also afforded same set of regioisomeric products **176c-1** and **176c-2** in identical yield and diastereomeric ratio (**Scheme 2.50b**). This suggests the formation of identical carbocation intermediate **a** and **b** respectively, leading to the production of the same THFs.



Scheme 2.50 Synthesis of THFs **176b** and **176c** *via* using regioisomeric allylic electrophiles

For cyclizations involving benzylic alcohols, using two different enantiopure 1-indanols gave the product as a racemate (**Scheme 2.51**). As the chirality of the indanols was lost during cyclization, it proved the formation of identical carbocation intermediate **a** from both (*R*)-(-)-1-indanol and (*S*)-(+)-1-indanol, leading to the formation of racemic product

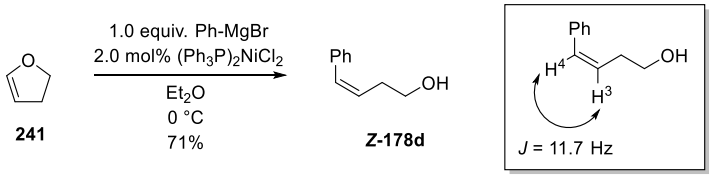
176y. The above results again supported the formation of carbocation for both allylic and benzylic alcohols, stabilized by the polar solvent HFIP, and then trapped by the nucleophilic alcohol to give desired product.



Scheme 2.51 Loss of chirality *via* formation of the carbocation intermediate

2.6.2. Influence of the homoallylic alcohol on the 2,3-diastereoselectivity

The influence of the alkene geometry of the homoallylic alcohol was then studied. The *cis* alcohol ***Z*-178d** was synthesized *via* a nickel-catalyzed addition of phenyl magnesium bromide to 2,3-dihydrofuran (**Scheme 2.52**). Alcohol ***Z*-178d** was obtained as a pure *Z*-isomer, which was confirmed by the small *J* coupling constant between 4-H and 3-H of the alkene (*J* = 11.7 Hz).

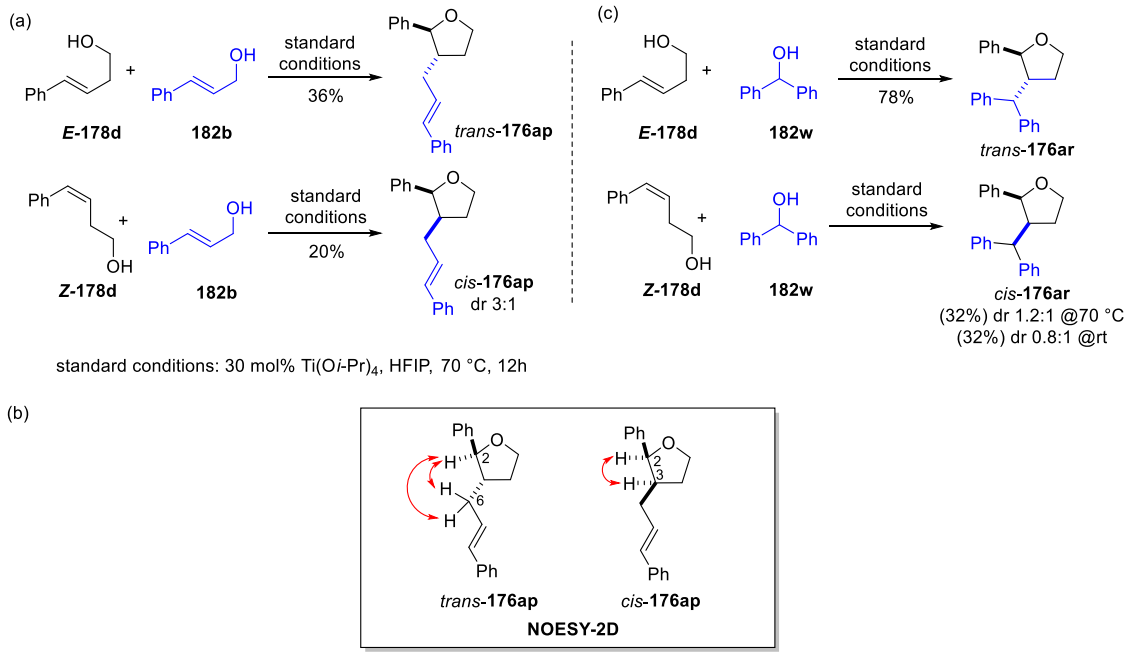


Scheme 2.52 Synthesis of *cis* homoallylic alcohol ***Z*-178d**

Treating *trans* alcohol ***E*-178d** and *cis* alcohol ***Z*-178d** with allyl alcohol **182b** under the standard conditions afforded pure *trans*-**176ap** with complete 2,3-diastereoselectivity and *cis*-**176ap** as a 3:1 partially separable mixture of *cis* to *trans* diastereomers, which

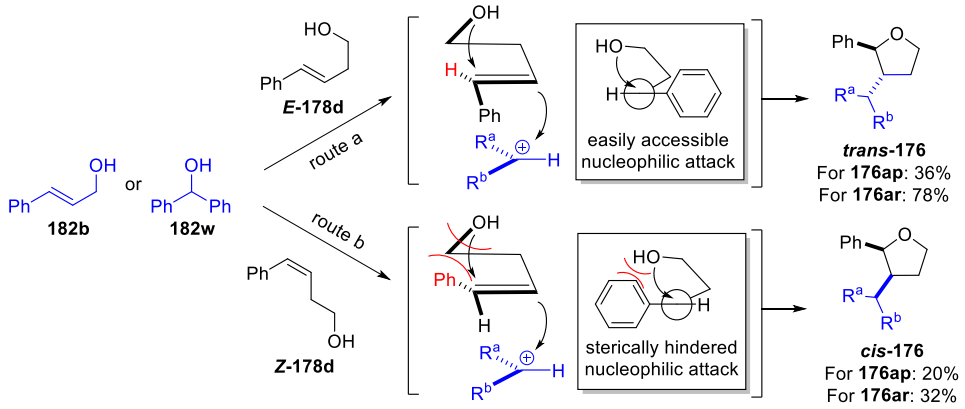
suggested that the *trans* alcohol was more likely to go through a concerted pathway, the *cis* alcohol reacted possibly *via* a stepwise pathway (**Scheme 2.53a**). The stereochemistry of THFs *trans*-**176ap** and *cis*-**176ap** was characterized by NOESY-2D experiments (**Scheme 2.53b**). Correlations could be seen between 2-H and 6-H_2 for THFs *trans*-**176ap**, suggesting the 2,3-*trans* geometry. Correlations could be seen between 2-H and 3-H for THFs *cis*-**176ap**, suggesting the 2,3-*cis* geometry.

Benzylic alcohol **182w** was then employed as the electrophile for the cyclization. *Trans* ***E*-178d** afforded the same result as allyl alcohol **182b**, producing *trans*-**176ar** with complete 2,3-diastereoselectivity. However, worse 2,3-diastereoselectivity was observed when using *cis* ***Z*-178d**, which gave a 1.2:1 mixture of *cis* to *trans* diastereomers under standard conditions, and an inverted 0.8:1 mixture of *cis* and *trans* diastereomers were produced when lowering the temperature to 0 °C. This worse 2,3-diastereoselectivity was possibly attributed to a combination of steric effects and a stepwise pathway for the cyclization of *cis* homoallylic alcohol, possibly because benzhydrol **182w** is a much bulkier electrophile than cinnamyl alcohol **182b**. The stereochemistry of THFs *trans*-**176ar** was signed by analogy with **176v** (see **Scheme 2.17**).



Scheme 2.53 (a) Cyclization of *trans* and *cis* homoallylic alcohols; (b) NOESY-2D experiments on THFs **176ap**

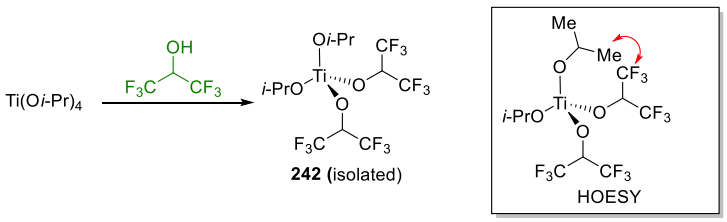
Another obvious difference between the *trans* and *cis* homoallylic alcohols was the higher yield obtained with the *trans* isomer. As the nucleophilic oxygen attacks the alkene bond, the large phenyl group was pointing directly to the approaching pathway in *cis* alcohol ***Z*-178d**, which was more difficult to cyclize and resulted a lower yield. While for *trans* alcohol ***E*-178d,** the phenyl group was pointing opposite to its approaching pathway, leading to a higher yield (**Scheme 2.54**).



Scheme 2.54 Synthesis of *trans* and *cis* THFs

2.6.3. Proposed mechanism for the cyclization

Next, effort was made to detect any reactive complex and intermediate *in situ*. Treating titanium tetraisopropoxide with 20 equivalents of HFIP at both rt and 70 °C led to the isolation of relatively stable titanium complex **242** as a white solid. Complex **242** was characterized by mass spectroscopy and HOESY experiment (correlation found between CF_3 and Me), whereby two of the isopropoxide ligands on titanium were substituted by two HFIP molecules (**Scheme 2.55**). Although the properties and usages of this type of titanium complex was unexplored, there have been similar complexes reported in the literature.[84]



Scheme 2.55 Synthesis of Titanium complex **242**

After complex **242** was prepared and successfully isolated, a few experiments were carried out to investigate its role in the cyclization. Treating alcohols **178a** and **182b** with

30 mol% of $Ti(O^iPr)_2(OHFIP)_2$ as an additive in HFIP afforded similar yield, which suggested the similar role of additive **242** with $Ti(O^iPr)_4$ (**Table 2.11**, **Entries 1 and 3**). While using $CHCl_3$ as solvent with either $Ti(O^iPr)_4$ or $Ti(O^iPr)_2(OHFIP)_2$ gave no desired product (**Table 2.11**, **Entries 2 and 4**). However, with only 20 equivalents of the HFIP added, THFs **176a** was obtained in 20% yield, which illustrated the importance of HFIP as a carbocation stabilizing agent for the cyclization (**Table 2.11**, **Entry 5**).

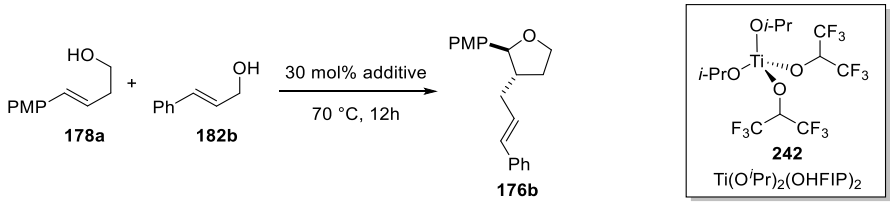
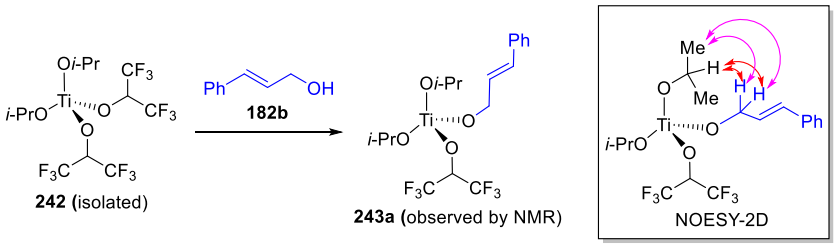


Table 2.11 synthesis of THFs **176a** with complex **242** as additive

Entry	Additive	Solvent	Yield **176b (%)**
1	30 mol% $Ti(O^iPr)_4$	HFIP	52
2	30 mol% $Ti(O^iPr)_4$	$CHCl_3$	0
3	30 mol% $Ti(O^iPr)_2(OHFIP)_2$	HFIP	48
4	30 mol% $Ti(O^iPr)_2(OHFIP)_2$	$CHCl_3$	0
5*	30 mol% $Ti(O^iPr)_2(OHFIP)_2$	$CHCl_3$	20

* 20 equivalents of HFIP was added

Mixing pre-formed complex **242** with cinnamyl alcohol **182b** in $CDCl_3$ for 10 minutes led to the rapid formation of complex **243a**, where one of the hexafluoroisopropoxy ligand was replaced by the cinnamyl alcohol **182b**. Although it was a relatively unstable oil which could not be detected by mass spectroscopy, NOESY-2D experiments showed correlations between the allylic protons with both the Me and α-proton of the isopropoxide ligand (**Scheme 2.56**).

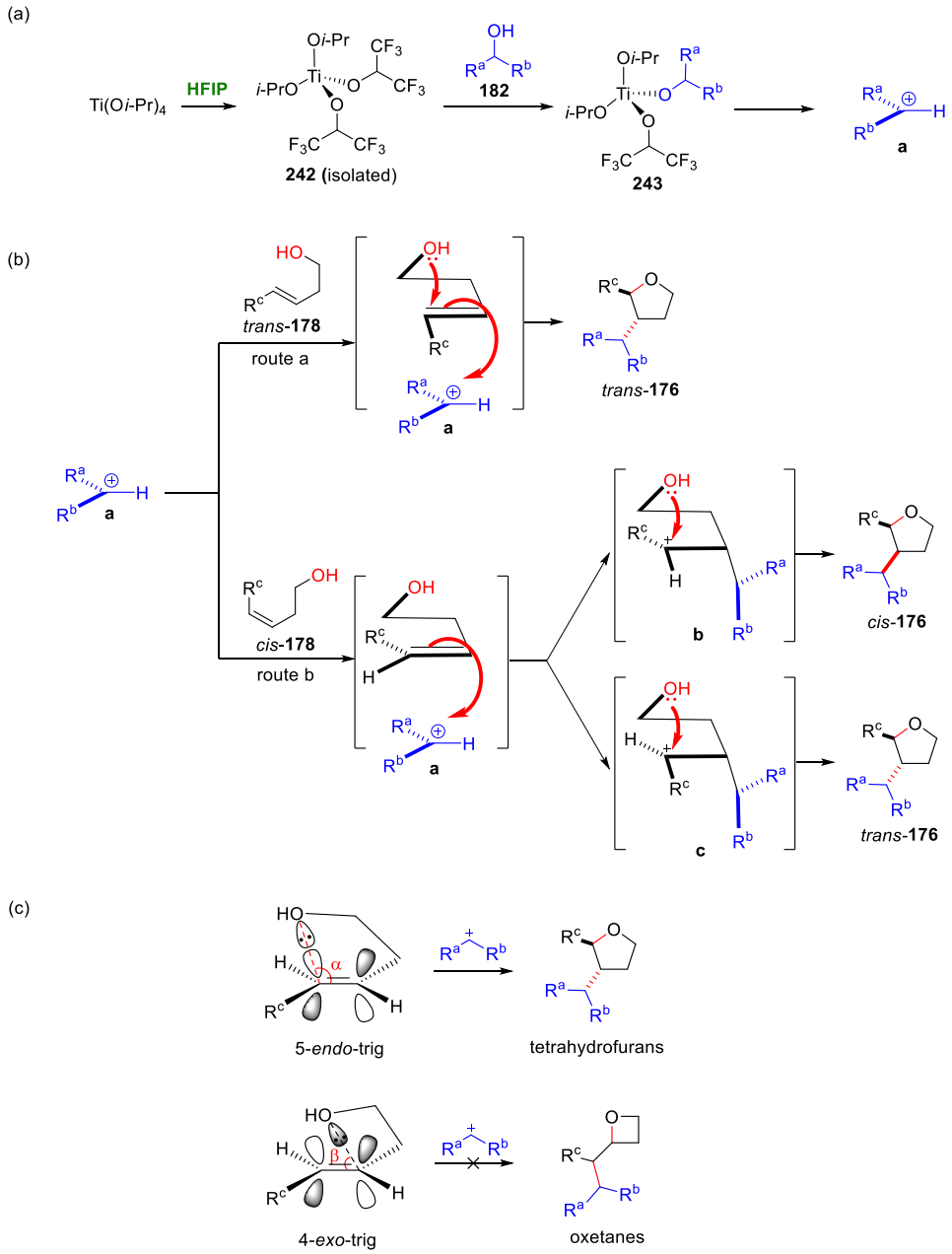


Scheme 2.56 Synthesis of Titanium complex **243a**

Combined with all the results obtained above. It is proposed that *trans* and *cis* homoallylic alcohol **178** possibly went through different reaction pathways. The complex **242** was firstly formed by the addition of two HFIP molecules to $Ti(O^iPr)_4$, whose hexafluoroisopropoxy ligand was substituted by one electrophilic alcohol **182** to give complex **243**. It then generated a key carbocation intermediate **a** (**Scheme 2.57a**). For most of the cyclizations involving *trans*-homoallylic alcohol **178** (except for the synthesis of THFs **176ae**, **176af** and **176am**, which went through a stepwise pathway, see **Scheme 2.22-2.23**), it is more likely to trap the carbocation **a** *via* a 5-*endo*-*trig* manner to afford the *trans*-THFs **176**, which explains the retention of geometry. However, a stepwise pathway is more likely for the cyclization of *cis*-homoallylic alcohol **178**, which generates intermediate **b**&**c** meaning a mixture of *cis* and *trans* diastereomers was obtained (**Scheme 2.57b**).

Additionally, not a single oxetane product was observed or isolated in the previous scope, which is possibly attributed to a disfavored 4-*exo*-trig cyclization. For nucleophilic attack on a sp^2 centre, orbital overlap between the oxygen lone pair and the alkene anti-bonding orbital will be maximized at 109° (Bürgi-Dunitz" trajectory), which is

relatively easier to achieve *via* a 5-*endo*-trig than 4-*exo*-trig cyclization (**Scheme 2.57c**).



Scheme 2.57 Proposed mechanism for the synthesis of THFs **176**

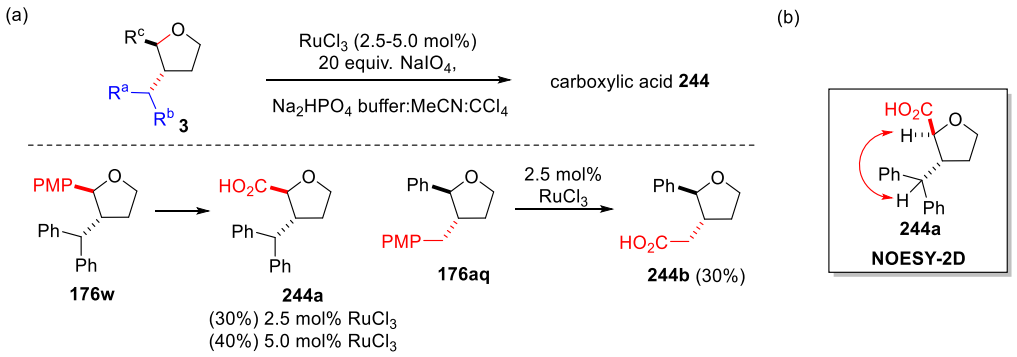
2.7. Selective Functionalization of the THFs

Selective functionalization of the heterocycles **176** provided an opportunity to modify these products into other synthetically useful substrates. Functionalization of the products would be focused in three main directions: oxidation of the electron-rich aromatic ring and the alkene functional group, reduction of the alkene functional group and alkylation/acylation of the lactones.

2.7.1. Oxidation: synthesis of carboxylic acid and aldehyde

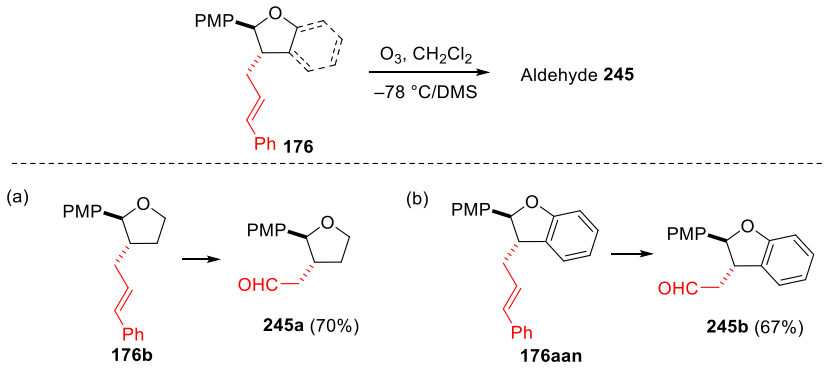
The functionalization of THFs **176** started with Ru-catalyzed oxidation of the aromatic rings as most of the products contained this motif (**Scheme 2.58a**). As only electron-rich aromatic rings can be oxidized, starting materials **176w** and **176aq** bearing an electron-rich PMP group were used. Carboxylic acid **244a** was then synthesized with 2.5 mol% of $RuCl_3$ in 30% yield and 30% of starting material **176w** recovered. In order to push the reaction to completion, 5 mol% of $RuCl_3$ was employed, which improved the yield to 40% without recovering any starting material. Treating THFs **176aq** with 2.5 mol% of $RuCl_3$ afforded **244b** in 30% yield with all of the starting material being consumed. Although this Ru-catalyzed oxidation is well-known in the literature, the reaction mechanism remained unknown and the yield was generally between 30-60%. The stereochemistry of carboxylic acid **244a** was characterized by NOESY-2D experiments (**Scheme 2.58b**). Correlations could be seen between 2-H and 6-H, suggesting the 2,3-*trans* geometry. The stereochemistry of carboxylic acid **244b** was assigned by

analogy with **244a**.



Scheme 2.58 (a) Synthesis of carboxylic acid **244** *via* Ru-catalyzed oxidation; (b) NOESY-2D experiments on carboxylic acid **244a**

As allyl alcohols were widely presented in the scope of the reaction, it was decided to perform ozonolysis of the allylic substituent to afford a synthetically useful aldehyde (**Scheme 2.59**). Treating THFs **176a** with the reaction condition gave aldehyde **245a** in 70% yield. Aldehyde **245b** was also synthesized from THFs **176aan** in similar yield.

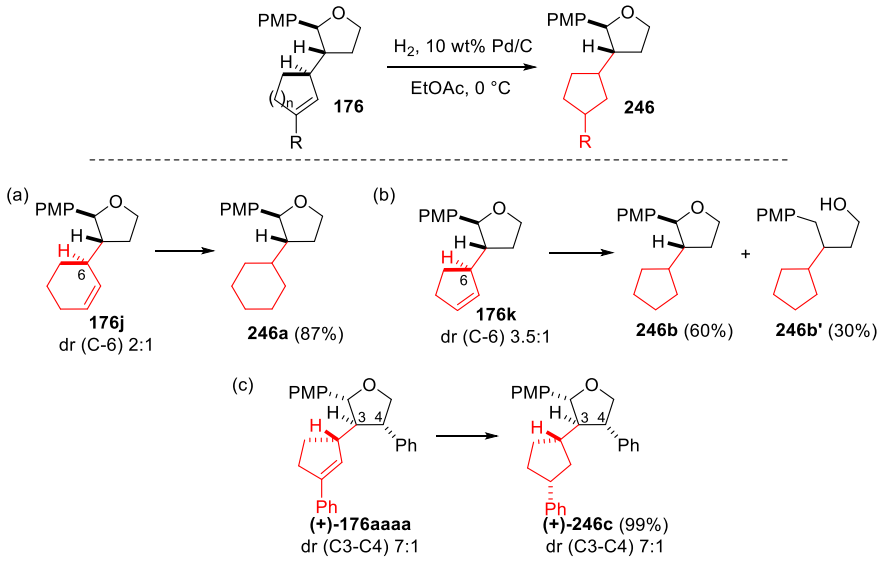


Scheme 2.59 Synthesis of aldehyde **245** *via* ozonolysis

2.7.2. Reduction: synthesis of THF derivatives bearing aliphatic cyclic substituent

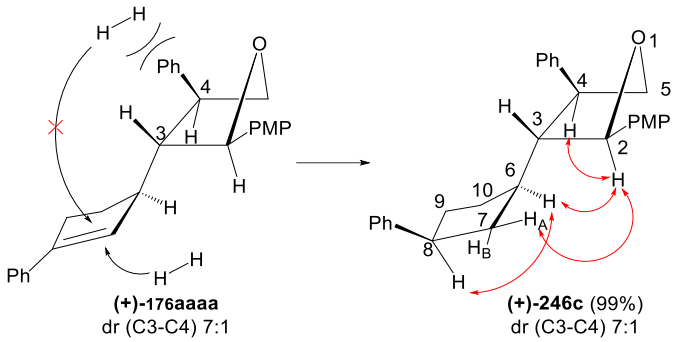
Employing hydrogenation of the THFs allowed the access to saturated ring substituents and could also convert a mixture of diastereomers into single diastereomer. Subjecting THFs **176j** to hydrogenation conditions afforded THFs **246a** in 87% yield as a single

diastereomer (**Scheme 2.60a**). However, the hydrogenation was difficult to control as it was strongly affected by the stirring rate and hydrogen concentration in solvent, which could lead to over-reduction or recovered starting materials. Treating THFs **176k** under the reaction conditions gave product **246b** in only 60% yield, and over-reduced product **246b'** was obtained in 30% yield (**Scheme 2.60b**).



Scheme 2.60 Hydrogenation of THF derivatives bearing allylic substituents

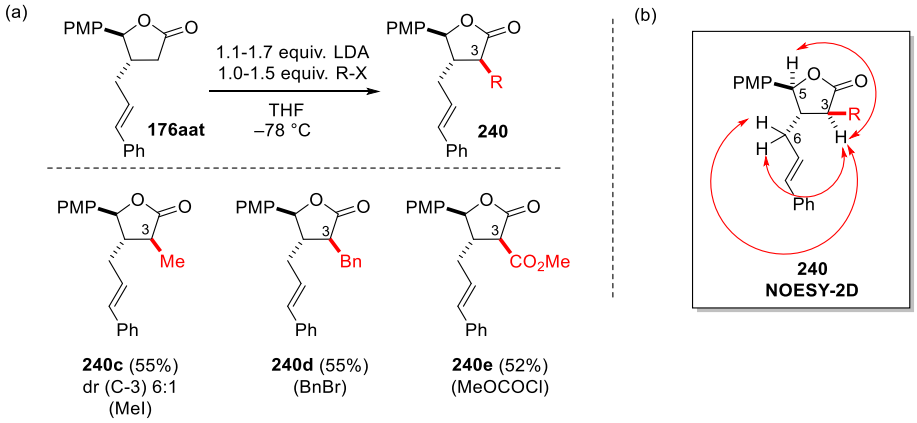
Using enantiopure **(+)-176aaaa** afforded enantiopure product **(+)-246c** in quantitative yield with an identical diastereomeric ratio observed. This meant the hydrogen attacked the alkene from only one face, which could be attributed to blocking of the top face by the large phenyl group at the C-4 position (**Scheme 2.61**). The stereochemistry of THFs **(+)-246c** was determined by a NOESY-2D experiment. Correlations could be seen between 2-H and 4-H, 2-H and 6-H, 2-H and 7-H_A, 6-H and 8-H, suggesting the 2,3,4-all *trans* geometry and 6,8-*cis* geometry.



Scheme 2.61 Hydrogenation of THFs **(+)-246aaaa**

2.7.3. Alkylation and acylation: synthesis of fully substituted lactones

Finally, functionalization of the lactones **176aat** was attempted (**Scheme 2.62a**). Treating **176aat** with a base followed by methyl iodide afforded fully substituted lactione **240c** in 55% yield as a 6:1 mixture of diastereomers. Previous results suggested that diastereselectivity between position C-3 and C-4 positions was controlled by the bulkiness of the substituents at these positions. Thus, a large alkylating or acylating agent was attempted to improve the diastereocontrol outcome. Utilizing BnBr and MeOCOCl afforded product fully substituted lactones **240d** and **240e** in 55% and 52% yield respectively, and both as a single diastereomer. All alkylated and acylated lactones possessed all-*trans* geometry, which was confirmed by NOESY-2D experiments, showing clear correlations between 5-H and 3-H, 3-H and 6-H_2 (**Scheme 2.62b**).



Scheme 2.62 (a) Alkylation and acylation of a lactone; (b) NOESY-2D experiment on lactones **240**

Chapter 3: Stereoselective Synthesis of Pyrrolidines

3.1. Improvement and Optimization of the Original Method

Substituted pyrrolidine derivatives are also widely found as a structural motif in a broad range of natural products and other biologically active molecules, including antitumor, antihelmic, antimalarial, antimicrobial, and antiprotozoal agents. For example, pyrrolidine-containing (–)-anisomycin has been clinically employed to treat amebic dysentery and trichomonas vaginitis, and (+) preussin possesses potent antifungal activities (**Figure 1.1**).[3]

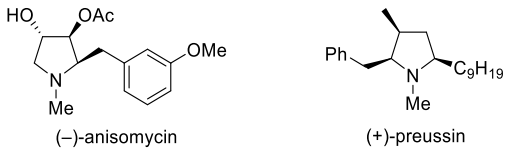
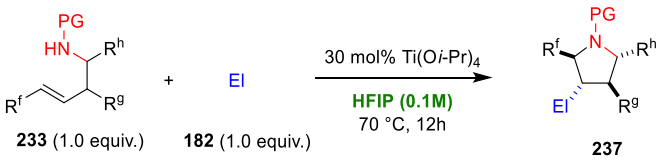


Figure 3.1 Pyrrolidine-containing natural products.

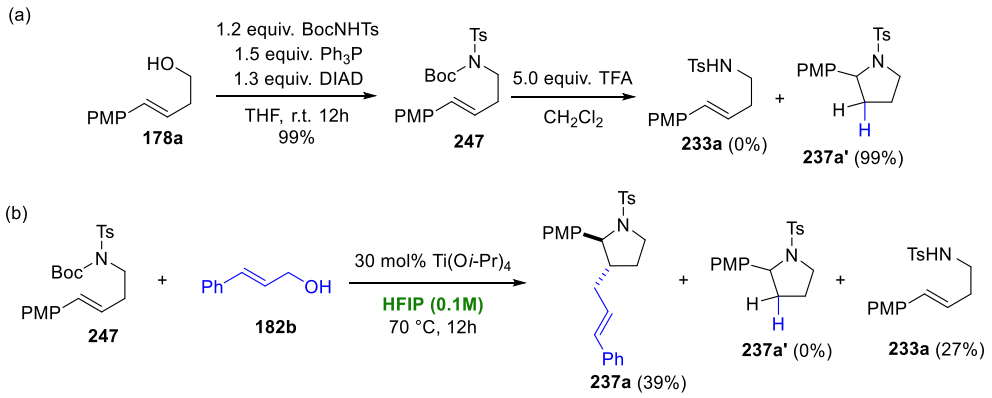
Due to the high diastereoselectivity and broad scope observed with the synthesis of THFs and previously successful synthesis of pyrrolidines **237a** (see **Scheme 2.40**), it was decided to further extend this methodology to the nitrogen cycles *via* using protected homoallylic amines **233** as nucleophiles while keeping the electrophile **182** unchanged (**Scheme 3.1**).



Scheme 3.1 Synthesis of pyrrolidine derivatives **237**

Initial attempts at synthesizing homoallylic amine **233a** started by treating alcohol **178a**

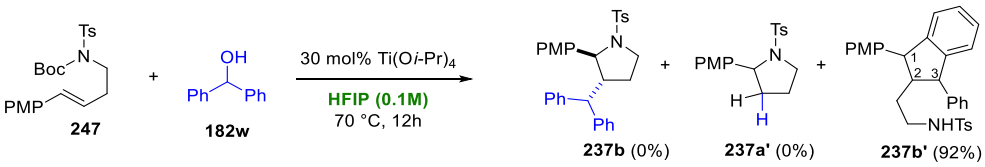
with BocNHTs under Mitsunobu conditions, leading to the production of **247** in quantitative yield. However, the Boc group deprotection of **247** using trifluoroacetic acid (TFA) consumed all the starting materials and led to the sole formation of protonated product **237a'** (**Scheme 3.2a**). This suggested deprotection of the Boc group and cyclization could be performed under the same acidic conditions. Thus, a one pot reaction was attempted in an effort to shorten the synthesis of starting materials into a single step reaction from the previously prepared homoallylic alcohols **1** (**Scheme 3.2b**). The formation of protonated product **237a'** was observed when no other reactive electrophiles were present, allyl alcohol **182b** was therefore added as a more competitive electrophile to inhibit the production of **237a'**. Pleasingly, the Boc group was removed followed by cyclization to produce desired product **237a** in 39% yield without forming protonated product **237a'**, and 27% of the de-Boc amine **233a** was also obtained.



Scheme 3.2 (a) First attempt at **s**ynthesizing homoallylic amine **233a**; (b) Cyclization of Boc-protected amine **247** with allyl alcohol **182b** as the electrophile

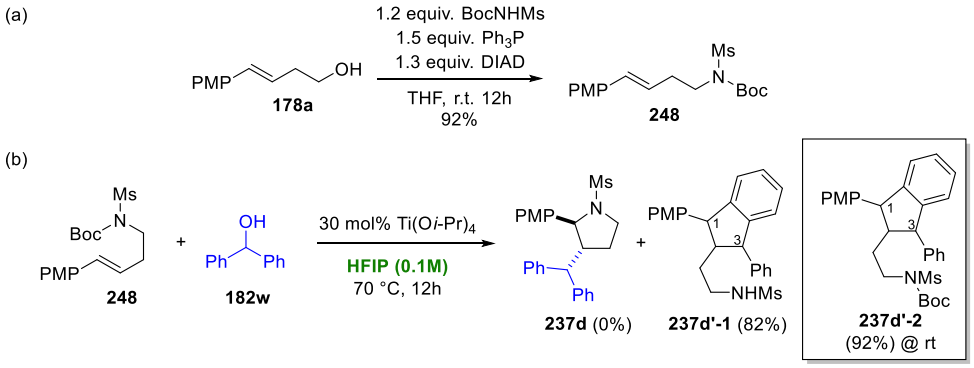
Benzhydrol **182w** was then subjected to the cyclization to examine its compatibility

(**Scheme 3.3**). Unfortunately, neither protonated product **237a'** nor pyrrolidines **237b** was observed, but side-product **237b'** was obtained in 92% yield. After the electrophile **182w** was trapped by compound **247**, instead of being attacked by the nitrogen to form the pyrrolidines **237b**, the alkene was attacked by the phenyl group from alcohol **182w** *via* a Friedel-Crafts type reaction to generate side product **237b'** as a single diastereomer (the stereochemistry of **237b'** was not determined).



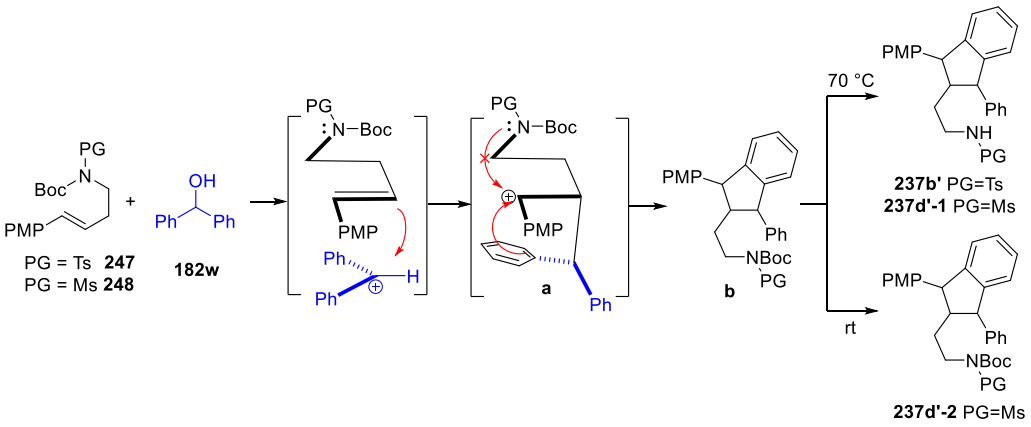
Scheme 3.3 Cyclization of Boc-protected amine **247** with benzylic alcohol **182w** as the electrophile

Different protecting groups were then screened to avoid this side reaction. Boc protected sulfonamide **248** was synthesized *via* treating alcohol **178a** with BocNHMs under Mitsunobu reaction (**Scheme 3.4a**). Treating Boc protected sulfonamide **248** with benzylic alcohol **182w** afforded same type of side-product **237d'-1**. Unfortunately lowering the temperature to room temperature was not helpful, and Boc protected side-product **237d'-2** was again obtained in the same yield (**Scheme 3.4b**) (The stereochemistry of **237d'-1** and **237d-2'** was not determined).



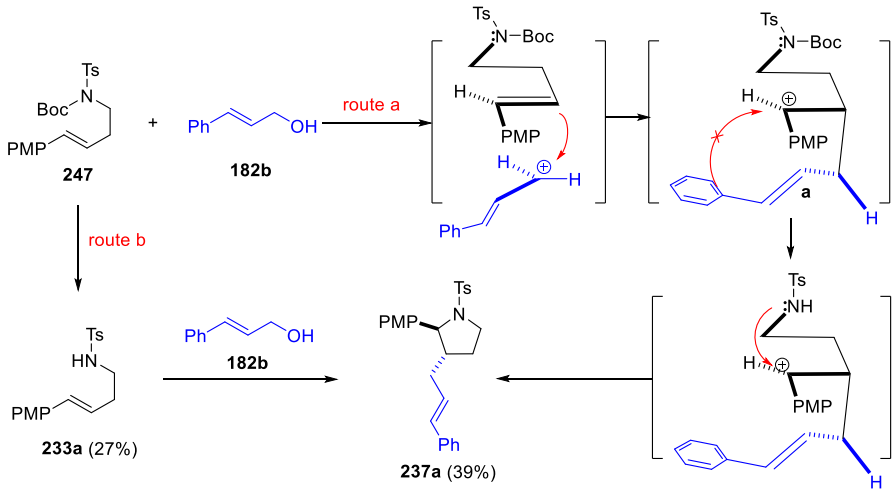
Scheme 3.4 (a) Synthesis of Boc-protected sulfonamide **248**; (b) Cyclization of sulfonamide **248** with alcohol **182w** as the electrophile

Based on the above results, a mechanism was proposed for the formation of side-products **237b'** and **237d-1'** (**Scheme 3.5**). The electron-rich alkene from the homoallylic amines firstly attacked the *in situ* generated di-benzylic carbocation to give intermediate **a**. However, the Boc group on the nitrogen atom was so bulky that it inhibited attack of the nitrogen on to the carbocation. The phenyl of the di-benzylic substituents then conducted a Friedel-Crafts type cyclization to form the intermediate **b**. Lastly, the Boc group was deprotected at high temperature to afford the final side-products, which was supported by the production of Boc protected side-product **237d'-2** at room temperature.



Scheme 3.5 Formation of side-product **237b'**, **237d'-1** and **237d'-2**

Note that no Friedel-Crafts type side-product was observed when employing allyl alcohol **182b** as the electrophile; here it was inhibited by the larger distance between the phenyl of the allylic substituent and the carbocation intermediate **a** (**Scheme 3.6**). Regarding the formation of de-Boc amine **233a**, the rate of generation of intermediate **a** was also slower which was attributed to the less reactive allyl alcohol **182b** being employed. This gave **247** the opportunity to undergo Boc-deprotection and generate amine **233a**. These results then supported two possible pathways to produce pyrrolidines **237a**. It either proceeded through trapping of the allylic carbocation followed by deprotection of the Boc group and ring closure (**Scheme 3.6-route a**) or by first deprotection of the starting material **247** followed by trapping of the electrophile and ring closure (**Scheme 3.6-route b**). As only one diastereomer *trans*-**237a** was produced, it suggested that the stepwise route a is less possible, and the cyclization should proceed through route b.



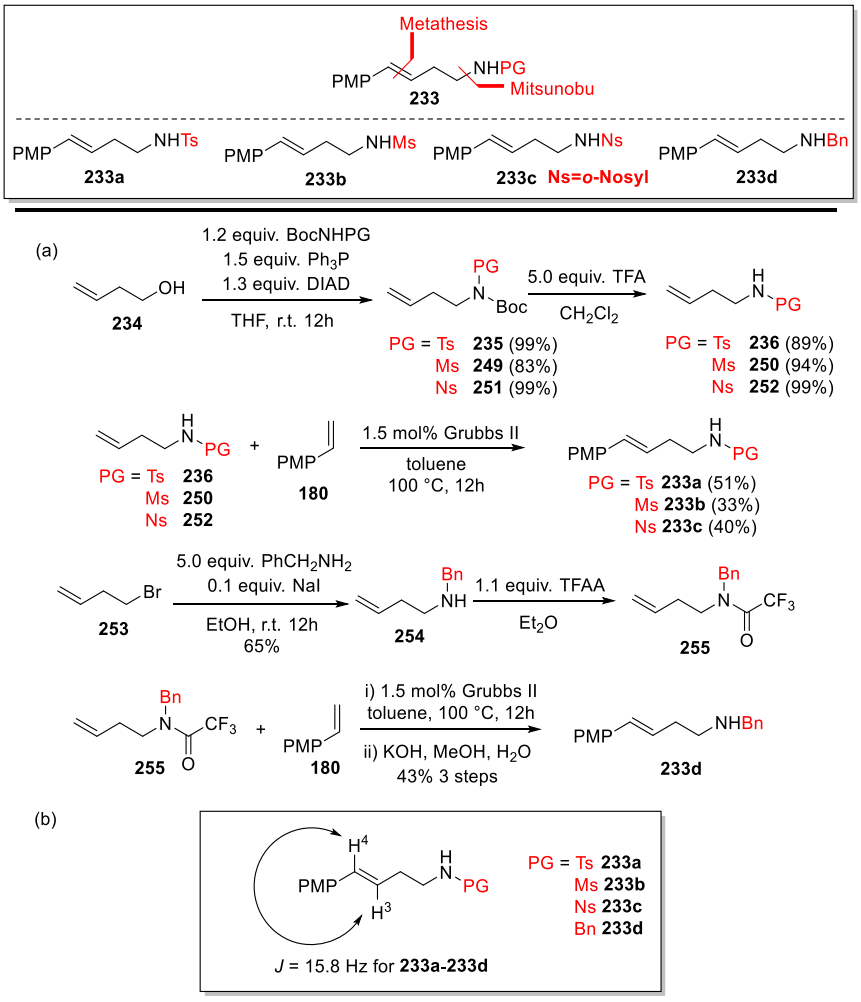
Scheme 3.6 Formation of pyrrolidines **237a** and de-Boc amine **233a**

The experiment shown in **Scheme 3.5** suggests that the Boc deprotection is slower than

the cyclization. It is therefore concluded that the nucleophilic homoallylic amine must not possess a Boc group on the nitrogen atom.

3.2. Screening of the Protecting Group

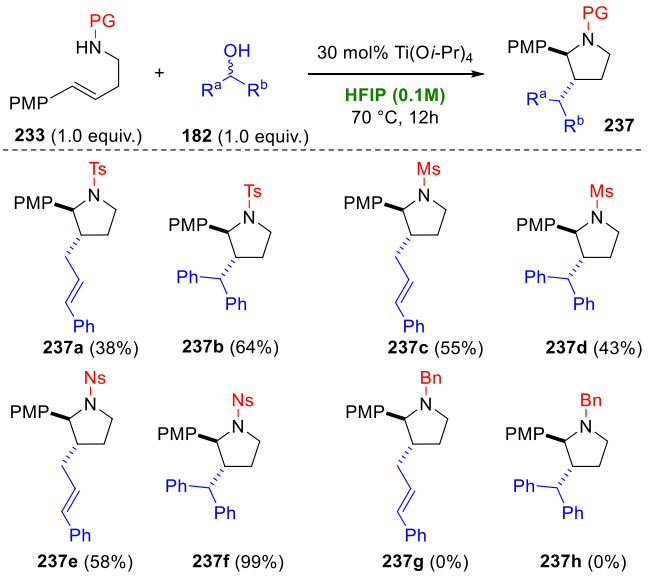
Synthesis of protected amines **233a-233c** started with a Mitsunobu reaction of non-activated homoallylic alcohol **234** using BocNHTs, BocNHMs and BocNHNs respectively, followed by deprotection of the Boc group and Ru-catalyzed metathesis with 4-methoxystyrene **180**.



Scheme 3.7 (a) Synthesis of protected amines **233a-233d**; (b) *J* coupling constants for amines **233a-233d**

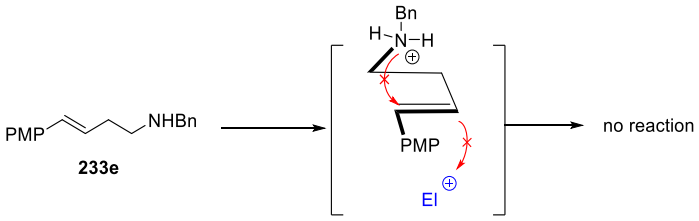
Protected amine **233d** was prepared firstly by alkylation of benzylamine to form **253**, followed by protection of amine to give **255**. It was then treated with 4-methoxystyrene **180** under Ru-catalyzed metathesis conditions and deprotection of the trifluoroacetyl group to afford protected amine **233d** (**Scheme 3.7a**). All homoallylic amines **233a**-**233d** were obtained as single *E*-isomers (again confirmed by a large *J* coupling constant of 15.8 Hz between 3-H and 4-H) (**Scheme 3.7b**).

Cinnamyl alcohol **182b** and benzhydrol **182w** were then utilized for the screening of protecting groups as they represented the two main type of electrophiles used for the synthesis of THFs (**Scheme 3.8**). Using Ts as a protecting group afforded pyrrolidines **237a** and **237b** in 38% and 64% respectively. Replacing the Ts group with a Ms group managed to bring the yield of **237c** to 55% but diminished the yield of **237d** to 43%. Using Ns (*ortho*-nitrobenzenesulfonyl) as a protecting group afforded pyrrolidines **237e** and **237f** in 58% and 99% yield respectively.



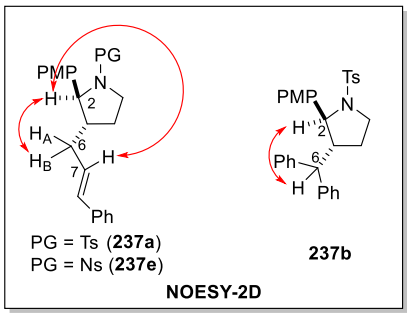
Scheme 3.8 Scope of the protecting group

Finally, attempting to use Bn as a protecting group gave none of the desired products **237g** and **237h**. This could be attributed to the enhanced basicity of the N-Bn group, leading to protonation of the nitrogen under the reaction conditions which then inhibited the cyclization (**Scheme 3.9**).



Scheme 3.9 Inhibition of cyclization *via* protonation of nitrogen

All pyrrolidines **237a**-**237f** were obtained as a single 2,3-*trans* diastereomer, which possessed the same relative stereochemistry as THFs **176**. The 2,3-*trans* stereochemistry was determined by NOESY-2D experiments on pyrrolidines **237a**&**237e** and **237b**, which bear allyl and benzylic substituents respectively. Pyrrolidines **237a** and **237e** showed correlation between 2-H and 6-H_B, 2-H and 7-H, and pyrrolidines **237b** showed correlation between 2-H and 6-H, proving its 2,3-*trans* geometry. The rest of the pyrrolidines were assigned by analogy (**Scheme 3.10**).



Scheme 3.10 NOESY-2D experiments on pyrrolidines **237a, 237e,** and **237b**

3.3. Optimization of the Reaction Conditions

The best protecting group was determined to be *o*-Ns, and optimization of the cyclization was therefore conducted using homoallylic amine **233c** as the nucleophile and cinnamyl alcohol **182b** as the electrophile. Using previously optimum conditions afforded pyrrolidines **237e** in 58% yield (**Table 3.1**, **Entry 1**). Neither adding an extra equivalent of alcohol **182b** nor lowering the temperature to 40 °C benefited the reaction (**Table 3.1**, **Entries 2-3**). Conducting the reaction at dilute concentration (0.05M) afforded similar yield (**Table 3.1**, **Entry 4**). Finally, the reaction was carried out at 40 °C for 36 hours, leading to only 40% yield (**Table 3.1**, **Entry 5**).

For conditions which led to high yield, only 0-5% of electrophilic alcohol **182b** was recovered while amine **233c** was recovered in a large amount (**Table 3.1**, **Entries 1 and 5**). Thus, more equivalents of alcohol **182b** were then utilized with harsher reaction conditions in order to push the reaction to completion. Using 2 equivalents of alcohol **182b** at 70 °C for 36 hours or at 95 °C for 12 hours led to 43% and 52% yield respectively, and with 33% of alcohol **182b** being recovered (**Table 3.1**, **Entries 6-7**). A higher loading of $Ti(O^iPr)_4$ was beneficial, affording pyrrolidines **237e** in 58% without recovering any alcohol **182b** (**Table 3.1**, **Entry 8**). Finally, 1 equivalent of alcohol **182b** was added after 6 hours of reaction time with 50% loading of $Ti(O^iPr)_4$, leading to a lowered yield and only 5% of alcohol **182b** was recovered (**Table 3.1**, **Entry 9**).

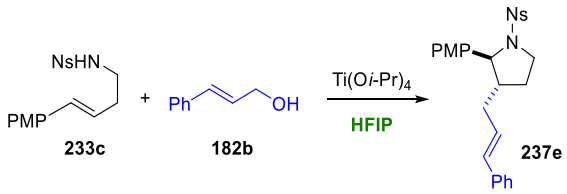


Table 3.1 Optimization of the synthesis of pyrrolidines **237e**

Entry	**233c**:**182b**	Loading of Ti(O^{i}Pr)$_4$	Temperature	Time	Concentration	Yield **237e** (%)	Recovered (%)	
							233c	**182b**
1	1:1	30mol%	70 °C	12h	0.1M	58	42	0
2	1:2	30mol%	70 °C	12h	0.1M	40	37	37
3	1:1	30mol%	40 °C	12h	0.1M	31	68	35
4	1:1	30mol%	70 °C	12h	0.05M	54	46	0
5	1:1	30mol%	40 °C	36h	0.1M	40	60	5
6	1:2	30mol%	70 °C	36h	0.1M	43	57	33
7	1:2	30mol%	95 °C	12h	0.1M	52	48	33
8	1:2	50mol%	70 °C	12h	0.1M	58	41	0
9*	1:2	50mol%	70 °C	12h	0.1M	43	57	5

***** 1 equivalent of **182b** was added after 6 hours

It was then decided that the best conditions identified so far were 30 mol% Ti(O^{i}Pr)$_4$ at 70 °C for 12 hours, as they gave the highest yield with less alcohol **182b** and Ti(O^{i}Pr)$_4$ required. Further optimization with HFIP solvent was then conducted. As the byproduct of this cyclization was water, extra water in HFIP could slow the rate of cyclization. Thus, distilled HFIP was used, but again the same yield was obtained (**Table 3.2**, **Entry 3**). Using undistilled HFIP with addition of extra 20 equivalents of water neither benefited the reaction nor harm the yield (**Table 3.2**, **Entry 2**). Both degassed and distilled degassed HFIP were utilized, but none of them was beneficial to the reaction, leading to identical yields (**Table 3.2**, **Entries 4-5**). Therefore, commercial HFIP was determined to be the most suitable solvent for cyclization of the amine.

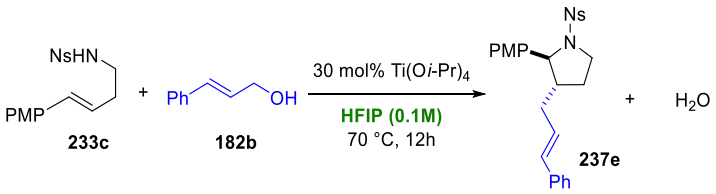
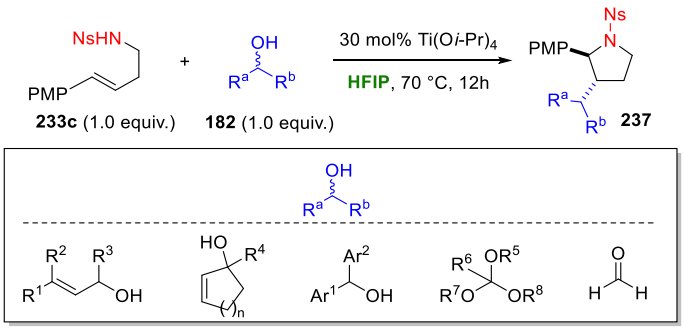


Table 3.2 Optimization of the synthesis of pyrrolidines **237e** using different batches of HFIP

Entry	HFIP	Yield **237e** (%)	Recovered **233c** (%)	Recovered **182b** (%)
1	From bottle, wet	58	42	0
2	From bottle, with extra 20 equiv. of H_2O	58	42	0
3	Distilled	57	42	0
4	Degassed HFIP	58	42	0
5	Distilled and degassed HFIP	58	42	0

3.4. Scope of the Reaction-electrophiles

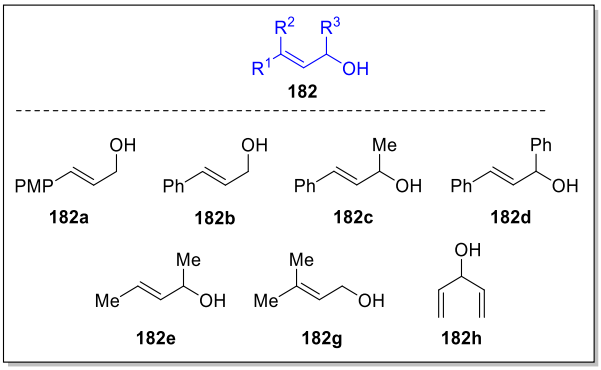
With the optimized conditions and best protecting group identified, it was then decided to further investigate the scope of the electrophile component **182**. As the reactivity of this system was similar to the synthesis of tetrahydrofurans, previously used electrophiles **182** were examined as they should tolerate the synthesis of pyrrolidines **237**. Amine **233c** with a PMP group attached was used as the nucleophile for the scope of the electrophile, as it was the simplest nucleophile and bears a reactive electron-rich alkene. Four different classes of electrophile were investigated; acyclic allyl alcohols, cyclic allyl alcohols, benzylic alcohols and other miscellaneous electrophiles that were tolerated in the reaction system (such as paraformaldehyde and orthoformate) (**Scheme 3.11**).



Scheme 3.11 Synthesis of pyrrolidine derivatives **237**

3.4.1. Acyclic allyl alcohols acting as electrophiles

Seven of the previously screened acyclic allyl alcohols, which afforded high yields and good diastereoselectivity in the synthesis of THFs, were selected for the exploration of the electrophile scope (**Scheme 3.12**). All modifications on the reaction conditions for the later cyclization reactions were based on the previous scope of the THFs forming reaction.

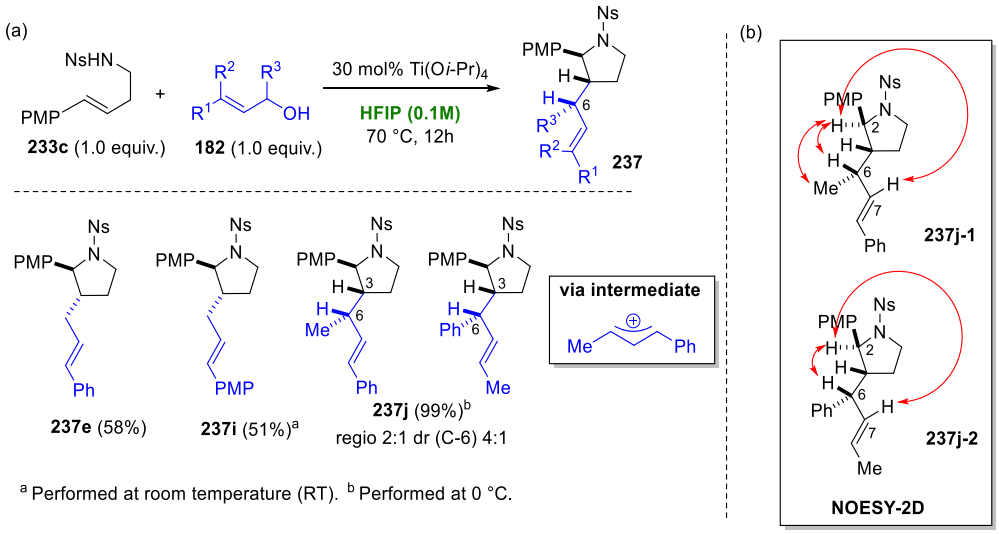


Scheme 3.12 Acyclic allyl alcohols

Pyrrolidines **237e** was previously prepared during the optimization process using alcohol **182b** as the electrophile, affording 58% yield. Conducting the cyclization of **233c** at room temperature using alcohol **182a** bearing an electron-rich aromatic ring gave pyrrolidines **237i** in 51% yield. Unsymmetrical allyl alcohol **182c** was then treated with

amine **233c** at 0 °C, leading to the formation of **237j** as a 2:1 mixture of regioisomeric products in 99% yield. Both of regioisomeric mixtures were obtained as a 4:1 mixture of diastereomers. The formation of regioisomeric mixtures was attributed to the generation of an unsymmetrical carbocation intermediate, which could be trapped by the amine at either end. The preference for trapping at the methyl end was due to the reduced steric hinderance at this position (**Scheme 3.13a**).

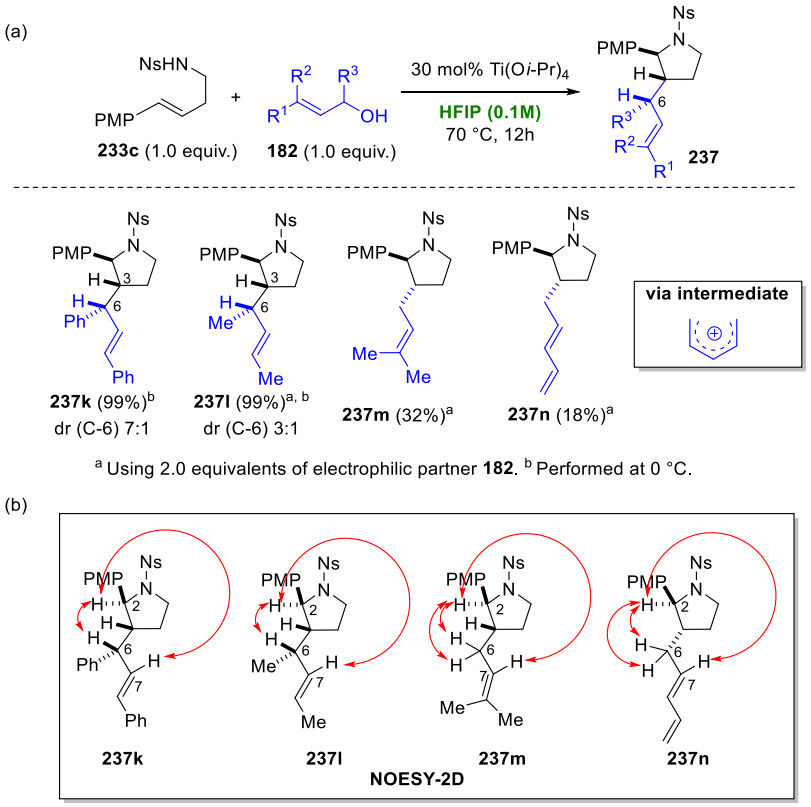
The stereochemistry of pyrrolidines **237j** was characterized by NOESY-2D experiments (**Scheme 3.13b**). Correlations could be seen between 2-H and 6-H, 2-H and Me, 2-H and 7-H for pyrrolidines **237j-1;** correlations could be seen between 2-H and 6-H, 2-H and 7-H for pyrrolidines **237j-2**, suggesting the 2,3-*trans* geometry. The stereochemistry of pyrrolidines **237i** was assigned by analogy with pyrrolidines **237e** (see **Scheme 3.10** on NOESY-2D analysis of **237e**).



Scheme 3.13 (a) Synthesis of pyrrolidines **237e**, **237i** and **237j**; (b) NOESY-2D experiments on pyrrolidines **237j**

Symmetrical allyl alcohols **182d** and **182e** could be used to avoid the regioisomer problem. Treating alcohol **182d** with amine **233c** afforded product **237k** in 99% yield with 7:1 dr. Using aliphatic allyl alcohol **182e** did not compromise the yield, affording pyrrolidines **237i** in 99% yield with 3:1 dr, although the reaction required two equivalents of alcohol **182e** and was conducted at 0 °C. Using less reactive aliphatic allyl alcohols **182g** and **182h** allowed the introduction of a non-aromatic substituent at the C-3 position in the pyrrolidines with diminished yield, affording **237m** and **237n** in 32% and 18% yield respectively. Pleasingly, for the latter diallyl alcohol **182h**, only one regioisomer was observed *via* attack at the primary end of the carbon cation intermediate, which again is the less sterically hindered position (**Scheme 3.14a**).

The stereochemistry of pyrrolidines **237k**-**237n** was characterized by NOESY-2D experiments (**Scheme 3.14b**). Correlations could be seen between 2-H and 6-H_2, 2-H and 7-H, suggesting the 2,3- *trans* geometry. The 3,6-*cis* geometry of pyrrolidines **237j**, **237k** and **237l** was assigned by analogy with THFs **240b** (see **Scheme 2.44**).



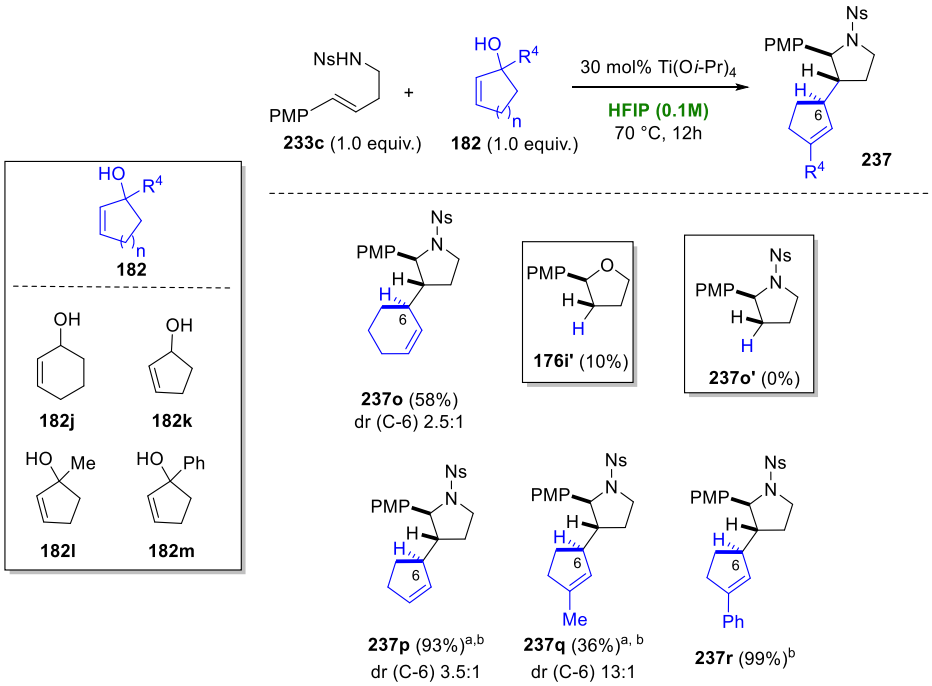
Scheme 3.14 (a) Synthesis of pyrrolidines **237k**-**237n**; (b) NOESY-2D experiments on pyrrolidines **237k**-**237n**.

3.4.2. Cyclic allyl alcohols acting as electrophiles

Cyclic allyl alcohols **182j**-**182m**, which were previously prepared, were also screened (**Scheme 3.15**). Treating cyclohexenyl alcohol **182j** with amine **233c** under the standard conditions led to the formation of pyrrolidines **237o** in 58% yield and pleasingly some level of diastereocontrol was observed at the C-6 position, giving the products as a 2.5:1 mixture of diastereomers. Unlike the synthesis of THF derivatives using alcohol **182j** as the electrophile, where protonated product **176i'** was obtained in 10% yield, there was no protonated product **237o'** observed in this case (see **Scheme 2.13**). This suggests a higher efficiency for the cyclization of homoallylic amines. Using cyclopentyl alcohol

182k gave a higher yield and better diastereocontrol, affording pyrrolidines **237p** in 93% yield with 3.5:1 dr; and the reaction could be carried out at room temperature, although two equivalents of the alcohol **182k** were required.

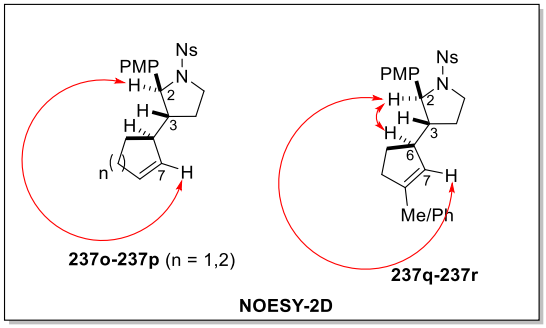
Tertiary cyclopentenyl allyl alcohols with aliphatic or aromatic substituents were investigated next (**Scheme 3.15, 237q-237r**). Employing two equivalents of methyl bearing tertiary alcohol **182l** at room temperature resulted in only 34% yield, but much better diasteroselectivity, giving pyrrolidines **237q** as a 13:1 mixture of diastereomers. Swapping the methyl group with a bulkier phenyl group led to complete diasterocontrol at the C-6 position, giving pyrrolidines **237r** in quantitative yield and as a single diastereomer.



[a] Using 2.0 equivalents of electrophilic partner **182**.[b] Performed at room temperature (RT).

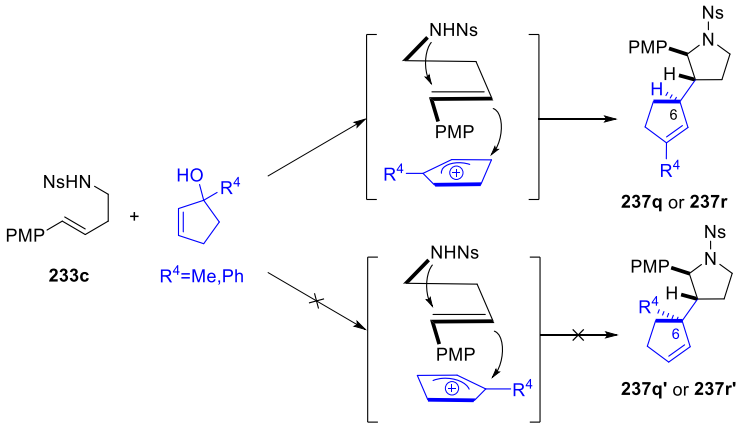
Scheme 3.15 Scope of the electrophiles-cyclic allyl alcohols

The stereochemistry of pyrrolidines **237o**-**237r** was characterized by NOESY-2D experiments (**Scheme 3.16**). Correlations could be seen between 2-H and 7-H for pyrrolidines **237o**-**237p**; correlations could be seen between 2-H and 6-H, 2-H and 7-H for pyrrolidines **237q** and **237r**, suggesting the 2,3-*trans* geometry. The 3,6-*trans* geometry of pyrrolidines **237o**-**237r** was assigned by analogy with THF derivative **176aad** (see **Scheme 2.33**).



Scheme 3.16 NOESY-2D experiments on pyrrolidines **237o**-**237r**

Note that the formation of both pyrrolidines **237q** and **237r** processed in a regiospecific manner, no regioisomeric product was obtained, and the trapping of carbocation intermediate only happened at the less hindered secondary position (**Scheme 3.17**).

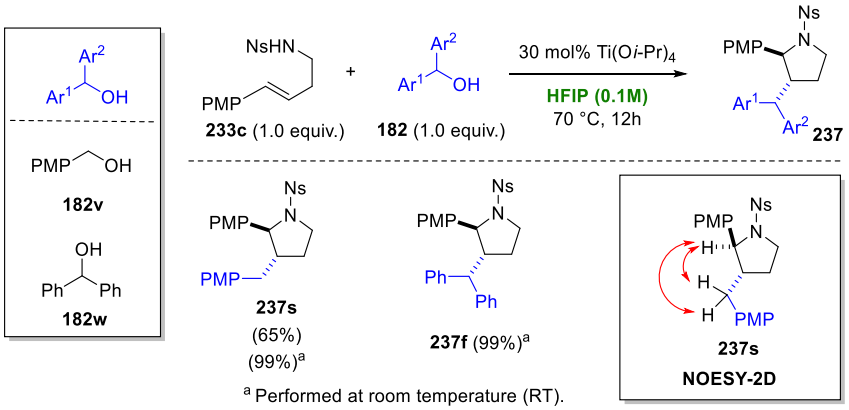


Scheme 3.17 Synthesis of pyrrolidines **237q** and **237r**

3.4.3. Benzylic alcohols acting as electrophiles

Next, primary and secondary benzylic alcohols were screened. Using primary electron-rich benzylic alcohol **182v** under the standard conditions afforded pyrrolidines **237s** in 65% yield without recovering any starting materials. This could be attributed to the destruction of either starting materials (amine **233c** and alcohol **182v**) or pyrrolidines **237s** at high temperature. The reaction was therefore conducted at room temperature, leading to production of pyrrolidines **237s** in 99% yield. With the re-optimized conditions in hand, treating di-benzylic alcohol **182w** with amine **233c** at room temperature afforded pyrrolidines **237f** in 99% yield (**Scheme 3.18**).

The stereochemistry of pyrrolidines **237s** was characterized by NOESY-2D experiments. Correlations could be seen between 2-H and 6-H_2 for pyrrolidines **237s**, suggesting the 2,3-*trans* geometry. The NOESY-2D experiment of pyrrolidines **237f** was previously discussed (see **Scheme 3.10**)



Scheme 3.18 Scope of benzylic alcohols as electrophiles and NOESY-2D experiment on pyrrolidines **237s**

3.4.4. Orthoformate and paraformaldehyde acting as electrophiles

Using trimethyl orthoformate **182ae** under the previous optimized conditions, where no other additive was used, afforded no desired product **237t** and 100% of recovered starting materials (**Table 3.3**, **Entry 1**). Raising the temperature to 70 °C was not helpful, and only starting materials were recovered (**Table 3.3**, **Entry 2**). Conducting the reaction with 30 mol% of $Ti(O^iPr)_4$ at 70 °C led to 11% conversion based on crude ^1H NMR spectroscopy, although a 1:1 mixture of diastereomers was obtained (**Table 3.3**, **Entry 3**). Ionic additive Ph_4PBF_4, which has been reported to strengthen the cation stabilizing ability of HFIP,[66] gave a promising result of 55% conversion, but there was no diastereocontrol at the C-3 position (**Table 3.3**, **Entry 4**). A final attempt was made at 0 °C using Ph_4PBF_4, but only a trace amount of product with 1:1 dr was observed (**Table 3.3**, **Entry 5**). Thus, trimethyl orthoformate **182ae** was determined to be an unsuitable electrophile for the synthesis of pyrrolidines and no further optimization was conducted.

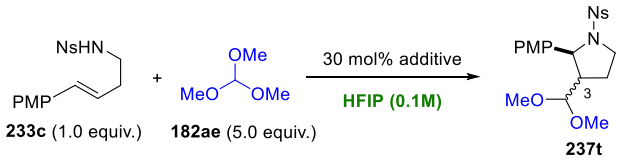


Table 3.3 Synthesis of pyrrolidines **237t**

Entry	Additives	Temperature	NMR Conversion **237t** (%)	dr (C-3)
1	None	rt	0	
2	None	70 °C	0	
3	$Ti(O^iPr)_4$	70 °C	11	1:1
4	Ph_4PBF_4	70 °C	55	1:1
5	Ph_4PBF_4	0 °C	Trace	1:1

Treating amine **233c** with 20 equivalents of paraformaldehyde **182am** under the standard conditions afforded pyrrolidines **237u** in 40% yield and as a 10:1 mixture of

trans to *cis* diastereomers. Surprisingly, side-product **237u'** was also obtained in 30% yield with an identical diastereomeric ratio. It was suspected that 30% of the pyrrolidines **237u** could further reacted with the paraformaldehyde **182am** at high temperature followed by a hydride shift to give side-product **237u'** (**Table 3.3**, **Entry 4**). In order to avoid production of overreacted product **237u'** and gain better diastereocontol, lower temperature was utilized. Treating the reaction at 0 °C led to the sole production of **237u** in 74% yield as a single *trans* diastereomer (**Table 3.3**, **Entry 5**).

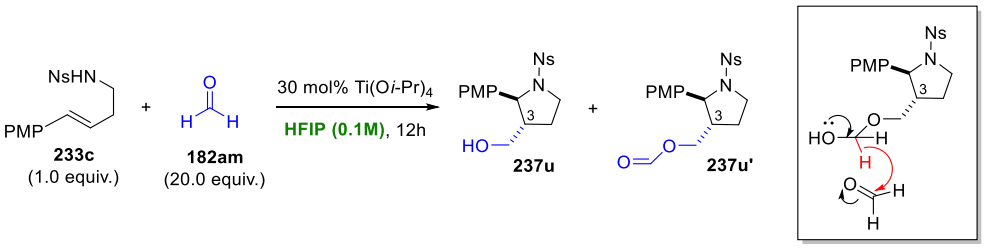
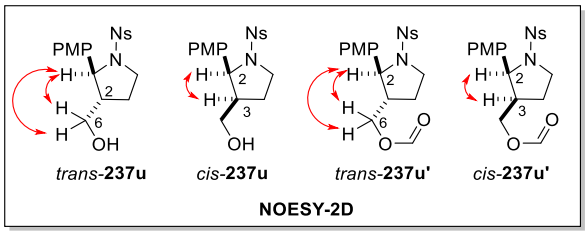


Table 3.4 Synthesis of pyrrolidium **237u** and side-product **237u'**

Entry	Temperature	Yield **237u** (%)	Yield **237u'** (%)
1	70 °C	40% dr (C-3) 10:1	30% dr (C-3) 10:1
2	0 °C	74	0

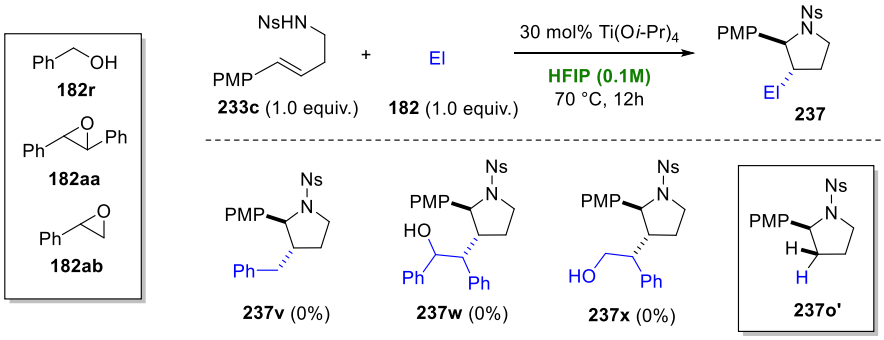
The stereochemistry of pyrrolidines **237u** and **237u'** was characterized by NOESY-2D experiments (**Scheme 3.19**). Correlations could be seen between 2-H and 6-H_2 for both *trans*-**237u** and *trans*-**237u'**, suggesting the 2,3-*trans* geometry. Correlations could be seen between 2-H and 3-H for both *cis*-**237u** and *cis*-**237u'**, suggesting the 2,3-*cis* geometry.



Scheme 3.19 NOESY-2D experiment on pyrrolidines **237u** and **237u'**

3.4.5. Miscellaneous

Better yields and diastereoselevtivity were observed in most of the syntheses of the pyrrolidines compared with the syntheses of tetrahydrofurans, which suggested that homoallylic amines were generally more reactive than homoallylic alcohols. Other previously failed electrophiles were therefore screened to complete the scope of the electrophiles (**Scheme 3.20**). Unfortunately, using electron-neutral benzylic alcohol **182r** as the electrophile afforded neither desired product **237v** nor protonated product **237o'**. Attempted reactions with 1,2-disubstituted epoxide **182aa** and terminal epoxide **182ab** produced no pyrrolidines **237w** and **237x**, and only starting materials were recovered.

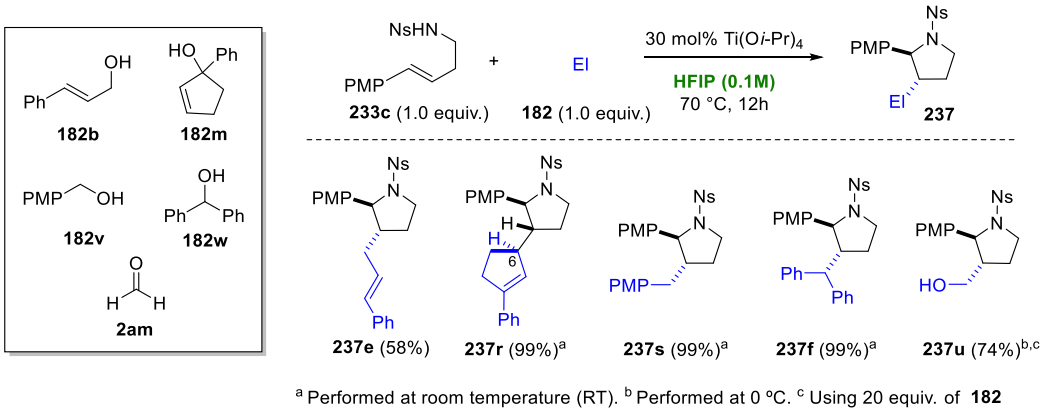


Scheme 3.20 Scope of the electrophiles-miscellaneous

3.4.6. Summary of the electrophile scope

With the completion of electrophile screening, it was suggested that the protected amine **233c** showed tolerance to a range of electrophilic alcohols and paraformaldehyde. Acyclic allyl alcohol **182b**, cyclic allyl alcohol **182m**, benzylic alcohols **182v** and **182w** were determined to be the most efficient and useful electrophilic alcohols as they led to high yield and complete diastereocontrol at up to three newly formed stereogenic

centres. Additionally, other than the alcohols, paraformaldehyde **182am** was found to afford promising results with amine **233c**, giving pyrrolidines **237u** bearing a synthetically useful primary alcohol substituent as a single *trans* diastereomer in high yield (**Scheme 3.21**). These five electrophiles were therefore chosen to be utilized for the later scope of the nucleophiles.

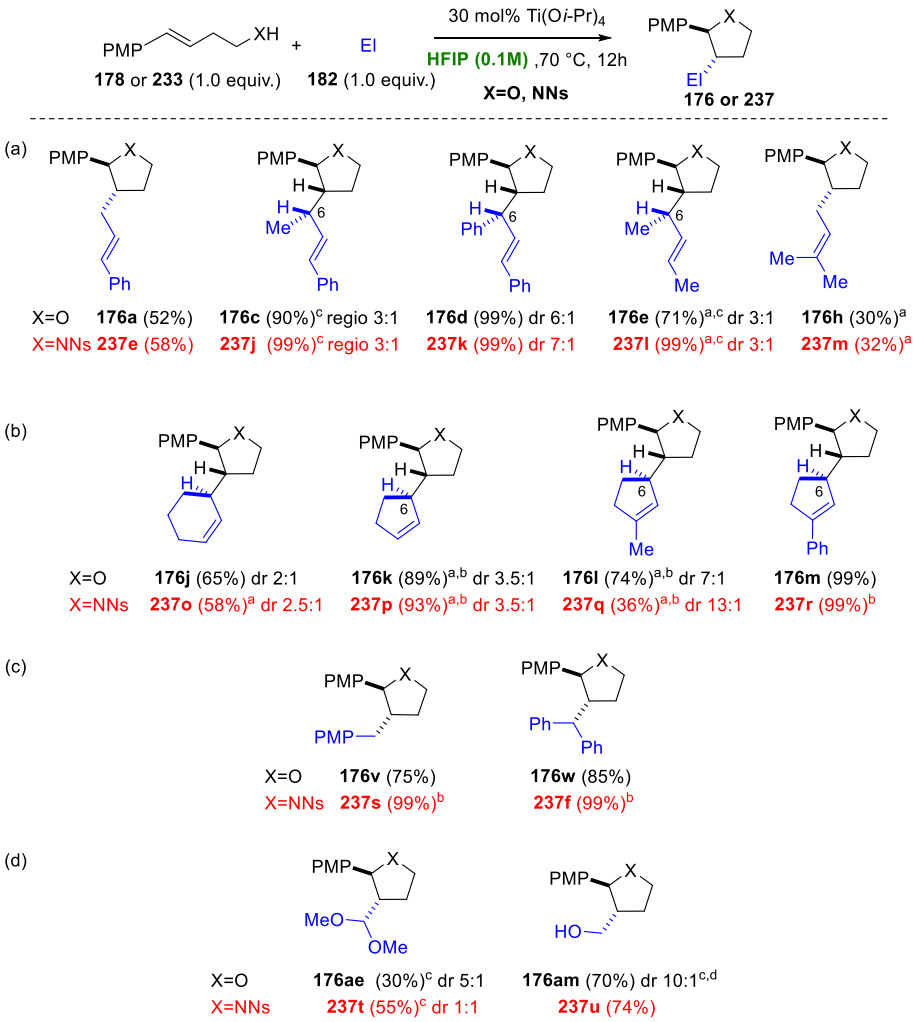


[a] Performed at room temperature (RT). [b] Performed at 0 °C. [c] Using 20 equiv. of **182**

Scheme 3.21 Best electrophiles found for the synthesis of pyrrolidines **237**

It was then decided to compare the results of the electrophile scope between the synthesis of THFs and pyrrolidines. When using acyclic alcohols as the electrophiles, the synthesis of pyrrolidines was generally more efficient, as higher yields were observed without harming the diastereoselectivity (**Scheme 3.22a**). With cyclic alcohols employed as the electrophiles, the yield and diastereoselectivity were similar except for THFs **176l** and pyrrolidines **237q**, where a much better diastereocontrol outcome at the C-6 position was observed using the amine as a nucleophile but its yield was halved (**Scheme 3.22b**). When using benzylic alcohols as the electrophiles, higher yields were obtained by using the amine as a nucleophilic partner (**Scheme 3.22c**). Finally, huge differences were observed among other non-alcoholic electrophiles. Treating

trimethylorthoformate with amine led to complete loss of stereocontrol at the C-3 position, giving pyrrolidines **237t** as a 1:1 mixture of diastereomers. In contrast, THFs **176ae** was obtained as a 5:1 mixture of *trans* to *cis* diastereomers. Employing paraformaldehyde as the electrophile afforded pyrrolidines **237u** in similar yield as THFs **176am** but gave product as a single *trans* diastereomer (**Scheme 3.22d**).



[a] Using 2.0 equiv. of **182**. [b] Performed at room temperature. [c] Performed at 0 °C. [d] Using 20 equiv. of **182**

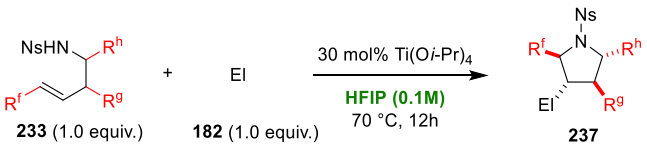
Scheme 3.22 Scope of the electrophiles-synthesis of THFs and pyrrolidines

To sum up, it was generally beneficial to both yield and *trans*-diastereoselectivity to switch the nucleophile to an amine. This could be attributed to the stronger

nucleophilicity of the nitrogen atom than the oxygen atom, leading to faster ring closure and trapping of the carbocation intermediate which was generated from the electrophile.

3.5. Scope of the Reaction-nucleophile

After obtaining the optimum reaction conditions and showing that a broad variety of electrophiles tolerated the cyclization, further exploration on the nucleophilic homoallyllic amine **233** was conducted. Examination of the nucleophilic amine focused on two parts; the versatility and diastereomeric outcome of substituents R^f-R^h and the synthesis of enantiopure products (**Scheme 3.23**).

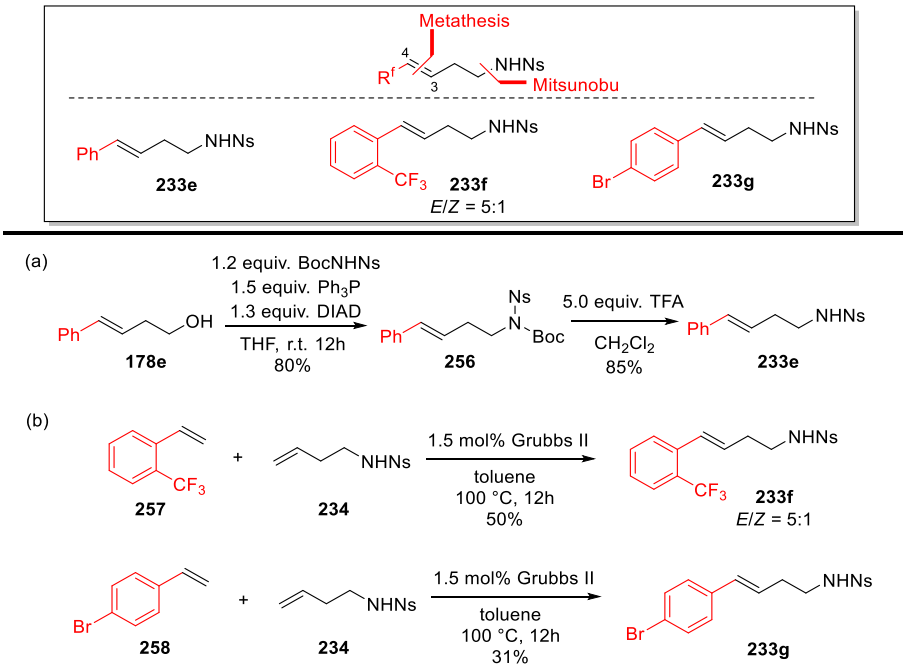


Scheme 3.23 Scope of the nucleophiles **233**

3.5.1. Versatility of the substituent R^f: alkyl and aryl substituted amine

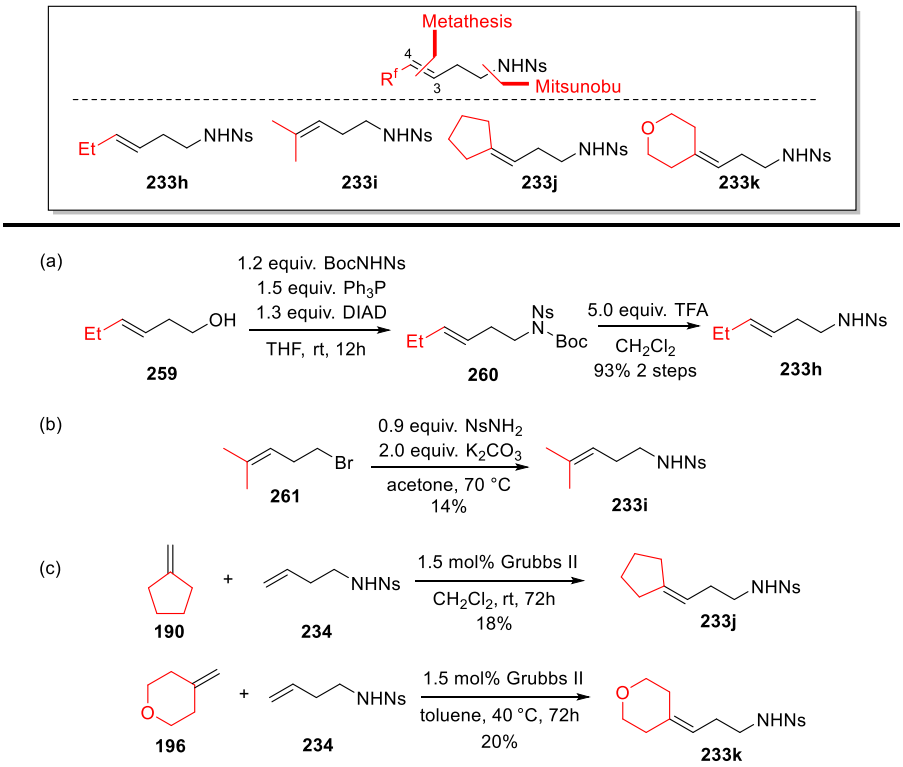
The scope of the nucleophiles was firstly explored by utilizing amine **233** bearing different alkyl and aryl substituents R^f. Treating previously synthesized alcohol **178e** under the Mitsunobu conditions afforded protected amine **256**, whose Boc group was deprotected to give amine **233e**. (**Scheme 3.24a**). Amines bearing electron-deficient aromatic rings were synthesized by using Ru-catalyzed metathesis of the corresponding styrenes with previously synthesized homoallylic amine **234**, giving amine **233f** in a

separable 5:1 mixture of *trans* to *cis* diastereomers and **233g** as a single *trans* diastereomer (**Scheme 3.24b**). Amine **233f** was obtained as a 5:1 mixture of *E* and *Z* alkenes, preferring the *E* alkene, and other amines were obtained as single *E*-isomers (*E*-isomer was confirmed by a large *J* coupling constant of 15.8 Hz between 3-H and 4-H; *Z*-isomer was confirmed by a small *J* coupling constant of 11.8 Hz between 3-H and 4-H).



Scheme 3.24 Synthesis of homoallylic amines **233e-233g**

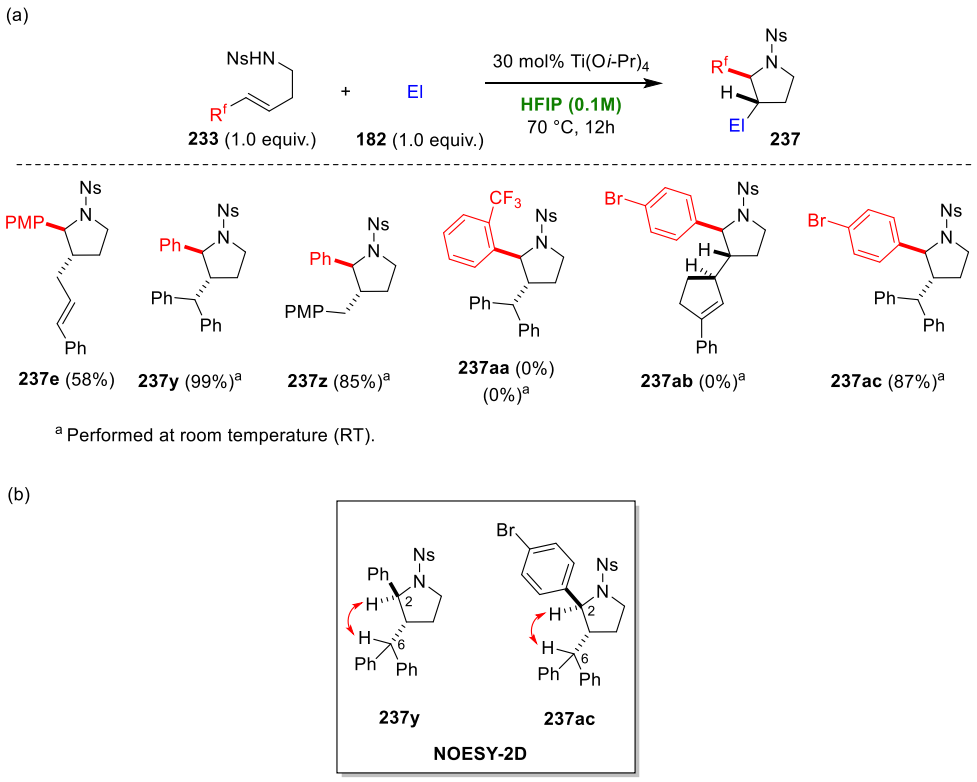
Disubstituted aliphatic amine **233h** was prepared by a Mitsunobu reaction of commercially available alcohol **259**, followed by removal of the Boc group (**Scheme 3.25a**). Trisubstituted acyclic aliphatic amine **233i** was synthesized by the coupling of *p*-nosyl amine and bromide **261** (**Scheme 3.25b**). Trisubstituted cyclic aliphatic amines **233j** and **233k** were synthesized by the Ru-catalyzed metathesis reaction of the corresponding 1,1-disubstituted alkenes with previously synthesized homoallylic amine **234** (**Scheme 3.25c**).



Scheme 3.25 Synthesis of homoallylic amines **233h-233k**

Evaluation of substituents R^f started by examining amines bearing different aromatic substituents (**Scheme 3.26a**). According to the previous scope of THFs synthesis, less activated nucleophiles required a better electrophile in order to achieve high yields. Benzhydrol **182w** was therefore employed as the electrophile with electron-neutral homoallylic amine **233e**, affording pyrrolidines **237y** in 99% yield. Utilizing alcohol **182v** as the electrophile also led to pyrrolidines **237z** in an excellent yield of 85%. Using electron-deficient aromatic substituted amine **233f** (pure *trans*) gave no desired product **237aa** at either room temperature or at 70 °C. Treating 4-bromophenyl substituted amine **233g** with alcohols **182v** gave no desired product **237ab**, but pyrrolidines **237ac** was obtained in 87% yield with alcohol **182w** as the electrophile. Thus, benzhydrol **182w** was determined to be the most suitable electrophile for the scope of less reactive

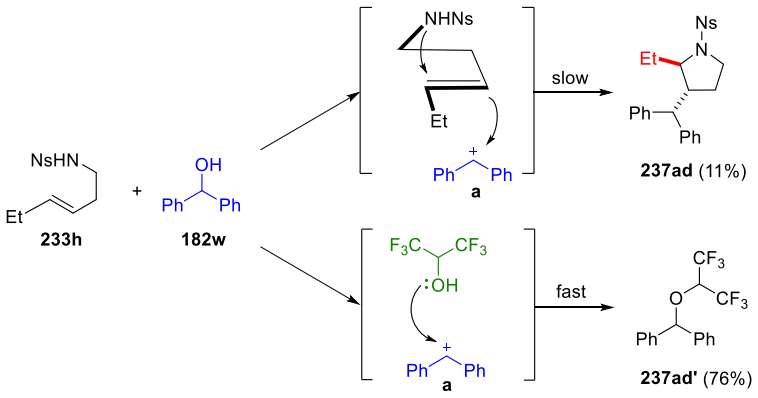
amines (see later). The stereochemistry of pyrrolidines **237y** and **237ac** was characterized by NOESY-2D experiments (**Scheme 3.26b**). Correlations could be seen between 2-H and 6-H for both **237y** and **237ac**, suggesting the 2,3-*trans* geometry. The stereochemistry of pyrrolidines **237e** was previously determined (see **Scheme 3.10**) and the stereochemistry of pyrrolidines **237z** was assigned by analogy with pyrrolidines **237s** (see **Scheme 3.18**).



Scheme 3.26 (a) Synthesis of pyrrolidines bearing different aromatic substituents (b) NOESY-2D experiments on pyrrolidines **237y** and **237ac**

Challenging disubstituted aliphatic homoallylic amine **233h** was treated with benzhydrol **182w** at 70 °C, giving 11% of pyrrolidines **237ad** which was not separable from the amine starting material **233h**, which was recovered in 89% yield (**Scheme 3.27**). Additionally, side-product **237ad'** was obtained in 76% yield, which was attributed to

the weak nucleophilicity of the alkene in **233h**. Under the reaction conditions, di-benzylic carbocation **a** was easily formed which was slowly trapped by the amine **233h** to give pyrrolidines **237ad**. Carbocation **a** survived long enough to be attacked by a HFIP molecule to afford side-product **237ad'**.



Scheme 3.27 Synthesis of pyrrolidines **237ad** and side-product **237ad'**

A further optimization study was then attempted. Conducting the reaction at room temperature led to full recovery of starting materials **233h** and **182w** (**Table 3.5**, **Entry 2**)**.** Using 100 mol% of $Ti(O^iPr)_4$ accelerated side-product formation, producing a quantitative amount of **237ad'** while only a trace of pyrrolidines **237ad** was observed. This could be attributed to faster formation of the di-benzylic carbocation, which was rapidly trapped by a HFIP molecule (**Table 3.5**, **Entry 3**). Employing 5 equivalents of the benzhydrol **182w** gave pyrrolidines **237ad** and side-product **237ad'** in similar yield (**Table 3.5**, **Entry 4**). Leaving the reaction for 72 hours was not beneficial, leading to similar results (**Table 3.5**, **Entry 5**). A final attempt was made using ionic additive Ph_4PBF_4, which has been reported to strengthen the cation stabilizing ability of HFIP,[66] but this gave a similar result (**Table 3.5**, **Entry 6**).

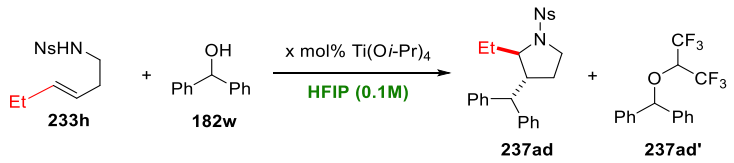
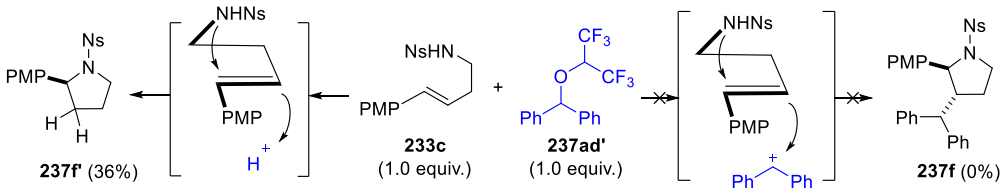


Table 3.5 Synthesis of pyrrolidines **237ad**

Entry	Loading of **182w**	Additive	Temperature	Time (h)	Yield (%)	
					237ad	**237ad'**
1	1.0 equiv.	30 mol% $Ti(O^iPr)_4$	70 °C	12	11	76
2	1.0 equiv.	30 mol% $Ti(O^iPr)_4$	rt	12	0	0
3	1.0 equiv.	100 mol% $Ti(O^iPr)_4$	70 °C	12	Trace	99
4	5.0 equiv.	30 mol% $Ti(O^iPr)_4$	70 °C	12	11	95
5	5.0 equiv.	30 mol% $Ti(O^iPr)_4$	70 °C	72	12	88
6	1.0 equiv.	100 mol% Ph_4PBF_4	70 °C	12	15	85

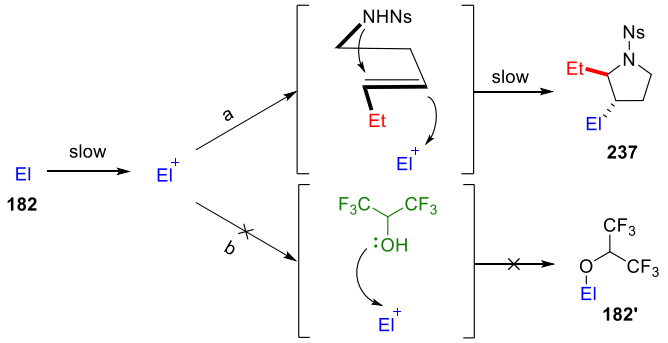
A control experiment was conducted to investigate whether the side-product **237ad'** was able to regenerate the carbocation or if it remained stable under the reaction conditions (**Scheme 3.28**). Treating amine **233c** with side-product **237ad'** produced protonated product **237f'** in 36% yield as the only available electrophile was proton, while no desired product **237f** was observed. This indicated that the generation of side-product **237ad'** from benzhydrol **182w** was irreversible. Combined with the fact that carbocation formation from benzhydrol **182w** was rapid and trapping of carbocation by amine **233h** was too slow, it was concluded that benzhydrol **182w** was not a suitable electrophile for the cyclization of amine **233h**.



Scheme 3.28 Attempted synthesis of pyrrolidines **237f** using **237ad'** as the electrophile

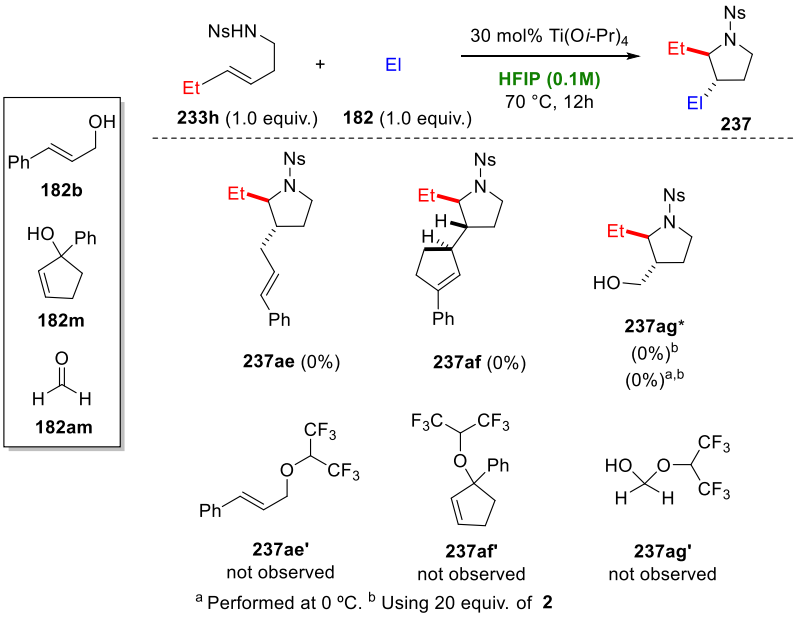
A suitable electrophile should either be able to generate the carbocation at a similar

rate to the trapping of the carbocation by amine **233h** (**Scheme 3.29-a**), and its generated carbocation should either be unable to form the HFIP-coupled product **182'** or form it reversibly (**Scheme 3.29-b**).



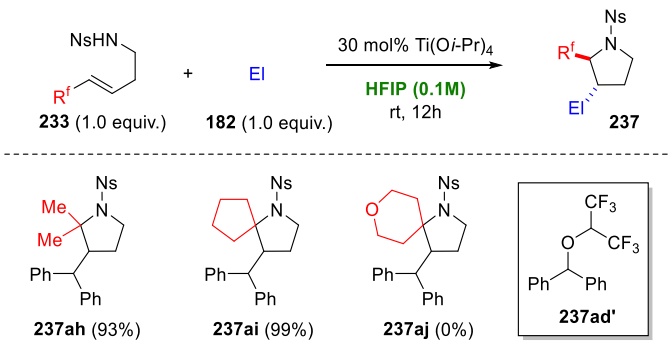
Scheme 3.29 Suitable electrophiles for the cyclization of amine **233h**

Less reactive allyl alcohols **182b** and **182m** were screened based on the above criteria (**Scheme 3.30**). With these electrophiles, none of the undesired HFIP-coupled side-products **237ae'-237af'** were observed. However, no pyrrolidines product was obtained either, and amine **233h** was recovered in quantitative yield with all the electrophiles being consumed. Employing paraformaldehyde **182am** as the electrophile produced a complex mixture with 40% of amine **233h** being recovered, and neither pyrrolidines **237ag** nor side-product **237ag'** were observed (**Scheme 3.30**, **237ag**). Instead of being trapped by the amine **233h** or HFIP, the above electrophiles were destroyed under the reaction conditions. Thus, no further cyclizations of amine **233h** were attempted due to the lack of suitable electrophiles.



Scheme 3.30 Attempted synthesis of β-alkyl pyrrolidines using different electrophiles

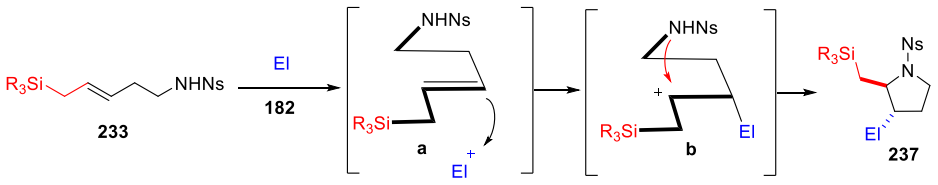
Aliphatic tri-substituted homoallylic amine **233i** was successfully reacted with benzhydrol **182w**, giving pyrrolidines **237ah** in 93% yield and no side-product **237ad'** was observed. Valuable five-membered spirocycle **237ai** was successfully obtained in quantitative yield as well. This could be attributed to the stronger nucleophilicity of the tri-substituted alkenes in amine **233i** and **233j**. However, treating amine **233k** bearing a six-membered ring with benzhydrol **182w** led to no formation of pyrrolidines **237aj** or side-product **237ad'** (**Scheme 3.31**).



Scheme 3.31 Synthesis of pyrrolidines using trisubstituted aliphatic homoallylic amines

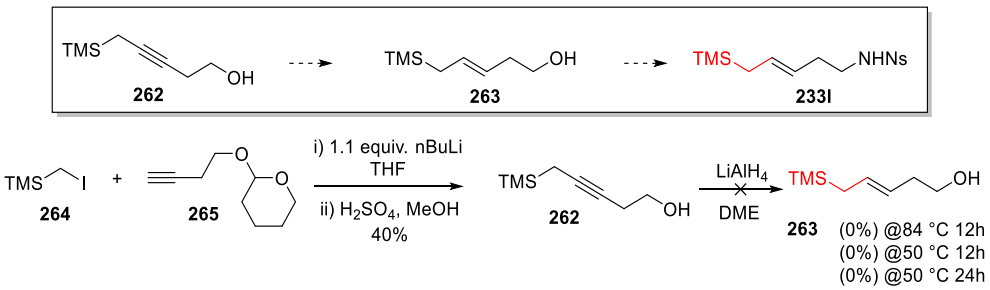
3.5.2. Versatility of the substituent R^f: allylic silyl substituted amines

Allylic silyl substituted amine **233** was next investigated. Silicon is known to stabilize β-carbocations *via* hyperconjugative effects, it was hoped that stabilizing the carbocation intermediate **b** could lead to formation of pyrrolidines **237** (**Scheme 3.32**).



Scheme 3.32 Synthesis of pyrrolidines using vinyl silyl amine

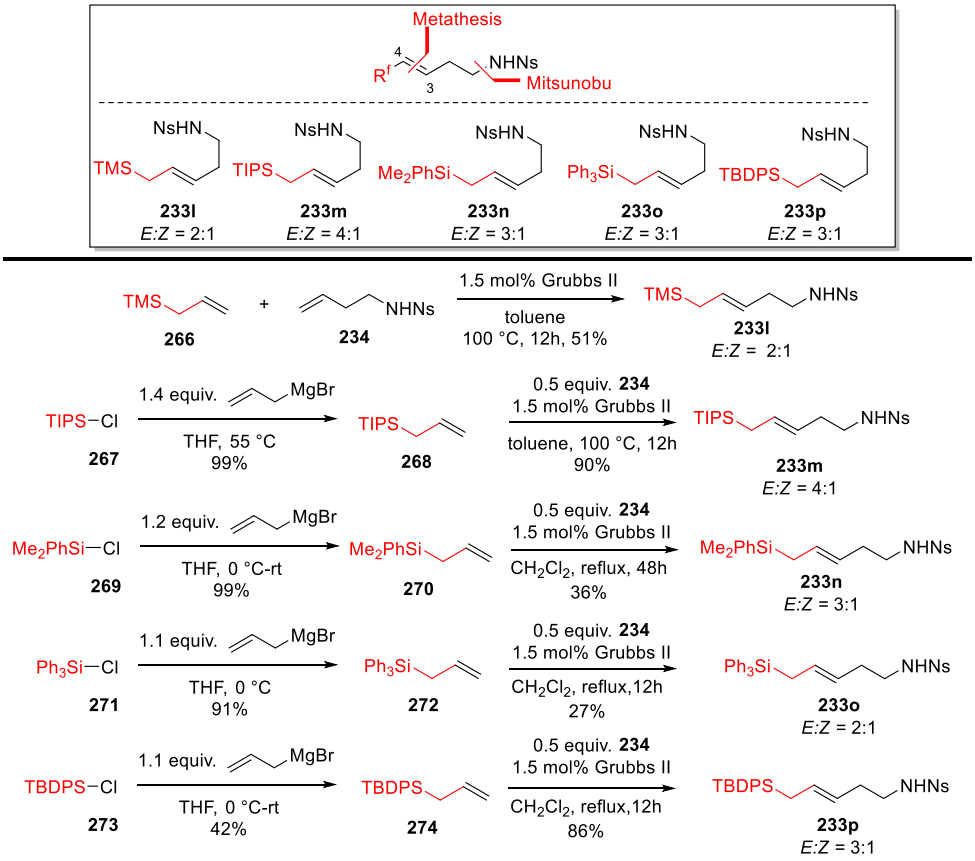
An initial attempt at synthesis of amine **233l** began with the preparation of alkyne variant **262**, followed by reduction of alkyne and amination of the alcohol (**Scheme 3.33**). However, reduction of alkyne **262** using $LiAlH_4$ at 84 °C afforded no desired product **263**, and only a complex mixture was obtained. Neither lowering the temperature to 50 °C nor leaving the reaction at 50 °C for 24 hours led to formation of product **263**, and only starting material was recovered.



Scheme 3.33 Synthesis of vinyl silyl alcohol **263**

It was instead decided to prepare allylic silyl amines *via* a Ru-catalyzed metathesis reaction (**Scheme 3.34**). Amine **233l** was synthesized using commercially available allylsilane **266** and previously prepared homoallylic amine **234**. Other allylsilanes were

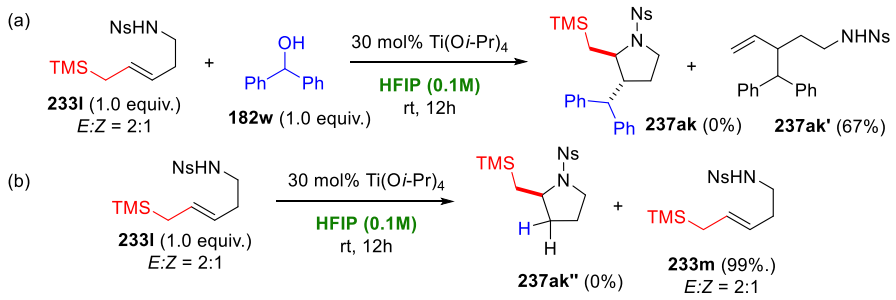
synthesized *via* the coupling of corresponding silyl chloride and allyl magnesium bromide, which were then treated with amine **234** under Ru-catalyzed metathesis conditions to afford amine **233m**-**233p**. However, although these amines were successfully prepared, all of them were obtained as mixtures of *E* and *Z* alkenes and only amine **233p** was partially separable (the *E*/*Z* ratio was based on crude ^{1}H NMR). The major *E*-alkene was confirmed by a large *J* coupling constant between 4-H and 3-H of the alkenes in amines ***E*-233l**-**233p** (*J* = 15.8 Hz), while the *J* coupling constant between 4-H and 3-H of the *Z*-alkenes was smaller in amines ***Z*-233l**-**233p** (*J* = 11.8 Hz).



Scheme 3.34 Synthesis of allylic silyl amines **233l**-**233p**

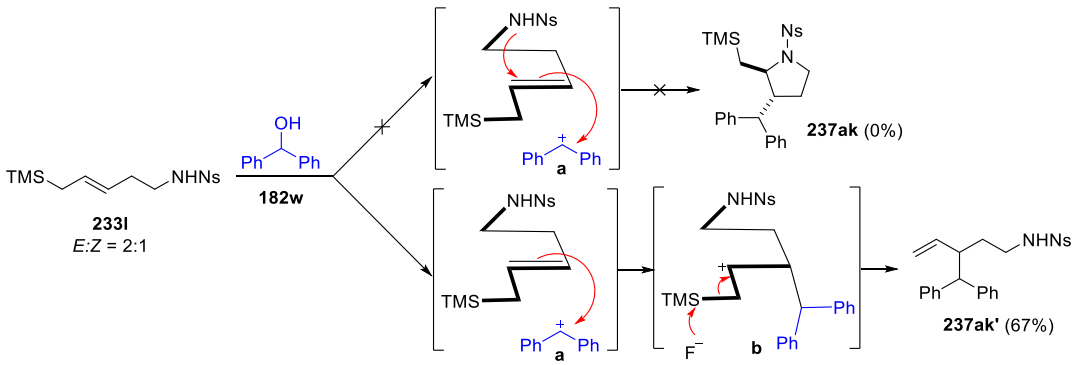
Employing amine **233l** along with benzhydrol **182w** at room temperature afforded no desired product **237ak**, and only eliminated product **237ak'** was observed in 67% yield

(**Scheme 3.35a**). A control experiment was conducted, in which amine **233l** was subjected to the standard conditions in the absence of external electrophiles. This led to neither production of protonated product **237ak''** nor eliminated product **237ak'**, suggesting the amine **233l** was stable under the reaction conditions (**Scheme 3.35b**).



Scheme 3.35 (a) Cyclization of amine **233l** with benzhydrol 18**2w**; (b) Stability test on amine **233l**

The above results suggested that the generation of eliminated product **237ak'** was likely to be triggered by the addition of benzhydrol **182w**. It was proposed that the amine **233l** trapped the di-benzylic carbocation **a** to give a silyl-stabilized carbocation. The **237ak'** was then generated *via* the elimination of the TMS group by a nucleophile (possibly a trace of fluoride from the HFIP solvent) (**Scheme 3.36**). This discovery might suggest there could be both concerted and stepwise reaction pathways for different substrates; in this case it preferred a stepwise reaction pathway.



Scheme 3.36 Proposed mechanism for the formation of eliminated product **237ak'**

A short optimization study was carried out to avoid this undesired side-product. As hydrogen fluoride and fluoride anion were known to exist in HFIP solvent, distillation of the reaction solvent was attempted.[81] Unfortunately, treating amine **233l** and benzhydrol **182w** with the distilled HFIP at room temperature afforded only eliminated product **237ak'** (**Table 3.6**, **Entry 2**). Lowering the temperature to 0 °C was not beneficial, and only eliminated product **237ak'** was observed (**Table 3.6**, **Entry 3**). Thus, the TMS group was concluded to be too labile to be a successful substrate.

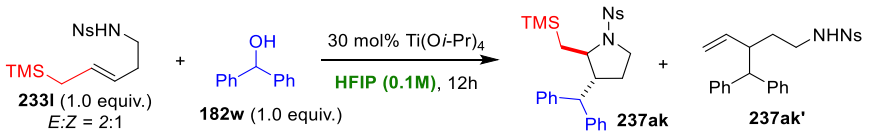


Table 3.6 Optimization of synthesizing pyrrolidines **237ak**

Entry	Temperature	Solvent	Yield **7ak** (%)	Yield **7ak'** (%)
1	rt	Undistilled HFIP	0	76
2	rt	Distilled HFIP	0	76
3	0 °C	Distilled HFIP	0	76

A bulky TIPS group was therefore installed on amine **233m** to inhibit this undesired elimination by retarding nucleophilic attack at silicon. Treating amine **233m** with either undistilled HFIP or distilled HFIP at room temperature successfully afforded pyrrolidines **237al** in quantitative yield (**Table 3.7**, **Entries 1-2**). Surprisingly, the product **237al** existed as a separable 1:3 mixture of *trans* to *cis* diastereomers, preferring the *cis* diastereomer. The geometry between starting material and product had been inverted and was completely different from all other heterocycles examples previously synthesized. Further reduction of the temperature to 0 °C using undistilled HFIP improved the diastereoselectivity, giving pyrrolidines **237al** as a 1:4 mixture of *trans* to

cis diastereomers (**Table 3.7**, **Entry 3**). The 2,3-*cis* geometry of the major diastereomer was confirmed by a NOESY-2D experiment, where clear correlations were found between 2-H and 3-H, 6-H and 7-H_2. While correlations were found between 2-H and 6-H for the minor diastereomer, suggesting the 2,3-*trans* geometry.

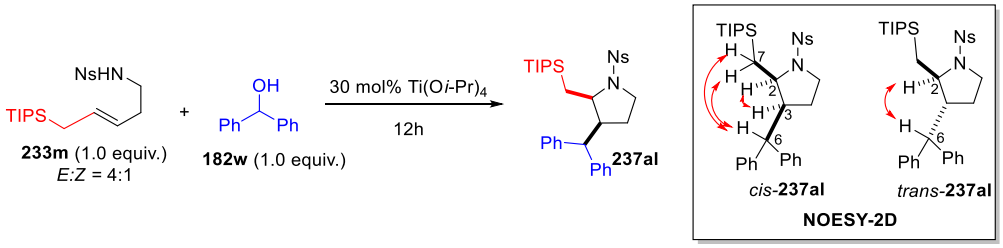


Table 3.7 Synthesis of pyrrolidines **237al**

Entry	Temperature	Solvent	Yield **237al** (%)	*trans:cis*
1	rt	Undistilled HFIP	99	1:3
2	rt	Distilled HFIP	99	1:3
3	0 °C	Undistilled HFIP	99	1:4

A further optimization study was conducted *via* varying the reaction temperatures. Raising the temperature to 70 °C changed the *trans* to *cis* ratio to 1:2 (**Table 3.8**, **Entry 2**). Leaving the reaction at 70 °C for 24 and 40 hours afforded pyrrolidines **237al** as 1:1.4 and 1:1.1 mixtures of *trans* to *cis* diastereomers respectively (**Table 3.8**, **Entries 3-4**). These results suggested that isomerization occurs in the amine starting material **233m** or in the pyrrolidines product **237al**.

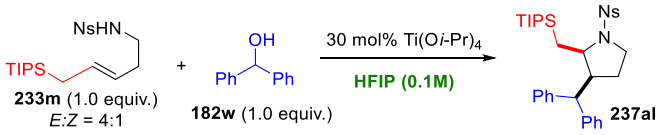
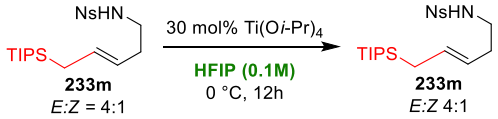


Table 3.8 Synthesis of pyrrolidines **237al** at different temperatures

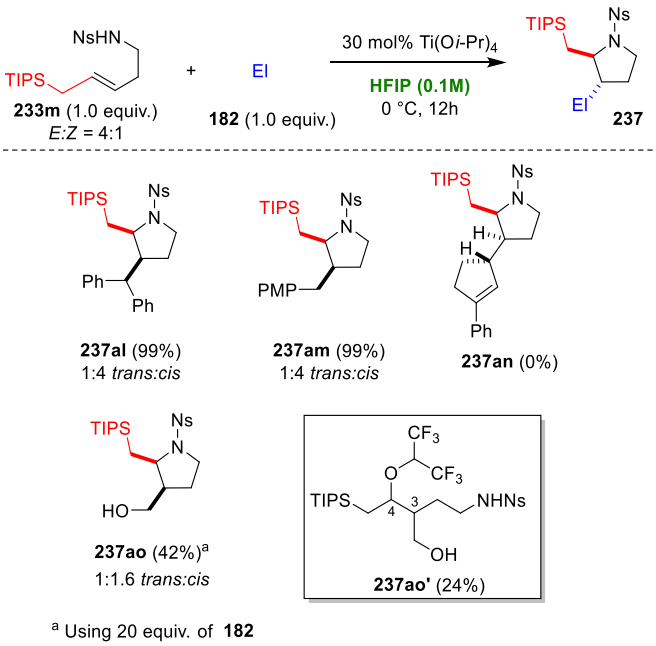
Entry	Temperature	Time	Yield **237al** (%)	*trans:cis*
1	0 °C	12h	99	1:4
2	70 °C	12h	99	1:2
3	70 °C	24h	99	1:1.4
4	70 °C	40h	99	1:1.1

A control experiment was therefore conducted, in which amine **233m** was subjected to the reaction conditions without the presence of additional electrophiles. Amine **233m** was recovered with the same diastereomeric ratio (**Scheme 3.37**). This helps to support the equilibration, at high temperature, between the *trans* and *cis* diastereomers of pyrrolidines **237al**; the *cis*-diastereomer is the kinetic product while the *trans* diastereomer is the thermodynamically more stable product.



Scheme 3.37 Control experiment investigating isomerization of amine **233m**

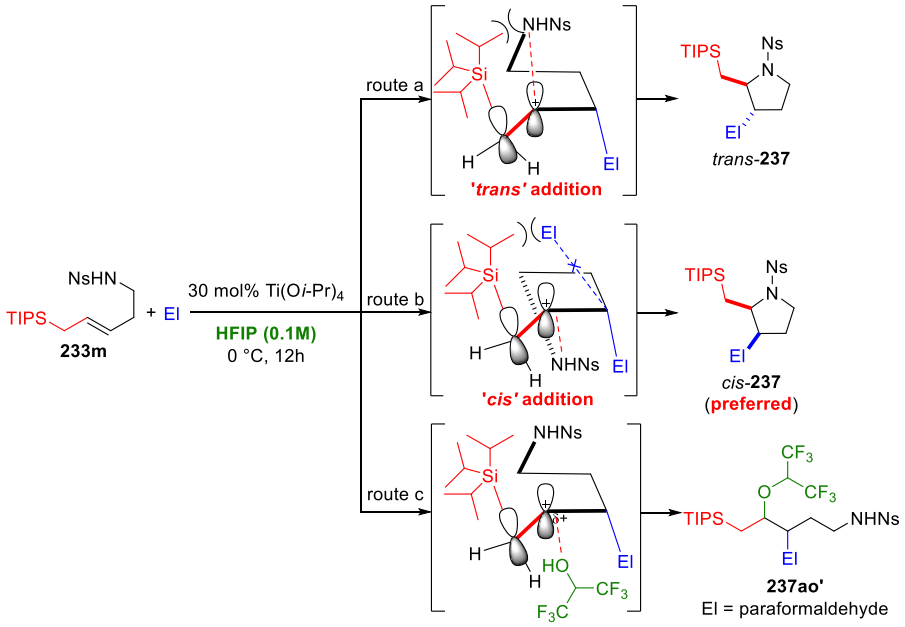
Further screening of amine **233m** was conducted to investigate the diastereoselectivity with different electrophiles. All cyclizations were conducted at 0 °C as this afforded the best diastereocontrol outcome for **237al**. Employing benzylic alcohol **182v** as the electrophile afforded pyrrolidines **237am** in quantitative yield with identical diastereomeric ratio. Using allyl alcohol **182m** as the electrophile afforded only recovered amine **233m**. Treating amine **233m** with paraformaldehyde **182am** gave pyrrolidines **237ao** in 42% yield with 1:1.6 dr, and an unexpected side-product **237ao'** was produced in 24% yield and as a single diastereomer (the stereochemistry between C-3 and C-4 was unassigned) (**Scheme 3.38**). The stereochemistry of pyrrolidines **237ao** and **237am** were assigned by analogy with the pyrrolidines **237al**.



Scheme 3.38 Cyclization of amine **233m** using different electrophiles

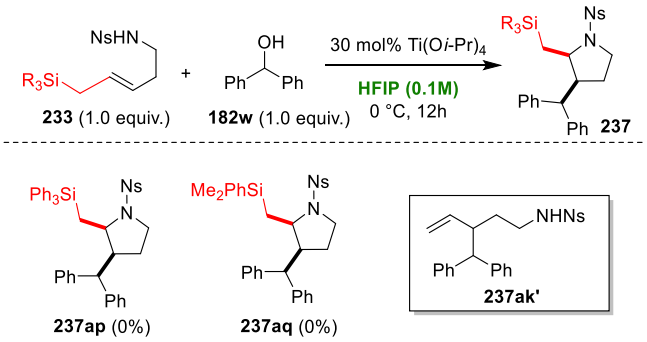
Note that the stereoselectivity for pyrrolidines **237al**-**237ao** were all opposite to the previous synthesized products; here 2,3-*cis* pyrrolidines were obtained as the major diastereomer. One possible explanation for this is that the they all went through a stepwise reaction pathway. The electrophile was firstly trapped by the alkene to generate a carbocation which could be stabilized by the silyl group. The silyl group adopted a conformation that was parallel to the empty p-orbital of the carbocation in order to provide hyperconjugative stabilization. However, this conformation might block both the initial trapping of the electrophile and the ensuing attack of the nitrogen nucleophile from the top face (by the bulky TIPS group); it could therefore only trap and cyclize from the bottom face (opposite to the TIPS group), which led to a '*cis*' addition of both nucleophile and electrophile across the alkene and generated 2,3-*cis* pyrrolidines as the major diastereomer (**Scheme 3.39-route a, b**). The formation of side product

237ao' was attributed to the trapping of the β-silyl carbocation by HFIP solvent rather than the nitrogen (**Scheme 3.39-route c**).



Scheme 3.39 Proposed mechanism for the cyclization of allylic silyl amine **233m** and formation of side product **237ao'**

As using benzhydrol **182w** afforded the highest yield and best diastereoselectivity, it was then utilized for the later scope of the amines **233n**-**233p**. Using amine **233n** under the reaction conditions led to the sole recovery of starting materials. Treating amine **233o** with benzhydrol **182w** afforded no desired product **237ap** but eliminated product **237ak'** was obtained in 76% yield (**Scheme 3.40**).



Scheme 3.40 Attempted synthesis of pyrrolidines **237ap** and **237aq**

Treating TBSPS-substituted amine **233p** (*E*:*Z* = 3:1) with benzhydrol **182w** gave pyrrolidines **237ar** in quantitative yield as a 1:2 separable mixture of *trans* to *cis* diastereomers (**Table 3.9**, **Entry 1**). A small amount of isomerically enriched amine **233p** (*E*:*Z* = 16:1) was obtained *via* slow flash chromatography, which was re-subjected to the reaction conditions, affording pyrrolidines **237ar** as a 1:5 mixture of *trans* to *cis* diastereomers (**Table 3.9**, **Entry 2**). The 2,3-*cis* geometry of the major diastereomer **237ar** was confirmed by a NOESY-2D experiment, where clear correlations were found between 2-H and 3-H, 6-H and 7-H_2. While correlations were found between 2-H and 6-H for the minor diastereomer, suggesting the 2,3-*trans* geometry.

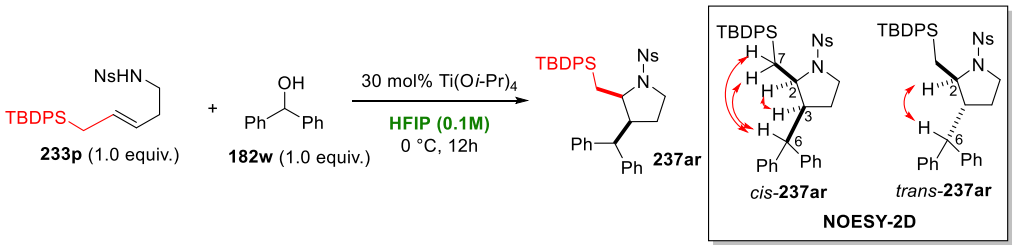
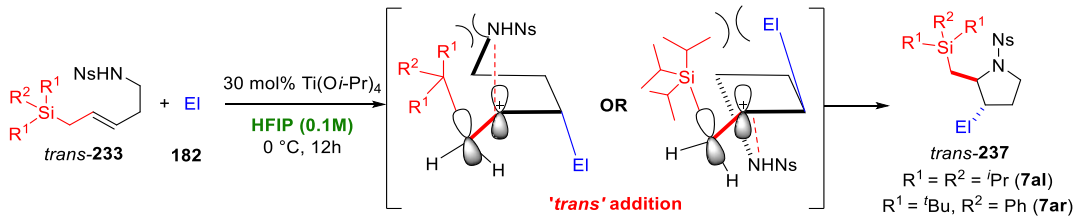


Table 3.9 Synthesis of pyrrolidines **7ar**

Entry	amine **233p** (*E*:*Z*)	Yield **237ar** (%)	Product **237ar** (*trans:cis*)
1	3:1	99	1:2
2	16:1	99	1:5

Compared with the synthesis of TIPS-substituted pyrrolidines **237al** (see **Scheme 3.36**), formation of *cis*-**237ar** was less preferred. Lightner and coworkers in conformational analysis suggested the relative steric size of a *tert*-butyl group is similar to isopropyl group and bulkier than a phenyl group.[82] This means that the TIPS group is bulkier than the TBDPS group, which means that it blocks the approaches of the nitrogen nucleophile and electrophile from top face of the alkene more effectively and therefore inhibits the formation of *trans* product (**Scheme 3.41**).



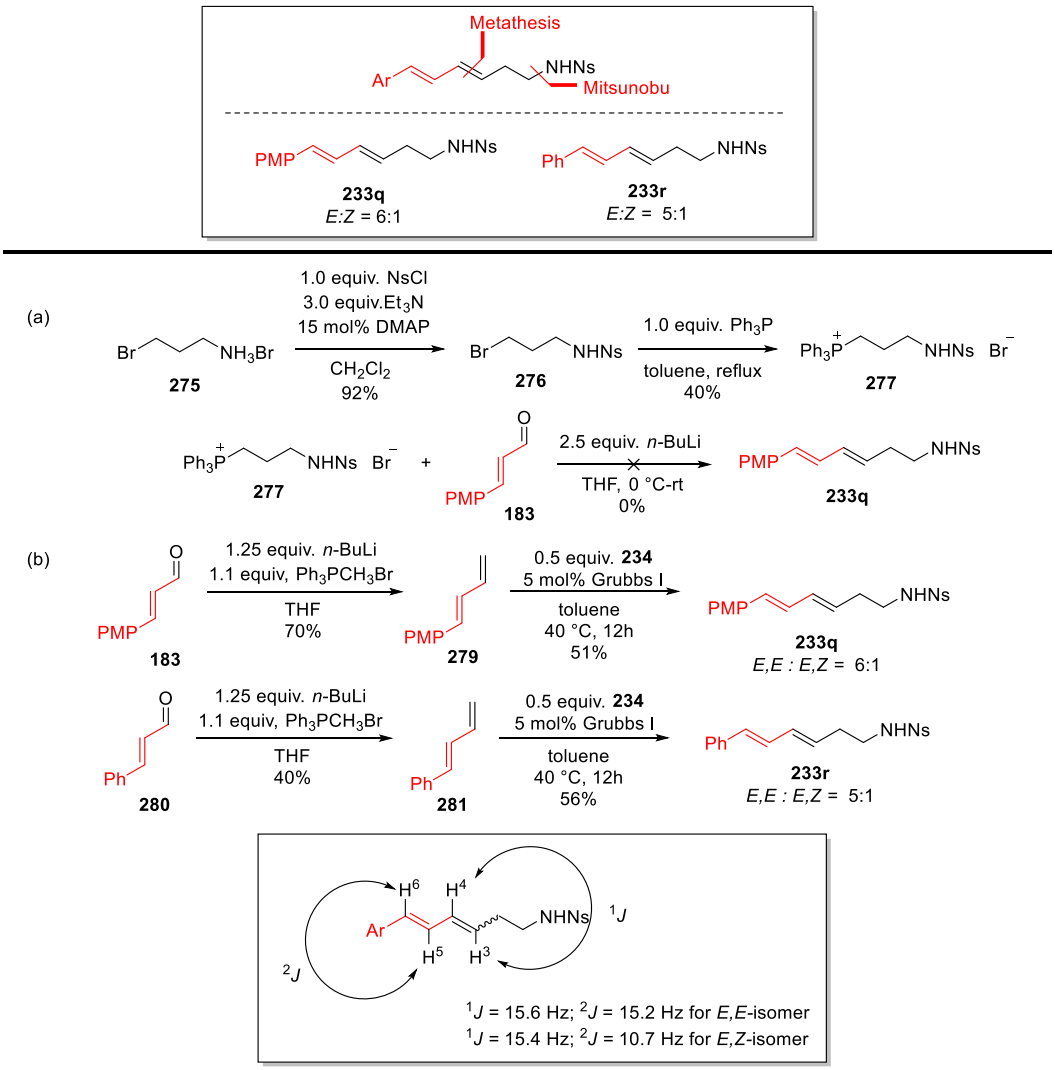
Scheme 3.41 Proposed mechanism for the synthesis of *trans* **237al** and **237ar**

3.5.3. Versatility of the substituent R^f: vinyl substituted amines

It was decided to examine amines bearing aromatic vinyl substituents, whose cyclized product could be easily transformed into other synthetically useful functional groups such as aldehydes and alcohols. Initial attempts at synthesizing the amine **233q** started with the nosyl protection of ammonium salt **275** followed by addition of triphenylphosphine to form the Wittig salt **277**. This was then treated with the aldehyde **183** under the standard Wittig conditions; however, no desired product was obtained and only aldehyde **183** was recovered (**Scheme 3.42a**).

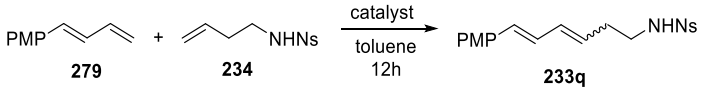
Diene **279** was then synthesized from aldehyde **183** under Wittig conditions, which was

treated with previously prepared homoallylic amine **234** using Grubbs 1st generation catalyst to afford amine **233q** as a 6:1 mixture of *E,E* to *E,Z* alkenes. Following the same synthetic route, phenyl-substituted amine **233r** was prepared as a 5:1 mixture of *E,E* to *E,Z* alkenes (*E*/*Z* ratio was based on crude ^{1}H NMR) (**Scheme 3.42b**). The major *E,E*-alkene was confirmed by large *J* coupling constants between both H^4-H^3 and H^5-H^6 of the alkenes *E,E*-**233q** and *E,E*-**233r** (^1J = 15.6 Hz; ^2J =15.2 Hz), while the ^2J coupling constants between H^4 and H^3 of the *E,Z*-**233q** and *E,Z*-**233r** was smaller (^1J = 15.4 Hz, ^2J =10.7 Hz).



Scheme 3.42 Synthesis of amines **233r** and **233s**

In order to improve the diastereselectivity, a short optimization study of the metathesis was attempted using different catalysts and temperatures. Raising the temperature to 100 °C harmed the diastereoselectivity, affording amine **233q** as a 4:1 mixture of *trans* to *cis* diastereomers (**Table 3.10**, **Entry 2**). Further attempts using common Ru-catalysts for cross metathesis,[85] such as Grubbs 2nd generation catalyst, Hoveyda-Grubbs2nd generation catalyst and Zhang's catalyst were unfruitful, and no desired product was generated at either 40 °C or 100 °C (**Table 3.10**, **Entries 3-8**). Pure *trans*-amines **233q** and **233r** were obtained from the mixtures *via* slow flash column chromatography for the later scope of the cyclization reactions.



279 **234** **233q**

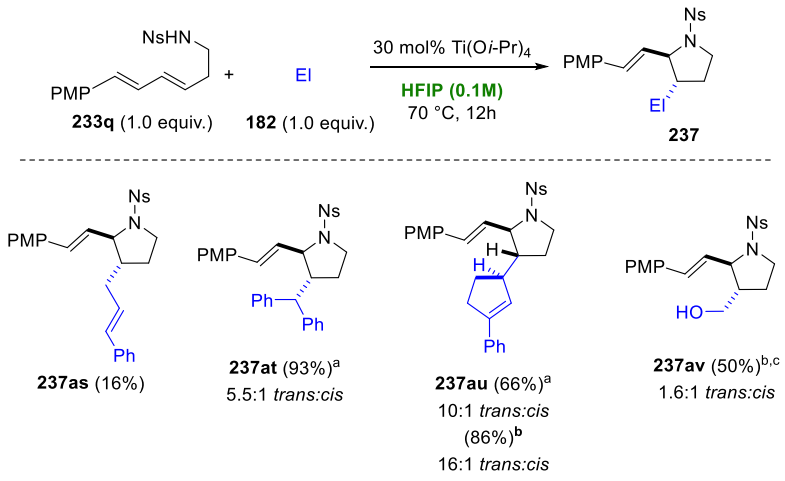
Entry	Catalyst	Temperature	Yield **233r** (%)	*E,E:E,Z*
1	Grubbs 1st generation	40 °C	51	6:1
2	Grubbs 1st generation	100 °C	51	4:1
3	Grubbs 2nd generation	40 °C	0	
4	Grubbs 2nd generation	100 °C	0	
5	Hoveyda-Grubbs2nd generation	40 °C	0	
6	Hoveyda-Grubbs2nd generation	100 °C	0	
7	Zhang's catalyst	40 °C	0	
8	Zhang's catalyst	100 °C	0	

Table 3.10 Synthesis of amine **233q** using different catalyst

In the cyclization experiments, employing cinnamyl alcohol **182b** as the electrophile afforded pyrrolidines **237as** in 16% yield as a pure *trans* diastereomer (**Scheme 3.43a**). Treating amine **233q** with benzhydrol **182w** at room temperature led to pyrrolidines **237at** in 93% yield. However, the diastereoselectivity was somewhat compromised,

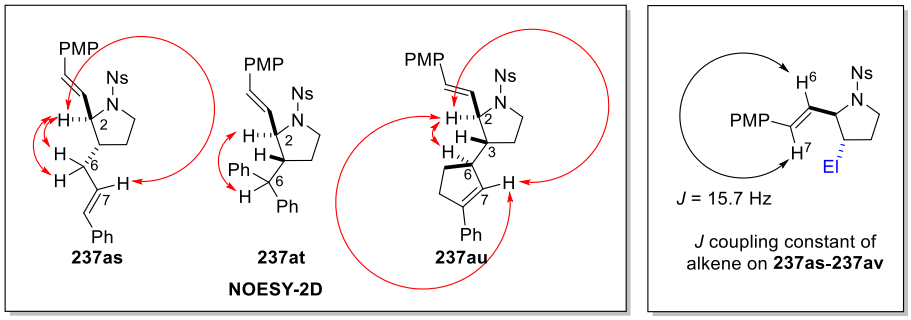
giving pyrrolidines **237at** in 5.5:1 dr. Switching the electrophile to alcohol **233m** afforded pyrrolidines **237au** in 66% yield with 10:1 dr. Further decreasing the temperature to 0 °C for 48 hours led to 86% yield with an improved 16:1 dr. Using paraformaldehyde **182am** at 0 °C for 48 hours afforded the lowest diastereoselectivity so far, giving pyrrolidines **237av** in 50% yield with 1.6:1 dr (**Scheme 3.43a**).

(a)



[a] Performed at room temperature (RT). [b] Performed at 0 °C. [c] Using 20 equiv. of **182**

(b)

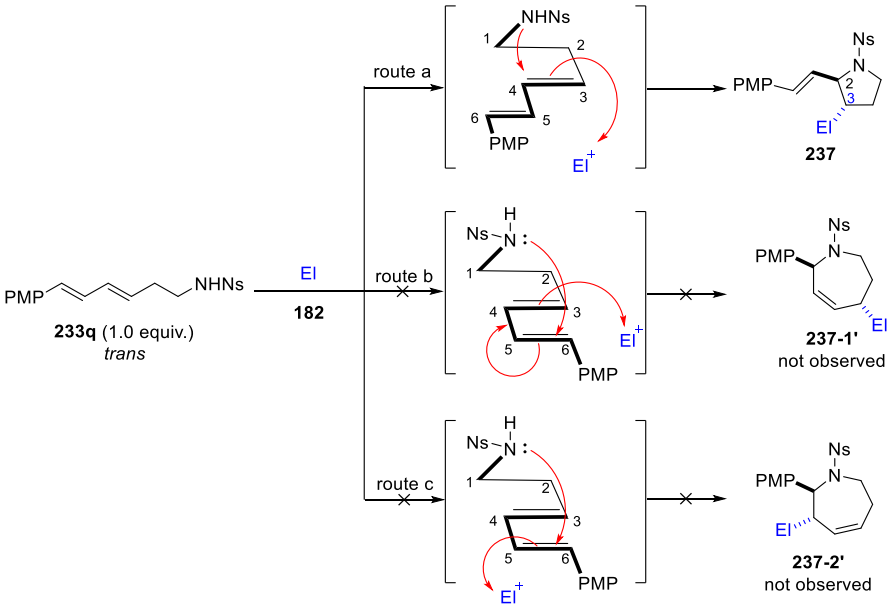


Scheme 3.43 (a) Cyclization of amine **233q** using different electrophiles; (b) NOESY-2D experiments on pyrrolidines **237as**-**237au** and *J* coupling constant of alkene on **237as**-**237av**

The stereochemistry of pyrrolidines **237as**-**237av** was characterized by NOESY-2D experiments (**Scheme 3.43b**). Correlations could be seen between 2-H and 7-H, 2-H and 6-H_2 for pyrrolidines **237as**; correlations could be seen between 2-H and 6-H for

pyrrolidines **237at**; correlations could be seen between 2-H and 6-H, 2-H and 7-H for pyrrolidines **237au**, suggesting the 2,3-*trans* geometry. The stereochemistry of pyrrolidines **237av** was assigned by analogy. The *E*-alkene geometry of pyrrolidines **237as**-**237av** was confirmed by the large *J* coupling constant between H^6-H^7 of the alkenes (*J* = 15.7 Hz).

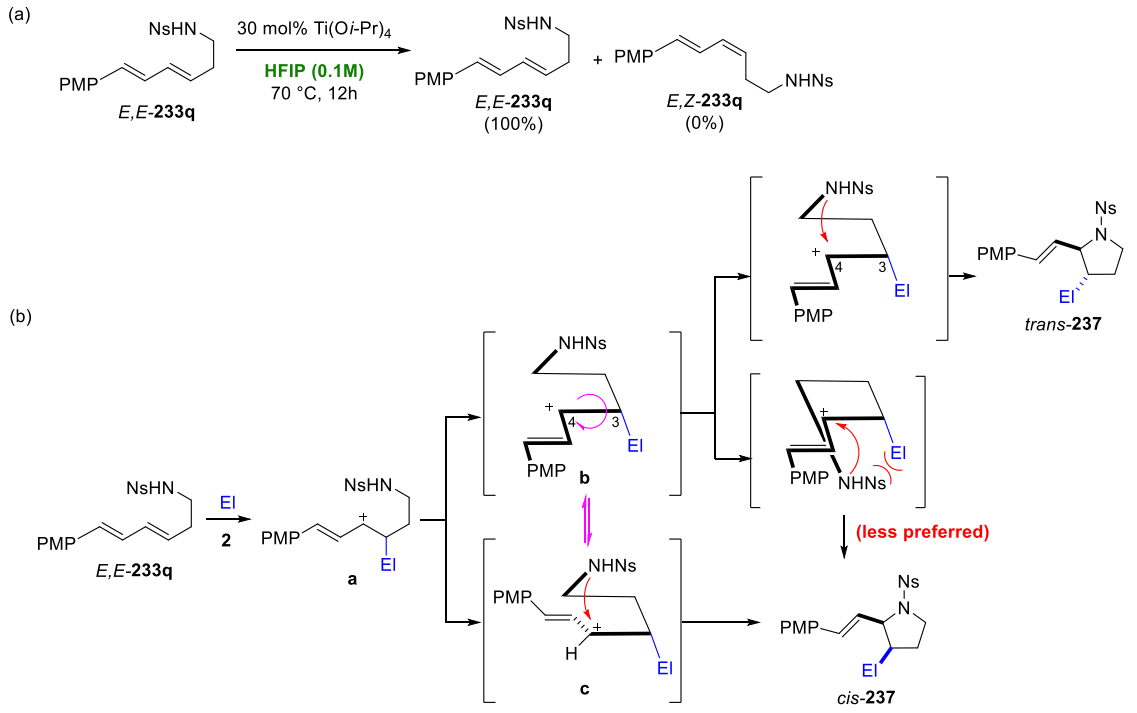
Pleasingly, none of the above examples afforded side-product **237-1'** or **237'-2** through the vinylogous attack of the nitrogen at the C-6 position of the diene (**Scheme 3.44**). The absence of both side-products was possibly due to two main reasons; firstly, there was a larger distance between the nitrogen and the C-6 position than the C-4 position, and secondly, it is generally more challenging to synthesize a seven-membered ring than five-membered ring.



Scheme 3.44 Proposed mechanism for the cyclization of amine **233q**

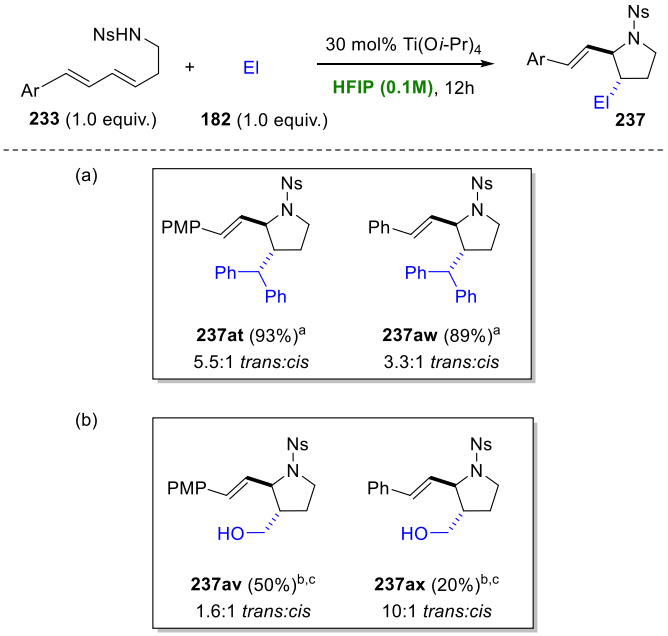
Treating pure all *trans* amine **233q** under the reaction conditions without additional

electrophiles afforded complete recovery of *E,E*-**233q** and no *E,Z*-**233q** was observed, which suggested that the starting material does not undergo alkene isomerization under the reaction conditions (**Scheme 3.45a**). The formation of mixture of *trans* and *cis* diastereomers for pyrrolidines **237as**-**237av** could be attributed a stepwise reaction pathway. The reaction firstly started with the trapping of the electrophile, generating carbocation **a** which was stabilized by the vinyl aromatic substituent. This led to formation of carbocation intermediate **b** and **c** due to free rotation of the C_3-C_4 bond, which resulted in a mixture of diastereomers (**Scheme 3.45b**). There were two possible ways to improve the *trans*-diastereoselectivity, either to slow down the trapping event by using a less reactive electrophile or weaken the nucleophilicity of the diene *via* using a less electron-rich aromatic substituent, so that the nitrogen would have more chance to attack the alkene before the trapping of electrophile and thus retaining the *trans*-geometry. The first hypothesis was supported by the production of pure *trans*-pyrrolidines **237as** using cinnamyl alcohol **182b**, which was a less reactive electrophile and generally afforded mild yield. Amine **233r** was then examined to verify the second hypothesis.



Scheme 3.45 (a) Resubjection experiment with amine **233q**; (b) Proposed mechanism for the formation of *trans* and *cis* diastereomers

Treating amine **233r** bearing an electron-neutral phenyl substituent with benzhydrol **182w** as the electrophile afforded pyrrolidines **237aw** in similar yield as **237at**. However, the diastereoselectivity was not improved as expected, leading to a 3.3:1 mixture of *trans* to *cis* diastereomers (**Scheme 3.46a**). This unexpected outcome was possibly due to a mismatch between the reactivity and the steric bulk of the trapped electrophile **182w**. Therefore, less steric bulky paraformaldehyde **182am** was employed as the electrophile, successfully improving the diastereoselectivity to 10:1 dr, but the yield was compromised, giving pyrrolidines **237ax** in 20% yield with 80% of recovered amine **233r**. The low yield of **237ax** was attributed to the relatively poor nucleophilicity of the alkene (**Scheme 3.46b**). The stereochemistry of pyrrolidines **237aw** and **237ax** were assigned by analogy with pyrrolidines **237as**-**237au**.



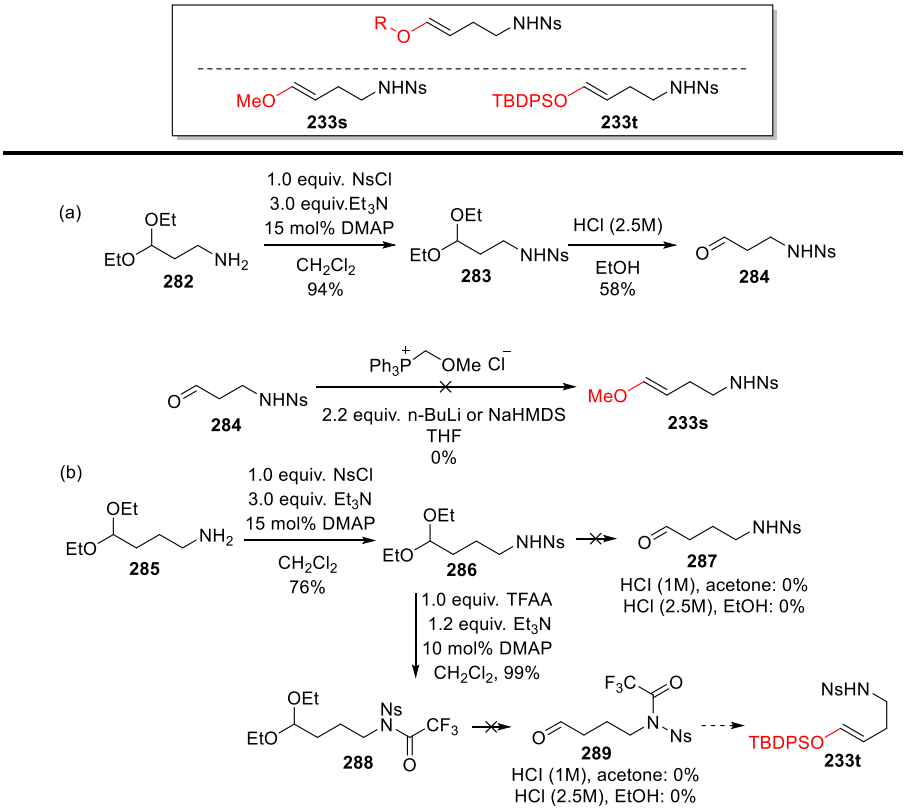
[a] Performed at room temperature (RT). [b] Performed at 0 °C. [c] Using 20 equiv. of **182**

Scheme 3.46 Synthesis of pyrrolidines using less electron-rich amine

3.5.4. Versatility of the substituent R^f: ether and silyl ether substituted amine

Next, a synthesis of silyl ether and ether substituted amines were attempted, which could be easily transformed into other synthetically useful functional groups. Synthesis of amine **233s** started with the nosyl protection of aminoacetal **282**, followed by hydrolysis to afford aldehyde **284**. This intermediate was then treated with methylmethoxy triphenylphosphine chloride under Wittig conditions, but using either *n*-BuLi or NaHMDS did not lead to production of the desired product **233s**, and only complex mixtures were obtained (**Scheme 3.47a**). Synthesis of amine **233t** started with a similar synthetic route, but the hydrolysis of acetal **286** afforded no desired aldehyde **287** using either acetone or ethanol as solvent. A complex mixture was obtained using acetone as solvent, while all starting materials was recovered using ethanol, which was

possibly due to poor solubility. Attempts to protect the amine with trifluoroacetic anhydride followed by hydrolysis were also unsuccessful and no desired aldehyde **289** was obtained (**Scheme 3.47b**). It was therefore decided to abandon synthesis of amines **233s** and **233t**.



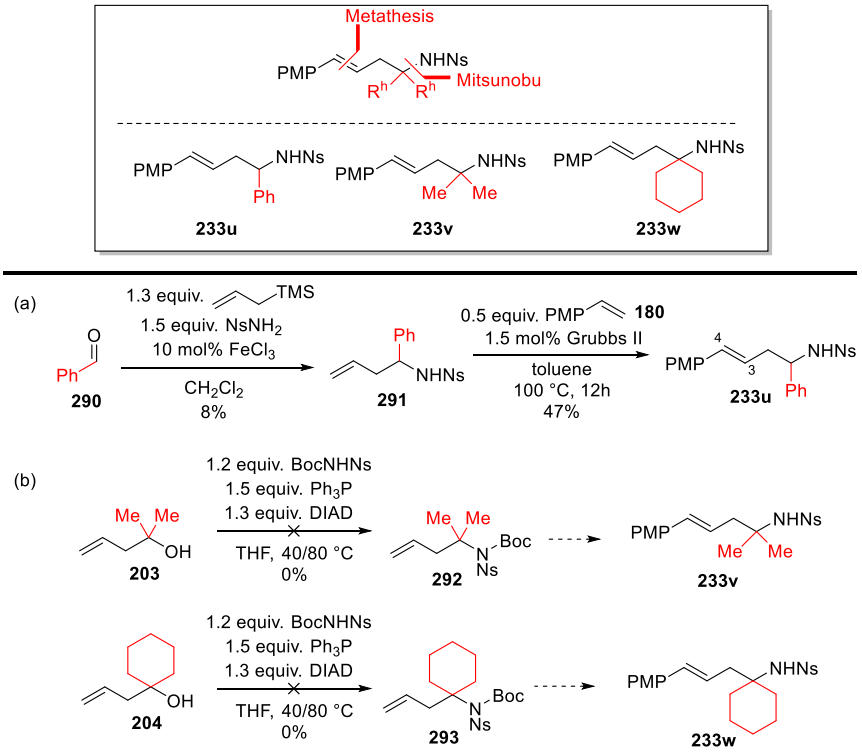
Scheme 3.47 Attempts to synthesize amines **233s** and **233t**

3.5.5. Scope of the nucleophiles: versatility of the substituent R^h

After an exploration of the substituent R^f of the homoallylic amine **233**, *para*-methoxyphenyl (PMP) was determined to be the most suitable substituent as it was easily accessible and gave high yield; this would be used for further screening of nucleophiles. Compatibility of the R^h substituent was then evaluated. Amine **233u** was

obtained by the Ru-catalyzed metathesis of 4-methoxystryrene **180** with α-substituted amine **291**, which was prepared *via* the condensation of aldehyde **290** with NH_2Ns followed by addition of allyl trimethylsilane. Amine **233u** was obtained as a single *E*-isomer (again confirmed by a large *J* coupling constant of 15.8 Hz between 3-H and 4-H) (**Scheme 3.48a**).

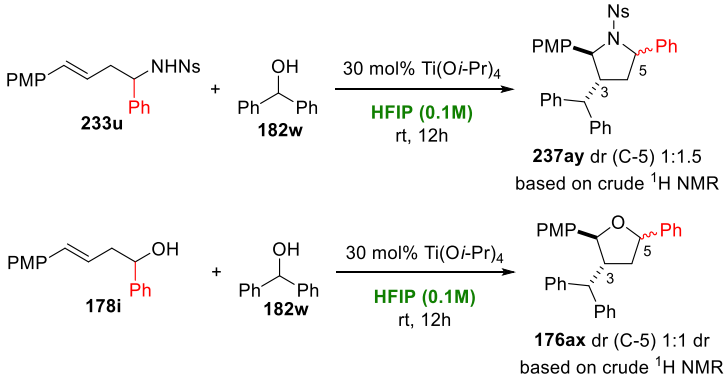
Attempts to synthesize tertiary amines **233v** and **233w** by treating both alcohols **203** and **204** under Mitsunobu conditions led to no production of amines **292** and **293** at either 40 °C or 80 °C. This could be attributed to the steric hinderance of the tertiary alcohols (**Scheme 3.48b**).



Scheme 3.48 Synthesis of amine **233u** and attempts to synthesize amines **233v** and **233w**

Unfortunately, treating α-substituted amine **233u** with the bulky electrophile

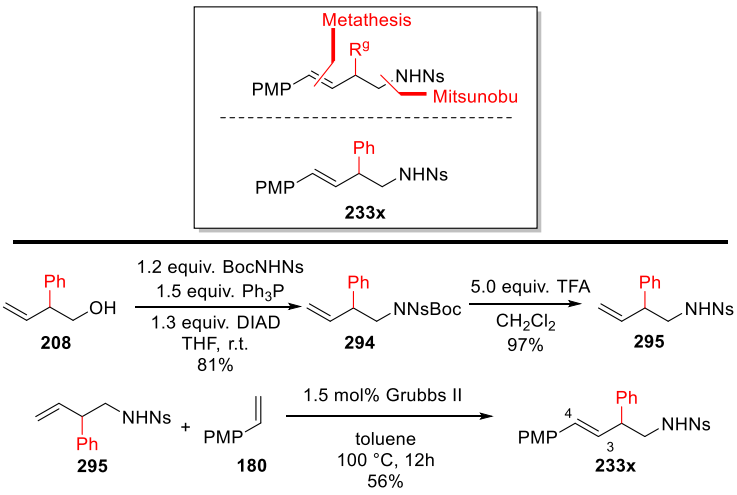
benzhydrol **182w** afforded pyrrolidines **237ay** as a 1.5:1 mixture of diastereomers based on crude ^{1}H NMR spectroscopy. A similar result was observed in the synthesis of THFs **176ax** where diastereocontrol at the C-5 position was impossible even with very bulky electrophiles (both pyrrolidines **237ay** and THFs **176ax** were not fully characterized because of their low selectivities). These results were attributed to the large distance between the C-5 position and electrophile at the C-3 position (**Scheme 3.49**).



Scheme 3.49 Synthesis of pyrrolidines **237ay** and THFs **176ax**

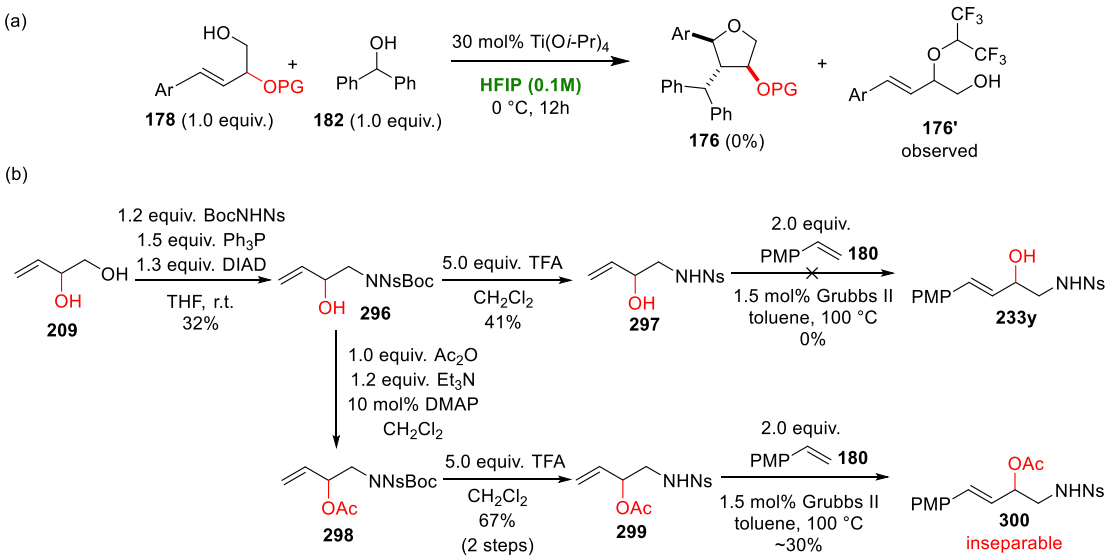
3.5.6. Scope of the nucleophiles: versatility of the substituent R^{g}

Retaining the PMP substituent on the amine, the versatility of the substituent R^{g} was next investigated. Subjecting the previously synthesized alcohol **208** to Mitsunobu conditions, followed by deprotection of the Boc group led to formation of homoallylic amine **295**, which was treated with 4-methoxystryrene **180** under Ru-catalyzed metathesis conditions to afford amine **233x** (**Scheme 3.50**). Amine **233x** was obtained as a single *E*-isomer (again confirmed by a large *J* coupling constant of 15.8 Hz between 3-H and 4-H).



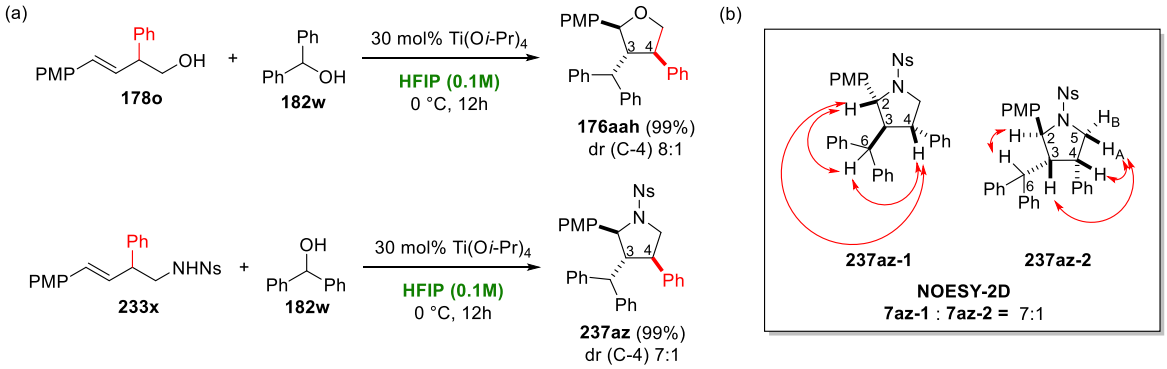
Scheme 3.50 Synthesis of amine **233x**

It would be interesting to install a free alcohol at R^g, as it could be easily modified to other synthetically useful functional groups. The synthesis of β-ether substituted amines was not attempted as its alcohol variant had previously been proven to be unstable under the cyclization conditions (**Scheme 3.51a**). Initial attempt was to synthesize alkanolamine **297** *via* the formation of doubly protected amine **296** from diol **209** followed by deprotection of the Boc group. However, Ru-catalyzed metathesis of 4-methoxystryrene **180** with alkanolamine **297** afforded only recovered starting materials. Acetyl protected alkanolamine **298** was therefore prepared, which gave amine **299** in 30% yield under Ru-catalyzed metathesis conditions. Unfortunately, amine **300** was not separable from the starting material **299**, and so the synthesis of amine **233y** was abandoned (**Scheme 3.51b**).



Scheme 3.51 (a) Previously unsuccessful attempt at the synthesis of THFs **176** using homoallylic alcohol bearing a β-ether substituent; (b) Attempts to synthesize amine **233y.**

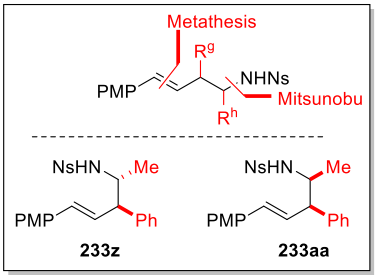
For the analogous THFs **176aah**, the best stereocontrol outcome at the C-4 position was obtained when conducting the reaction at 0 °C and using benzhydrol **182w** as the electrophile (**Scheme 3.52a**). Amine **233x** was therefore treated with benzhydrol **182w** at 0 °C, affording pyrrolidines **237az** in quantitative yield with a good diastereomeric ratio of 7:1 (**Scheme 3.52b**). The stereochemistry of pyrrolidines **237az** was characterized by a NOESY-2D experiment (**Scheme 3.52b**). Correlations could be seen between 2-H and 6-H, 2-H and 4-H, 4-H and 6-H for the major diastereomer **237az-1**, suggesting the 2,3,4-all *trans* geometry. Correlations could be seen between 2-H and 6-H, 4-H and 5-H_A, 3-H and 5-H_A, for the minor diastereomer **237az-2**, suggesting the 2,3,4-*trans cis* geometry.

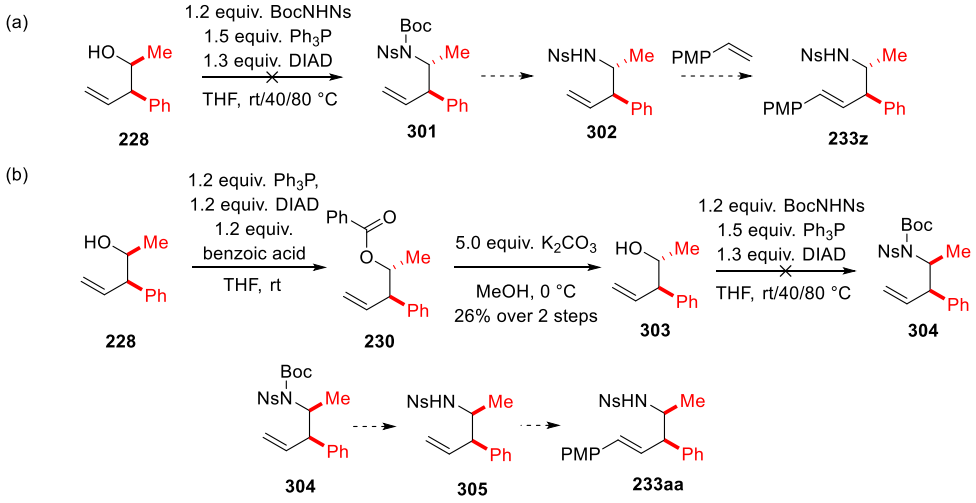


Scheme 3.52 (a) Syntheses of THFs **176aah** and pyrrolidines **237az;** (b) NOESY-2D experiments on pyrrolidines **237az**

3.5.7. Scope of the nucleophiles: versatility of the substituents R^g and R^h

In an effort to synthesize fully substituted pyrrolidines, preparation of amines bearing substituents at both R^g and R^h was attempted. Unfortunately, treating previously synthesized alcohol **228** (see **chapter 2.4.4** for its synthesis and stereochemistry study) with BocNHNs under Mitsunobu conditions afforded only recovered starting materials. Neither raising the temperature to 40 °C nor 80 °C was helpful, and only a complex mixture was obtained (**Scheme 3.53a**). Although employing benzoic acid as a nucleophile with alcohol **228** under Mitsunobu conditions successfully produced ester **230**, using BocNHNs led to no production of the desired protected amine **304** (**Scheme 3.53b**). This could be attributed to the steric hindrance of the secondary alcohol and the bulkier nucleophile BocNHNs employed.



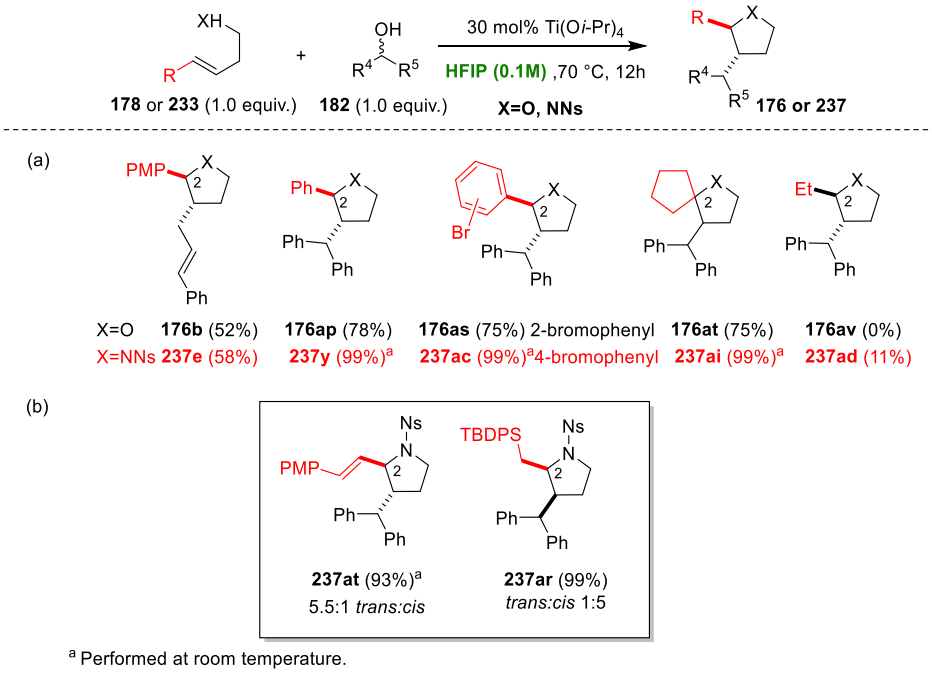


Scheme 3.53 Attempts to synthesize amine **233z-233aa**

3.5.8. Summary of the nucleophile scope

With the pleasing results obtained from the scope of the nucleophilic amines, it was then decided to compare the results from the nucleophile scope between the synthesis of THFs and pyrrolidines. Both systems tolerated electron-rich and electron-deficient aromatic substituents at the C-2 position, with generally higher yields observed for pyrrolidines without harming the diastereoselectivity. Additionally, tolerance was observed with di-alkyl substituents at the C-2 positions, and good yields were obtained. Note that no β-alkyl substituted THFs was obtained, but β-alkyl substituted pyrrolidines **237ad** was produced in 11% yield (**Scheme 3.54a**). Further exploration of the pyrrolidines synthesis provided a way to access both 2,3-*trans* and *cis* diastereomers.

Using a vinyl substituted amine afforded pyrrolidines **237at** as a 5.5:1 mixture of *trans* to *cis* diastereomers, while employing allylic silyl substituted amine (15:1 *trans*/*cis*) as the nucleophile gave pyrrolidines **237ar** as a 1:5 mixture of *trans* to *cis* diastereomers. Additionally, these substituents could be readily transformed into synthetically useful functional groups (**Scheme 3.54b**).

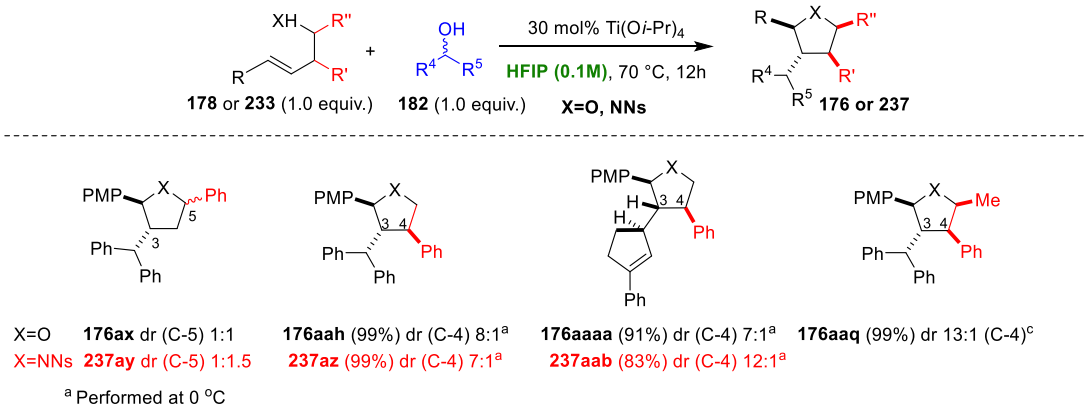


[a] Performed at room temperature.

Scheme 3.54 Scope of the nucleophiles-syntheses of THFs and pyrrolidines

Both C-5 substituted THFs and pyrrolidines showed poor stereocontrol at the C-5 positions, leading to 1:1 and 1:1.5 mixtures of diastereomers respectively. This was possibly due to large distance between substituents at the C-3 and C-5 positions, so that they cannot affect the stereoselectivity. Conversely, C-4 substituted THFs and pyrrolidines were synthesized in excellent yield with good diastereoselectivity. Synthesis of fully substituted THFs was accomplished in excellent yield, while the synthesis of fully substituted pyrrolidines remained unexplored due to failure of synthesizing starting

materials (**Scheme 3.55**).

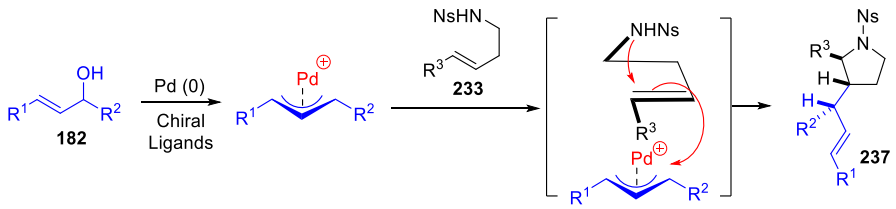


Scheme 3.55 Summary of the scope of the nucleophiles-syntheses of THFs and pyrrolidines

3.6. Synthesis of Enantiopure Pyrrolidines

3.6.1. Asymmetric synthesis of pyrrolidines *via* Pd(0) catalysis

Based on the previous mechanistic study in the synthesis of THFs and similar reactivity observed in the synthesis of pyrrolidines, it was proposed that a π-carbocation intermediate was generated from electrophile **182**, which was trapped by the nucleophilic homoallylic amine to afford pyrrolidines **237**. It was hoped that it might be possible to utilize Pd(0) to induce chirality to the product as this type of asymmetric synthesis is well developed and known in the literature (**Scheme 3.56**).



Scheme 3.56 Proposed asymmetric synthesis of pyrrolidines **237**

Exploration of the asymmetric synthesis of pyrrolidines was attempted using amine **233c** and alcohol **182b** as model substrates. Production of pyrrolidines **237e** was not observed without the presence of additional additives (**Table 3.11a**, **Entry 1**). Addition of 30 mol% of $Pd_2(dba)_3$ and 1.2 equivalents of Ph_3P were not helpful, and only trace amount of pyrrolidines **237e** was observed (**Table 3.11a**, **Entry 2**).

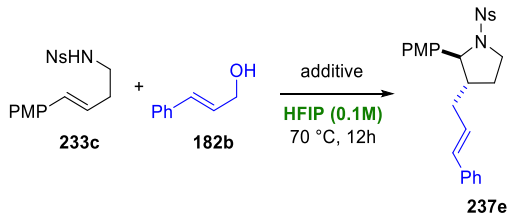


Table 3.11a Synthesis of pyrrolidines **237e** using $Pd_2(dba)_3$ as additive

Entry	Additive	Yield **237e** (%)
1	None	0
2	30 mol% $Pd_2(dba)_3$ 1.2 equiv. Ph_3P	Trace

It was soon discovered that allylic acetates and carbonates are commonly used in Pd-catalyzed asymmetric synthesis. Carbonate **182ao** was therefore employed as the electrophile for the cyclization. Surprisingly, pyrrolidines **237e** was obtained in 66% yield without the presence of additional reagents (**Table 3.11b**, **Entry 1**). The addition of $Pd_2(dba)_3$ and Ph_3P seemed to inhibit the cyclization, and only 4% of pyrrolidines **237e** was obtained (**Table 3.11b**, **Entry 2**). Switching the solvent to THF, toluene or CH_2Cl_2 was not beneficial, affording only recovered starting materials (**Table 3.11b**, **Entry 3-5**). A final attempt using a 1:1 solvent mixture led to a complex mixture with both amine **233c** and carbonate **182ao** being consumed. (**Table 3.11b**, **Entries 6-8**).

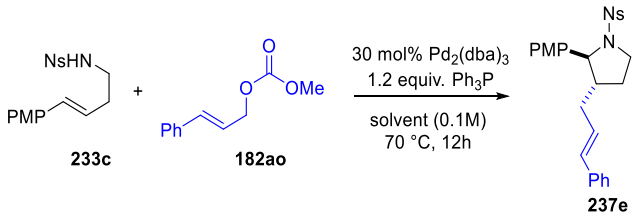


Table 3.11b Synthesis of pyrrolidines **237e** using $Pd_2(dba)_3$ as an additive

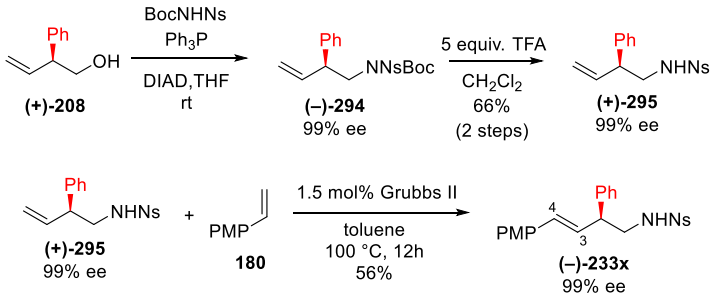
Entry	Solvent	Yield **237e** (%)
1*	HFIP	66
2	HFIP	4
3	THF	0
4	Toluene	0
5	CH_2Cl_2	0
6	THF:HFIP 1:1	0
7	Toluene:HFIP 1:1	0
8	CH_2Cl_2:HFIP 1:1	0

*no additional reagents were used

3.6.2. Synthesis of enantiopure pyrrolidines *via* using enantiopure nucleophilic amines 233

It was then considered to follow the previous route to synthesize enantiopure THFs, which transferred the chirality from a previously established stereogenic centre in the starting materials. Amine **233x** was selected as the nucleophilic partner because it gave good diastereoseletivity and high yield. Enantiopure **(+)-295** was firstly synthesized from previously prepared enantiopure alcohol **(+)-208** (see **chapter 2.5.2** for its synthesis and stereochemistry study) under Mitsunobu conditions followed by deprotection of the Boc group. It was then treated with 4-methoxystyrene **180** under the Ru-catalyzed metathesis conditions to afford enantiopure amine **(–)-233x**. Amine **(–)-233x** was obtained as a pure *E*-isomer (again confirmed by a large *J* coupling constant of 15.8 Hz

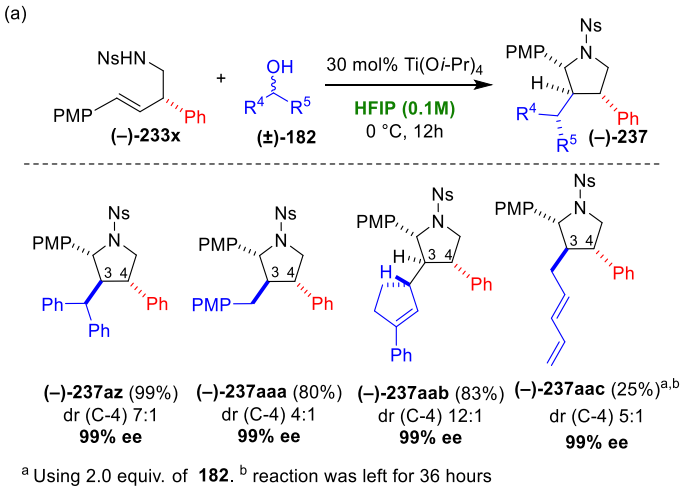
between 3-H and 4-H). (**Scheme 3.57**).

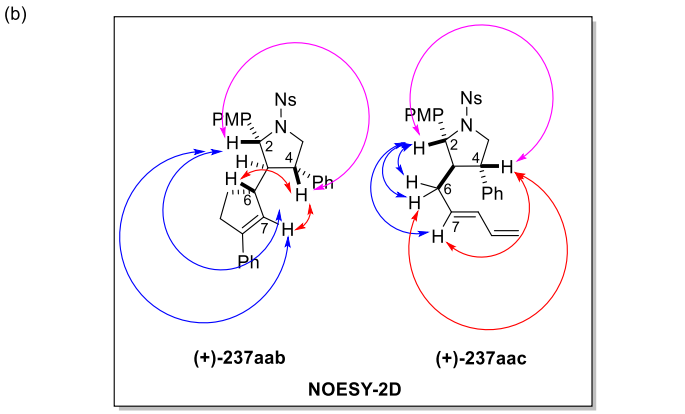


Scheme 3.57 Synthesis of enantiopure homoallylic amine **(–)-233x**

Employing benzhydrol **182w** as the electrophile at 0 °C afforded enantiopure pyrrolidines **(–)-237az** in 99% yield with 7:1 dr, suggesting a successful transfer of chirality from the starting material to the product. Other electrophiles were then examined to explore its scope. Using 4-methoxybenzylic alcohol **182v** gave enantiopure pyrrolidines **(–)-237aaa** in 80% yield with 4:1 dr. Treating alcohol **182m** with amine **(–)-233x** led to formation of pyrrolidines **(–)-237aab** in 91% yield with a pleasing 13:1 dr. Finally, utilizing diallyl alcohol **182h** gave pyrolidine **(–)-237aac** bearing a diene substituent in 25% yield with 5:1 dr, but the reaction required 36 hours. Therefore, utilizing enantiopure homoallylic amine could allow access to enantiopure pyrrolidines with up to three new stereogenic centers in a single step (**Scheme 3.58a**). The stereochemistry of pyrrolidines **(–)-237aab**-**(–)-237aac** was characterized by NOESY-2D experiments (**Scheme 3.58b**). Correlations could be seen between 2-H and 4-H, 2-H and 6-H, 2-H and 7-H, 4-H and 6-H, 4-H and 7-H for the major diastereomer of **(–)-237aab**, suggesting the 2,3,4-all *trans* geometry. Correlations could be seen between 2-H and 4-H, 2-H and 6-H_2, 2-H and 7-H, 4-H and 6-H_2, 4-H and 7-H major diastereomer of **(–)-237aac**,

suggesting the 2,3,4-all *trans* geometry. Pyrrolidines **(–)-237aaa** were assigned by analogy with pyrrolidines **237az** whose stereochemistry was previously characterized (see **Scheme 3.52b**). The enantiomeric excess of pyrrolidines **(–)-237az-(–)-237aac** was determined by HPLC analysis (see experimental chapter in detail).

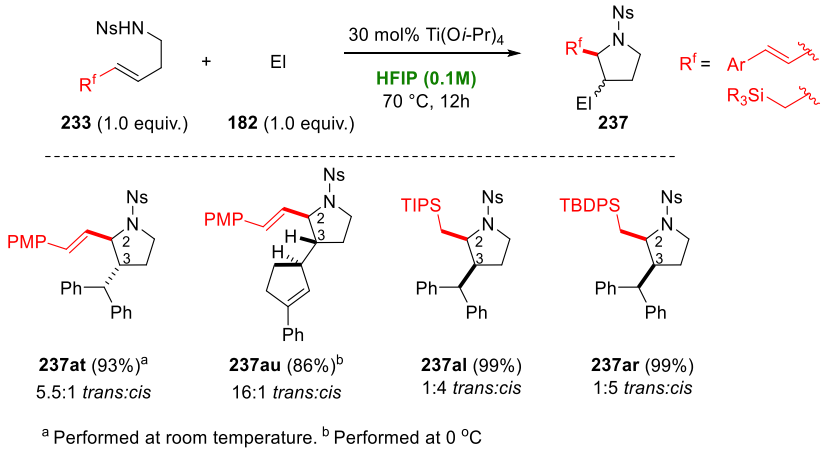




Scheme 3.58 (a) Synthesis of enantiopure pyrrolidines; (b) NOESY-2D experiment on pyrrolidines **(–)-237aab** and **(–)-237aac**

3.7. Mechanistic Study

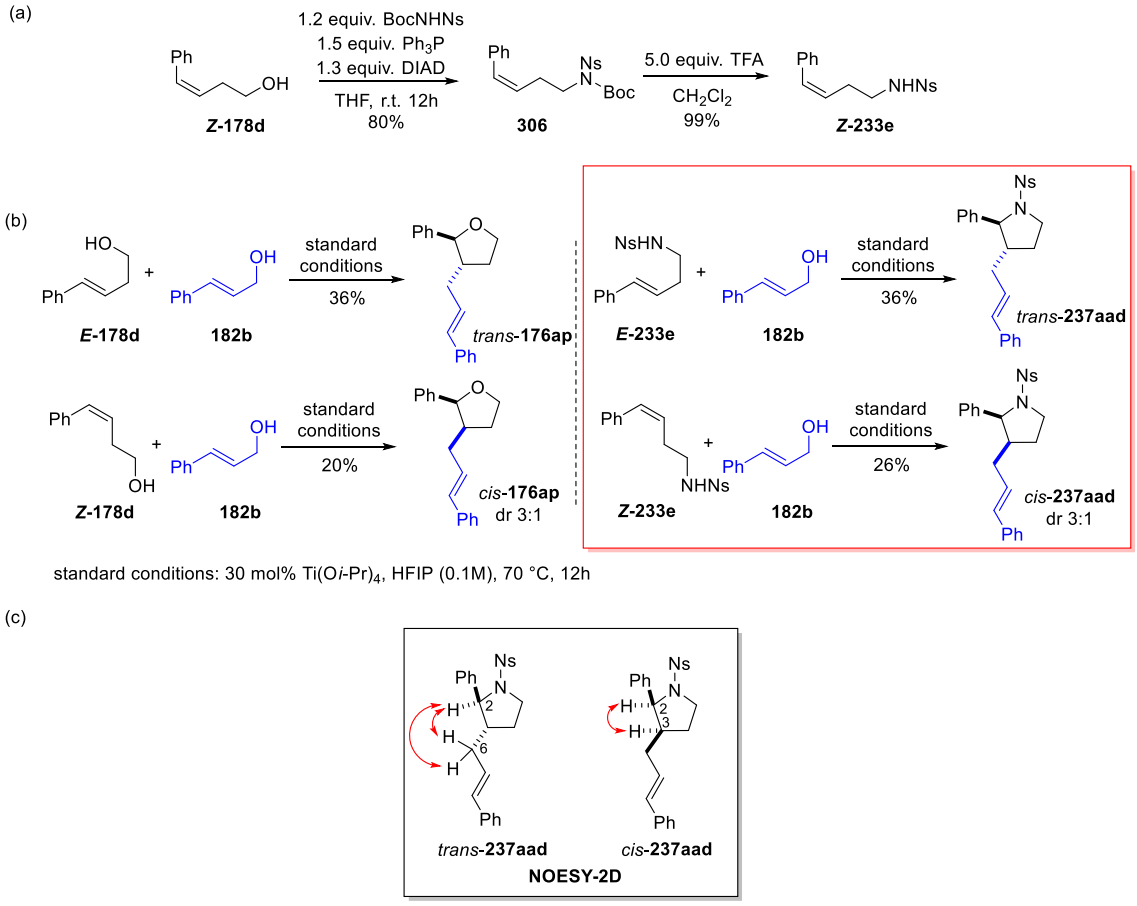
Based on the previous mechanistic study on the synthesis of THFs, and similar stereoselectivity observed. It was possible that the synthesis of pyrrolidines possesses some degree of similarity. However, unlike the synthesis of THFs where only 2,3-*trans* products were observed, different diastereoselectivity at the 2,3-positions of pyrrolidines was observed when using vinyl or silyl substituted homoallylic amines as nucleophiles (**Scheme 3.59**). For instance, pyrrolidines **237at** and **237au** were obtained as mixtures of *trans* and *cis* diastereomers. Additionally, completely opposite diastereoselectivity was observed in pyrrolidines **237al** and **237ar**, giving *cis* pyrrolidines as the major diastereomer.



Scheme 3.59 Synthesis of pyrrolidines **237** with different stereocontrol outcome

To further investigate its reaction pathway, *cis* homoallylic amine ***Z*-233e** was synthesized by treating the previously prepared alcohol ***Z*-178d** under Mitsunobu conditions followed by deprotection of the Boc group (**Scheme 3.60a**). Treating amine ***E*-233e** with cinnamyl alcohol **182b** afforded pyrrolidines *trans*-**237aad** in 36% yield and

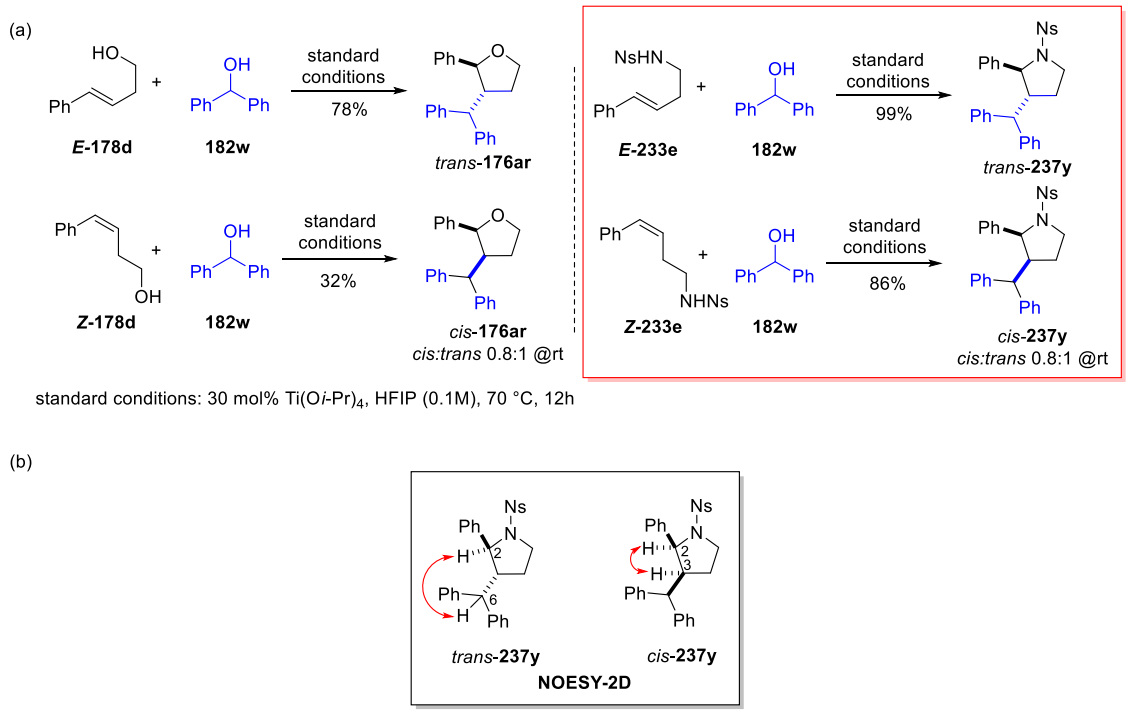
as a single diastereomer, while the isomeric alcohol ***Z*-233e** possibly reacted *via* a stepwise pathway, producing pyrrolidines **237aad** as a 3:1 mixture of *cis* to *trans* diastereomers. This gave identical distereomeric ratio as the synthesis of *cis*-**176ap** (**Scheme 3.60b**). The stereochemistry of pyrrolidines *trans*-**237aad** and *cis*-**237aad** was characterized by NOESY-2D experiments (**Scheme 2.60c**). Correlations could be seen between 2-H and 6-H_2 for *trans*-**237aad**, suggesting the 2,3-*trans* geometry. Correlations could be seen between 2-H and 3-H for *cis*-**237aad**, suggesting the 2,3-*cis* geometry.



Scheme 3.60 (a) Synthesis of *cis*-amine ***Z*-233e**; (b) Cyclization of homoallylic alcohol and amine with electrophile **182b**; (c) NOESY-2D experiments on pyrrolidines **237aad**

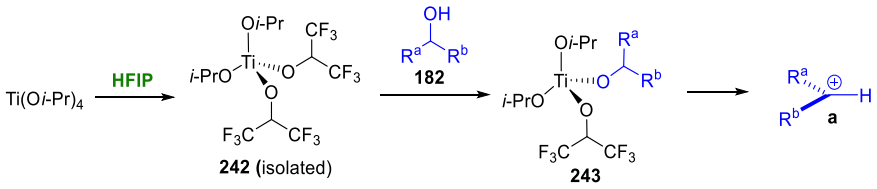
Employing benzhydrol **182w** as the electrophile led to a similar outcome. Both reactions

produced pure *trans* products *trans*-**176ar** and *trans*-**237y** from *trans* starting materials and led to a 0.8:1 mixture of *cis* to *trans* diastereomers from *cis* starting materials. The only difference was that pyrrolidines were obtained in higher yields than the corresponding THFs (**Scheme 3.61a**). The abnormal diastereoselectivity observed when treating *cis* starting materials with benzhydrol **182w** could be attributed to a combination of steric bulk of the electrophile and a stepwise reaction pathway as previously discussed. The stereochemistry of pyrrolidines *trans*-**237y** and *cis*-**237y** was characterized by NOESY-2D experiments (**Scheme 2.61b**). Correlations could be seen between 2-H and 6-H for pyrrolidines *trans*-**237y**, suggesting the 2,3-*trans* geometry. Correlations could be seen between 2-H and 3-H for pyrrolidines *cis*-**237y**, suggesting the 2,3-*cis* geometry.



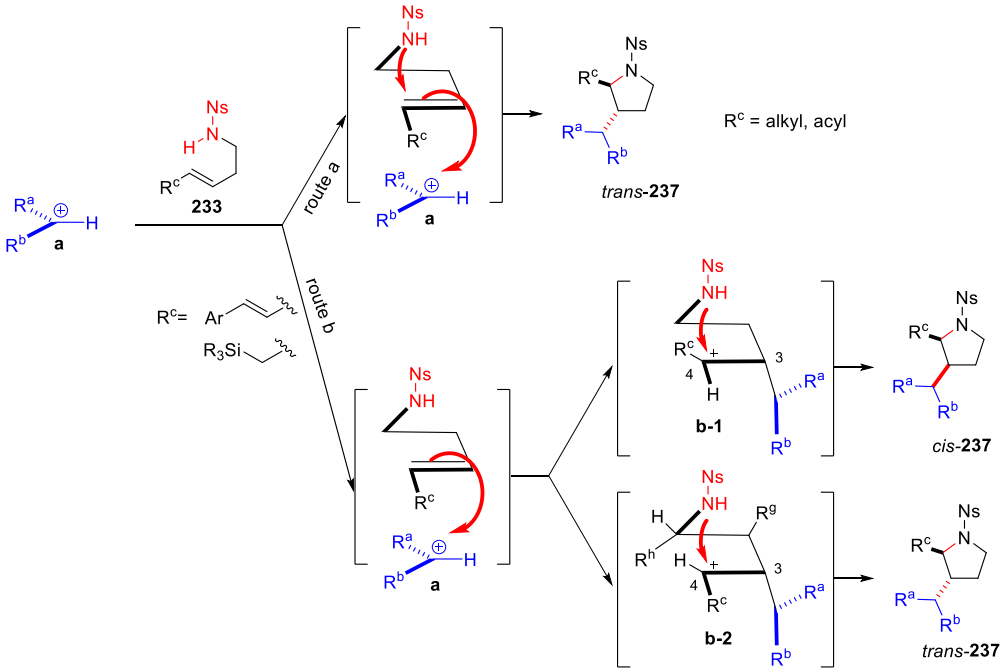
Scheme 3.61 (a) Cyclization of homoallylic alcohol and amine with electrophile **182w**; (c) NOESY-2D experiments on pyrrolidines **237y**

The identical pattern of diastereoselectivity between THFs and pyrrolidines suggests that the cyclization of amines (except the allylic silyl substituted amine, see **chapter 3.5.2** for detailed mechanistic discussion) likely occurs through the same reaction pathway as the synthesis of THFs. The electrophilic carbocation **a** was firstly generated from complex **242** (**Scheme 3.62**). (see **chapter 2.6.3** for detailed discussion).



Scheme 3.62 Proposed mechanism for the generation of carbocation **a**

For most of *trans* homoallylic amines bearing an alkyl or acyl substituent at R^c, the cyclization was more likely proceeded in a concerted 5-*endo*-trig manner and retained the *trans* geometry from the starting material, as only *trans*-diastereomers was obtained (**Scheme 3.63-route a**). However, for *cis* homoallylic amines and vinyl or allylic silyl substituted *trans*-homoallylic amines, the cyclization proceeded through a less stereoselective pathway, possibly in a stepwise manner, where the amine firstly trapped the carbocation **a** to form intermediate **b-1** and **b-2** due to C_3-C_4 bond rotation. It was then trapped by the nitrogen to generate *cis* and *trans* pyrrolidines respectively (**Scheme 3.63-route b**).



Scheme 3.63 Proposed mechanism for the synthesis of pyrrolidines **237**

3.8. Selective Functionalization of the Pyrrolidine Products

Selective functionalization of the pyrrolidines **237** would provide an opportunity to modify products into other synthetically useful compounds. Functionalization of the pyrrolidines would be focused on three main directions; removal of the Ns protecting group, and oxidation of the electron-rich aromatic ring, vinyl and silyl substituted pyrrolidines.

3.8.1. Removal of Ns protecting group

Removal of Ns protecting group was considered essential as this would produce the more useful free secondary amine. The Ns group is generally deprotected by treating

with a sulfide source under basic conditions, where the sulfide attacks the 2-nitrophenyl ring in a S_NAr manner to produce the desired product and release SO_2. Treating pyrrolidines **237e** with thiophenol with K_2CO_3 as the base at 50 °C led to full recovery of starting material (**Table 3.12**, **Entry 1**). Neither raising the temperature to 70 °C nor 90 °C was helpful, and only starting material was recovered (**Table 3.12**, **Entries 2-3**). Employing Cs_2CO_3 as the base afforded no desired product as well (**Table 3.12**, **Entry 4**). Finally, switching the sulfide source to mercaptoacetic acid with LiOH as the base at room temperature successfully afforded desired product **307a** in 67% yield. (**Table 3.12**, **Entry 5**).

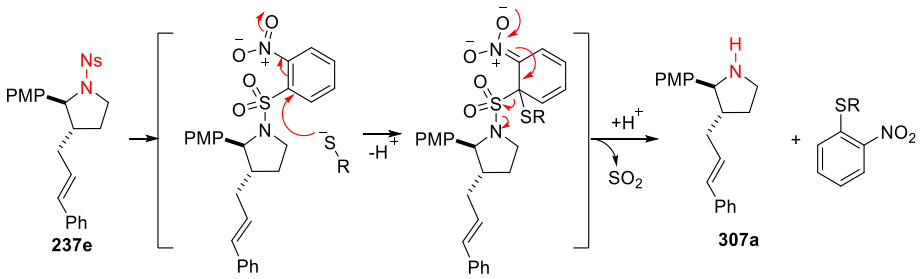
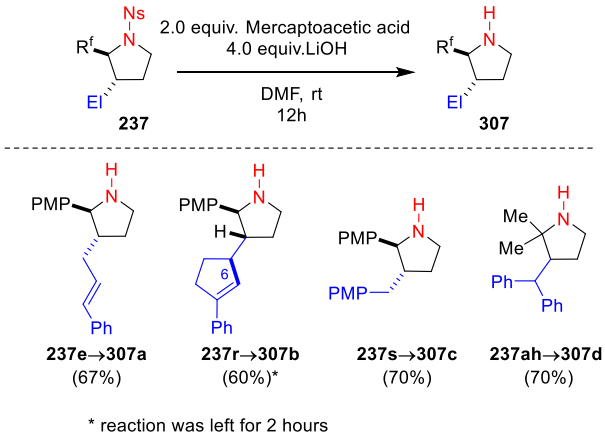


Table 3.12 Removal of Ns protecting group

Entry	Sulfide source	Base	Solvent	Temperature	Time	Yield **307a** (%)
1	3 equiv. PhSH	4 equiv. K_2CO_3	MeCN	50 °C	12h	0
2	3 equiv. PhSH	4 equiv. K_2CO_3	MeCN	70 °C	12h	0
3	3 equiv. PhSH	4 equiv. K_2CO_3	MeCN	90 °C	12h	0
4	3 equiv. PhSH	4 equiv. Cs_2CO_3	MeCN	50 °C	12h	0
5	2 equiv. $HSCH_2COOH$	4 equiv. LiOH	DMF	rt	12h	67

With suitable deprotection conditions identified, it was decided to examine the generality of this method (**Scheme 3.64**). Treating pyrrolidines **237r** under the reaction conditions for 2 hours led to full consumption of starting materials, giving amine **307b** in

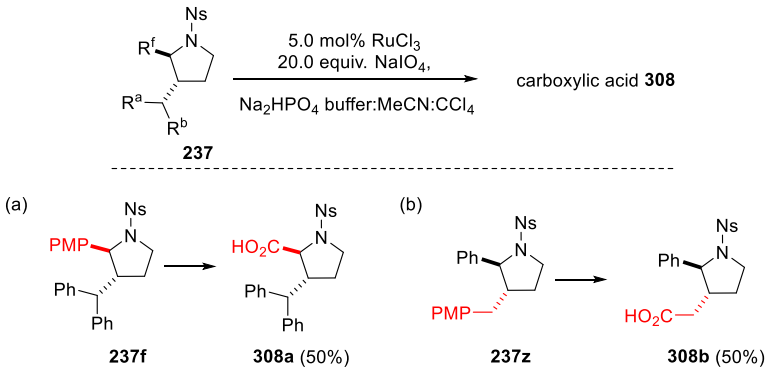
60% yield. Under the same reaction conditions, amines **307c** and **307d** were both obtained in 70% yield by deprotection of pyrrolidines **237s** and **237ah**.



Scheme 3.64 Deprotection of pyrrolidines **237**

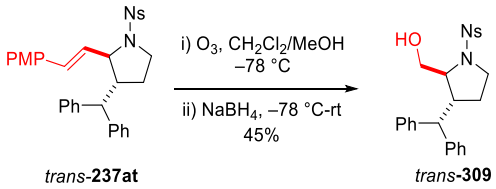
3.8.2. Oxidation: synthesis of carboxylic acid and alcohol

The oxidation of the electron-rich aromatic ring in pyrrolidines **237** was attempted by using 5mol% of $RuCl_3$ as primary oxidant and $NaIO_4$ as co-oxidant. Pyrrolidines **237f** and **237z** were examined as they contained electron-rich PMP group, which led to full consumption of starting materials and afforded both carboxylic acid **308a** and **308b** in both 50% yield without damaging the pyrrolidine ring (**Scheme 3.65**).



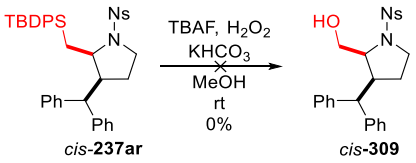
Scheme 3.65 Synthesis of carboxylic acid **308** *via* Ru-catalyzed oxidation

Ozonolysis was performed with α-vinyl substituted pyrrolidines *trans*-**237at** as it could transform it to the more synthetically useful alcohols. Treating pyrrolidines *trans*-**237at** with ozone followed by a reductive quench using $NaBH_4$ successfully afforded alcohol *trans*-**309** in 45% yield (**Scheme 3.66**).



Scheme 3.66 Synthesis of alcohol *trans*-**309** *via* ozonolysis followed by reductive quench

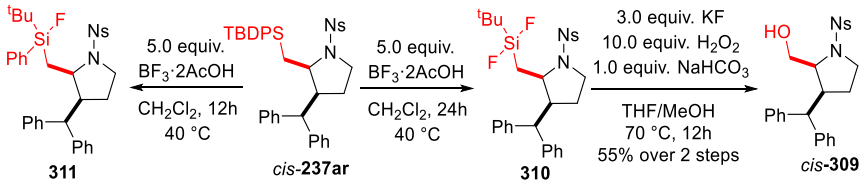
Fleming-Tamao Oxidation of α-silyl substituted pyrrolidines was also attempted, which would be complementary as it would form diastereomeric alcohol substituted products. Unfortunately, treating *cis*-**237ar** with TBAF and hydrogen peroxide at room temperature afforded only recovered starting materials (**Scheme 3.67**).



Scheme 3.67 Attempts to oxidize the TBDPS *via* Fleming-Tamao Oxidation

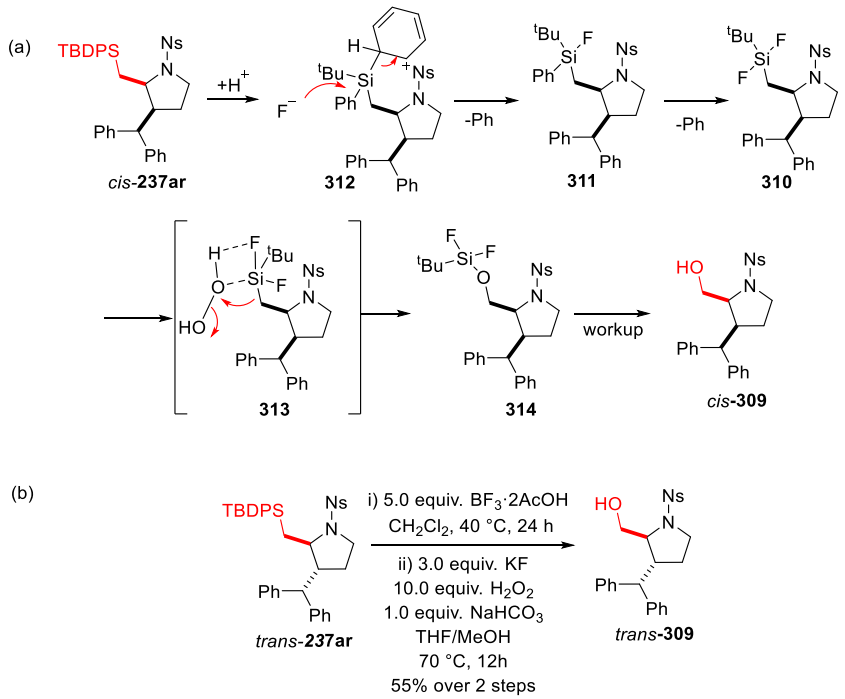
It was then decided to firstly transform TBDPS group to the more reactive di-fluoro-*tert*-butyl silyl group so that the sequent oxidation could be achieved (**Scheme 3.68**). Treating *cis*-**237ar** with $BF_3{\cdot}2AcOH$ at 40 °C for 12 hours afforded the mono-fluoro-substituted silane **311**. Increasing the reaction time to 24 hours successfully produced di-fluoro-*tert*-butyl silane **310**, which was then treated with potassium fluoride and hydrogen peroxide at 70 °C to afford desired alcohol *cis*-**309** in

55% yield.



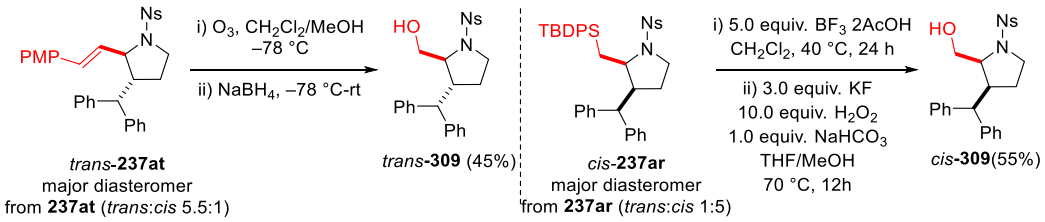
Scheme 3.68 Fleming-Tamao Oxidation of pyrrolidines *cis*-**237ar**.

The di-fluoride insertion thought to proceed *via* trapping of proton by the phenyl ring followed by attack of the fluoride anion to the silane. The di-fluoro silane **310** is more electrophilic and can be attacked by the hydrogen peroxide. A C-Si bond migration then occurs to produce **314**, which leads to formation of alcohol *cis*-**309** upon hydrolysis (**Scheme 3.69a**). The oxidation of *trans*-**237ar** was also performed using the optimized conditions, leading to production of alcohol *trans*-**309** in identical yield (**Scheme 3.69b**).



Scheme 3.69 (a) Mechanism for the synthesis of alcohol *cis*-**309**; (b) Fleming-Tamao Oxidation of pyrrolidines *trans*-**237ar**.

It is particularly noteworthy that either diastereoisomer of alcohol product *trans*-**309** or *cis*-**309** can be produced from this chemistry *via* using either vinyl or silyl substituted homoallylic amine. (**Scheme 3.70**).



trans-**237at**
major diasteromer
from **237at** (*trans*:*cis* 5.5:1)

trans-**309** (45%)

cis-**237ar**
major diasteromer
from **237ar** (*trans*:*cis* 1:5)

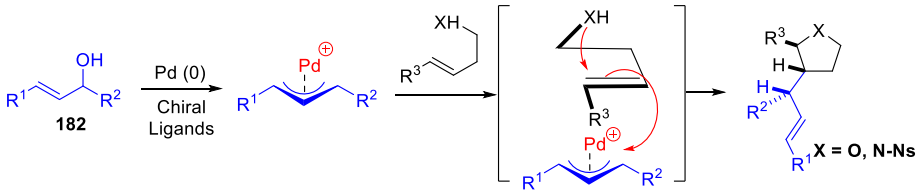
cis-**309**(55%)

Scheme 3.70 Synthesis of *cis* and *trans*-**309**

Chapter 4: Future Work

4.1. Asymmetric Syntheses of Pyrrolidines and Tetrahydrofurans

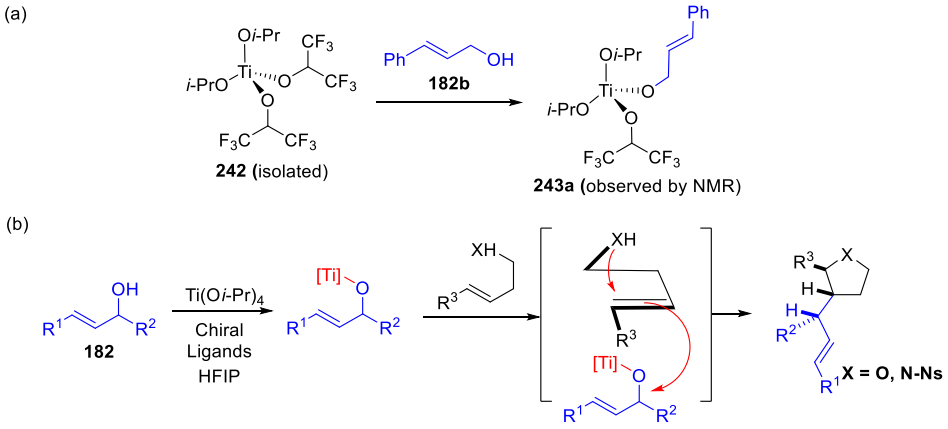
Although previous attempts to synthesize enantiopure heterocycles using Pd(0) catalyst were unsuccessful, this would ultimately be the most powerful and well-developed methods to induce chirality through a π-carbocation intermediate (**Scheme 4.1**). Previous results suggest that the Pd(0) catalyst is not compatible with the HFIP solvent, which is one of the key components for this cyclization as it helps stabilize the carbocation intermediate. Finding a suitable solvent mixture, which allows the formation of key Pd chelated π-carbocation intermediate, is one of the possible solutions. Additionally, identifying a suitable Pd catalyst and ligand is another alternative way to allow the asymmetric synthesis of the heterocycle rings.



Scheme 4.1 Proposed Pd-catalysed asymmetric synthesis of heterocycles

Using chiral Ti catalyst to achieve asymmetric synthesis would be another alternative, and should compatible with the necessary HFIP solvent. During the mechanistic study, a Ti-complex **243a**, where hexafluoroisopropoxy ligand of complex **242** was substituted by one electrophilic alcohol **182b**, was isolated and identified by NMR study (**Scheme 4.2a**). Introducing a bidentate chiral ligand, which could generate a key chelated intermediate with electrophilic alcohol **182**, could provide a feasible way to synthesize enantiopure

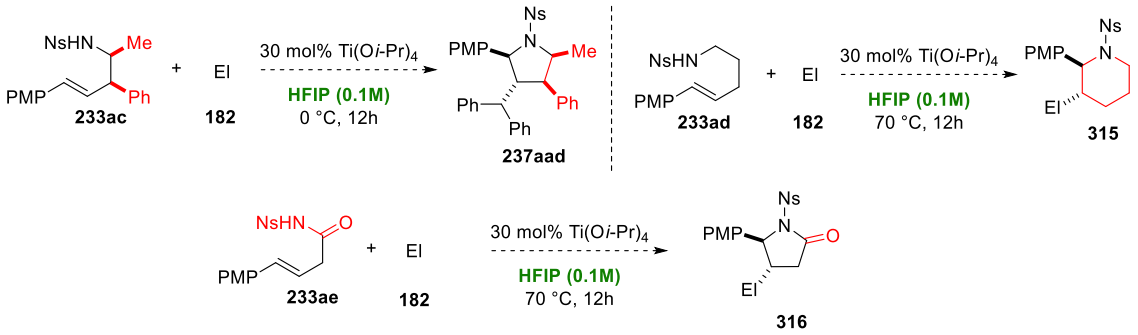
heterocycles (**Scheme 4.2b**).



Scheme 4.2 (a) Formation of Titanium complex **243a**; (b) Proposed Ti-catalysed asymmetric synthesis of heterocycles.

4.2. Syntheses of Fully Substituted Pyrrolidine, Piperidine and Lactam derivatives

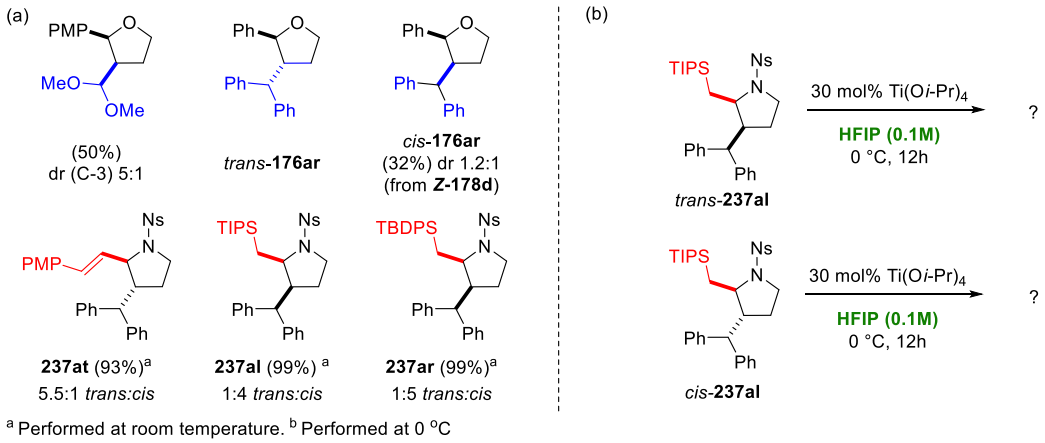
Another clear extension of this work would be to further explore this methodology to more diverse and useful nitrogen-containing heterocycles (**Scheme 4.3**). Although previous attempts to synthesize α,β-substituted homoallylic amine **233ac** bearing a bulky β-substituent were unsuccessful *via* a Mitsunobu reactions, synthesis of secondary homoallylic amines is known in the literature. Synthesis of fully substituted pyrrolidines could then be achieved. Additionally, explorations of piperidine **315** and lactam **316** are required to complete the scope of nitrogen-containing heterocycles.



Scheme 4.3 Syntheses of fully substituted pyrrolidine, peperidine and lactam derivatives

4.3. Investigation of the reaction mechanism

Although work has been carried out in investigating the reaction pathway and a mechanism was proposed, there was still some abnormal 2,3-*cis* diastereoselectivity that needed to be explained (**Scheme 4.4a**). One of the obvious experiments would be re-subjection of *cis*- and *trans*-**237al**, which could clarify the existence of equilibration in the cyclization (**Scheme 4.4b**). Additionally, a computational study would be a great tool to provide a complementary understanding of the reaction mechanism.



[a] Performed at room temperature. [b] Performed at 0 °C

Scheme 4.3 (a) THFs and pyrrolidines substrates with abnormal diastereoselectivity; (b) Re-subjection of pyrrolidines *trans*-**237al** and *cis*-**237al**

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Chapter 5: Experimental

5.1 General Experimental Details

^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz or 500MHz spectrometer in $CDCl_3$ and referenced to residual solvent peaks. Chemical shifts were quoted in ppm (parts per million) to the nearest 0.01 ppm with signal splitting recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint) septet (sept), multiplet (m) and broad singlet (br s). Coupling constants, *J*, were measured in Hz to the nearest 0.1 Hz. ^{1}H and ^{13}C NMR spectra were recorded at room temperature. All diastereomeric ratio values (dr) were based on the crude NMR spectroscopy. The numbering system drawn on the structures and used to assign the NMR peaks is not the same system that was used to generate the chemical name. Infrared spectra were recorded as thin films of neat samples on a Bruker Tensor 27 FT-IR spectrometer equipped with Attenuated Total Reflectance sampling accessories. High resolution mass spectra were given to four decimal places and were recorded on a Bruker MicroTof (resolution = 10000 FWHM) under conditions of electrospray ionization (ESI), electronic ionization (EI) or chemical ionization (CI). Melting points (m.p.) were obtained from recrystallized samples using a Lecia VMTG heated-stage microscope and were uncorrected. The solvent systems used for recrystallization were quoted in parentheses. Flash column chromatography (FCC) was performed using silica gel (60 Å, 0.033-0.070 mm, BDH). TLC analyses were performed on Merck Kiesegel 60 F_{254} 0.25 mm precoated silica plates or Macherey-Nagel Alugram Alox N/UV_{254} 0.20 mm precoated alumina plates. Reagents obtained from Sigma-Aldrich, Alfa, Fluorochem and TCI suppliers were used directly as supplied All anhydrous reactions were carried out in flame dried glassware and under an inert atmosphere of argon provided by a balloon. All reactions were stirred with magnetic followers. THF, toluene and CH_2Cl_2 were dried by purification through two activated alumina purification columns. Brine refers to a saturated aqueous solution of NaCl.

5.2 General Procedures

5.2.1 General procedure A: synthesis of styrenes *via* Wittig reaction

A solution of triphenylphosphonium halide (1.1-2.3 equiv.) in dry solvent (THF or Et_2O) was placed in a flame-dried round-bottomed flask. The solution was cooled to 0 °C, and the base (1.2-4.5 equiv. of base-^{t}BuOK or of NaH (60%) or *n*-BuLi) was added in one portion. After stirring at 0 °C for 30 min, the aldehyde (1.0 equiv.) was added. The reaction mixture was gradually warmed to room temperature. After 12 hours, the reaction was quenched by slow addition of saturated NH_4Cl. The phases were separated, and the aqueous phase was extracted twice with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give the corresponding styrene, that was purified by chromatography on silica gel using the appropriate mixture of eluents.

5.2.2 General procedure B: synthesis of styrenes using Ru-catalyzed methatesis reaction

To a flame-dried r.b.f., charged with 1.5 mol% of Ru-catalyst, under Ar, at room temperature, was added 4.0 mL/mmol of dry CH_2Cl_2 (previously degassed, bubbling Ar during 30 min.). A solution of the mixture of alkenes in dry and degassed CH_2Cl_2 (1.0 mL/mmol) was added and the mixture was stirred under reflux. The reaction was monitored by TLC until completion, and the solvent was evaporated under reduced pressure to give the corresponding alkene, that was purified by chromatography on

silica gel using the appropriate mixture of eluents.

5.2.3 General procedure C: synthesis of alcohol from acetate deprotection

To a solution of acetate in MeOH (10.0 mL/mmol), 5.0 equiv. of K_2CO_3 were added in one portion at 0 °C. The reaction was monitored by TLC until completion. The mixture was filtered, and the solvent was evaporated under reduced pressure to give the corresponding alcohol, that was purified by chromatography on silica gel using the appropriate mixture of eluents.

5.2.4 General procedure D: synthesis of *E*-styrenes with a carboxylic acid moiety

To a solution of triphenylphosphonium salt (1.2 equiv.) in THF (2 mL) was added dropwise a 1 M solution of NaHMDS (3.5 equiv.) at 0 °C. The solution was then stirred for 30 min. After cooling to –78 °C, aldehyde (1.0 equiv.) was added dropwise. The reaction was allowed to warm up to r.t. overnight. Add water and Et_2O and pour the mixture into a separatory funnel. Separate the aqueous layer and acidify with 1 M HCl until pH=1. Extract the aqueous layer with Et_2O twice. The organic layer was dried with $MgSO_4$, and the solvent was evaporated under reduced pressure to give the corresponding carboxylic acid, that was purified by chromatography on silica gel using the appropriate mixture of eluents.

5.2.5 General procedure E: synthesis of *E*-styrenes with a carbamate moiety

To a stirred solution of alcohol (1.0 equiv.), triphenylphosphine (1.5 equiv.) and

tosyl/mesyl/*o*-nosyl/benzyl methyl carbamate (1.2 equiv.) in THF (3 mL/mmol of alcohol) was slowly added diisopropyl azodicarboxylate (DIAD) (1.3 equiv.) at 0 °C. The reaction mixture was gradually warmed to room temperature. After 12 hours, it was concentrated under reduced pressure to give the corresponding carbamate, that was purified by chromatography on silica gel using the appropriate mixture of eluents.

5.2.6 General procedure F: deprotection of Boc-group

To a stirred solution of carbamate (1.0 equiv.) in CH_2Cl_2 (3 mL/mmol of carbamate) was slowly added trifluoroacetic acid (TFA) (5.0 equiv.) at 0 °C. The reaction mixture was gradually warmed to room temperature. After 12 hours, it was quenched with saturated $NaHCO_3$ solution. The aqueous layer was separated and extract with CH_2Cl_2 twice. The organic layer was combined and dried over $MgSO_4$ and concentrated under reduced pressure to afford the corresponding amine.

5.2.7 General procedure G: synthesis of allylic silane

To a stirred solution of chlorosilane (1.0 equiv.) in dry THF (5 mL/mmol) was slowly added allyl magnesium bromide (1M, 1.1 equiv.) at 0 °C. The reaction mixture was gradually warmed to room temperature. After 12 hours, it was cooled to 0 °C and quenched with saturated NH_4Cl solution. The aqueous layer was separated and extract with Et_2O twice. The organic layer was combined and dried over $MgSO_4$ and concentrated under reduced pressure to give the corresponding allylic silane, that was purified by chromatography on silica gel using the appropriate mixture of eluents.

5.2.8 General procedure H: synthesis of THFs via cyclization of homoallylic alcohol

To a microwave vial charged with a stirring bar, 1.0 equiv. of alcohol **A**, 1.0 equiv. of alcohol **B** and HFIP (10 mL/mmol of **A**) was added under argon. After fully dissolving the substrate, 30 mol% $Ti(O^iPr)_4$ was added. The reaction was stirred for 12 hours at 70 °C. Then the solvent was removed under vacuum. The residue was purified by silica gel column chromatography to give the corresponding heterocycle.

5.2.9 General procedure I: synthesis carboxylic acids *via* Ru-catalyzed oxidation of aromatic rings

To a cold (0 °C) solution of THFs or pyrrolidines in 10.0 mL/mmol of a 2:2:3 mixture of CCl_4:MeCN:pH 7 buffer (Na_2HPO_4), $NaIO_4$ (20.0 equiv) was added in one portion. The mixture was stirred at that temperature for 15 min. and $RuCl_3$ (5 mol%) was added in one portion. The mixture was warmed up to room temperature. The reaction was monitored by TLC until completion, diluted with Et_2O and H_2O and extracted with Et_2O (3 x 3 mL/mmol). The water layer was acidified until pH=1 using concentrated HCl, and extracted with Et_2O (3 x 3 mL/mmol). The combined organic layers were dried using Na_2SO_4, filtered and the solvent was evaporated under reduced pressure to give the corresponding carboxylic acid, that was purified by chromatography on silica gel using the appropriate mixture of eluents.

5.2.10 General procedure J: ozonolysis of alkene

Alkene and CH_2Cl_2 were added to a r.b.f. charged with a stirring bar under –78°C.

The solution was bubbled with O_3 for 7-10 min until the blue color was observed, leave it for 2-3 min. Then bubbling O_2 for few min. and switch to N_2 bubbling for 3-4 min. until no blue color was seen. DMS was added under dry-ice bath, leave it for 10min. and let it warm up to room temperature. The crude mixture was concentrated under reduced pressure to give the corresponding aldehyde, that was purified by chromatography on silica gel using the appropriate mixture of eluents.

5.2.11 General procedure K: hydrogenation of alkene

Alkene (1 equiv.), EtOAc (2 mL) and 10 wt. % of Pd/C (10 wt. %) were added to a two-necked r.b.f. The flask was submerged in an ice bath, and then evacuated and backfilled with hydrogen five times. The reaction mixture was stirred vigorously under hydrogen atmosphere (balloon pressure) at 0 °C for 2 hours. The reaction mixture was filtered through celite and flushed with EtOAc. The filtrate was concentrated under reduced pressure and purified by flash column chromatography to afford the corresponding products.

5.2.12 General procedure L: acylation and alkylation of lactones

To a solution of diisopropylamine (1.15 equiv.) in dry THF (1.92 mL/mmol) at −78 °C was added *n*-butyllithium (2.5 M in hexanes, 1.10 equiv.) dropwise. The solution was stirred at 0 °C for 30 min and then cooled to −78 °C at which time lactones (1.00 equiv.) in THF (0.22 mL/mmol) was added over 10 min. The mixture was stirred at −78 °C for 0.5 hours and electrophile (1.0-1.5 equiv.) was added quickly. The mixture

was allowed to warm to room temperature, stirred for 3 hours, and quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O three times, and the organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the corresponding product.

5.2.13 General procedure M: removal of Ns protecting group

To a solution of Ns protected pyrrolidines (1.0 equiv.) in dry DMF (1.00 mL/mmol) under Argon was added LiOH (4.0 equiv.) and mercaptoacetic acid (2.0 equiv.). After stirring stirred at room temperature for 16 hours, the reaction was quenched with H_2O. The mixture was extracted with EtOAc three times, and the organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the corresponding amine.

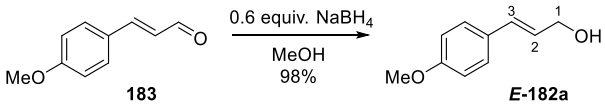
5.2.14 General procedure N: Flemming-Tamao oxidation of TBDPS substituted pyrrolidines

To a solution of TBDPS substituted pyrrolidines (1.0 equiv.) in dry CH_2Cl_2 (10 mL/mmol) was added Boron trifluoride/acetic acid complex (BF3·2 HOAc, 5.0 equiv.). The reaction mixture was heated at reflux for 24 hours, and then it was quenched with a saturated $NaHCO_3$ solution. The aqueous layer was separated and extracted three times with CH_2Cl_2, and the combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was dissolved in a mixture of

THF and MeOH (1:1, 14mL/mmol), followed by the addition of $NaHCO_3$ (1.0 equiv.), KF (3.0 equiv.) and H_2O_2 (30%, 10 equiv.). The reaction mixture was refluxed for 6 hours, then quenched with saturated $Na_2S_2O_3$ solution. The aqueous layer was separated and extracted three times with EtOAc, and the combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the corresponding alcohol.

5.3 Synthesis of Allyl Alcohols

5.3.1 (2*E*)-3-(4-Methoxyphenyl)prop-2-en-1-ol (*E*-182a)

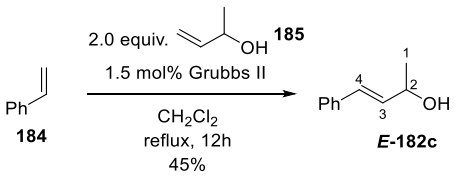


To a stirring solution of 4-methoxycinnamaldehyde **183** (4.800 g, 29.62 mmol) in MeOH (56 mL) under Ar, $NaBH_4$ (0.840 g, 17.8 mmol) is slowly added at 0 ℃**.** After 30 min. the ice bath is removed**.** The reaction was allowed to stir for 12 hours at room temperature. The reaction is quenched with saturated NH_4Cl solution and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Recrystallization afforded alcohol ***E*-182a** as a white solid (4.850 g, 98%). Spectroscopic properties matched those previously reported.[1]

Data for ***E*-182a**: $\mathbf{R_f}$ 0.5 (80% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.32 (2H, d, *J* = 8.7 Hz, Ar), 6.86 (2H, d, *J* = 8.7 Hz, Ar), 6.56 (1H, d, *J* = 15.9 Hz, 3-H), 6.24 (1H,

dt, *J* = 15.8, 6.0 Hz, 2-H), 4.29 (2H, dd, *J* = 5.9, 1.2 Hz, 1-H_2), 3.81 (3H, s, OMe), 1.53 (1H, br s, OH). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.5 (C Ar), 131.1 (C-3), 129.6 (C Ar), 127.8 (2 x CH Ar), 126.4 (C-2), 114.2 (2 x CH Ar), 64.07 (C-1), 55.43 (OMe). **HRMS** (Cl): calculated for $C_{10}H_{13}O_2$ $[M+H]^+$ requires *m/z* 165.0916, found *m/z* 165.0919.

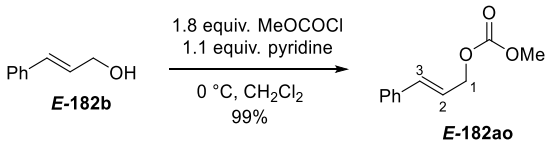
5.3.2 (±)-(3*E*)-4-Phenylbut-3-en-2-ol (*E*-182c)



Styrene **184** (1.000 g, 9.606 mmol), but-3-en-2-ol **185** (1.380 g, 19.14 mmol) and Grubbs II (122.0 mg, 0.1438 mmol) were subjected to the general procedure B (FCC: 30% Et_2O - pentane) to yield ***E*-182c** as a yellow oil (0.712 g, 50%). Spectroscopic properties matched those previously reported.[2]

Data for ***E*-182c**: **R_f** 0.30 (80% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.36-7.41 (2H, m, Ar), 7.29-7.35 (2H, m, Ar), 7.21-7.27 (1H, m, Ar), 6.57 (1H, d, *J* = 15.8 Hz, 4-H), 6.27 (1H, dd, *J* = 15.9, 6.4 Hz, 3-H), 4.44-4.55 (1H, m, 2-H), 1.66 (1H, br s, OH), 1.38 (3H, d, *J* = 6.4 Hz, Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 136.8 (C Ar), 133.7 (C-3), 129.5 (C-4), 128.7 (2 x C-H Ar), 127.8 (C-H Ar), 126.6 (2 x C-H Ar), 69.1 (C-2), 23.5 (Me).

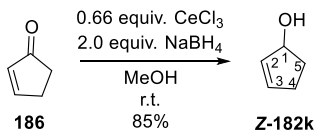
5.3.3 Cinnamyl methyl carbonate (*E*-182ao)



To a stirred solution of alcohol ***E*-182b** (0.220 g, 1.65 mmol, 1.0 equiv.), pyridine (0.15 mL, 2.96 mmol, 1.8 equiv.), in CH_2Cl_2 (10 mL) was slowly added methyl chloroformate (0.15 mL, 2.96 mmol, 1.8 equiv.) at 0 °C. The reaction mixture was warmed up and stirred for 2 hours before quenching with 1N HCl solution. The aqueous layer was separated and extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure to yield ***E*-182ao** (FCC: gradient elution: 5% → 15% Et_2O - pentane) as a colorless oil (0.316 g, 99%). Spectroscopic properties matched those previously reported.

Data for ***E*-182ao**: $\mathbf{R_f}$ 0.40 (30% Et_2O - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 7.37-7.41 (2H, m, Ar), 7.29-7.35 (2H, m, Ar), 7.24-7.29 (1H, m, Ar), 6.69 (1H, dt, *J* = 15.8, 1.3 Hz, 3-H), 6.30 (1H, dt, *J* = 15.9, 6.4 Hz, 2-H), 4.80 (2H, dd, *J* = 6.5, 1.3 Hz, 1-H_2), 3.81 (3H, s, OMe). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 155.8 (C=O), 136.2 (C Ar), 134.9 (C-3), 128.8 (2 x CH Ar), 128.2 (CH Ar), 126.8 (2 x CH Ar), 122.6 (C-2), 68.5 (C-1), 55.0 (OMe).

5.3.4 (±)-(2*Z*)-Cyclopent-2-en-1-ol (*Z*-182k)

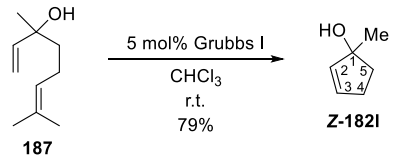


Cerium trichloride (2.000 g, 8.197 mmol) was dissolved in 20 mL of methanol. Then cyclopent-2-enone **186** (1.00 g, 12.3 mmol) was added. After 5 min. of vigorous

stirring, sodium borohydride (934 mg, 24.6 mmol) was carefully added portionwise and the resulting heterogeneous mixture was stirred for 15 min. at r. t. Water was added dropwise until a clear solution is seen and then the mixture was extracted twice with Et_2O. The organic layers were collected, dried over $MgSO_4$ and the solvents were removed under vacuum. FCC (20% Et_2O) afforded ***Z*-182k** as a colorless oil (0.580 g, 85%). Spectroscopic properties matched those previously reported.[3]

Data for ***Z*-182k**: $\mathbf{R_f}$ 0.45 (50% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 5.93-5.99 (1H, m, 3-H), 5.78-5.84 (1H, m, 2-H), 4.82-4.88 (1H, m, 1-H), 2.49 (1H, ddt, *J* = 16.6, 10.9, 5.4 Hz, 4-H_A), 2.17-2.31 (2H, m, 4-H_B and 5-H_A), 1.95 (1H, br s, OH), 1.61-1.76 (1H, m, 5-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 135.2 (C-3), 133.4 (C-2), 77.6 (C-1), 33.3 (C-5), 31.1 (C-4). **HRMS** (EI): calculated for C_5H_7O $[M-H]^+$ requires *m/z* 83.0491, found *m/z* 83.049.

5.3.5 (±)-1-Methylcyclopent-2-en-1-ol (*Z*-182l)



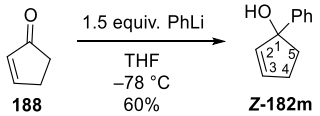
187 ***Z*-182l**

Linalool **21** (0.500 g, 3.23 mmol) and Grubbs I (0.133 g, 0.161 mmol) were subjected to the general procedure B except conducting the reaction at room temperature in $CHCl_3$ (FCC: gradient elution: 20% → 50% Et_2O - pentane) to yield ***Z*-182l** as a yellow oil (0.250 g, 79%). Spectroscopic properties matched those previously reported.[4]

Data for ***Z*-182l**: $\mathbf{R_f}$ 0.40 (80% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 5.81

(1H, dt, *J* = 5.4, 2.3 Hz, 3-H), 5.69 (1H, dt, *J* = 5.4, 2.3 Hz, 2-H), 2.48 (1H, m, 4-H_A), 2.30 (1H, m, 4-H_B), 1.96 (1H, ddd, *J* = 13.4, 8.1, 4.8 Hz, 5-H_A), 1.89 (1H, ddd, *J* = 13.4, 8.1, 4.8 Hz, 5-H_B), 1.37 (3H, s, Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 138.0 (C-2), 132.8 (C-3), 83.6 (C-1), 39.8 (C-5), 31.2 (C-4), 27.6 (Me).

5.3.6 (±)-(*Z*)-1-Phenylcyclopent-2-en-1-ol (*Z*-182m)



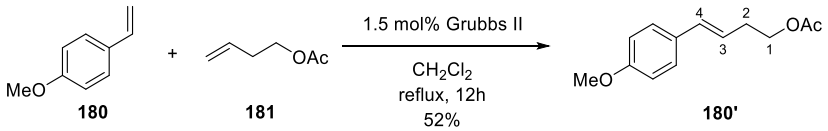
188 **Z-182m**

To a solution of Cyclopent-2-enone **188** (0.51 mL, 6.1 mmol) in THF (40 mL) at –78 °C was added 1.88M PhLi (4.9 mL, 9.1 mmol). After the mixture was stirred at –78 °C for 1 hour, H_2O was added and allowed to warm to room temperature. The mixture was extracted with Et_2O and the organic extract was washed with brine, dried over $MgSO_4$ and the solvents were removed under vacuum. The residue was purified (FCC: gradient elution: 5% → 7% Et_2O - pentane) to yield ***Z*-182m** as a white solid (0.584 g, 60%). Spectroscopic properties matched those previously reported.[5]

Data for ***Z*-182m**: **R_f** 0.5 (60% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.43-7.47 (2H, m, Ar), 7.32-7.38 (2H, m, Ar), 7.23-7.28 (1H, m, Ar), 6.12 (1H, dt, *J* = 5.6, 2.4 Hz, 3-H), 5.88 (1H, dt, *J* = 5.5, 2.2 Hz, 2-H), 2.60-2.70 (1H, m, 4-H_A), 2.43-2.52 (1H, m, 4-H_B), 2.24-2.29 (1H, m, 5-H_2),1.98 (1H, br s, OH). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 147.0 (C Ar), 136.6 (C-2), 134.9 (C-3), 128.2 (2 x CH Ar), 126.8 (CH Ar), 124.9 (2 x CH Ar), 87.0 (C-1), 42.0 (C-5), 31.5 (C-4).

5.4 Synthesis of Homoallylic Alcohols

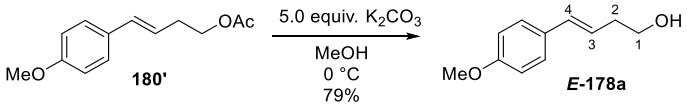
5.4.1 (3*E*)-4-(4-Methoxyphenyl)but-3-en-1-yl acetate (180')



4-Methoxystyrene **180** (5.000 g, 37.28 mmol), but-3-en-1-yl acetate **181** (8.510 g, 74.58 mmol) and Grubbs II (0.470 g, 0.554 mmol) were subjected to the general procedure **B** (FCC: 5% Et_2O - pentane) to yield **180'** as a yellow oil (4.250 g, 52%). Spectroscopic properties matched those previously reported.[6]

Data for **180'**: $\mathbf{R_f}$ 0.30 (10% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.28 (2H, d, *J* = 8.4 Hz, Ar), 6.84 (2H, m, *J* = 8.8 Hz, Ar), 6.41 (1H, d, *J* = 15.9 Hz, 4-H), 6.02 (1H, dt, *J* = 15.8 and 7.0 Hz, 3-H), 4.17 (1H, t, *J* = 6.8 Hz, 1-H_2), 3.79 (3H, s, OMe), 2.52 (1H, qd, *J* = 6.9 and 1.5 Hz, 2-H_2), 2.05 (3H, s, Ac Me). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 171.1 (C=O), 159.0 (C Ar), 131.8 (C-4), 130.1 (C Ar), 127.2 (2 x CH Ar), 123.3 (C-3), 114.0 (2 x CH Ar), 63.9 (C-1), 55.3 (OMe), 32.4 (C-2), 21.0 (Ac Me). **HRMS** (ESI): calculated for $C_{13}H_{16}O_3Na$ $[M+Na]^+$ requires *m/z* 243.0991, found *m/z* 243.0994.

5.4.2 (3*E*)-4-(4-Methoxyphenyl)but-3-en-1-ol (*E*-178a)

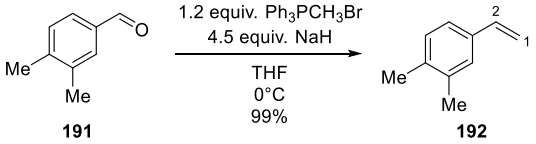


Acetate **180'** (3.510 g, 15.95 mmol) and K_2CO_3 (6.580 g, 47.68 mmol) were subjected to the general procedure **C** (FCC: gradient elution: 50% → 100% Et_2O - pentane) to yield ***E*-178a** as a white solid (2.230 g, 79%). Spectroscopic properties

matched those previously reported.[7]

Data for ***E*-178a**: R_f 0.33 (75 % Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.30 (2H, d, *J* = 8.9 Hz, Ar), 6.84 (2H, d, *J* = 8.8 Hz, Ar), 6.45 (1H, d, *J* = 15.9 Hz, 4-H), 6.05 (1H, dt, *J* = 15.8, 7.2 Hz, 3-H), 3.80 (3H, s, OMe), 3.75 (2H, t, *J* = 7.5 Hz, 1-H_2), 2.43-2.50 (2H, m, 2-H_2), 1.47 (1H, br s, OH). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.0 (C Ar), 132.3 (C-4), 130.1 (C Ar), 127.2 (2 x CH Ar), 124.0 (C-3), 114.0 (2 x CH Ar), 62.1 (C-1), 55.3 (OMe), 36.4 (C-2). **HRMS** (Cl): calculated for $C_{11}H_{15}O_2$ $[M+H]^+$ requires *m/z* 179.1072, found *m/z* 179.1067.

5.4.3 2,4-Dimethyl-1-vinylbenzene (192)



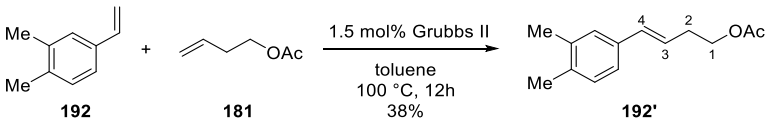
191 **192**

Methyltriphenylphosphonium bromide (6.400 g, 17.92 mmol), NaH (60%, 1.613 g, 67.20 mmol), 3,4-dimethoxybenzaldehyde **191** (2.000 g, 14.91 mmol) and THF (74.5 mL) were subjected to the general procedure **A** (FCC: pentane) to yield **192** as a colorless oil (2.000 g, 99%). Spectroscopic properties matched those previously reported.[8]

Data for **192**: R_f 0.50 (pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.23 (1H, s, Ar), 7.19 (1H, d, *J* = 7.8 Hz, Ar), 7.12 (1H, d, *J* = 7.7 Hz, Ar), 6.70 (1H, dd, *J* = 17.6, 10.9 Hz, 2-H), 5.73 (1H, d, *J* = 17.6 Hz, 1-H_A), 5.20 (1H, d, *J* = 10.8 Hz, 1-H_B), 2.30 (3H, s, Me), 2.29 (3H, s, Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 136.9 (C-2), 136.7 (C Ar), 136.4 (C Ar), 135.4 (C Ar), 129.9 (CH Ar), 127.6 (CH Ar), 123.8 (CH Ar), 112.7 (C-1), 19.9 (Me), 19.7 (Me). **HRMS**

(ESI): calculated for $C_{10}H_{13}$ $[M+H]^+$ requires *m/z* 133.10118, found *m/z* 133.10120.

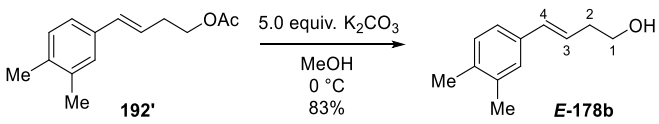
5.4.4 (3*E*)-4-(3,4-Dimethylphenyl)but-3-en-1-yl acetate (192')



Styrene **192** (0.513 g, 3.89 mmol), but-3-en-1-yl acetate **181** (0.885 g, 7.77 mmol) and Grubbs II (49.0 mg, 0.0578 mmol) were subjected to the general procedure **B** except conducting the reaction in toluene at 100°C (FCC: 10% Et_2O - pentane) to yield **192'** as a colorless oil (0.351 g, 38%).

Data for **192'**: **R_f** 0.3 (20% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.15 (1H, s, Ar), 7.12-7.06 (2H, m, Ar), 6.43 (1H, d, *J* = 15.8 Hz, 4-H), 6.12 (1H, dt, *J* = 16.0, 7.0 Hz, 3-H), 4.19 (2H, t, *J* = 6.7 Hz, 1-H_2), 2.54 (2H, qd, *J* = 6.9, 1.4 Hz, 2-H_2), 2.26 (3H, s, Me), 2.25 (3H, s, Me), 2.07 (3H, s, Ac Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 171.2 (C=O), 136.7 (C Ar), 135.8 (C Ar), 135.0 (C Ar), 132.4 (C-4), 129.9 (C-H Ar), 127.4 (C-H Ar), 124.4 (C-3), 123.6 (C-H Ar), 63.9 (C-1), 32.5 (C-2), 21.1 (Ac Me), 19.9 (Me), 19.6 (Me). **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max} : 3656, 2980, 1736, 1232, 1033, 965 cm^{-1}.

5.4.5 (3*E*)-4-(3,4-Dimethylphenyl)but-3-en-1-ol (*E*-178b)

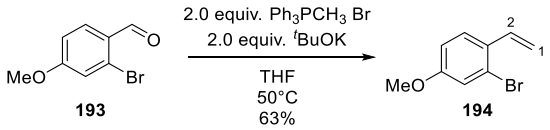


Acetate **192'** (0.351 g, 1.50 mmol) and K_2CO_3 (1.039 g, 7.529 mmol) were subjected to the general procedure **C** (FCC: gradient elution: 40% → 50% Et_2O - pentane)

to yield ***E*-178b** as a yellow oil (0.251 g, 83%).

Data for ***E*-178b**: **R_f** 0.45 (80 % Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.15 (1H, d, *J* = 1.7 Hz, Ar), 7.03-7.12 (2H, m, Ar), 6.45 (1H, d, *J* = 15.9 Hz, 4-H), 6.14 (1H, dt, *J* = 15.8, 7.2 Hz, 3-H), 3.74 (2H, t, *J* = 6.3 Hz, 1-H_2), 2.47 (2H, qd, *J* = 6.3, 1.4 Hz, 2-H_2), 2.25 (3H, s, Me), 2.24 (3H, s, Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 136.7 (C Ar), 135.9 (C Ar), 135.0 (C Ar), 132.9 (C-4), 129.9 (CH Ar), 127.5 (CH Ar), 126.1 (C-3), 123.7 (CH Ar), 62.2 (C-1), 36.6 (C-2), 19.9 (Me), 19.6 (Me). **HRMS** (EI): calculated for $C_{12}H_{16}O$ $[M]^+$ requires *m/z* 176.1196, found *m/z* 176.1194. **IR** (film) ν_{max} : 3335, 2980, 1382, 1154, 1045, 965 cm^{-1}.

5.4.6 2-Bromo-4-methoxy-1-vinylbenzene (194)

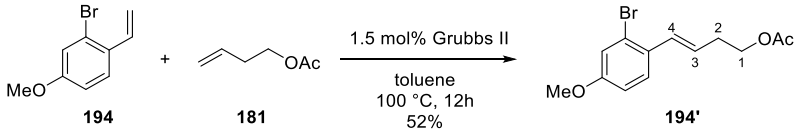


Methyltriphenylphosphonium bromide (3.800 g, 10.64 mmol), ^{t}BuOK (1.200 g, 10.71 mmol), solution of 2-bromo-4-methoxybenzaldehyde **193** (1.150 g, 5.333 mmol in 2.3 mL THF) and THF (4.6 mL) were subjected to the general procedure **A** except the reaction was heated to 50°C after the KO^{t}Bu was added and before adding the aldehyde (FCC: pentane) to yield **194** as a colorless oil (0.720 g, 63%). Spectroscopic properties matched those previously reported.[9]

Data for **194**: **R_f** 0.50 (5% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.48 (1H, d, *J* = 8.7 Hz, Ar), 7.09 (1H, d, *J* = 2.4 Hz, Ar), 6.99 (1H, dd, *J* = 17.4, 10.9 Hz, 2-H), 6.85 (1H, dd, *J* = 8.7, 2.5 Hz, Ar), 5.59 (1H, d, *J* = 17.4 Hz, 1-H_A), 5.25 (1H, d, *J* = 10.9 Hz, 1-H_B), 3.80

(3H, s, OMe). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.7 (C Ar), 135.2 (C-2), 130.2 (C Ar), 127.3 (CH Ar), 124.1 (C Ar), 117.6 (CH Ar), 114.7 (C-1), 114.2 (CH Ar), 55.7 (OMe). **HRMS** (ESI): calculated for $C_9H_{10}BrO$ $[M+H]^+$ requires *m/z* 212.9910, found *m/z* 212.9909.

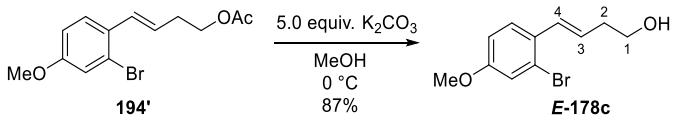
5.4.7 (3*E*)-4-(2-Bromo-4-methoxyphenyl)but-3-en-1-yl acetate (194')



Styrene **194** (0.648 g, 3.04 mmol), but-3-en-1-yl acetate **181** (0.693 g, 6.08 mmol) and Grubbs II (39.0 mg, 0.0460 mmol) were subjected to the general procedure **B** except conducting the reaction in toluene at 100°C (FCC: 5% Et_2O - pentane) to yield **194'** as a colorless oil (0.471 g, 52%).

Data for **194'**: **R_f** 0.3 (30% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.40 (1H, d, *J* = 8.7 Hz, Ar), 7.07 (1H, d, *J* = 2.7 Hz, Ar), 6.82 (1H, dd, *J* = 8.7, 2.7 Hz, Ar), 6.72 (1H, d, *J* = 15.8 Hz, 4-H), 5.99 (1H, dt, *J* = 15.7, 7.0 Hz, 3-H), 4.19 (2H, t, *J* = 6.6 Hz, 1-H_2), 3.79 (3H, s, OMe), 2.56 (2H, qd, *J* = 6.8, 1.4 Hz, 2-H_2), 2.06 (3H, s, Ac Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 171.2 (C=O), 159.2 (C Ar), 130.7 (C-4), 129.7 (C Ar), 127.4 (C-H Ar), 126.7 (C-3), 123.5 (C Ar), 117.5 (C-H Ar), 114.2 (C-H Ar), 63.6 (C-1), 55.6 (OMe), 32.4 (C-2), 21.0 (Ac Me). **HRMS** (CI): calculated for $C_{13}H_{15}BrO_3Na$ $[M+Na]^+$ requires *m/z* 321.00968, found *m/z* 321.00946. **IR** (film) ν_{max} : 2980, 2360, 1734, 1600, 1232, 1026 cm^{-1}.

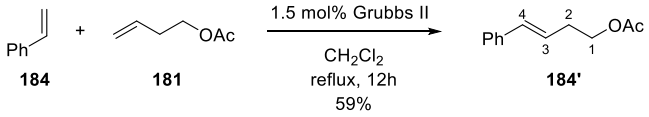
5.4.8 (3*E*)-4-(2-Bromo-4-methoxyphenyl)but-3-en-1-ol (*E*-178c)



Acetate **194'** (0.396 g, 1.32 mmol) and K_2CO_3 (0.913 g, 6.62 mmol) were subjected to the general procedure C (FCC: gradient elution: 30% → 100% Et_2O - pentane) to yield ***E*-178c** as a yellow oil (0.296 g, 87%).

Data for ***E*-178c**: **R_f** 0.30 (80 % Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.42 (1H, d, *J* = 8.7 Hz, Ar), 7.07 (1H, d, *J* = 2.6 Hz, Ar), 6.82 (1H, dd, *J* = 8.7, 2.6 Hz, Ar), 6.75 (1H, d, *J* = 15.8 Hz, 4-H), 6.03 (1H, dt, *J* = 16.0, 7.1 Hz, 3-H), 3.78 (3H, s, OMe), 3.76 (2H, t, *J* = 6.7 Hz, 1-H_2), 2.51 (2H, dq, *J* = 6.3, 1.3 Hz, 2-H_2), 1.59 (1H, br s, OH). **^{13}C NMR (100 MHz, $CDCl_3$) δ**159.3 (C Ar), 131.1 (C-4), 129.8 (C Ar), 127.6 (C-3), 127.5 (CH Ar), 123.6 (C Ar), 117.6 (CH Ar), 114.3 (CH Ar), 62.1 (C-1), 55.7 (OMe), 36.5 (C-2). **HRMS** (Cl): calculated for $C_{11}H_{14}O_2Br$ $[M+H]^+$ requires *m/z* 257.01717, found *m/z* 257.01703. **IR** (film) ν_{max} : 3341, 2980, 1599, 1487, 1281, 1025 cm^{-1}.

5.4.9 (3*E*)-4-Phenylbut-3-en-1-yl acetate (184')

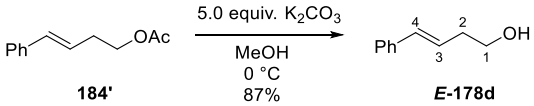


Styrene **184** (0.456 g, 4.38 mmol), but-3-en-1-yl acetate **181** (1.000 g, 8.764 mmol) and Grubbs II (56.0 mg, 0.0660 mmol) were subjected to the general procedure **B** (FCC: gradient elution: 5% → 8% Et_2O - pentane) to yield **184'** as a white solid (0.494 g, 59%). Spectroscopic properties matched those previously reported.[10]

Data for **184'**: **R_f** 0.50 (20% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ**

7.28-7.38 (4H, m, Ar), 7.19-7.25 (1H, m, Ar), 6.48 (1H, d, *J* = 15.9 Hz, 4-H), 6.18 (1H, dt, *J* = 15.9, 7.0 Hz, 3-H), 4.20 (2H, t, *J* = 6.7 Hz, 1-H_2), 2.55 (2H, qd, *J* = 6.8, 1.5 Hz, 2-H_2), 2.06 (3H, s, Ac Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 171.1 (C=O), 137.3 (C Ar), 132.4 (C-4), 128.6 (2 x CH Ar), 127.3 (CH Ar), 126.1 (2 x CH Ar), 125.6 (C-3), 63.8 (C-1), 32.4 (C-2), 21.0 (Ac Me). **HRMS** (ESI): calculated for $C_{12}H_{14}O_2Na$ $[M+Na]^+$ requires *m/z* 213.0886, found *m/z* 213.0888.

5.4.10 (3*E*)-4-Phenylbut-3-en-1-ol (*E*-178d)

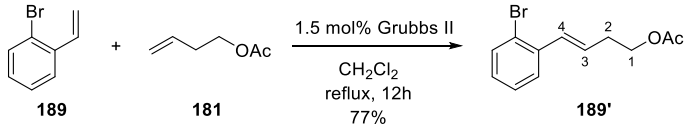


184' **E-178d**

Acetate **184'** (0.541 g, 2.85 mmol) and K_2CO_3 (1.970 g, 14.28 mmol) were subjected to the general procedure C (FCC: gradient elution: 40% → 60% Et_2O - pentane) to yield ***E*-178d** as a colorless oil (0.369 g, 87%). Spectroscopic properties matched those previously reported.[11]

Data for ***E*-178d**: **R_f** 0.4 (75% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.28-7.39 (4H, m, Ar), 7.19-7.25 (1H, m, Ar), 6.51 (1H, d, *J* = 15.8 Hz, 4-H), 6.21 (1H, dt, *J* = 15.9, 7.1 Hz, 3-H), 3.73-3.81 (2H, m, 1-H_2), 2.47-2.53 (2H, m, 2-H_2), 1.47 (1H, br s, OH). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 137.2 (C Ar), 132.9 (C-4), 128.6 (2 x CH Ar), 127.3 (CH Ar), 126.3 (C-3), 126.1 (2 x CH Ar), 62.0 (C-1), 36.4 (C-2). **HRMS** (CI): calculated for $C_{10}H_{17}ON$ $[M+NH_4]^+$ requires *m/z* 166.1232, found *m/z* 166.1227.

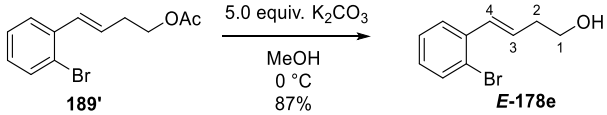
5.4.11 (3*E*)-4-(2-Bromophenyl)but-3-en-1-yl acetate (189')



2-Bromostyrene **189** (1.370 g, 7.527 mmol), but-3-en-1-yl acetate **181** (0.855 g, 7.49 mmol) and Grubbs II (48.0 mg, 0.0566 mmol) were subjected to the general procedure **B** (FCC: gradient elution: 4% → 5% Et_2O - pentane) to yield **189'** as a colorless oil (1.550 g, 77%).

Data for **189'**: **R_f** 0.40 (20% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.53 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.48 (1H, dd, *J* = 7.8, 1.7 Hz, Ar), 7.22-7.28 (1H, m, Ar), 7.05-7.12 (1H, m, Ar), 6.80 (1H, d, *J* = 15.8 Hz, 4-H), 6.11 (1H, dt, *J* = 15.8, 7.0 Hz, 3-H), 4.22 (2H, t, *J* = 6.6 Hz, 1-H_2), 2.59 (2H, qd, *J* = 6.7, 1.5 Hz, 2-H_2), 2.07 (3H, s, Ac Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 171.2 (C=O), 137.3 (C Ar), 133.0 (CH Ar), 131.5 (C-4), 128.9 (C-3), 128.7 (CH Ar), 127.6 (CH Ar), 127.1 (CH Ar), 123.4 (C Ar), 63.6 (C-1), 32.6 (C-2), 21.1 (Ac Me). **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max} : 2963, 1735, 1472, 1233, 1041, 753 cm^{-1}.

5.4.12 (3*E*)-4-(2-Bromophenyl)but-3-en-1-ol (*E*-178e)

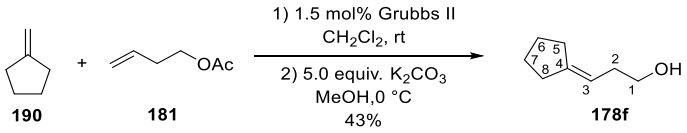


Acetate **189'** (1.550 g, 5.784 mmol) and K_2CO_3 (4.000 g, 28.99 mmol) were subjected to the general procedure C (FCC: gradient elution: 20% → 30% Et_2O - pentane) to yield ***E*-178e** as a colorless oil (1.138 g, 87%). Spectroscopic properties matched those

previously reported.[22]

Data for ***E*-178e**: $\mathbf{R_f}$ 0.4 (80% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.53 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.50 (1H, dd, *J* = 7.8, 1.7 Hz, Ar), 7.22-7.28 (1H, m, Ar), 7.05-7.10 (1H, m, Ar), 6.83 (1H, d, *J* = 15.8 Hz, 4-H), 6.16 (1H, dt, *J* = 15.8, 7.1 Hz, 3-H), 3.79 (1H, t, *J* = 6.3 Hz, 1-H_2), 2.53 (1H, dtd, *J* = 7.7, 6.3, 1.5 Hz, 2-H_2), 1.57 (1H, br s, OH). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 137.3 (C Ar), 133.0 (CH Ar), 131.7 (C-4), 129.8 (C-3), 128.7 (CH Ar), 127.6 (CH Ar), 127.1 (CH Ar), 123.4 (C Ar), 62.1 (C-1), 36.6 (C-2). **HRMS** (CI): calculated for $C_{10}H_{10}OBr$ $[M-H]^+$ requires *m/z* 224.99113, found *m/z* 224.99095.

5.4.13 3-Cyclopentylidenepropan-1-ol (178f)

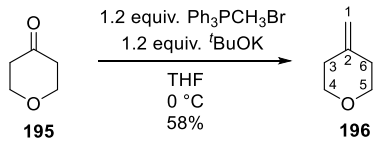


To a solution of but-3-en-1-yl acetate **181** (0.246 g, 2.19 mmol) in methylenecyclopentane **190** (0.898 g, 11.0 mmol) at room temperature was added Grubbs II (26.0 mg, 0.0307 mmol). The mixture was stirred for 72 hours and concentrated under reduced pressure. To the crude was then added K_2CO_3 (1.600 g, 11.59 mmol) in MeOH (12 mL) at 0 °C. The reaction was monitored by TLC until completion. The mixture was filtered and the solvent was evaporated under reduced pressure, that was purified (FCC: gradient elution: 20% → 30% Et_2O - pentane) to afford **178f** as a colorless oil (0.120 g, 43%).

Data for **178f**: $\mathbf{R_f}$ 0.4 (50% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 5.20-5.27 (1H, m, 3-H), 3.63 (1H, t, *J* = 6.3 Hz, 1-H_2), 2.17-2.31 (6H, m, 2-H_2, 5-H_2 and 8-H_2),

1.56-1.72 (4H, m, 6-H_2 and 7-H_2), 1.49 (1H, br s, OH). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 147.3 (C-4), 115.5 (C-3), 62.6 (C-1), 33.9 and 33.3 (C-5 and C-8), 29.0 (C-2), 26.52 and 26.45 (C-6 and C-7). **HRMS** (ESI): calculated for $C_8H_{15}O$ $[M+H]^+$ requires *m/z* 127.11174, found *m/z* 127.11185. **IR** (film) ν_{max} : 3332, 2980, 2887, 1432, 1251, 1047 cm^{-1}.

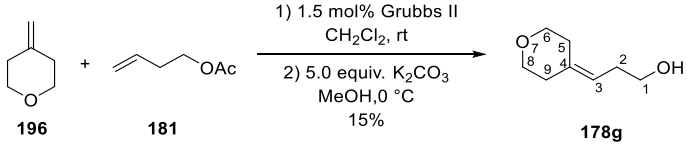
5.4.14 Methylenecyclohexane (196)



Methyltriphenylphosphonium bromide (17.000 g, 47.592 mmol), ^{t}BuOK (5.370 g, 48.00 mmol), 4-oxotetrahydropyran **195** (4.000 g, 40.00 mmol) and Et_2O (130 mL) were subjected to the general procedure **A** (FCC: gradient elution: 3% → 5% Et_2O - pentane) to yield **196** as a colorless oil (2.270 g, 58%). Spectroscopic properties matched those previously reported.[12]

Data for **196**: **R_f** 0.40 (15% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 4.71 (2H, s, 1-H_2), 3.68 (4H, t, *J* = 5.5 Hz, 4-H_2 and 5-H_2), 2.25 (4H, t, *J* = 5.5 Hz, 3-H_2 and 6-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 144.7 (C-2), 108.4 (C-1), 69.5 (C-4 and C-5), 35.7 (C-3 and C-6). **HRMS** (EI): calculated for $C_6H_{10}O$ $[M]^+$ requires *m/z* 98.0726, found *m/z* 98.0729.

5.4.15 3-(Tetrahydro-4*H*-pyran-4-ylidene)propan-1-ol (178g)

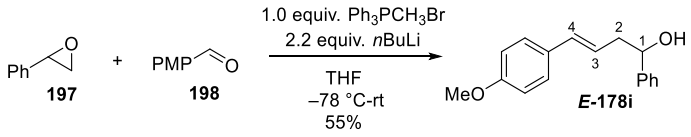


To a solution of but-3-en-1-yl acetate **181** (0.182 g, 1.53 mmol), alkene **196**

(0.300 g, 3.06 mmol) in CH_2Cl_2 (8 mL) at room temperature was added Grubbs II (20.0 mg, 0.0236 mmol). The mixture was stirred for 72 hours and concentrated under reduced pressure. To the crude was then added K_2CO_3 (1.060 g, 7.681 mmol) in MeOH (7.7 mL) at 0°C. The reaction was monitored by TLC until completion. The mixture was filtered and the solvent was evaporated under reduced pressure, that was purified by chromatography on silica gel (FCC: gradient elution: 50% → 100% Et_2O - pentane) to afford **178g** as a colorless oil (0.033 g, 15%). Spectroscopic properties matched those previously reported.[13]

Data for **178g**: **R_f** 0.30 (100% Et_2O). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 5.20 (1H, t, *J* = 7.5 Hz, 3-H), 3.59-3.73 (6H, m, 1-H_2, 6-H_2 and 8-H_2), 2.19-2.35 (6H, m, 2-H_2, 5-H_2 and 9-H_2), 1.62 (1H, br s, OH). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 137.7 (C-4), 119.9 (C-3), 69.8 and 69.0 (C-6 and C-8), 62.6 (C-1), 37.1 and 30.6 (C-5 and C-9), 30.0 (C-2). **HRMS**: stable ion was not found in ESI, EI and CI.

5.4.16 (±)-(E)-4-(4-methoxyphenyl)-1-phenylbut-3-en-1-ol (*E*-178i)



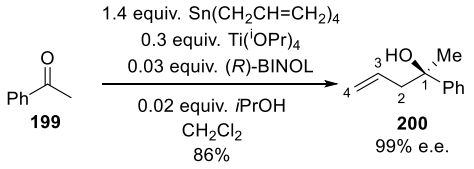
In a three-necked round-bottomed flask methyltriphenylphosphonium bromide (3.580 g, 10.00 mmol) were dissolved in 20 mL of dry THF. Ar gas was bubbled in this solution for about 20 minutes while maintaining the temperature at –78 °C. The reaction mixture was kept under Ar for another 15 minutes in order to ensure an inert atmosphere. The whole reaction assembly was kept airtight. To this solution of *n*-BuLi

(10M, 11.0 mL, 11.0 mmol) was added carefully dropwise in a period of 15 minutes. A yellow solution was obtained. The stirring was continued for another 10 minutes at –78 °C and then the temperature was slowly raised to 23 °C and the stirring was continued for 2.5 hours. The yellow solution turned into orange suspension. The resulting suspension was cooled to 0 °C and to this was added styrene epoxide **197** (1.320 g, 11.00 mmol). The reaction mixture was left overnight at 23 °C. The orange suspension turned to a yellow suspension. To this resulting reaction mixture, which was cooled to –78 °C, *n*-BuLi (10M, 11.0 mL, 11.0 mmol) was added dropwise *via* syringe pump. Let the temperature slowly raised to 23 °C and then the reaction mixture was stirred for 2.5 hours. This gave orange suspension which was cooled to –78 °C. To this cooled suspension was added 4-methoxybenzaldehyde **198** in dry THF (10.00 mmol, 1.360 g dissolved in 7.5 mL of THF). The reaction was kept stirring for 6 hours at 23 °C. Then the reaction mixture was worked up by adding it to crushed ice in a beaker. The resulting mixture was extracted with Et_2O, dried over $MgSO_4$ and the solvent was removed under reduced pressure. FCC (30% Et_2O - pentane) afforded alcohol ***E*-178i** as white solid (1.397 g, 55%). Spectroscopic properties matched those previously reported.[14]

Data for ***E*-178i**: $\mathbf{R_f}$ 0.5 (60% Et_2O - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 7.43-7.34 (4H, m, Ar), 7.32-7.25 (3H, m, Ar), 6.84 (2H, d, *J* = 8.7 Hz, Ar), 6.46 (1H, d, *J* = 15.9 Hz, 4-H), 6.06 (1H, dt, *J* = 15.8, 6.8 Hz, 3-H), 4.83-4.77 (1H, m, 1-H), 3.80 (3H, s, OMe), 2.69-2.58 (2H, m, 2-H_2), 2.10 (1H, br s, OH). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 159.2 (C Ar), 144.1 (C Ar), 133.1 (C-4), 130.1 (C Ar), 128.6 (2 x C-H Ar), 127.7 (C-H Ar), 127.4 (2 x

C-H Ar), 125.9 (2 x C-H Ar), 123.7 (C-3), 114.1 (2 x C-H Ar), 73.9 (C-1), 55.4 (OMe), 43.3 (C-2).

5.4.17 (+)-(*R*)-2-Phenylpent-4-en-2-ol (200)

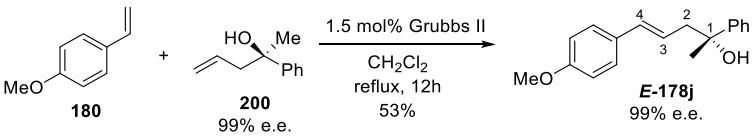


To a solution of (*R*)-BINOL (362 mg, 1.27 mmol) in CH_2Cl_2 (9.5 mL) were sequentially added $Ti(O^iPr)_4$ (0.37 mL, 1.27 mmol), ^{i}PrOH (6.5 mL, 0.085 mol), and tetraallylstannane (1.5 mL, 6.3 mmol) and the mixture was stirred at room temperature for 1 day. Then acetophenone **199** (0.49 mL, 4.16 mmol) was added and the mixture was stirred at room temperature for a further day. The reaction mixture was diluted with aqueous NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in hexanes, filtered through Celite, and evaporated under reduced pressure to afford the crude oil. FCC (gradient elution: 10% → 20% Et_2O - pentane) afforded **200** as a colorless liquid (583 mg, 86%). Spectroscopic properties matched those previously reported.[15]

Data for **200**: $\mathbf{R_f}$ 0.4 (30% Et_2O - pentane). $[\alpha]_D$: +19.3 (c 0.39 CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 7.47-7.42 (2H, m, Ar), 7.37-7.31 (2H, m, Ar), 7.27-7.21 (1H, m, Ar), 5.63 (1H, dddd, *J* = 16.8, 10.1, 8.3, 6.4 Hz, 2-H), 5.18-5.10 (2H, m, 1-H_2), 2.70 (1H, dd, *J* = 13.7, 6.5 Hz, 3-H_A), 2.51 (1H, dd, *J* = 13.7, 8.3 Hz, 3-H_B), 2.05 (1H, s, OH), 1.55 (3H, s, Me).

^{13}C NMR (100 MHz, $CDCl_3$) **δ** 147.8 (C Ar), 133.8 (C-2), 128.3(2 x C-H Ar), 126.8 (C-H Ar), 124.9 (2 x C-H Ar), 119.6 (C-1), 73.7 (C-4), 48.6 (C-3), 30.1 (Me).

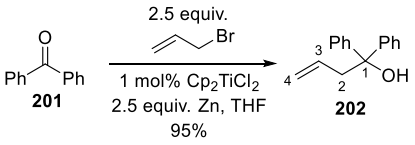
5.4.18 (2*S*,4*E*)-5-(4-Methoxyphenyl)-2-phenylpent-4-en-2-ol (*E*-178j)



4-Methoxystyrene **180** (150 mg, 1.18 mmol), (+)-(*R*)-2-phenylpent-4-en-2-ol **200** (384 mg, 2.24 mmol) and Grubbs II (14 mg, 0.017 mmol) were subjected to general procedure **B** (gradient elution: 10% → 15% Et_2O - pentane) to yield ***E*-178j** as a brown oil (169 mg, 53%).

Data for ***E*-178j**: $\mathbf{R_f}$ 0.4 (60% Et_2O - pentane). $[\alpha]_D$: +15.0 (c 0.39 CH_2Cl_2). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 7.49-7.45 (2H, m, Ar), 7.39-7.33 (2H, m, Ar), 7.29-7.24 (1H, m, Ar), 7.22 (2H, d, *J* = 8.7 Hz, Ar), 6.81 (2H, d, *J* = 8.7 Hz, Ar), 6.43 (1H, d, *J* = 15.7 Hz, 1-H), 5.87 (1H, ddd, *J* = 15.8, 8.5, 6.5 Hz, 2-H), 3.79 (3H, s, OMe), 2.81 (1H, ddd, *J* = 13.8, 6.6, 1.5 Hz, 3-H_A), 2.63 (1H, ddd, *J* = 13.8, 8.5, 1.1 Hz, 3-H_B), 2.10 (1H, s, OH), 1.59 (3H, s, Me). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 159.2 (C Ar), 147.9 (C Ar), 134.1 (C-1), 130.0 (C Ar), 128.4 (2 x C-H Ar), 127.5 (2 x C-H Ar), 126.8 (C-H Ar), 124.9 (2 x C-H Ar), 122.8 (C-2), 114.1 (2 x C-H Ar), 74.2 (C-4), 55.4 (OMe), 47.9 (C-3), 30.1 (Me). **HRMS** (ESI): calculated for $C_{18}H_{21}O_2$ $[M+H]^+$ requires *m/z* 269.1542, found *m/z* 269.1537. **IR** (film) ν_{max}: 3445, 2980, 1606, 1509, 1244, 1030 cm^{-1}.

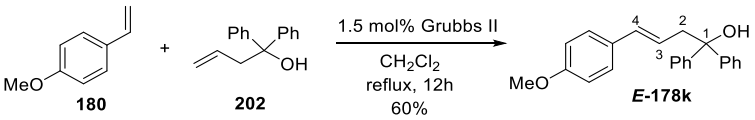
5.4.19 1,1-Diphenylbut-3-en-1-ol (202)



A clean, oven-dried 4 dram screw cap vial was charged with Cp_2TiCl_2 (7.5 mg, 0.030 mol) and zinc dust (488.0 mg, 7.746 mmol) under an atmosphere of Ar at room temperature, THF (15 mL) was added via syringe and the reaction stirred for 10 min or until the solution had turned from red to green. A solution of benzophenone **201** (546.0 mg, 3.000 mmol) and allyl bromide (0.65 mL, 7.5 mmol) in THF (15 mL) was then added via syringe. The reaction was stirred for 20 min or until all starting material was consumed as monitored by TLC. The mixture was diluted with saturated aqueous NH_4Cl and Et_2O and the layers were separated. The aqueous layer was extracted with Et_2O three times, and the combined organic fractions were washed with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated under reduced pressure. FCC (gradient elution: 10% → 20% Et_2O - pentane) afforded the **202** as a white solid (640 mg, 95%). Spectroscopic properties matched those previously reported.[16]

Data for **202**: $\mathbf{R_f}$ 0.45 (30% Et_2O - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 7.29-7.25 (4H, m, Ar), 7.18-7.09 (4H, m, Ar), 7.06-7.01 (2H, m, Ar), 5.48 (1H, ddt, *J* = 17.3, 10.1, 7.2 Hz, 2-H), 5.09-4.97 (2H, m, 1-H_2), 2.90 (2H, d, *J* = 7.2 Hz, 3-H_2), 2.37 (1H, s, OH). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 146.6 (2 x C Ar), 133.6 (C-2), 128.3(4 x C-H Ar), 127.0 (2 x C-H Ar), 126.1 (4 x C-H Ar), 120.7 (C-1), 77.0 (C-4), 46.9 (C-3).

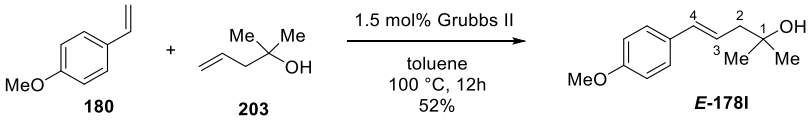
5.4.20 (*E*)-4-(4-Methoxyphenyl)-1,1-diphenylbut-3-en-1-ol (*E*-178k)



4-Methoxystyrene **180** (100 mg, 0.75 mmol), alcohol **202** (334 mg, 1.5 mmol) and Grubbs II (9.5 mg, 0.011 mmol) were subjected to general procedure **B** using CH_2Cl_2 (FCC: 5% Et_2O - pentane) to yield ***E*-178k** as a white solid (162 mg, 66%).

Data for ***E*-178k**: $\mathbf{R_f}$ 0.3 (30% Et_2O - pentane). **M.p.**: 70 °C (10% EtOAc - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 7.51-7.47 (4H, m, Ar), 7.37-7.31 (4H, m, Ar), 7.25 (2H, d, *J* = 7.0 Hz, Ar), 7.21 (2H, d, *J* = 8.8 Hz, Ar), 6.81 (2H, d, *J* = 8.7 Hz, Ar), 6.54 (1H, d, *J* = 15.8 Hz, 1-H), 5.89 (1H, dt, *J* = 15.8 Hz, 7.5 Hz, 2-H), 3.79 (3H, s, OMe), 3.21 (2H, dd, *J* = 7.3, 1.2 Hz, 3-H_2), 2.65 (1H, s, OH) . **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 159.3 (C Ar), 146.7 (2 x C Ar), 135.1 (C-1), 129.8 (C Ar), 128.3 (4 x C-H Ar), 127.6 (2 x C-H Ar), 127.0 (2 x C-H Ar), 126.1 (4 x C-H Ar), 122.2 (C-2), 114.0 (2 x C-H Ar), 77.4 (C-4), 55.4 (OMe), 46.2 (C-3). **HRMS** (ESI): calculated for $C_{23}H_{23}O_2$ $[M+H]^+$ requires *m/z* 331.1698, found *m/z* 331.1688. **IR** (film) ν_{max}: 3548, 2980, 2361, 1491, 1176, 841 cm^{-1}.

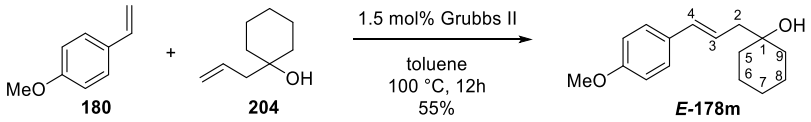
5.4.21 (3*E*)-4-(4-Methoxyphenyl)-1,1-dimethylbut-3-en-1-ol (*E*-178l)



4-Methoxystyrene **180** (0.937 g, 6.99 mmol), 2-methylpent-4-en-2-ol **203** (0.350 g, 3.50 mmol) and Grubbs II (45.0 mg, 0.0531 mmol) were subjected to the general procedure **B** except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 20% → 50% Et_2O - pentane) to yield ***E*-178l** as a yellow oil (0.376 g, 52%).

Data for ***E*-178l**: **R_f** 0.40 (80% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.31 (2H, d, *J* = 8.3 Hz, Ar), 6.85 (2H, d, *J* = 8.3 Hz, Ar), 6.41 (1H, d, *J* = 15.8 Hz, 4-H), 6.41 (1H, dt, *J* = 15.8, 7.6 Hz, 3-H), 3.81 (3H, s, OMe), 2.36 (2H, d, *J* = 7.6 Hz, 2-H_2), 1.63 (1H, br s, OH), 1.27 (6H, s, 2 x Me).**^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.1 (C Ar), 133.3 (C-4), 130.3 (C Ar), 127.4 (2 x CH Ar), 123.5 (C-3), 114.1 (2 x CH Ar), 71.0 (C-1), 55.5 (OMe), 47.5 (C-2), 29.4 (2 x Me) . **HRMS** (ESI): calculated for $C_{13}H_{18}O_2$ $[M]^+$ requires *m/z* 206.1301, found *m/z* 206.1306. **IR** (film) ν_{max} : 3385, 2970, 1576, 1244, 1174, 1033 cm^{-1}.

5.4.22 (3*E*)-1-[3-(4-Methoxyphenyl)allyl]cyclohexan-1-ol (*E*-178m)

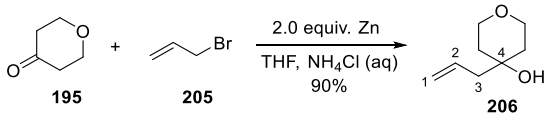


4-Methoxystyrene **180** (1.900 g, 14.17 mmol), 1-allylcyclohexanol **204** (1.000 g, 7.138 mmol) and Grubbs II (90.0 mg, 0.106 mmol) were subjected to the general procedure **B** except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 12% → 20% Et_2O - pentane) to yield ***E*-178m** as a yellow oil (0.964 g, 55%).

Data for ***E*-178m**: **R_f** 0.3 (50% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.30 (2H, d, *J* = 8.7 Hz, Ar), 6.84 (2H, d, *J* = 8.7 Hz, Ar), 6.40 (1H, d, *J* = 15.8 Hz, 4-H), 6.15 (1H, dt, *J* = 15.5, 7.6 Hz, 3-H), 3.80 (3H, s, OMe), 2.34 (2H, dd, *J* = 7.6, 1.2 Hz, 2-H_2), 1.42-1.67 (9H, m, 5-H_2, 6-H_2, 8-H_2, 9-H_2 and 7-H_A), 1.22-1.36 (1H, m, 7-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.5 (C Ar), 133.2 (C-4), 130.3 (C Ar), 127.4 (2 x CH Ar), 123.1 (C-3), 114.0 (2 x CH Ar), 71.7 (C-1), 55.4 (OMe), 46.0 (C-2), 37.6 (2 x CH_2 cyclohexenyl), 25.9 (CH_2 cyclohexenyl), 22.3 (2 x CH_2 cyclohexenyl). **HRMS** (CI): calculated for $C_{16}H_{22}O_2Na$

$[M+Na]^+$ requires *m/z* 269.15120, found *m/z* 269.15106. **IR** (film) ν_{max} : 3426, 2928, 1608, 1509, 1244, 967 cm^{-1}

5.4.23 4-Allyltetrahydro-2*H*-pyran-4-ol (206)

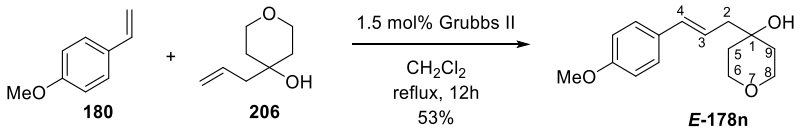


Zinc dust (3.900 g, 61.03 mmol) was slowly added under vigorous stirring to a mixture of tetrahydro-4*H*-pyran-4-one **195** (3.000 g, 30.00 mmol) and allyl bromide **205** (9.000 g, 75.00 mmol) in 10 mL THF, and 30 mL of a saturated aqueous solution of ammonium chloride in such a way that the temperature did not exceed 40°C. The mixture was then stirred for 10 hours at room temperature, 100 ml of 10% aqueous sulfuric acid was added and the mixture was filtered. The organic phase was separated, and the aqueous phase was saturated with sodium chloride and extracted with diethyl ether. The extracts were combined with the organic phase and dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified (FCC: gradient elution: 15% → 25% Et_2O - pentane) to yield **206** as a colorless oil (3.830 g, 90%). Spectroscopic properties matched those previously reported.[17]

Data for **206**: $\mathbf{R_f}$ 0.30 (60% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 5.86 (1H, ddt, *J* = 17.6, 10.2, 7.5 Hz, 2-H), 5.10-5.22 (2H, m, 1-H_2), 3.68-3.78 (4H, m, 2 x CH_2 tetrahydropyranyl), 2.23 (1H, d, *J* = 7.5 Hz, 3-H_2), 1.69 (2H, ddd, *J* = 13.8, 10.4, 5.8 Hz, CH_2 tetrahydropyranyl), 1.60 (1H, br s, OH), 1.42-1.51 (2H, m, CH_2 tetrahydropyranyl).

^{13}C NMR (100 MHz, $CDCl_3$) δ 132.6 (C-2), 119.8 (C-1), 68.4 (C-4), 63.9 (2 x CH_2 tetrahydropyranyl), 47.6 (C-3), 37.7 (2 x CH_2 tetrahydropyranyl).

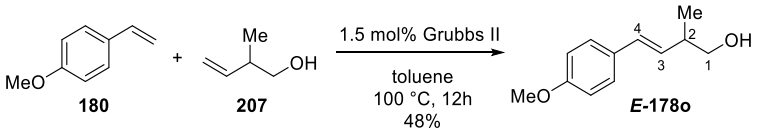
5.4.24 (3*E*)-1-[3-(4-Methoxyphenyl)allyl]tetrahydro-2*H*-pyran-1-ol (*E*-178n)



4-Methoxystyrene **180** (0.734 g, 5.48 mmol), alcohol **206** (0.389 g, 2.73 mmol) and Grubbs II (35.0 mg, 0.0413 mmol) were subjected to the general procedure **B** (FCC: gradient elution: 15% → 50% Et_2O - pentane) to yield ***E*-178n** as a yellow oil (0.365 g, 53%).

Data for ***E*-178n**: **R_f** 0.30 (80% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.30 (2H, d, *J* = 8.7 Hz, Ar), 6.85 (2H, d, *J* = 8.7 Hz, Ar), 6.44 (1H, d, *J* = 15.8 Hz, 4-H), 6.12 (1H, dt, *J* = 15.5, 7.6 Hz, 3-H), 3.80 (3H, s, OMe), 3.74-3.80 (4H, m, 6-H_2 and 8-H_2), 2.37 (2H, dd, *J* = 7.7, 1.3 Hz, 2-H_2), 1.70-1.81 and 1.50-1.56 (4H, m, 5-H_2 and 9-H_2). .**^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.3 (C Ar), 134.3 (C-4), 130.0 (C Ar), 127.5 (2 x CH Ar), 131.6 (C-3), 114.1 (2 x CH Ar), 69.0 (C-1), 64.0 (C-6 and C-8), 55.5 (OMe), 46.8 (C-2), 37.8 (C-5 and C-9). **HRMS** (EI): calculated for $C_{15}H_{20}O_3$ $[M]^+$ requires *m/z* 248.1407, found *m/z* 248.1408. **IR** (film) ν_{max} : 3408, 2950, 1606, 1509, 1244, 1096 cm^{-1}.

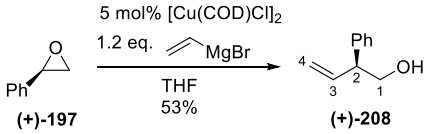
5.4.25 (*E*)-4-(4-Methoxyphenyl)-2-methylbut-3-en-1-ol (*E*-178o)



4-Methoxystyrene **180** (2.3 g, 17.4 mmol), 2-methyl-3-buten-1-ol **207** (300 mg, 3.48 mmol) and Grubbs II (47 mg, 0.054 mmol) were subjected to general procedure **B** except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 30% → 60% Et_2O - pentane) to yield ***E*-178o** as a yellow solid (320 mg, 48%).

Data for ***E*-178o**: $\mathbf{R_f}$ 0.45 (80% Et_2O - pentane). **M.p.**: 68 °C (20% EtOAc - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 7.30 (2H, d, *J* = 8.9 Hz, Ar), 6.85 (2H, d, *J* = 8.8 Hz, Ar), 6.43 (1H, d, *J* = 15.9 Hz, 1-H), 5.93 (1H, dd, *J* = 15.9, 8.0 Hz, 2-H), 3.81 (3H, s, OMe), 3.65-3.53 (1H, m, 4-H_A), 3.53-3.45 (1H, m, 4-H_B), 2.51 (1H, hept, *J* = 7.0 Hz, 3-H), 1.50 (1H, br s, OH), 1.10 (3H, d, *J* = 6.8 Hz, Me). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 159.1 (C Ar), 130.6 (C-1), 130.3 (C-2), 130.1 (C Ar), 127.4 (2 x CH Ar), 114.1 (2 x CH Ar), 67.6 (C-4), 55.4 (OMe), 40.3 (C-3), 16.7 (Me). **HRMS** (ESI): calculated for $C_{12}H_{17}O_2$ $[M+H]^+$ requires *m/z* 193.1229, found *m/z* 193.1226. **IR** (film) ν_{max} : 3657, 2980, 1382, 1249, 1152, 1072 cm^{-1}

5.4.26 (+)-(*S*)-2-Phenylbut-3-en-1-ol [(+)-208]



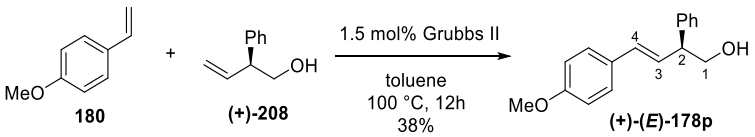
To a solution of (*R*)-phenyloxirane **(+)-197** (1.000 g, 8.326 mmol, 1.0 equiv.) and $[Cu(COD)Cl]_2$ (0.172 g, 0.415 mmol) in THF (12 mL) at –78°C was added vinylmagnesium bromide (10.0 mL, 10.0 mmol, 1.0 M solution in THF). The reaction was allowed to

warm to room temperature over 8 hours, then it was quenched by the addition of saturated NH_4Cl solution and extracted with EtOAc. The combined organics were dried over $MgSO_4$ and concentrated. The crude residue was purified (FCC: gradient elution: 15% → 20% Et_2O - pentane) to yield **(+)-208** as a colorless oil (0.650 g, 53%). Spectroscopic properties matched those previously reported.[18]

Data for **(+)-208**: $\mathbf{R_f}$ 0.40 (40% Et_2O - pentane). $[\alpha]_D^{25}$ = +62.1 (0.01 g/mL, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.20-7.37 (2H, m, Ar), 7.20-7.27 (3H, m, Ar), 6.00 (1H, ddd, *J* = 17.6, 10.4, 7.7 Hz, 3-H), 5.15-5.23 (2H, m, 4-H_2), 3.81 (2H, t, *J* = 6.0 Hz, 1-H_2), 3.52 (1H, q, *J* = 7.3 Hz, 2-H), 1.57 (1H, br s, OH). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 140.7 (C Ar), 138.3 (C-3), 128.9 (2 x C-H Ar), 128.1 (2 x C-H Ar), 127.1 (C-H Ar), 117.2 (C-4), 66.2 (C-1), 52.6 (C-2). **HRMS** (Cl): calculated for $C_{10}H_{12}O$ $[M]^+$ requires *m/z* 148.0883, found *m/z* 148.0882.

Racemic **208** (55% yield) was made *via* the same procedure without using $[Cu(COD)Cl]_2$.

5.4.27 (+)-(2*S*,3*E*)-4-(4-Methoxyphenyl)-2-phenylbut-3-en-1-ol [(+)-(*E*)-178p]



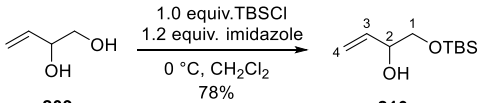
4-Methoxystyrene **180** (0.708 g, 5.28 mmol), alcohol **(+)-208** (0.391 g, 2.64 mmol) and Grubbs II (33.6 mg, 0.0396 mmol) were subjected to the general procedure **B** except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 15% → 20% Et_2O - pentane) to yield **(+)-(*E*)-178p** as a yellow solid (0.256 g, 38%). Spectroscopic

properties matched those previously reported.[18]

Data for **(+)-(*E*)-178p**: $\mathbf{R_f}$ 0.40 (60% Et_2O - pentane). $[\alpha]_D^{25}$ = +61.2 (0.01 g/mL, $CHCl_3$) .**^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.23-7.40 (7H, m, Ar), 6.84 (2H, d, *J* = 8.8 Hz, Ar), 6.48 (1H, d, *J* = 15.8 Hz, 4-H), 6.23 (1H, dd, *J* = 15.9, 8.0 Hz, 3-H), 3.87-3.93 (2H, m, 1-H_2), 3.80 (3H, s, OMe), 3.68 (1H, q, *J* = 7.2 Hz, 2-H), 1.53 (1H, s, OH). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.3 (C Ar), 141.2 (C Ar), 131.8 (C-4), 129.9 (C Ar), 129.0 (2 x CH Ar), 128.1 (2 x CH Ar), 127.6 (2 x CH Ar), 127.5 (C-3), 127.1 (CH Ar), 114.1 (2 x CH Ar), 66.6 (C-1), 55.4 (OMe), 52.0 (C-2). **HRMS** (CI): calculated for $C_{17}H_{18}O_2$ $[M]^+$ requires *m/z* 254.1301, found *m/z* 254.1295.

Racemic **(±)-(*E*)-178p** (38%) was made via the same procedure using racemic alcohol **208**.

5.4.28 (±)-1-[(*tert*-Butyldimethylsilyl)oxy]but-3-en-2-ol (210)



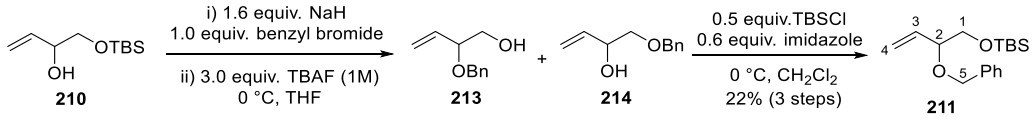
209 **210**

To a r.b.f., charged with diol **209** (300.0 mg, 3.409 mmol) and imidazole (300.0 mg, 4.091 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C, was slowly added TBSCl (511.4 mg, 3.409 mmol) in CH_2Cl_2 (2.0 mL). The reaction mixture was gradually warmed to room temperature and stirred for 12 hours. FCC afforded the product **210** (FCC: gradient elution: 25% → 50% Et_2O - pentane) as a colorless oil (537.1 mg, 78%). Spectroscopic properties matched those previously reported.[19]

Data for **210**: $\mathbf{R_f}$ 0.40 (60% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 5.81 (1H,

ddd, *J* = 17.3, 10.6, 5.7 Hz, 3-H), 5.29-5.37 (1H, m, 4-H_A), 5.13-5.22 (1H, m, 4-H_B), 4.11-4.21 (1H, m, 2-H), 3.66 (1H, dd, *J* = 10.0, 3.7 Hz, 1-H_A), 3.45 (1H, dd, *J* = 10.0, 7.7 Hz, 1-H_B), 2.57 (1H, d, *J* = 3.5 Hz, OH), 0.90 (9H, s, 3 x Me TBS), 0.08 (6H, s, 2 x Me TBS). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 136.8 (C-3), 116.6 (C-4), 73.2 (C-2), 67.1 (C-1), 26.0 (3 x Me TBS), 18.5 (CMe_3 TBS), -5.20 (Me TBS), -5.23 (Me TBS).

5.4.29 (±)-{[2-(Benzyloxy)but-3-en-1-yl]oxy}(*tert*-butyl)dimethylsilane (211)

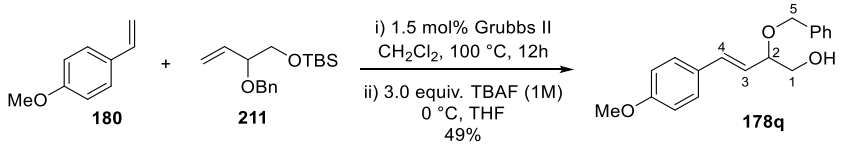


To a flame-dried r.b.f. charged with 60% sodium hydride (43.1 mg, 1.08 mmol) and 2 mL of dry THF was slowly added alcohol **210** (300.0 mg, 0.6733 mmol) in 6 mL of THF. After stirring for 30 min, the flask was cooled to 0 °C, and benzyl bromide (113.8 mg, 0.6733 mmol) in 6 mL THF was added dropwise. The mixture was gradually warmed to room temperature. After 12 hours, the reaction was quenched by slow addition of saturated NH_4Cl solution. The phases were separated, and the aqueous phase was extracted two additional times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated by rotary evaporation. The crude oil was added TBAF (1M in THF, 2.00 mL, 2.00 mmol) in THF (3mL) at 0 °C. After 5 hours, the solvent was removed under reduced pressure. The crude oil was dissolved in CH_2Cl_2 (5.0 mL), and was added imidazole (27.5 mg, 0.404 mmol) at 0 °C. After stirring for 5 min. the TBSCl (50.5 mg, 0.337 mmol) in CH_2Cl_2 (2.0 mL) was slowly added and let the reaction stirring for 12 hours. FCC afforded the product **211** (FCC: gradient elution: 15%

→ 20% Et_2O - pentane) as a colorless oil (43.3 mg, 22%). Spectroscopic properties matched those previously reported.[20]

Data for **211**: **R_f** 0.40 (60% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.30-7.38 (4H, m, Ar), 7.24-7.29 (1H, m, Ar), 5.78 (1H, ddd, *J* = 17.4, 10.4, 6.6 Hz, 3-H), 5.23-5.35 (2H, m, 4-H_2), 4.66 (1H, d, *J* = 12.1 Hz, 5-H_A), 4.48 (1H, d, *J* = 12.1 Hz, 5-H_B), 3.89 (1H, td, *J* = 6.6, 5.1 Hz, 2-H), 3.74 (1H, dd, *J* = 10.6, 6.6 Hz, 1-H_A), 3.62 (1H, dd, *J* = 10.6, 5.1 Hz, 1-H_B), 0.90 (9H, s, 3 x Me TBS), 0.06 (6H, s, 2 x Me TBS). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 138.9 (C Ar), 136.3 (C-3), 128.4 (2 x CH Ar), 127.8 (2 x CH Ar), 127.5 (CH Ar), 118.2 (C-4), 81.3 (C-2), 70.8 (C-5), 66.5 (C-1), 26.1 (3 x Me TBS), 18.5 (CMe_3 TBS), -5.1 (Me TBS), -5.2 (Me TBS).

5.4.30 (±)-(3*E*)-2-(Benzyloxy)-4-(4-methoxyphenyl)but-3-en-1-ol (178q)

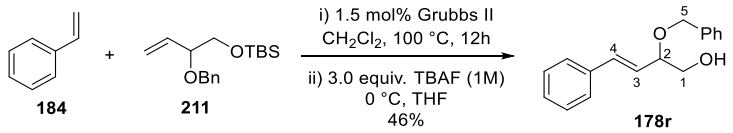


4-Methoxystyrene **180** (134.0 mg, 1.000 mmol), alkene **211** (146.0 mg, 0.5000 mmol) and Grubbs II (12.7 mg, 0.015 mmol) were subjected to general procedure **B**. After 12 hours, the crude mixture was concentrated under reduced pressure and dissolved in THF, and TBAF (1M in THF, 1.50 mL, 1.50 mmol) was added at 0 °C. After 5 hours, the solvent was removed under reduced pressure. FCC afforded the alcohol **178q** (FCC: gradient elution: 15% → 20% Et_2O - pentane) as a colorless oil (139.2 mg, 49%).

Data for **178q**: **R_f** 0.40 (60% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.27-7.38 (7H, m, Ar), 6.88 (2H, d, *J* = 8.7 Hz, Ar), 6.62 (1H, d, *J* = 16.0 Hz, 4-H), 5.98 (1H,

dd, *J* = 16.0, 8.0 Hz, 3-H), 4.71 (1H, d, *J* = 11.7 Hz, 5-H_A), 4.45 (1H, d, *J* = 11.7 Hz, 5-H_B), 4.06-4.13 (1H, m, 2-H), 3.83 (3H, s, OMe), 3.62-3.73 (1H, m, 1-H_2), 2.20 (1H, br s, OH). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 159.7 (C Ar), 138.3 (C Ar), 134.2 (C-4), 129.1 (C Ar), 128.6 (2 x CH Ar), 128.1 (2 x CH Ar), 128.0 (2 x CH Ar), 127.9 (CH Ar), 123.9 (C-3), 114.2 (2 x CH Ar), 81.1 (C-2), 70.5 (C-5), 65.8 (C-1), 55.5 (OMe). **HRMS** (ESI): calculated for $C_{18}H_{20}O_3Na$ $[M+Na]^+$ requires *m/z* 307.1310, found *m/z* 307.1310. **IR** (film) ν_{max}: 3416, 2980, 2886, 1606, 1510, 1391 cm^{-1}.

5.4.31 (±)- (3*E*)-2-(Benzyloxy)-4-phenylbut-3-en-1-ol (178r)



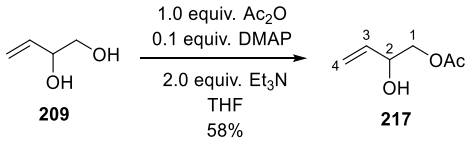
184 **211** **178r**

Styrene **184** (104.0 mg, 1.000 mmol), alkene **211** (146.0 mg, 0.5000 mmol) and Grubbs II (12.7 mg, 0.015 mmol) were subjected to general procedure **B**. After 12 hours, the crude mixture was concentrated under reduced pressure and dissolved in THF, and TBAF (1M in THF, 1.50 mL, 1.50 mmol) was added at 0 °C. After 5 hours, the solvent was removed under reduced pressure. FCC afforded the alcohol **178r** (FCC: gradient elution: 15% → 20% Et_2O - pentane) as a colorless oil (116.8 mg, 46%).

Data for **178r**: **R_f** 0.40 (60% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.26-7.46 (10H, m, Ar), 6.69 (1H, d, *J* = 16.0 Hz, 4-H), 6.15 (1H, dd, *J* = 16.0, 7.8 Hz, 3-H), 4.72(1H, d, *J* = 11.7 Hz, 5-H_A), 4.47 (1H, d, *J* = 11.7 Hz, 5-H_B), 4.14 (1H, ddd, *J* = 7.7, 6.2, 5.2 Hz, 2-H), 3.64-3.75 (1H, m, 1-H_2), 2.24 (1H, br s, OH). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 138.2 (C Ar), 136.3 (C Ar), 134.6 (C-4), 128.8 (2 x CH Ar), 128.6 (2 x CH Ar), 128.2 (CH Ar),

128.0 (2 x CH Ar), 127.9 (CH Ar), 126.7 (2 x CH Ar), 126.2 (C-4), 80.9 (C-2), 70.7 (C-5), 65.7 (C-1). **HRMS** (ESI): calculated for $C_{17}H_{18}O_2Na$ $[M+Na]^+$ requires *m/z* 277.1204, found *m/z* 277.1198. **IR** (film) ν_{max}: 3425, 2972, 1382, 1062, 968, 746 cm^{-1}.

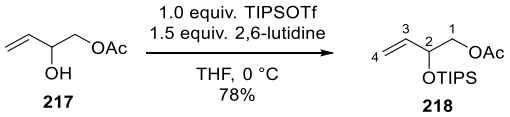
5.4.32 (±)-2-Hydroxybut-3-en-1-yl acetate (217)



Diol **209** (0.500 g, 5.68 mmol) was dissolved in THF (57.0 mL) and the solution was cooled to 0 °C. Triethylamine (1.60 mL, 11.36 mmol) and 4-dimethylaminopyridine (69.3 mg, 0.568 mmol) were added, followed by addition of acetic anhydride (0.580 g, 5.68 mmol). After 30 min, the reaction mixture was warmed up to room temperature and stirred for 2 hours. The mixture was quenched with saturated $NaHCO_3$ solution and the aqueous layer was separated and extracted with Et_2O. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. FCC (40% Et_2O - pentane) afforded the acetate **217** as a colorless oil (0.428 g, 58%). Spectroscopic properties matched those previously reported.[21]

Data for **217**: $\mathbf{R_f}$ 0.40 (60% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 5.83 (1H, ddd, *J* = 17.3, 10.5, 5.6 Hz, 3-H), 5.31-5.40 (1H, m, 4-H_A), 5.18-5.25 (1H, m, 4-H_B), 5.32-4.38 (1H, m, 2-H), 4.14 (1H, dd, *J* = 11.5, 3.5 Hz, 1-H_A), 4.00 (1H, dd, *J* = 11.5, 7.4 Hz, 1-H_B), 2.57 (1H, br s, OH), 2.08 (3H, s, Me Ac). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 171.4 (C=O Ac), 136.2 (C-3), 117.2 (C-4), 71.0 (C-2), 67.9 (C-1), 21.0 (Me Ac).

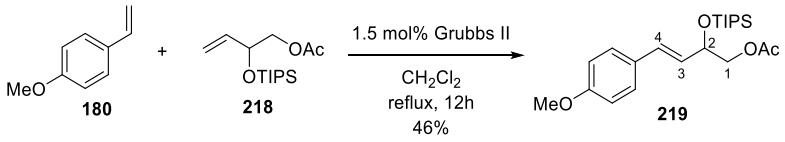
5.4.33 (±)-2-[(Triisopropylsilyl)oxy]but-3-en-1-yl acetate (218)



To a r.b.f., charged with acetate **217** (400.0 mg, 3.077 mmol) and 2,6-lutidine (0.54 mL, 4.6 mmol) in dry CH_2Cl_2 (5.0 mL) at 0 °C, was slowly added TIPSOTf (0.56 mL, 3.077 mmol). The reaction mixture was gradually warmed to room temperature and stirred for 12 hours. The mixture was quenched with saturated aq. $NaHCO_3$ and the aqueous layer was separated and extracted with Et_2O. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. FCC afforded the **218** (FCC: gradient elution: 25% → 50% Et_2O - pentane) as a colorless oil (537.1 mg, 78%).

Data for **218**: **R_f** 0.40 (60% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 5.82 (1H, ddd, *J* = 16.9, 10.4, 6.2 Hz, 3-H), 5.24-5.33 (1H, m, 4-H_A), 5.13-5.21 (1H, m, 4-H_B), 4.45 (1H, qt, *J* = 6.2, 1.3 Hz, 2-H), 4.01 (2H, d, *J* = 5.9 Hz, 1-H_2), 2.05 (3H, s, Me Ac), 0.99-1.10 (21H, m, 6 x CH_3 *i*Pr and 3 x CH *i*Pr). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 170.9 (C=O Ac), 138.1 (C-3), 116.3 (C-4), 71.9 (C-2), 68.3 (C-1), 20.9 (Me Ac), 17.97 (6 x CH_3 *i*Pr), 17.96 (3 x CH *i*Pr). **HRMS** (ESI): calculated for $C_{15}H_{30}O_3NaSi$ $[M+Na]^+$ requires *m/z* 309.1862, found *m/z* 309.1856. **IR** (film) ν_{max}: 2971, 2889, 1746, 1382, 1229, 1151 cm^{-1}.

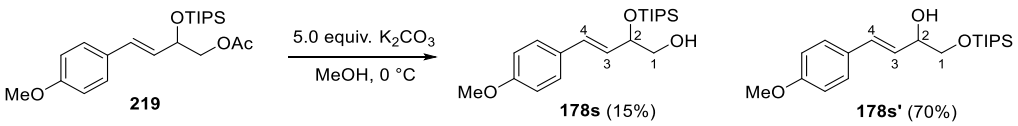
5.4.34 (±)-(3*E*)-4-(4-Methoxyphenyl)-2-[(triisopropylsilyl)oxy]but-3-en-1-yl acetate (219)



4-Methoxystyrene **180** (653.9 mg, 4.88 mmol), acetate **218** (697.8 mg, 2.44 mmol) and Grubbs II (31.0 mg, 0.087 mmol) were subjected to general procedure **B** (FCC: gradient elution: 10% → 30% Et_2O - pentane) to yield **219** as a colorless oil (440.0 mg, 46%).

Data for **219**: $\mathbf{R_f}$ 0.40 (30% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.30 (2H, d, *J* = 8.7 Hz, Ar), 6.86 (2H, d, *J* = 8.7 Hz, Ar), 6.55 (1H, dd, *J* = 16.0, 1.1 Hz, 4-H), 6.02 (1H, dd, *J* = 16.0, 6.8 Hz, 3-H), 4.60 (1H, dtd, *J* = 7.1, 6.0, 1.1 Hz, 2-H), 4.08 (2H, d, *J* = 6.0 Hz, 1-H_2), 3.81 (3H, s, OMe), 2.05 (3H, s, Me Ac), 1.03-1.11 (21H, m, 6 x CH_3 *i*Pr and 3 x CH *i*Pr). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 171.1 (C=O Ac), 159.5 (C Ar), 131.0 (C-4), 129.5 (C Ar), 127.8 (2 x CH Ar), 127.3 (C-3), 114.2 (2 x CH Ar), 71.9 (C-2), 68.7 (C-1), 55.5 (OMe), 21.1 (Me Ac), 18.14 (3 x CH_3 *i*Pr), 18.12 (3 x CH_3 *i*Pr), 12.5 (3 x CH *i*Pr). **IR** (film) ν_{max}: 2971, 2888, 1756, 1392, 1329, 1251 cm^{-1}.

5.4.35 (±)-(3*E*)-4-(4-Methoxyphenyl)-2-[(triisopropylsilyl)oxy]but-3-en-1-ol (178s) (±)-(3*E*)-4-(4-methoxyphenyl)-1-[(triisopropylsilyl)oxy]but-3-en-2-ol (178s')



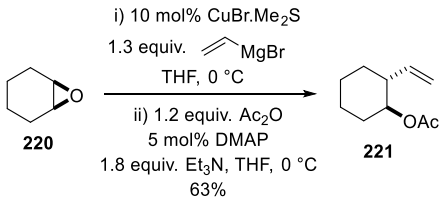
Acetate **219** (392.0 mg, 1.000 mmol) and K_2CO_3 (69.0 mg, 5.000 mmol) were

subjected to general procedure **C** (FCC: gradient elution: 10% → 50% Et_2O - pentane) to yield **178s** (52.5 mg, 15%) and **178s'** (245.0 mg, 70%) as colorless oil.

Data for **178s**: $\mathbf{R_f}$ 0.35 (70% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.31 (2H, d, *J* = 8.7 Hz, Ar), 6.86 (2H, d, *J* = 8.7 Hz, Ar), 6.53 (1H, dd, *J* = 16.0, 1.0 Hz, 4-H), 6.05 (1H, dd, *J* = 16.0, 7.3 Hz, 3-H), 4.46 (1H, dddd, *J* = 7.3, 5.8, 4.6, 1.0 Hz, 2-H), 3.80 (3H, s, OMe), 3.53-3.66 (2H, m, 1-H_2), 2.10 (1H, t, *J* = 5.8 Hz, OH) 1.03-1.17 (21H, m, 6 x CH_3 *i*Pr and 3 x CH *i*Pr). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 159.5 (C Ar), 131.3 (C-4), 129.4 (C Ar), 127.8 (2 x CH Ar), 127.5 (C-3), 114.1 (2 x CH Ar), 74.8 (C-2), 67.4 (C-1), 55.4 (OMe), 18.21 (3 x CH_3 *i*Pr), 18.16 (3 x CH_3 *i*Pr), 12.5 (3 x CH *i*Pr). **HRMS** (ESI): calculated for $C_{20}H_{34}O_3NaSi$ $[M+Na]^+$ requires *m/z* 373.2175, found *m/z* 373.2171. **IR** (film) ν_{max}: 3358, 298, 2889, 1511, 1382, 1248 cm^{-1}.

Data for **178s'**: $\mathbf{R_f}$ 0.40 (70% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.32 (2H, d, *J* = 8.7 Hz, Ar), 6.85 (2H, d, *J* = 8.7 Hz, Ar), 6.63 (1H, dd, *J* = 16.0, 1.1 Hz, 4-H), 6.04 (1H, dd, *J* = 16.0, 6.5 Hz, 3-H), 4.35 (1H, dddd, *J* = 9.3, 6.5, 3.9, 1.1 Hz, 2-H), 3.81 (1H, dd, *J* = 8.1, 3.9 Hz, 1-H_A), 3.80 (3H, s, OMe), 3.61 (1H, dd, *J* = 9.3, 8.1 Hz, 1-H_B), 2.81 (1H, d, *J* = 2.7 Hz, OH), 1.03-1.17 (21H, m, 6 x CH_3 *i*Pr and 3 x CH *i*Pr). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 159.4 (C Ar), 131.5 (C-4), 129.6 (C Ar), 127.8 (2 x CH Ar), 125.6 (C-3), 114.1 (2 x CH Ar), 73.3 (C-2), 67.7 (C-1), 55.4 (OMe), 18.1 (6 x CH_3 *i*Pr), 12.1 (3 x CH *i*Pr). **HRMS** (ESI): calculated for $C_{20}H_{34}O_3NaSi$ $[M+Na]^+$ requires *m/z* 373.2175, found *m/z* 373.2171. **IR** (film) ν_{max}: 3358, 298, 2889, 1511, 1382, 1248 cm^{-1}.

5.4.36 (±)-(1*S*,2*R*)-2-Vinylcyclohexyl acetate (221)

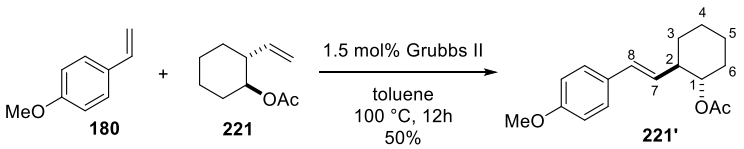


To a solution of cyclohexene oxide **220** (0.75 mL, 7.5 mmol) in dry diethyl ether (3 mL) at –78 °C, was added CuBr·Me_2S (154 mg, 0.75 mmol) and a solution of vinylmagnesium bromide (1 M in THF, 15 mL, 10 mmol). The solution was allowed to warm to room temperature. Then, the reaction was quenched with a solution of saturated NH_4Cl and the product was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The crude oil then was combined with acetic anhydride (0.922 g, 9.05 mmol), triethylamine (0.134 g, 13.3 mmol), and DMAP (4.6 mg, 0.038 mmol) in THF (15 mL) at 0 °C. The reaction mixture was maintained at 0 °C for 1 hour and then was allowed to stir at room temperature overnight. The solvent was removed under reduced pressure, and the resulting material was diluted with EtOAc and washed with water and brine and dried over $MgSO_4$. FCC (0.5% Et_2O - pentane) afforded **221** as a colorless oil (800 mg, 63%). Spectroscopic properties matched those previously reported.[21]

Data for **221**: $\mathbf{R_f}$ 0.40 (10% Et_2O - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 5.64 (1H, ddd, *J* = 16.8, 10.2, 8.1 Hz, 7-H), 5.01 (1H, dd, *J* = 16.9, 1.8 Hz, 8-H_A), 4.95 (1H, dd, *J* = 10.3, 1.8 Hz, 8-H_B), 4.60 (1H, td, *J* = 10.2, 4.4 Hz, 1-H), 2.15-2.02 (1H, m, 2-H), 1.99 (3H, s, Me Ac), 1.97-1.92 (1H, m, 5-H_A), 1.81-1.63 (3H, m, 5-H_B and 4-H_2), 1.36-1.27 (2H, m, 6-H_2), 1.27-1.17 (2H, m, 3-H_2). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 170.7 (C=O), 140.2 (C-7),

115.0 (C-8), 75.3 (C-1), 47.3 (C-2), 31.5 (CH_2 Cy), 31.2 (CH_2 Cy), 24.8 (CH_2 Cy), 24.5 (CH_2 Cy), 21.3 (Me Ac).

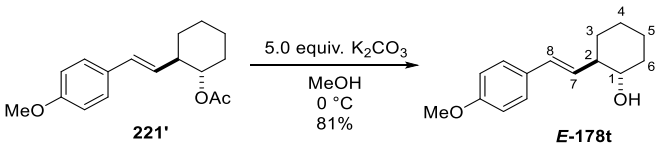
5.4.37 (±)-(1*S*,2*R*)-2-[(*E*)-4-methoxystyryl]cyclohexyl acetate (221')



4-Methoxystyrene **180** (653 mg, 4.88 mmol), acetate **221** (410 mg, 2.44 mmol) and Grubbs II (31 mg, 0.087 mmol) were subjected to general procedure **B** (FCC: gradient elution: 4% → 10% Et_2O - pentane) to yield **221'** as a colorless oil (337 mg, 50%).

Data for **221'**: $\mathbf{R_f}$ 0.3 (20% Et_2O - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 7.25 (2H, d, *J* = 6.7 Hz, Ar), 6.83 (2H, d, *J* = 6.7 Hz, Ar), 6.33 (1H, d, *J* = 15.8 Hz, 8-H), 5.87 (1H, dd, *J* = 15.9, 8.5 Hz, 7-H), 4.73-4.62 (1H, m, 1-H), 3.79 (3H, s, OMe), 2.29-2.17 (1H, m, 2-H), 2.06-1.95 (1H, m, 5-H_A), 1.95 (3H, s, Ac Me), 1.88-1.66 (3H, m, 5-H_B and 4-H_2), 1.42-1.22 (4H, m, 3-H_2 and 6-H_2). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 170.8 (C=O), 158.9 (C Ar), 130.5 (C Ar), 130.0 (C-7), 129.9 (C-8), 127.3 (2 x CH Ar), 113.7 (2 x CH Ar), 75.7 (C-1), 55.4 (OMe), 47.4 (C-2), 31.9 (CH_2 Cy), 31.7 (CH_2 Cy), 25.1 (CH_2 Cy), 24.7 (CH_2 Cy), 21.4 (Ac Me). **HRMS** (ESI): calculated for $C_{17}H_{22}O_3Na$ $[M+Na]^+$ requires *m/z* 297.1467, found *m/z* 297.1460. **IR** (film) ν_{max} : 2933, 1730, 1607, 1510, 1239, 1030 cm^{-1}

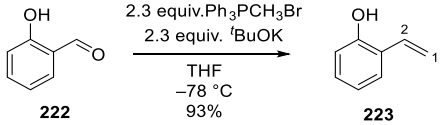
5.4.38 (±)-(1*S*,2*R*)-2-[(E)-4-Methoxystyryl]cyclohexan-1-ol (*E*-178t)



Acetate **221'** (337 mg, 1.23 mmol) and K_2CO_3 (850 mg, 6.15 mmol) were subjected to general procedure **C** (FCC: gradient elution: 20% → 30% Et_2O - pentane) to yield ***E*-178t** as a white solid (232 mg, 81%).

Data for ***E*-178t**: $\mathbf{R_f}$ 0.30 (60 % Et_2O - pentane). **M.p.**: 67 °C (10% EtOAc - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 7.31 (2H, d, *J* = 8.9 Hz, Ar), 6.85 (2H, d, *J* = 8.9 Hz, Ar), 6.47 (1H, d, *J* = 15.8 Hz, 8-H), 5.92 (1H, dd, *J* = 15.8, 8.9 Hz, 7-H), 3.81 (3H, s, OMe), 3.32 (1H, td, *J* = 9.8, 4.1 Hz, 1-H), 2.10-2.05 (1H, m, 6-H_A), 2.05-2.00 (1H, m, 2-H), 1.97 (1H, br s, OH), 1.85-1.76 (2H, m, 3-H_A and 5-H_A), 1.73-1.66 (1H, m, 4-H_A), 1.37-1.20 (4H, m, 3-H_B, 4-H_B, 5-H_B and 6-H_B). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 159.1 (C Ar), 131.6 (C-8), 130.0 (C Ar and C-7), 127.4 (2 x CH Ar), 114.1 (2 x CH Ar), 73.4 (C-1), 55.4 (OMe), 50.8 (C-2), 33.9 (CH_2 Cy), 31.7 (CH_2 Cy), 25.4 (CH_2 Cy), 25.0 (CH_2 Cy). **HRMS** (EI): calculated for $C_{15}H_{20}O_2$ $[M]^+$ requires *m/z* 232.1463, found *m/z* 232.1461. **IR** (film) ν_{max}: 3658, 2980, 2888, 2360, 1382, 1247 cm^{-1}.

5.4.39 2-Vinylphenol (223)

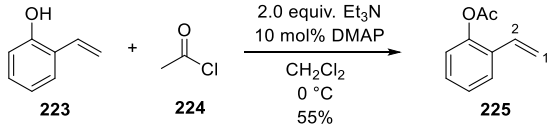


Methyltriphenylphosphonium bromide (8.220 g, 23.01 mmol), ^{t}BuOK (2.580 g, 23.04 mmol), salicylaldehyde **222** (1.220 g, 10.00 mmol) and THF (53 mL) were

subjected to the general procedure **A** except adding the salicylaldehyde at –78°C (FCC: gradient elution: 20% → 30% Et_2O - pentane) to yield **223** as a colorless liquid (1.120 g, 93%). Spectroscopic properties matched those previously reported.[22]

Data for **223**: $\mathbf{R_f}$ 0.5 (40% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.40 (1H, dd, *J* = 7.6, 1.7 Hz, Ar), 7.15 (1H, ddd, *J* = 8.1, 7.3, 1.6 Hz, Ar), 6.96 (1H, dd, *J* = 17.7, 11.2 Hz, 2-H), 6.90-6.95 (1H, m, Ar), 6.80 (1H, dd, *J* = 8.0, 1.2 Hz, Ar), 5.75 (1H, dd, *J* = 17.7, 1.4 Hz, 1-H_A), 5.37 (1H, dd, *J* = 11.2, 1.4 Hz, 1-H_B), 5.16 (1H, s, OH). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 152.9 (C Ar), 131.6 (C-2), 129.0 (C-H Ar), 127.5 (C-H Ar), 124.9 (C Ar), 121.0 (C-H Ar), 116.0 (C-H Ar and C-1). **HRMS** (Cl): calculated for C_8H_9O $[M+H]^+$ requires *m/z* 121.06479, found *m/z* 121.06465.

5.4.40 2-Vinylphenyl acetate (225)

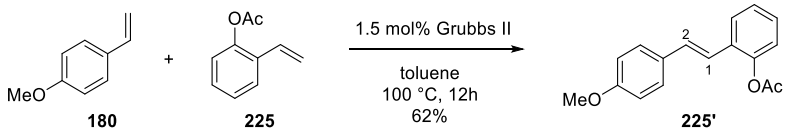


2-Vinylphenol **223** (0.480 g, 4.000 mmol) was dissolved in CH_2Cl_2 (40 mL) and the solution was cooled to 0 °C. Triethylamine (0.808 g, 8.000 mmol) and 4-dimethylaminopyridine **224** (50.0 mg, 0.409 mmol) were added, followed by addition of acetyl chloride (0.468 g, 6.000 mmol). After 30 min, the reaction mixture was warmed up to room temperature and stirred for 2 hours. The mixture was quenched with saturated $NaHCO_3$ solution and the aqueous layer was separated and extracted with Et_2O. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. FCC (5% Et_2O - pentane) afforded the acetate

225 as a colorless oil (0.357 g, 55%). Spectroscopic properties matched those previously reported.[24]

Data for **225**: $\mathbf{R_f}$ 0.4 (20% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.59 (1H, d, *J* = 7.7 Hz, Ar), 7.30 (1H, t, *J* = 7.6 Hz, Ar), 7.24 (1H, t, *J* = 7.5 Hz, Ar), 7.06 (1H, d, *J* = 8.0 Hz, Ar), 6.77 (1H, dd, *J* = 17.6, 11.1 Hz, 2-H), 5.78 (1H, dd, *J* = 17.7, 1.8 Hz, 1-H_A), 5.36 (1H, dd, *J* = 11.0, 1.8 Hz, 1-H_B), 2.35 (3H, s, Ac Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 169.4 (C=O), 148.1 (C Ar), 130.4 (C-2), 130.3 (C Ar), 128.8 (CH Ar), 126.6 (CH Ar), 126.3 (CH Ar), 122.7 (CH Ar), 116.5 (C-1), 21.0 (Ac Me). **HRMS** (EI): calculated for $C_{10}H_{10}O_2$ $[M]^+$ requires *m/z* 162.0675, found *m/z* 162.0678.

5.4.41 (1*E*)-2-(4-Methoxystyryl)phenyl acetate (225')

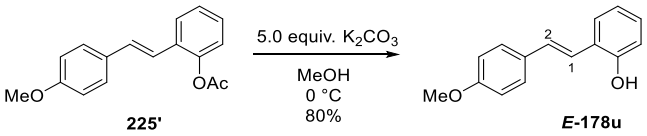


4-Methoxystyrene **180** (0.590 g, 4.40 mmol), acetate **225** (0.357 g, 2.20 mmol) and Grubbs II (28.0 mg, 0.0330 mmol) were subjected to the general procedure **B** except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 10% → 12% Et_2O - pentane) to yield **225'** as a white solid (0.365 g, 62%). Spectroscopic properties matched those previously reported.[25]

Data for **225'**: $\mathbf{R_f}$ 0.40 (40% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.64-7.69 (1H, m, Ar), 7.43 (2H ,d, *J* = 8.4 Hz, Ar), 7.21-7.29 (2H, m, Ar), 7.03-7.10 (2H, m, Ar and 2-H), 6.98 (1H, d, *J* = 16.3 Hz, 1-H), 6.90 (2H, d, *J* = 8.7 Hz, Ar), 3.84 (3H, s, OMe), 2.37 (3H, s, Ac Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 169.5 (C=O), 159.7 (C Ar), 148.1 (C Ar),

130.7 (C-2), 130.4 (C Ar), 130.1 (C Ar), 128.1 (CH Ar), 128.0 (2 x CH Ar), 126.5 (CH Ar), 126.4 (CH Ar), 122.8 (CH Ar), 119.8 (C-1), 114.3 (2 x CH Ar), 55.5 (OMe), 21.1 (Ac Me). **HRMS** (ESI): calculated for $C_{17}H_{16}O_3Na$ $[M+Na]^+$ requires *m/z* 291.09917, found *m/z* 291.09909.

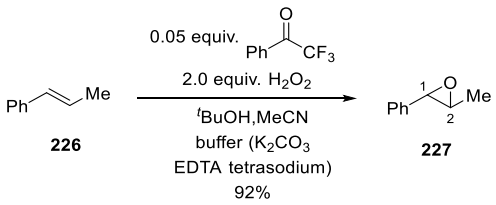
5.4.42 (1*E*)-2-(4-Methoxystyryl)phenol (*E*-178u)



Acetate **225'** (0.345 g, 1.29 mmol) and K_2CO_3 (0.888 g, 6.44 mmol) were subjected to the general procedure **C** (FCC: gradient elution: 20% → 50% Et_2O - pentane) to yield ***E*-178u** as a white solid (0.230 g, 80%). Spectroscopic properties matched those previously reported.[26]

Data for ***E*-178u**: R_f 0.4 (50 % Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.42-7.52 (3H, m, Ar), 7.21 (1H, d, *J* = 16.4 Hz, 2-H), 7.11 (1H, t, *J* = 7.5 Hz, Ar), 7.05 (1H, d, *J* = 16.4 Hz, 1-H), 6.93 (1H, t, *J* = 7.8 Hz, Ar), 6.89 (2H, d, *J* = 8.5 Hz, Ar), 6.79 (1H, d, *J* = 8.0 Hz, Ar), 5.12 (1H, s, OH), 3.82 (3H, s, OMe). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.4 (C Ar), 153.0 (C Ar), 130.5 (C Ar), 129.9 (C-1), 128.4 (CH Ar), 127.9 (2 x CH Ar), 127.1 (CH Ar), 125.1 (C Ar), 121.2 (CH Ar), 121.0 (C-2), 116.0 (CH Ar), 114.2 (2 x CH Ar), 55.5 (OMe). **HRMS** (CI): calculated for $C_{15}H_{15}O_2$ $[M+H]^+$ requires *m/z* 227.10666, found *m/z* 227.10658.

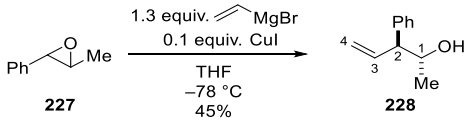
5.4.43 (±)-2-Methyl-3-phenyloxirane (227)



Trans-β-Methylstyrene **226** (2.000 g, 16.95 mmol) was placed in a round-bottom flask followed by 2,2,2-trifluoro-1-phenylethanone (147 mg, 0.846 mmol). *tert*-Butyl alcohol (25 mL), aqueous buffer solution (25 mL, 0.6 M K_2CO_3, 4 × 10^{-5} M EDTA tetrasodium salt), acetonitrile (1.9 mL), and 30% aqueous H_2O_2 (3.9 mL, 34 mmol) were added consecutively. The reaction mixture was allowed to stir for 1 hour at room temperature. Then the reaction was quenched by addition of sodium thiosulfate solution, and the mixture was extracted twice with Et_2O. The organic layers were collected, dried over $MgSO_4$ and the solvents were removed under reduced pressure. FCC (2% Et_2O) afforded **227** as a colorless oil (2.090 g, 92%). Spectroscopic properties matched those previously reported.[27]

Data for **227**: **R_f** 0.45 (50% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.22-7.39 (5H, m, Ar), 3.58 (1H, d, *J* = 2.1 Hz, 1-H), 3.05 (1H, qd, *J* = 5.1, 2.1 Hz, 2-H), 1.46 (3H, d, *J* = 5.1 Hz, Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 137.9 (C Ar), 128.6 (2 x C-H Ar), 128.2 (C-H Ar), 125.7 (2 x C-H Ar), 59.2 (C-1), 59.2 (C-2), 18.1 (Me). **HRMS** (Cl): calculated for $C_9H_{10}O$ $[M]^+$ requires *m/z* 134.0726, found *m/z* 134.072.

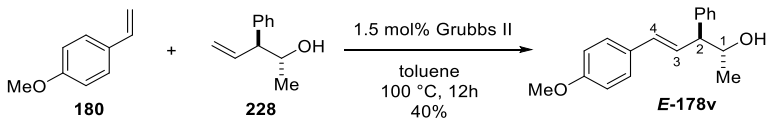
5.4.44 (±)- (2*R*,3*S*)-3-Phenylpent-4-en-2-ol (228)



A 50 mL round bottom flask was flame dried and charged with a solution of copper (I) iodide (85.0 mg, 0.448 mmol) in diethyl ether (3.2 mL) and cooled to –78 °C. The vinyl magnisium bromide solution (1M, 5.8 mL, 5.8 mmol) was added slowly. The resulting solution was stirred for 30 min. and then epoxide **227** (0.600 g, 4.48 mmol) was added slowly. The solution was stirred overnight and allowed to warm to room temperature. The solution was cooled to 0 °C and saturated NH_4Cl solution was added. The aqueous layer was extracted three times with diethyl ether, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude residue was purified (FCC: gradient elution: 10% → 15% Et_2O - pentane) to yield **228** as a yellow oil (0.325 g, 45%). Spectroscopic properties matched those previously reported.[28]

Data for **228**: **R_f** 0.40 (40% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.32-7.37 (2H, m, Ar), 7.24-7.28 (3H, m, Ar), 6.04 (1H, ddd, *J* = 17.5, 9.8, 8.7 Hz, 3-H), 5.09-5.18 (2H, m, 4-H_2), 4.00-4.10 (1H, m, 1-H), 3.25 (1H, t, *J* = 8.2 Hz, 2-H), 1.51 (1H, br s, OH), 1.25 (3H, d, *J* = 6.2 Hz, Me). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 141.0 (C Ar), 138.5 (C-3), 129.0 (2 x C-H Ar), 128.5 (2 x C-H Ar), 127.1 (C-H Ar), 117.0 (C-4), 70.6 (C-1), 59.1 (C-2), 20.8 (Me).

5.4.45 (±)-(2*R*,3*S*,3*E*)-5-(4-Methoxyphenyl)-3-phenylpent-4-en-2-ol (*E*-178v)

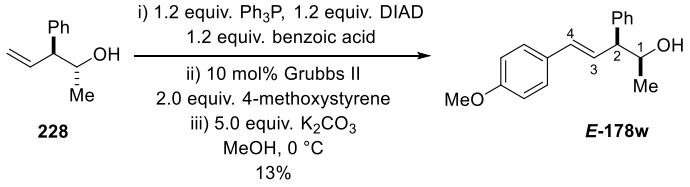


4-Methoxystyrene **180** (0.358 g, 2.67 mmol), alcohol **228** (0.217 g, 1.34 mmol)

and Grubbs II (17.0 mg, 0.0200 mmol) were subjected to the general procedure **B** except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 13% → 20% Et_2O - pentane) to yield ***E*-178v** as a yellow oil (0.149 g, 40%).

Data for ***E*-178v**: R_f 0.40 (60% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.23-7.40 (7H, m, Ar), 6.83 (2H, d, *J* = 8.8 Hz, Ar), 6.43 (1H, d, *J* = 15.8 Hz, 4-H), 6.26 (1H, dd, *J* = 15.8, 8.8 Hz, 3-H), 4.08-4.18 (1H, m, 1-H), 3.80 (3H, s, OMe), 3.38 (1H, t, *J* = 8.3 Hz, 2-H), 1.54 (1H, br s, OH), 1.29 (3H, d, *J* = 6.2 Hz, Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.2 (C Ar), 141.4 (C Ar), 131.5 (C-4), 130.1 (C Ar), 129.0 (2 x C-H Ar), 128.6 (2 x C-H Ar), 127.9 (C-3), 127.5 (2 x C-H Ar), 127.1 (C-H Ar), 114.1 (2 x C-H Ar), 71.0 (C-1), 58.4 (C-2), 55.4 (OMe), 21.0 (Me). **HRMS (EI):** calculated for $C_{18}H_{20}O_2$ [M]+ requires *m/z* 268.1458, found *m/z* 268.1466. **IR** (film) ν_{max}: 3657, 2980, 1387, 1249, 1151, 1026 cm^{-1}.

5.4.46 (±)-(2*S*,3*S*,3*E*)-5-(4-Methoxyphenyl)-3-phenylpent-4-en-2-ol (*E*-178w)

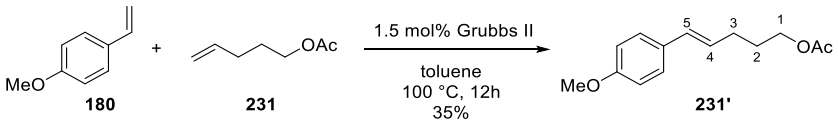


To a mixture of alcohol **228** (0.060 g, 0.37 mmol), PPh_3 (0.116 g, 0.443 mmol) and benzoic acid (0.072 g, 0.44 mmol) in THF (1 mL) at –20 °C was added dropwise DIAD (0.09 mL, 0.44 mmol) over a period of 30 min. The mixture was then stirred for 1 hour while allowing the reaction warm to 0 °C and then diluted with Et_2O and washed with an aqueous solution of $NaHCO_3$. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and

concentrated. The crude was flushed through a layer of slica gel with 10% Et_2O in pentane, then the filtrate was concentrated and added to flame-dried flask, charged with 4-Methoxystyrene **180** (0.013 g, 0.097 mmol), Grubbs II (4.1 mg, 0.0048 mmol) and degassed toluene (0.24 mL). The solution was heat at 100 °C for 24 hours. Then the solvent was evaporated, and the crude was added to a flask charged with K_2CO_3 (23.0 mg, 0.162 mmol) and MeOH (1 mL) at 0 °C. The solution was sitrred for 2 hours, then concentrated in reduced pressure to give the crude residue which was purified (FCC: gradient elution: 13% → 20% Et_2O - pentane) to yield ***E*-178w** as a yellow oil (12.9 mg, 13%).

Data for ***E*-178w**: **R_f** 0.50 (70% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.28-7.35 (4H, m, Ar), 7.20-7.27 (3H, m, Ar), 6.83 (2H, d, *J* = 8.7 Hz, Ar), 6.50 (1H, d, *J* = 15.8 Hz, 4-H), 6.32 (1H, dd, *J* = 15.8, 9.2 Hz, 3-H), 4.04 (1H, quint, *J* = 6.7 Hz, 1-H), 3.79 (3H, s, OMe), 3.29 (1H, t, *J* = 8.4 Hz, 2-H), 1.92 (1H, br s, OH), 1.10 (3H, d, *J* = 6.1 Hz, Me). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.3 (C Ar), 132.1 (C Ar), 132.7 (C-4), 129.8 (C Ar), 128.9 (2 x C-H Ar), 128.1 (2 x C-H Ar), 127.63 (2 x C-H Ar), 127.57 (C-3), 126.9 (C-H Ar), 114.1 (2 x C-H Ar), 70.8 (C-1), 58.5 (C-2), 55.5 (OMe), 20.9 (Me). **HRMS** (EI): calculated for $C_{18}H_{20}O_2$ $[M]^+$ requires *m/z* 268.1458, found *m/z* 268.1466. **IR** (film) ν_{max}: 3657, 2980, 1387, 1249, 1151, 1026 cm^{-1}.

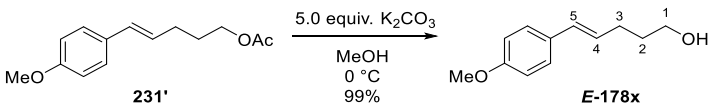
5.4.47 (4*E*)-5-(4-Methoxyphenyl)pent-4-en-1-yl acetate (231')



4-Methoxystyrene **180** (0.499 g, 3.72 mmol), pent-4-en-1-yl acetate **231** (0.952 mg, 7.44 mmol) and Grubbs II (47.0 mg, 0.0554 mmol) were subjected to the general procedure **B** except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 8% → 10% Et_2O - pentane) to yield **231'** as a colorless oil (0.302 g, 35%). Spectroscopic properties matched those previously reported.[29]

Data for **231'**: **R_f** 0.40 (40% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.27 (2H, d, *J* = 8.6 Hz, Ar), 6.83 (2H, d, *J* = 8.7 Hz, Ar), 6.35 (1H, d, *J* = 15.9 Hz, 5-H), 6.05 (1H, dt, *J* = 15.8, 6.9 Hz, 4-H), 4.11 (2H, t, *J* = 6.6 Hz, 1-H_2), 3.79 (3H, s, OMe), 2.26 (2H, qd, *J* = 7.0, 1.5 Hz, 3-H_2), 2.05 (3H, s, Ac Me), 1.80 (2H, tt, *J* = 7.6, 6.4 Hz, 2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 171.6 (C=O), 159.2 (C Ar), 130.8 (C Ar), 130.4 (C-5), 127.54 (C-4), 127.48 (2 x CH Ar), 114.3 (2 x CH Ar), 64.4 (C-1), 55.7 (OMe), 29.8 (C-3), 29.7 (C-2), 21.5 (Ac Me). **HRMS** (Cl): calculated for $C_{14}H_{19}O_3$ $[M+H]^+$ requires *m/z* 235.13287, found *m/z* 235.13284.

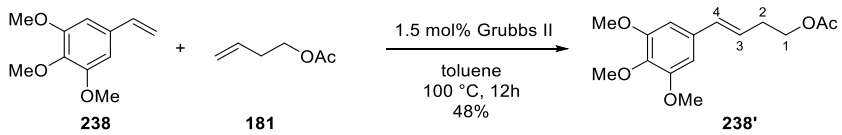
5.4.48 (4*E*)-5-(4-Methoxyphenyl)pent-4-en-1-ol (*E*-178x)



Acetate **231'** (0.304 g, 1.30 mmol) and K_2CO_3 (0.896 g, 6.50 mmol) were subjected to the general procedure **C** (FCC: gradient elution: 40% → 100% Et_2O - pentane) to yield ***E*-178x** as a white solid (0.249 g, 99%). Spectroscopic properties matched those previously reported.[30]

Data for ***E*-178x**: **R_f** 0.30 (60% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.28 (2H, d, *J* = 8.7 Hz, Ar), 6.84 (2H, d, *J* = 8.7 Hz, Ar), 6.36 (1H, d, *J* = 15.8 Hz, 5-H), 6.09 (1H, dt, *J* = 15.7, 6.9 Hz, 4-H), 3.80 (3H, s, OMe), 3.70 (2H, t, *J* = 6.5 Hz, 1-H_2), 2.29 (2H, qd, J = 7.3, 1.5 Hz, 3-H_2), 1.74 (2H, tt, *J* = 7.7, 6.4 Hz, 2-H_2), 1.44 (1H, br s, OH). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.8 (C Ar), 130.6 (C Ar), 129.8 (C-5), 128.0 (C-4), 127.2 (2 x CH Ar), 114.0 (2 x CH Ar), 62.6 (C-1), 55.4 (OMe), 32.5 (C-2), 29.4 (C-3). **HRMS** (CI): calculated for $C_{12}H_{17}O_2$ $[M+H]^+$ requires *m/z* 193.12231, found *m/z* 193.12245.

5.4.49 (3*E*)-4-(3,4,5-Trimethoxyphenyl)but-3-en-1-yl acetate (238')

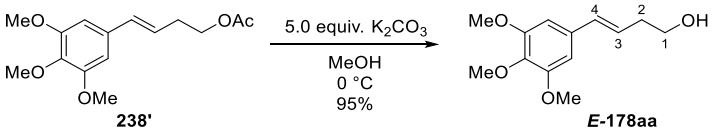


3,4,5-Trimethoxy styrene **238** (0.194 g, 1.00 mmol), but-3-en-1-yl acetate **181** (0.114 g, 0.500 mmol) and Grubbs II (12.7 mg, 0.0150 mmol) were subjected to the general procedure **B** except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 30% → 40% Et_2O - pentane) to yield **238'** as a colorless oil (0.067 g, 48%).

Data for **238'**: **R_f** 0.50 (70% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.56 (2H, s, Ar), 6.39 (1H, d, *J* = 15.9 Hz, 4-H), 6.07 (1H, dt, *J* = 15.9, 7.0 Hz, 3-H), 4.18 (2H, t, *J* = 6.8 Hz, 1-H_2), 3.86 (6H, s, 2 x OMe), 3.83 (3H, s, OMe), 2.53 (2H, qd, *J* = 6.8, 1.5 Hz, 2-H_2), 2.05 (3H, s, Ac Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 171.2 (C=O), 153.3 (2 x C Ar), 137.8 (C Ar), 133.2 (C Ar), 135.4 (C-4), 125.2 (C-3), 103.3 (2 x CH Ar), 63.8 (C-1), 61.0 (OMe), 56.2 (2 x OMe), 32.4 (C-2), 21.1 (Ac Me). **HRMS** (ESI): calculated for $C_{15}H_{20}O_5Na$ $[M+Na]^+$ requires *m/z* 303.1208, found *m/z* 303.1203. **IR** (film) ν_{max}: 3657, 2980, 2889, 1735,

1582, 1382 cm^{-1}.

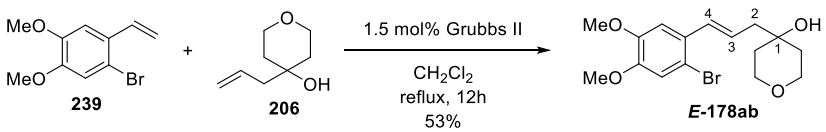
5.4.50 (3*E*)-4-(3,4,5-Trimethoxyphenyl)but-3-en-1-ol (*E*-178aa)



Acetate **238'** (0.314 g, 0.480 mmol) and K_2CO_3 (0.331 g, 2.40 mmol) were subjected to the general procedure **C** (FCC: gradient elution: 40% → 60% EtOAc - pentane) to yield ***E*-178aa** as a colorless oil (0.109 g, 95%).

Data for ***E*-178aa**: R_f 0.4 (70% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.58 (2H, s, Ar), 6.42 (1H, d, *J* = 15.8 Hz, 4-H), 6.07 (1H, dt, *J* = 15.8, 7.2 Hz, 3-H), 3.87 (6H, s, 2 x OMe), 3.83 (3H, s, OMe), 3.76 (2H, t, *J* = 6.3 Hz, 1-H_2), 2.48 (2H, dtd, *J* = 7.6, 6.3, 1.4 Hz, 2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 153.5 (2 x C Ar), 133.2 (2 x C Ar), 132.8 (C-4), 126.1 (C-3), 103.3 (2 x CH Ar), 63.2 (C-1), 61.1 (OMe), 56.2 (2 x OMe), 36.4 (C-2). **HRMS** (CI): calculated for $C_{13}H_{18}O_4Na$ $[M+Na]^+$ requires *m/z* 261.1103, found *m/z* 261.1099. **IR** (film) ν_{max} : 3436, 2930, 1618, 1519, 1245, 967 cm^{-1}

5.4.51 (3*E*)-4-[(2-Bromo-4,5-dimethoxyphenyl)allyl)]tetrahydro-2H-pyran-1-ol (*E*-178ab)

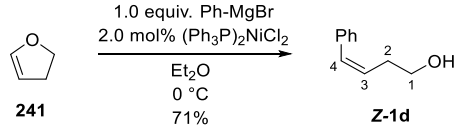


1-Bromo-4,5-dimethoxy-2-vinylbenzene **239** (0.800 g, 3.32 mmol), 1-allylcyclohexanol **206** (0.236 g, 1.66 mmol) and Grubbs II (42.2 mg, 0.0498 mmol)

were subjected to the general procedure **B** except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 12% → 20% Et_2O - pentane) to yield ***E*-178ab** as a yellow oil (0.313 g, 53%).

Data for ***E*-178ab**: R_f 0.3 (50% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.30 (2H, d, *J* = 8.7 Hz, Ar), 6.84 (2H, d, *J* = 8.7 Hz, Ar), 6.40 (1H, d, *J* = 15.8 Hz, 4-H), 6.15 (1H, dt, *J* = 15.5, 7.6 Hz, 3-H), 3.80 (3H, s, OMe), 2.34 (2H, dd, *J* = 7.6, 1.2 Hz, 2-H_2), 1.42-1.67 (9H, m, 5-H_2, 6-H_2, 8-H_2, 9-H_2 and 7-H_A), 1.22-1.36 (1H, m, 7-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.5 (C Ar), 133.2 (C-4), 130.3 (C Ar), 127.4 (2 x CH Ar), 123.1 (C-3), 114.0 (2 x CH Ar), 71.7 (C-1), 55.4 (OMe), 46.0 (C-2), 37.6 (2 x CH_2 cyclohexenyl), 25.9 (CH_2 cyclohexenyl), 22.3 (2 x CH_2 cyclohexenyl). **HRMS** (Cl): calculated for $C_{16}H_{22}O_2Na$ $[M+Na]^+$ requires *m/z* 269.15120, found *m/z* 269.15106. **IR** (film) ν_{max}: 3426, 2928, 1608, 1509, 1244, 967 cm^{-1}

5.4.52 (3*Z*)-4-Phenylbut-3-en-1-ol (*Z*-178d)



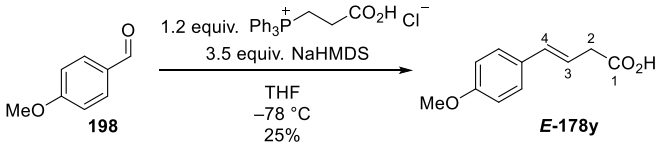
To $(PPh_3)_3NiCl_2$ dry powder (0.094 g, 0.14 mmol), 2,3-dihydrofuran **241** (0.54 mL, 7.1 mmol) in dry Et_2O (8.0 mL) was transferred dropwise *via* a cannula. The resulting suspension was cooled to 0 °C and PhMgBr (2.8 M, 2.56 mL, 7.14 mmol) was slowly added dropwise. After stirring for 1 h at 0 °C, the mixture was stirred at room temperature for 6 h, and then poured into sat. NH_4Cl solution (40 mL). The crude product was extracted with Et_2O (3 x 20 mL), then the organic layer was dried over

Na_2SO_4, filtered and concentrated to dryness giving a crude residue. Purification using silica gel flash chromatography (cyclohexane/EtOAc, 80:20) afforded the alcohol ***Z*-178d** as a colorless oil (0.750 g, 71%). Spectroscopic properties matched those previously reported.[31]

Data for ***Z*-178d**: R_f: 0.5 (100% EtOAc). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.28-7.38 (4H, m, Ar), 7.21-7.27 (1H, m, Ar), 6.59 (1H, d, *J* = 11.7 Hz, 4-H), 5.70 (1H, dt, *J* = 11.7, 7.4 Hz, 3-H), 3.75 (2H, t, *J* = 6.5 Hz, 1-H_2), 2.62 (2H, qd, *J* = 6.6, 1.8 Hz, 2-H_2), 1.54 (1H, br s, OH). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 137.3 (C Ar), 131.7 (C-4), 128.8 (2 x CH Ar), 128.4 (C-3), 128.3 (2 x CH Ar), 126.9 (CH Ar), 62.6 (C-1), 32.1 (C-2). **HRMS** (EI): calculated for $C_{10}H_{12}O$ $[M]^+$ requires *m/z* 148.0883, found *m/z* 148.0888.

5.5 Synthesis of Homoallylic Carboxylic Acids

5.5.1 (3*E*)-4-(4-Methoxyphenyl)but-3-enoic acid (*E*-178y)

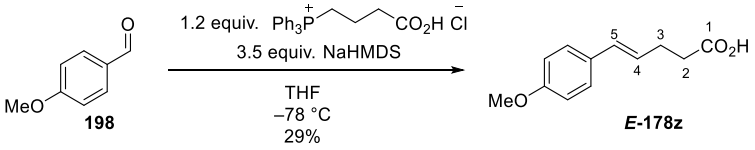


(2-Carboxyethyl)(triphenyl)phosphonium chloride (1.500 g, 4.054 mmol), NaHMDS (1M, 11.5 mL, 11.5 mmol) and 4-methoxybenzaldehyde **198** (0.460 g, 3.37 mmol) were subjected to the general procedure **D** (FCC: 100% EtOAc) to yield ***E*-178y** as a yellow solid (0.161 g, 25%). Spectroscopic properties matched those previously reported.[32]

Data for ***E*-178y**: R_f: 0.5 (100% EtOAc). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 10.07 (1H, br s,

CO_2H), 7.31 (2H, d, *J* = 8.7 Hz, Ar), 6.85 (2H, d, *J* = 8.7 Hz, Ar), 6.46 (1H, d, *J* = 15.9 Hz, 4-H), 6.14 (1H, dt, *J* = 15.8, 7.1 Hz, 3-H), 3.81 (3H, s, OMe), 3.28 (2H, dd, *J* = 7.1, 1.5 Hz, 2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 178.3 (C=O), 159.35 (C Ar), 133.5 (C-4), 129.6 (C Ar), 127.6 (2 x CH Ar), 118.7 (C-3), 114.1 (2 x CH Ar), 55.4 (OMe), 38.2 (C-2). **HRMS** (Cl): calculated for $C_{11}H_{12}O_3$ $[M]^+$ requires *m/z* 192.0786, found *m/z* 192.0788.

5.5.2 (4*E*)-5-(4-Methoxyphenyl)pent-4-enoic acid (*E*-178z)

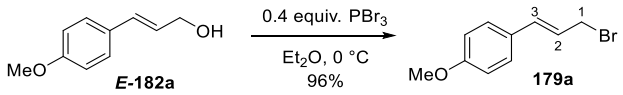


(2-Carboxypropyl)(triphenyl)phosphonium chloride (1.560 g, 4.063 mmol), NaHMDS (1M, 11.5 mL, 11.5 mmol) and 4-methoxybenzaldehyde **198** (0.460 g, 3.37 mmol) were subjected to the general procedure **D** (FCC: 100% EtOAc) to yield ***E*-178z** as a white solid (0.187 g, 29%). Spectroscopic properties matched those previously reported.[24]

Data for ***E*-178z**: **R_f**: 0.5 (100% EtOAc). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.28 (2H, d, *J* = 8.6 Hz, Ar), 6.84 (2H, d, *J* = 8.6 Hz, Ar), 6.39 (1H, d, *J* = 15.9 Hz, 5-H), 5.99-6.12 (1H, m, 4-H), 3.80 (3H, s, OMe), 2.50- 2.55 (4 H, m, 2-H_2 and 3-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 179.0 (C=O), 159.0 (C Ar), 130.7 (C-5), 130.2 (C Ar), 127.3 (2 x CH Ar), 125.9 (C-4), 114.1 (2 x CH Ar), 55.4 (OMe), 34.0 (C-3), 28.1 (C-2). **HRMS** (Cl): calculated for $C_{12}H_{14}O_3$ $[M]^+$ requires *m/z* 206.0943, found *m/z* 206.0947.

5.6 Synthesis of Ether Dienes

5.6.1 (*E*)-1-(3-Bromoprop-1-en-1-yl)-4-methoxybenzene (179a)

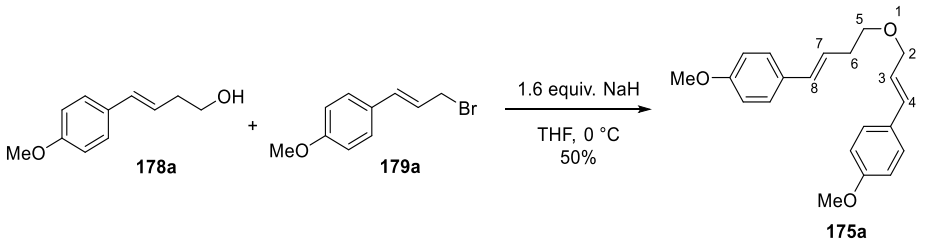


E-182a 179a

To a stirred solution of (*E*)-3-(4-Methoxyphenyl)prop-2-en-1-ol ***E*-182a** (1.06 g, 6.45 mmol) in dry Et_2O (50 mL) at 0 °C under Ar was added PBr_3 (0.24 mL, 2.58 mmol). The reaction was stirred until complete by TLC analysis (typically 0.25-1 hour) and poured into saturated $NaHCO_3$ solution. The layers were separated, and the aqueous layer extracted with Et_2O twice. The combined organics were washed with brine, dried over MgSO4, filtered and concentrated under reduced pressure to give the bromide **179a** as a white solid (1.40 mg, 96%). Spectroscopic properties matched those previously reported.[33]

Data for **179a**: $\mathbf{R_f}$ 0.80 (80% Et_2O - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 7.33 (2H, d, *J* = 8.4 Hz, Ar), 6.87 (2H, d, *J* = 8.8 Hz, Ar), 6.60 (1H, d, *J* = 15.5 Hz, 3-H), 6.27 (1H, dt, *J* = 15.7, 7.9 Hz, 2-H), 4.17 (2H, dd, *J* = 7.8, 1.0 Hz, 1-H_2), 3.82 (3H, s, OMe). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 159.8 (C Ar), 134.2 (C-3), 128.5 (C Ar), 128.1 (2 x CH Ar), 123.0 (C-2), 114.1 (2 x CH Ar), 55.4 (OMe), 34.3 (C-1). **HRMS** (Cl): calculated for $C_{10}H_{12}BrO$ $[M+H]^+$ requires *m/z* 227.0072, found *m/z* 227.0069.

5.6.2 1-Methoxy-4-{(*E*)-4-[(*E*)-3-(4-methoxyphenyl)allyloxy]but-1-en-1-yl}benzene (175a)



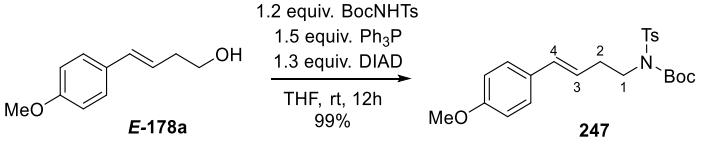
A flame-dried r.b.f. was charged with 60% sodium hydride (35.0 mg, 0.86 mmol) and 2 mL of dry THF. (*E*)-4-(4-methoxyphenyl)but-3-en-1-ol ***E*-178a** in 6 mL of THF (96 mg, 0.54 mmol) was added dropwise, and the reaction was stirred for 30 min. The flask was cooled to 0 °C, and bromide **179a** in 6 mL THF (170 mg, 0.76 mmol) was added dropwise. The mixture was gradually warmed to room temperature. After 12 hours, the reaction was quenched by slow addition of saturated NH_4Cl solution. The phases were separated, and the aqueous phase was extracted two additional times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure (FCC: gradient elution: 10% → 12% Et_2O - pentane) to yield **175a** as a white solid (122 mg, 70%).

Data for **175a**: **R_f** 0.45 (50% Et_2O - pentane). **M.p.**: 59 °C (30% diethyl ether in pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.33 (2H, d, *J* = 8.7 Hz, Ar), 7.29 (2H, d, *J* = 8.7 Hz, Ar), 6.85 (2H, d, *J* = 8.7 Hz, Ar), 6.84 (2H, d, *J* = 8.8 Hz, Ar), 6.56 (1H, d, *J* = 15.9 Hz, 4-H), 6.42 (1H, d, *J* = 15.9 Hz, 8-H), 6.18 (1H, dt, *J* = 15.8, 6.2 Hz, 3-H), 6.11 (1H, dt, *J* = 15.8, 7.0 Hz, 7-H), 4.15 (2H, dd, *J* = 6.2, 1.4 Hz, 2-H_2), 3.81 and 3.80 (6H, s, 2 x OMe), 3.59 (2H, t, *J* = 6.8 Hz, 5-H_2), 2.51 (2H, qd, *J* = 6.9, 1.5 Hz, 6-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.3 (C Ar), 158.8 (C Ar), 132.1 (C-4), 131.0 (C-8), 130.4 (C Ar), 129.5 (C Ar), 127.7 (2 x CH Ar),

127.2 (2 x CH Ar), 124.8 (C-7), 123.9 (C-3), 114.0 (2 x CH Ar), 113.9 (2 x CH Ar), 71.8 (C-2), 69.9 (C-5), 55.3 (2 x OMe), 33.6 (C-6). **IR** (film) ν_{max} 2980, 1512, 1382, 1251, 1152, 1091, 968 cm^{-1}. **HRMS** (CI): calculated for $C_{21}H_{25}O_3$ $[M+H]^+$ requires *m/z* 325.1804, found *m/z* 325.1795.

5.7 Synthesis of Homoallylic Amines

5.7.1 *tert*-Butyl (3*E*)-[4-(4-methoxyphenyl)but-3-en-1-yl](tosyl)carbamate (247)

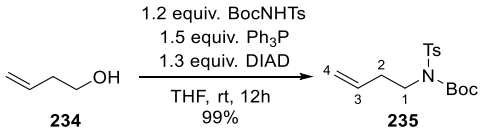


Alcohol ***E*-178a** (0.111 g, 0.627 mmol), BocNHTs (0.204 g, 0.752 mmol), triphenylphosphine (0.246 g, 0.941 mmol) and DIAD (0.164 g, 0.815 mmol) were subjected to the general procedure **E** (FCC: gradient elution: 15% → 20% Et_2O - pentane) to yield **247** as a colorless oil (0.269 g, 99%).

Data for **247**: $\mathbf{R_f}$ 0.40 (40% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.79 (2H, d, *J* = 8.7 Hz, Ar), 7.23-7.29 (4H, m, Ar), 6.83 (2H, d, *J* = 8.7 Hz, Ar), 6.41 (1H, d, *J* = 15.9 Hz, 4-H), 6.04 (1H, dt, *J* = 15.8, 7.3 Hz, 3-H), 3.90-3.97 (2H, m, 1-H_2), 3.80 (3H, s, OMe), 2.63 (2H, qd, *J* = 7.2, 1.3 Hz, 2-H_2), 2.43 (3H, s, Me Ts), 1.31 (9H, s, 3 x Me Boc). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.1 (C Ar), 151.1 (C=O Boc), 144.2 (C Ar), 137.7 (C Ar), 132.2 (C-4), 130.4 (C Ar), 129.3 (2 x CH Ar), 128.1 (2 x CH Ar), 127.4 (2 x CH Ar), 124.0 (C-3), 114.0 (2 x CH Ar), 84.3 (CMe_3 Boc), 55.4 (OMe), 46.9 (C-1), 34.0 (C-2), 28.0 (3 x Me Boc), 21.7 (Me Ts). **HRMS** (ESI): calculated for $C_{23}H_{29}NO_5SNa$ $[M+Na]^+$ requires *m/z* 454.1664, found *m/z*

454.1600. **IR** (film) ν_{max} : 2979, 1723, 1607, 1577, 1510, 1350 cm^{-1}.

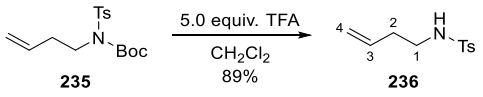
5.7.2 *tert*-Butyl but-3-en-1-yl(tosyl)carbamate (235)



But-3-en-1-ol **234** (1.000 g, 13.89 mmol), BocNHTs (4.492 g, 16.56 mmol), triphenylphosphine (4.700 g, 17.94 mmol) and DIAD (4.180 g, 20.70 mmol) were subjected to the general procedure **E** (FCC: gradient elution: 10% → 35% EtOAc - pentane) to yield **235** as a colorless oil (4.514 g, 99%). Spectroscopic properties matched those previously reported.[35]

Data for **235**: $\mathbf{R_f}$ 0.40 (40% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.78 (2H, d, *J* = 8.7 Hz, Ar), 7.29 (2H, d, *J* = 8.7 Hz, Ar), 5.73-5.86 (1H, m, 3-H), 5.03-5.16 (2H, m, 4-H_2), 3.83-3.90 (2H, m, 1-H_2), 2.50 (2H, qd, *J* = 7.2, 1.3 Hz, 2-H_2), 2.43 (3H, s, Me Ts), 1.33 (9H, s, 3 x Me Boc). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 151.1 (C=O Boc), 144.2 (C Ar), 137.6 (C Ar), 134.5 (C-3), 129.3 (2 x CH Ar), 128.0 (2 x CH Ar), 117.6 (C-4), 84.3 (CMe_3 Boc), 46.5 (C-1), 34.7 (C-2), 28.0 (3 x Me Boc), 21.7 (Me Ts). **HRMS** (ESI): calculated for $C_{16}H_{23}NO_4SNa$ $[M+Na]^+$ requires *m/z* 348.1245, found *m/z* 348.1242.

5.7.3 *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide (236)

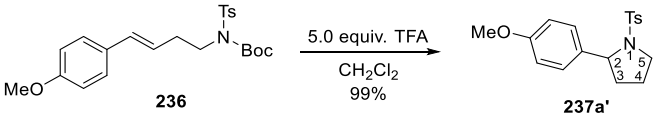


Carbamate **235** (0.989 g, 3.043 mmol) and TFA (1.16 mL, 15.2 mmol) were

subjected to general procedure **F** to yield **236** as a colorless oil (0.613 g, 89%). Spectroscopic properties matched those previously reported.[35]

Data for **236**: **R_f** 0.40 (50% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.74 (2H, d, *J* = 8.7 Hz, Ar), 7.30 (2H, d, *J* = 8.7 Hz, Ar), 5.61 (1H, ddt, *J* = 17.0, 10.5 and 7.0 Hz, 3-H), 4.98-5.07 (2H, m, 4-H_2), 4.63 (1H, br s, NH), 3.00 (2H, q, *J* = 6.5 Hz, 1-H_2), 2.42 (3H, s, Me Ts), 2.18 (2H, qt, *J* = 7.2, 1.3 Hz, 2-H_2). **^{13}C NMR (100 MHz, CDCl3) δ** 143.6 (C Ar), 137.1 (C Ar), 134.3 (C-3), 129.9 (2 x CH Ar), 127.2 (2 x CH Ar), 118.2 (C-4), 42.2 (C-1), 33.7 (C-2), 21.7 (Me Ts).

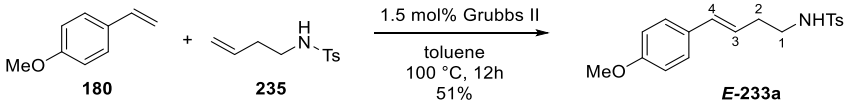
5.7.4 (±)-2-(4-Methoxyphenyl)-1-tosylpyrrolidine (237a')



Carbamate **247** (0.431 g, 1.00 mmol) and TFA (0.38 mL, 5.00 mmol) were subjected to general procedure **F** to yield side product **237a'** as a yellow solid (0.331 g, 99%). Spectroscopic properties matched those previously reported.[36]

Data for **237a'**: **R_f** 0.50 (40% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ**7.66 (2H, d, *J* = 8.3 Hz, Ar), 7.27 (2H, d, *J* = 8.3 Hz, Ar), 7.22 (2H, d, *J* = 8.7 Hz, Ar), 6.83 (2H, d, *J* = 8.7 Hz, Ar), 4.72 (1H, dd, J = 7.8, 4.0 Hz, 2-H), 3.79 (3H, s, OMe), 3.61-3.58 (1H, m, 5-H_A), 3.51-3.30 (1H, m, 5-H_B), 2.42 (3H, s, Me Ts), 1.98-1.92 (1H, m, 3-H_A), 1.90-1.74 (2H, m, 4-H_A and 3-H_B), 1.69-1.62 (1H, m, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.6 (2 x C Ar), 143.2 (C Ar), 135.1 (C Ar), 129.5 (2 x CH Ar), 127.4 (2 x CH Ar), 127.3 (2 x CH Ar), 113.6 (2 x CH Ar), 62.8 (C-2), 55.3 (OMe), 49.3 (C-5), 35.7 (C-3), 23.9 (C-4), 21.5 (Me).

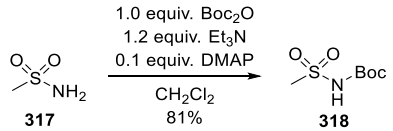
5.7.5 (3*E*)-*N*-[4-(4-methoxyphenyl)but-3-en-1-yl]-4-methylbenzenesulfonamide (*E*-233a)



4-methoxystyrene **180** (0.715 g, 5.34 mmol), sulfonamide **235** (0.600 g, 2.67 mmol) and Grubbs II (34.0 mg, 0.0401 mmol) were subjected to the general procedure **B** except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 20% → 50% Et_2O - pentane) to yield ***E*-233a** as a colorless oil (0.455 g, 51%). Spectroscopic properties matched those previously reported.[37]

Data for ***E*-233a**: $\mathbf{R_f}$ 0.50 (70% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.74 (2H, d, *J* = 8.7 Hz, Ar), 7.29 (2H, d, *J* = 8.7 Hz, Ar), 7.21 (2H, d, *J* = 8.7 Hz, Ar), 6.83 (2H, d, *J* = 8.7 Hz, Ar), 6.30 (1H, d, *J* = 15.8 Hz, 4-H), 5.82 (1H, dt, *J* = 15.8, 7.1 Hz, 3-H), 4.41 (1H, t, *J* = 6.5 Hz, NH), 3.81 (3H, s, OMe), 3.09 (2H, q, *J* = 6.5 Hz, 1-H_2), 2.43 (3H, s, Me Ts), 2.34 (2H, qd, *J* = 6.5, 1.4 Hz, 2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.3 (2 x C Ar), 143.6 (2 x C Ar), 132.9 (C-4), 129.9 (2 x CH Ar), 127.4 (2 x CH Ar), 127.3 (2 x CH Ar), 123.3 (C-3), 114.1 (2 x CH Ar), 55.5 (OMe), 42.8 (C-1), 33.1 (C-2), 21.7 (Me Ts). **HRMS** (ESI): calculated for $C_{18}H_{22}NO_3S$ $[M+H]^+$ requires *m/z* 332.1320, found *m/z* 332.1317.

5.7.6 *tert*-Butyl (methylsulfonyl)carbamate (318)

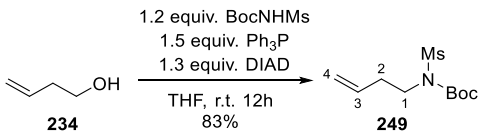


A 500-mL r.b.f. was charged with $MsNH_2$ **317** (3.000 g, 31.58 mmol, 1.0 equiv.),

DMAP (0.3855 g, 3.158 mmol, 0.1 equiv.) and 60 mL CH_2Cl_2. The mixture was cooled to 0 °C in an ice bath, and then Et_3N (5.3 mL, 37.92 mmol, 1.2 equiv.) was slowly added. Then Boc_2O (6.890 g, 31.58 mmol, 1.0 equiv.) was added, and the mixture was stirred at room temperature for 8 h. The resulting yellow mixture was concentrated under reduced pressure and re-dissolved in EtOAc. The solution was washed with 1N HCl twice, and the aqueous layer was extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4. The filtrate was concentrated under reduced pressure, and 50 mL hexanes was added to the crude residue. The mixture was refluxed under air for 1 hour. The resulting mixture was filtered, and the solids were washed with hexanes and dried under reduced pressure. The compound **318** was obtained as a white solid (4.960 g, 81%). Spectroscopic properties matched those previously reported. Spectroscopic properties matched those previously reported.[34]

Data for **318**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.52 (1H, br s, NH), 3.26 (3H, s, Me Ms), 1.50 (9H, s, 3 x Me Boc). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 150.0 (C=O Boc), 84.6 (CMe_3 Boc), 41.3 (Me Ms), 28.1 (3 x Me Boc). **HRMS** (ESI): calculated for $C_6H_{13}NO_4SNa$ $[M+Na]^+$ requires *m/z* 218.0463, found *m/z* 218.0458.

5.7.7 *tert*-Butyl but-3-en-1-yl(methylsulfonyl)carbamate (249)

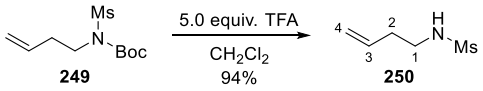


But-3-en-1-ol **234** (1.000 g, 13.89 mmol), BocNHMs **318** (3.230 g, 16.56 mmol), triphenylphosphine (4.700 g, 17.94 mmol) and DIAD (4.180 g, 20.70 mmol) were

subjected to the general procedure **E** (FCC: gradient elution: 10% → 35% EtOAc - pentane) to yield **249** as a colorless oil (2.840 g, 83%).

Data for **249**: $\mathbf{R_f}$ 0.45 (40% EtOAc - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 5.77 (1H, ddt, *J* = 17.2, 10.1, 7.1 Hz, 3-H), 5.03-5.13 (2H, m, 4-H_2), 3.76 (1H, t, *J* = 7.1 Hz, 1-H_2), 3.27 (3H, s, Me Ms), 2.38 (2H, qd, *J* = 7.1, 1.3 Hz, 2-H_2), 1.54 (9H, s, 3 x Me Boc). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 151.6 (C=O Boc), 134.8 (C-3), 177.8 (C-4), 84.5 (CMe_3 Boc), 45.7 (C-1), 42.5 (Me Ms), 34.4 (C-2), 28.1 (3 x Me Boc). **HRMS** (ESI): calculated for $C_{10}H_{19}NO_4SNa$ $[M+Na]^+$ requires *m/z* 272.0932, found *m/z* 272.0928. **IR** (film) ν_{max}: 3556, 2980, 1722, 1348, 1133, 1046 cm^{-1}.

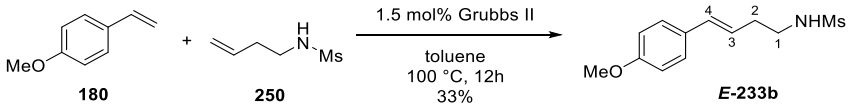
5.7.8 *N*-(but-3-en-1-yl)methanesulfonamide (250)



Carbamate **249** (1.713 g, 6.880 mmol) and TFA (2.67 mL, 34.40 mmol) were subjected to general procedure **F** to yield **250** as a colorless oil (0.979 g, 94%). Spectroscopic properties matched those previously reported.[38]

Data for **250**: $\mathbf{R_f}$ 0.40 (60% Et_2O - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 5.74 (1H, ddt, *J* = 17.1, 10.3, 6.8 Hz, 3-H), 5.09-5.18 (2H, m, 4-H_2), 4.63 (1H, br s, NH), 3.20 (2H, q, *J* = 6.5 Hz, 1-H_2), 2.95 (3H, s, Me Ms), 2.33 (2H, qt, *J* = 7.2, 1.3 Hz, 2-H_2). **^{13}C NMR** (100 MHz, CDCl3) **δ** 134.3 (C-3), 118.4 (C-4), 42.4 (C-1), 40.5 (Me Ms), 34.3 (C-2). **HRMS** (ESI): calculated for $C_5H_{11}NO_2SNa$ $[M+Na]^+$ requires *m/z* 172.0408, found *m/z* 172.0405.

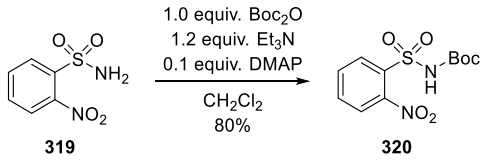
5.7.9 *tert*-Butyl (3*E*)-[4-(4-methoxyphenyl)but-3-en-1-yl](tosyl)carbamate (*E*-233b)



4-methoxystyrene **180** (0.715 g, 5.47 mmol), sulfonamide **250** (0.397 g, 2.73 mmol) and Grubbs II (34.0 mg, 0.0401 mmol) were subjected to the general procedure **B** except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 20% → 40% EtOAc - pentane) to yield ***E*-233b** as a colorless oil (0.229 g, 33%).

Data for ***E*-233b**: **R_f** 0.50 (60% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.28 (2H, d, *J* = 8.7 Hz, Ar), 6.85 (2H, d, *J* = 8.7 Hz, Ar), 6.43 (1H, d, *J* = 15.8 Hz, 4-H), 5.97 (1H, dt, *J* = 15.8, 7.1 Hz, 3-H), 4.50 (1H, t, *J* = 6.5 Hz, NH), 3.80 (3H, s, OMe), 3.09 (2H, q, *J* = 6.5 Hz, 1-H_2), 2.94 (3H, s, Me Ms), 2.46 (2H, qd, *J* = 6.5, 1.4 Hz, 2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.3 (C Ar), 132.9 (C-4), 129.7 (C Ar), 127.4 (2 x CH Ar), 123.3 (C-3), 114.1 (2 x CH Ar), 55.4 (OMe), 42.9 (C-1), 40.5 (Me Ms), 33.7 (C-2). **HRMS** (ESI): calculated for $C_{12}H_{17}NO_3SNa$ $[M+Na]^+$ requires *m/z* 278.0827, found *m/z* 278.0821. **IR** (film) ν_{max} : 3283, 2980, 2360, 1576, 1511, 1313 cm^{-1}.

5.7.10 *tert*-Butyl [(2-nitrophenyl)sulfonyl]carbamate (320)

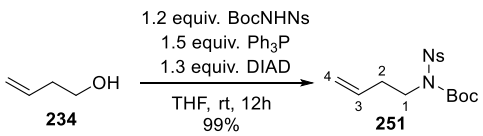


A 500-mL r.b.f. was charged with *o*-$NsNH_2$ **319** (1.000 g, 4.950 mmol, 1.0 equiv.), DMAP (0.604 g, 0.495 mmol, 0.1 equiv.) and 10 mL CH_2Cl_2. The mixture was cooled to 0 °C in an ice bath, and then Et_3N (0.83 mL, 5.940 mmol, 1.2 equiv.) was slowly added.

Then Boc_2O (1.079 g, 4.950 mmol, 1.0 equiv.) was added, and the mixture was stirred at room temperature for 8 h. The resulting yellow mixture was concentrated under reduced pressure and re-dissolved in EtOAc. The solution was washed with 1N HCl twice, and the aqueous layer was extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4. The filtrate was concentrated under reduced pressure, and 50 mL hexanes was added to the crude residue. The mixture was refluxed under air for 1 h. The resulting mixture was filtered, and the solids were washed with hexanes and dried under vacuum. The compound **320** was obtained as a white solid (1.340 g, 80%). Spectroscopic properties matched those previously reported.[39]

Data for **320**: **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 8.31-8.36 (1H, m, Ar), 7.83-7.88 (1H, m, Ar), 7.74-7.82 (2H, m, Ar), 1.43 (9H, s, 3 x Me Boc). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 148.8 (C=O Boc), 148.2 (C Ar), 134.8 (CH Ar), 133.4 (CH Ar), 132.6 (CH Ar), 132.2 (C Ar), 125.2 (CH Ar), 84.9 (CMe_3 Boc), 28.0 (3 x Me Boc). **HRMS** (ESI): calculated for $C_{11}H_{14}N_2O_6SNa$ $[M+Na]^+$ requires *m/z* 325.0470, found *m/z* 325.0463.

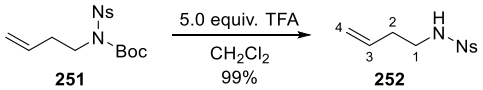
5.7.11 *tert*-Butyl but-3-en-1-yl[(2-nitrophenyl)sulfonyl]carbamate (251)



But-3-en-1-ol **234** (0.150 g, 2.08 mmol), BocNHNs (0.755 g, 2.50 mmol), triphenylphosphine (0.709 g, 2.70 mmol) and DIAD (0.630 g, 3.12 mmol) were subjected to the general procedure **E** (FCC: gradient elution: 15% → 25% EtOAc - pentane) to yield **251** as a colorless oil (0.740 g, 99%).

Data for **251**: R_f 0.50 (60% EtOAc - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 8.27-8.32 (1H, m, Ar), 7.69-7.76 (3H, m, Ar), 5.82 (1H, ddt, *J* = 17.2, 10.2, 7.0 Hz, 3-H), 5.07-5.19 (2H, m, 4-H_2), 3.79-3.86 (2H, m, 1-H_2), 2.50 (2H, qd, *J* = 7.1, 1.3 Hz, 2-H_2), 1.36 (9H, s, 3 x Me Boc). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 150.5 (C=O Boc), 147.8 (C Ar), 134.3 (C-3), 134.2 (CH Ar), 133.7 (C Ar), 133.5 (CH Ar), 131.8 (CH Ar), 124.5 (CH Ar), 117.9 (C-4), 85.1 (CMe_3 Boc), 47.5 (C-1), 34.8 (C-2), 28.0 (3 x Me Boc). **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max}: 2980, 1721, 1607, 1510, 1348, 1246 cm^{-1}.

5.7.12 *N*-(but-3-en-1-yl)-2-nitrobenzenesulfonamide (252)

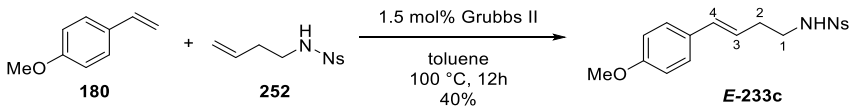


251 **252**

Carbamate **251** (0.720 g, 2.02 mmol) and TFA (0.77 mL, 10.1 mmol) were subjected to general procedure **F** to yield **252** as a colorless oil (0.535 g, 99%). Spectroscopic properties matched those previously reported.[40]

Data for **252**: R_f 0.40 (70% Et_2O - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 8.11-8.16 (1H, m, Ar), 7.84-7.89 (1H, m, Ar), 7.71-7.77 (2H, m, Ar), 5.66 (1H, ddt, *J* = 17.1, 10.3, 6.9 Hz, 3-H), 5.34 (1H, t, *J* = 6.5 Hz, NH), 5.00-5.10 (2H, m, 4-H_2), 3.18 (2H, q, *J* = 6.5 Hz, 1-H_2), 2.28 (qt, *J* = 6.5, 1.3 Hz, 2-H_2). **^{13}C NMR** (100 MHz, CDCl3) **δ** 134.0 (C Ar), 133.9 (C-3), 133.7 (CH Ar and C Ar), 132.9 (CH Ar), 131.2 (CH Ar), 125.5 (CH Ar), 118.5 (C-4), 43.0 (C-1), 33.8 (C-2). **HRMS**: stable ion was not found in ESI, EI and CI.

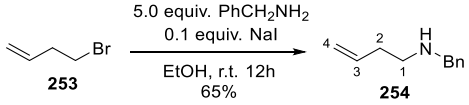
5.7.13 (3*E*)-*N*-[4-(4-methoxyphenyl)but-3-en-1-yl]-2-nitrobenzenesulfonamide (*E*-233c)



4-methoxystyrene **180** (0.715 g, 5.47 mmol), sulfonamide **252** (0.397 g, 2.73 mmol) and Grubbs II (34.0 mg, 0.0401 mmol) were subjected to the general procedure B except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 20% → 40% EtOAc - pentane) to yield ***E*-233c** as a colorless oil (0.229 g, 33%).

Data for ***E*-233c**: $\mathbf{R_f}$ 0.50 (60% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.28 (2H, d, *J* = 8.7 Hz, Ar), 6.85 (2H, d, *J* = 8.7 Hz, Ar), 6.43 (1H, d, *J* = 15.8 Hz, 4-H), 5.97 (1H, dt, *J* = 15.8, 7.1 Hz, 3-H), 4.50 (1H, t, *J* = 6.5 Hz, NH), 3.80 (3H, s, OMe), 3.09 (2H, q, *J* = 6.5 Hz, 1-H_2), 2.94 (3H, s, Me Ms), 2.46 (2H, qd, *J* = 6.5, 1.4 Hz, 2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.3 (C Ar), 132.9 (C-4), 129.7 (C Ar), 127.4 (2 x CH Ar), 123.3 (C-3), 114.1 (2 x CH Ar), 55.4 (OMe), 42.9 (C-1), 40.5 (Me Ms), 33.7 (C-2). **HRMS** (ESI): calculated for $C_{12}H_{17}NO_3SNa$ $[M+Na]^+$ requires *m/z* 278.0827, found *m/z* 278.0821. **IR** (film) ν_{max} : 3283, 2980, 2360, 1576, 1511, 1313 cm^{-1}.

5.7.14 *N*-benzylbut-3-en-1-amine (254)

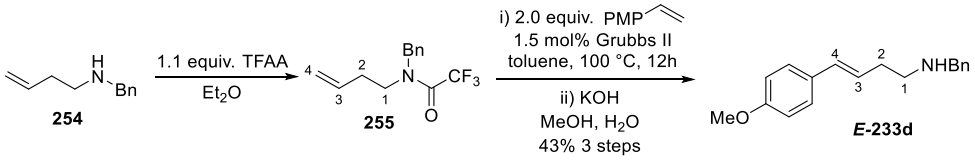


To a solution of benzylamine (4.04 mL, 37.1 mmol, 5.0 equiv.) and 4-bromo-1-butene **253** (0.75 mL, 7.41 mmol, 1.0 equiv.) in EtOH was added NaI (0.110 g, 0.741 mmol, 0.1 equiv.). The mixture was stirred and refluxed for 4 hours. Then the

solvent was removed under reduced pressure, followed by the addition of CH_2Cl_2 (5mL) and KOH (1M, 5mL). The organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified (FCC: gradient elution: 20% → 100% EtOAc - pentane) to yield **254** as a colorless oil (0.780 g, 65%). Spectroscopic properties matched those previously reported.[41]

Data for **254**: $\mathbf{R_f}$ 0.20 (60% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.29-7.34 (4H, m, Ar), 7.23-7.27 (1H, m, Ar), 5.79 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz, 3-H), 4.99-5.13 (2H, m, 4-H_2), 3.80 (2H, s, CH_2 Bn), 2.71 (2H, t, *J* = 6.9 Hz, 1-H_2), 2.29 (2H, qt, *J* = 6.9, 1.4 Hz, 2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 140.5 (C Ar), 136.6 (C-3), 128.5 (2 x CH Ar), 128.2 (2 x CH Ar), 127.0 (CH Ar), 116.5 (C-4), 54.1 (CH_2 Bn), 48.4 (C-1), 34.4 (C-2). **HRMS** (ESI): calculated for $C_{11}H_{16}N$ $[M+H]^+$ requires *m/z* 162.1283, found *m/z* 162.1277.

5.7.15 (3*E*)-*N*-benzyl-4-(4-methoxyphenyl)but-3-en-1-amine (*E*-6d)

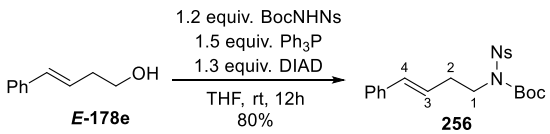


To a solution of benzylamine **254** (0.254 g, 1.56 mmol, 1.0 equiv.) in Et_2O (1.7 mL) at 0 °C was added dropwise trifluoroacetic anhydride (TFAA) (0.24 mL, 1.71 mmol, 1.1 equiv.). After stirring for 2 hours at room temperature, it was then quenched with water and the solution was extracted with Et_2O. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield **255** as a colorless oil (0.401 g) (**255** was used for the next step without purification). **255** (0.285 g), 4-methoxystyrene **180** (0.290 g, 2.16 mmol), and Grubbs II (13.8 mg, 0.0162

mmol) were subjected to the general procedure **B** except conducting the reaction in toluene at 100 °C. Finally, the crude mixture was concentrated under reduced pressure and added KOH (0.123 g, 2.16 mmol), MeOH (4 mL) and H_2O (0.5 mL); the reaction was heat under reflux for 2 hours and cooled to room temperature. It was then quenched with brine and extracted with EtOAc. The combined organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified (FCC: gradient elution: 20% → 50% EtOAc - pentane) to yield ***E*-233d** as a colorless oil (0.130 g, 43%).

Data for ***E*-233d**: **R_f** 0.50 (40% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.22-7.37 (7H, m, Ar), 6.83 (2H, d, *J* = 8.7 Hz, Ar), 6.39 (1H, d, *J* = 15.8 Hz, 4-H), 6.02 (1H, dt, *J* = 15.8, 7.1 Hz, 3-H), 3.84 (2H, s, CH_2 Bn), 3.80 (3H, s, OMe), 2.78 (2H, t, *J* = 6.9 Hz, 1-H_2), 2.45 (2H, qd, *J* = 7.0, 1.4 Hz, 2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.9 (C Ar), 139.2 (C Ar), 131.2 (C-4), 130.3 (C Ar), 128.5 (2 x CH Ar), 128.4 (2 x CH Ar), 127.2 (CH Ar), 127.1 (2 x CH Ar), 125.5 (C-3), 113.9 (2 x CH Ar), 55.3 (OMe), 53.6 (CH_2 Bn), 48.5 (C-1)**,** 33.1 (C-2). **HRMS** (ESI): calculated for $C_{18}H_{22}NO$ $[M+H]^+$ requires *m/z* 268.1701, found *m/z* 268.1695. **IR** (film) ν_{max}: 2980, 1606, 1576, 1509, 1453, 1245 cm^{-1}.

5.7.16 *tert*-Butyl (3*E*)-[(2-nitrophenyl)sulfonyl](4-phenylbut-3-en-1-yl)carbamate (256)

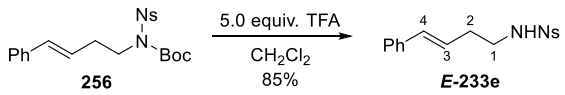


Alcohol ***E*-178e** (0.201 g, 1.36 mmol), BocNHNs (0.442 g, 1.63 mmol), triphenylphosphine (0.535 g, 2.04 mmol) and DIAD (0.359 g, 1.77 mmol) were subjected

to the general procedure **E** (FCC: gradient elution: 15% → 25% Et_2O - pentane) to yield **256** as a colorless oil (0.474 g, 80%).

Data for **256**: $\mathbf{R_f}$ 0.50 (60% Et_2O - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 8.27-8.33 (1H, m, Ar), 7.68-7.76 (3H, m, Ar), 7.33-7.39 (2H, m, Ar), 7.26-7.32 (2H, m, Ar), 7.17-7.23 (1H, m, Ar), 6.52 (1H, d, *J* = 15.8 Hz, 4-H), 6.21 (1H, dt, *J* = 15.8, 7.3 Hz, 3-H), 3.88-3.96 (2H, m, 1-H_2), 2.66 (2H, qd, *J* = 7.3, 1.4 Hz, 2-H_2), 1.33 (9H, s, 3 x Me Boc). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 150.5 (C=O Boc), 147.8 (C Ar), 137.5 (C Ar), 134.2 (CH Ar), 133.8 (C Ar), 133.4 (CH Ar), 133.0 (C-4), 131.8 (CH Ar), 128.6 (2 x CH Ar), 127.3 (CH Ar), 126.4 (2 x CH Ar), 126.0 (C-3), 124.5 (CH Ar), 85.1 (CMe_3 Boc), 47.7 (C-1), 34.1 (C-2), 28.0 (3 x Me Boc). **IR** (film) ν_{max}: 2980, 2888, 1731, 1542, 1369, 1152cm^{-1}.

5.7.17 (3*E*)-2-Nitro-*N*-(4-phenylbut-3-en-1-yl)benzenesulfonamide (*E*-233e)



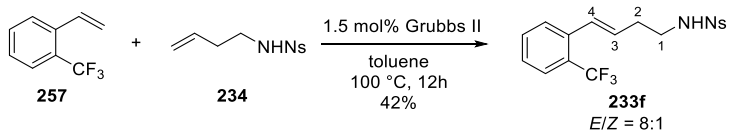
Carbamate **256** (0.454 g, 1.05 mmol) and TFA (0.40 mL, 5.26 mmol) were subjected to general procedure **F** to yield ***E*-233e** as a colorless oil (0.312 g, 85%).

Data for ***E*-233e**: $\mathbf{R_f}$ 0.40 (40% EtOAc - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 8.13 (1H, dd, *J* = 7.6, 1.6 Hz, Ar), 7.75 (1H, dd, *J* = 7.7, 1.6 Hz, Ar), 7.62-7.72 (2H, m, Ar), 7.18-7.30 (5H, m, Ar), 6.36 (1H, d, *J* = 15.8 Hz, 4-H), 5.99 (1H, dt, *J* = 15.8, 7.1 Hz, 3-H), 5.43 (1H, t, *J* = 6.5 Hz, NH), 3.29 (2H, q, *J* = 6.5 Hz, 1-H_2), 2.43 (qd, *J* = 7.1, 1.4 Hz, 2-H_2). **^{13}C NMR** (100 MHz, CDCl3) **δ** 147.9 (C Ar), 36.8 (C Ar), 133.8 (C Ar), 133.5 (C-4), 133.4 (CH Ar), 132.8 (CH Ar), 130.9 (CH Ar), 128.6 (2 x CH Ar), 127.6 (CH Ar), 126.2 (2 x CH Ar),

125.4 (CH Ar), 125.3 (C-3). **HRMS** (ESI): calculated for $C_{16}H_{16}N_2O_4SNa$ $[M+Na]^+$ requires *m/z* 355.0728, found *m/z* 355.0722. **IR** (film) ν_{max}: 3325, 2980, 2888, 1537, 1382, 1159 cm^{-1}.

5.7.18 (3*E*)-2-Nitro-*N*-{4-[2-(trifluoromethyl)phenyl]but-3-en-1-yl}benzenesulfonamide (*E*-233f)

(3*Z*)-2-Nitro-*N*-{4-[2-(trifluoromethyl)phenyl]but-3-en-1-yl}benzenesulfonamide (*Z*-233f)



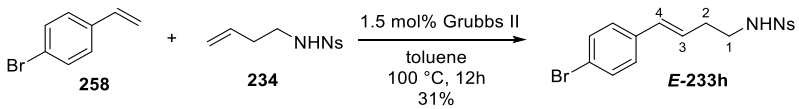
1-(Trifluoromethyl)-2-vinylbenzene **257** (0.153 g, 0.888 mmol), sulfonamide **234** (0.114 g, 0.445 mmol) and Grubbs II (5.7 mg, 0.067 mmol) were subjected to the general procedure **B** except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 15% → 25% EtOAc - pentane) to yield a 8:1 mixture of ***E*-233f** and ***Z*-233f** (0.075 g, 42%), which was partially separable into 2 fractions: first fraction of ***E*-233f** (0.018g, 10%) as a yellow oil, and second fraction of 6:1 of diastereomers ***E*-233f** and ***Z*-233f** as a yellow oil (0.060 mg, 32%).

Data for ***E*-233f**: $\mathbf{R_f}$ 0.45 (35% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.15 (1H, dd, *J* = 7.2, 1.9 Hz, Ar), 7.82 (1H, dd, *J* = 7.2, 1.9 Hz, Ar), 7.66-7.33 (2H, m, Ar), 7.57-7.61 (1H, m, Ar), 7.44-7.53 (2H, m, Ar), 7.29-7.34 (1H, m, Ar), 6.73 (1H, d, *J* = 15.5 Hz, 4-H), 6.05 (1H, dt, *J* = 15.5, 7.1 Hz, 3-H), 5.40 (1H, t, *J* = 6.6 Hz, NH), 3.31 (2H, q, *J* = 6.6 Hz, 1-H_2), 2.49 (2H, qd, *J* = 6.6, 1.5 Hz, 2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 148.2 (C

Ar), 136.0 (C Ar), 134.1 (C Ar), 133.6 (CH Ar), 132.9 (CH Ar), 132.0 (CH Ar), 131.1 (CH Ar), 129.9 (C Ar and C-3), 129.5 (C-4), 127.47 (CH Ar), 127.45 (CH Ar), 127.4 (CH Ar), 125.9 (q, *J* = 5.6 Hz, CF_3), 125.6 (CH Ar), 43.5 (C-1), 33.5 (C-2). **IR** (film) ν_{max}: 3342, 2980, 2888, 2360, 1538, 1381 cm^{-1}.

Data for ***Z*-233f** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.02-8.05 (1H, m, Ar), 7.83-7.86 (1H, m, Ar), 7.79-7.82 (1H, m, Ar), 7.64-7.74 (1H, m, Ar), 7.61-7.64 (1H, m, Ar), 7.42-7.48 (1H, m, Ar), 7.34-7.37 (1H, m, Ar), 7.21-7.25 (1H, m, Ar), 6.70-6.75 (1H, m, 4-H), 5.69 (1H, dt, *J* = 11.5, 7.4 Hz, 3-H), 5.35 (1H, t, *J* = 6.9 Hz, NH), 3.15 (2H, q, *J* = 6.9 Hz, 1-H_2), 2.34 (qd, *J* = 6..9, 1.7 Hz, 2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 148.1 (C Ar), 135.5 (C Ar), 133.7 (CH Ar), 133.6 (C Ar), 132.89 (C Ar), 132.86 (CH Ar), 131.7 (CH Ar), 131.2 (CH Ar), 131.0 (CH Ar), 130.8 (CH Ar), 129.34 (C-3), 129.32 (C-4), 127.3 (CH Ar), 125.9 (q, *J* = 5.6 Hz, CF_3), 125.5 (CH Ar), 46.1 (C-1), 28.9 (C-2).

5.7.19 (3*E*)-*N*-[4-(4-bromophenyl)but-3-en-1-yl]-2-nitrobenzenesulfonamide (*E*-233g)

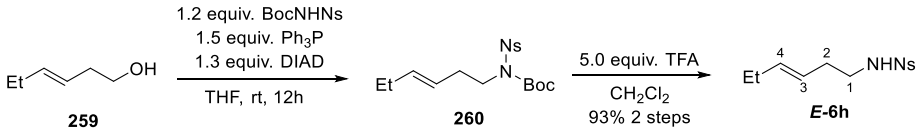


1-Bromo-4-vinylbenzene **258** (0.11 mL, 0.814 mmol), sulfonamide **234** (0.104 g, 0.407 mmol) and Grubbs II (5.2 mg, 0.061 mmol) were subjected to the general procedure **B** except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 15% → 25% EtOAc - pentane) to yield ***E*-233g** (0.052 g, 31%) as a colorless oil.

Data for ***E*-233g**: **R_f** 0.45 (40% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.14 (1H, dd, *J* = 7.6, 1.7 Hz, Ar), 7.79 (1H, dd, *J* = 7.6, 1.6 Hz, Ar), 7.65-7.74 (2H, m, Ar), 7.40

(2H, d, *J* = 8.5 Hz, Ar), 7.11 (2H, d, *J* = 8.5 Hz, Ar), 6.31 (1H, d, *J* = 15.9 Hz, 4-H), 6.00 (1H, dt, *J* = 15.8, 7.1 Hz, 3-H), 5.37 (1H, t, *J* = 6.5 Hz, NH), 3.28 (2H, q, *J* = 6.5 Hz, 1-H_2), 2.43 (2H, qd, *J* = 6.5, 1.4 Hz, 2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 135.8 (C Ar), 134.0 (2 x C Ar), 133.6 (CH Ar), 132.9 (CH Ar), 132.5 (C-4), 131.8 (2 x CH Ar), 131.1 (CH Ar), 127.8 (2 x CH Ar), 126.2 (C-3), 125.6 (CH Ar), 121.4 (C Ar), 43.4 (C-1), 33.3 (C-2). **HRMS** (ESI): calculated for $C_{16}H_{15}N_2O_4SBrNa$ $[M+Na]^+$ requires *m/z* 432.9834, found *m/z* 432.9828. **IR** (film) ν_{max}: 3334, 2980, 2888, 2360, 1536, 1382cm^{-1}.

5.7.20 (3*E*)-*N*-(hex-3-en-1-yl)-2-nitrobenzenesulfonamide (*E*-233h)

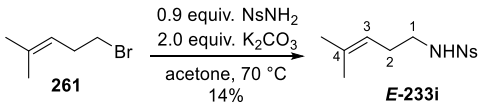


Alcohol **259** (0.100 g, 1.00 mmol), BocNHNs (0.362 g, 1.20 mmol), triphenylphosphine (0.393 g, 1.50 mmol) and DIAD (0.263 g, 1.30 mmol) were subjected to the general procedure **E**. The resulting yellow oil and TFA (0.570 g, 5.00 mmol) were subjected to the general procedure **F** (FCC: gradient elution: 25% → 45% EtOAc - pentane) to yield ***E*-233h** as a colorless oil (0.264 g, 93%).

Data for ***E*-233h**: **R_f** 0.50 (60% EtOAc - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 8.11-8.16 (1H, m, Ar), 7.84-7.89 (1H, m, Ar), 7.70-7.77 (2H, m, Ar), 5.49 (1H, dtt, *J* = 15.3, 6.3, 1.4 Hz, 3-H), 5.33 (1H, t, *J* = 5.4 Hz, NH), 5.21 (1H, dtt, *J* = 15.3, 6.9, 1.4 Hz, 4-H), 3.14 (2H, td, *J* = 6.3, 5.4 Hz, 1-H_2), 2.14-2.24 (2H, m, 2-H_2), 1.97 (1H, qdd, *J* = 7.5, 6.2, 1.4 Hz, CH_2 Et), 0.93 (3H, t, *J* = 7.5 Hz, CH_3 Et). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 147.4 (C Ar), 136.8 (C-3), 134.1 (C Ar), 133.6 (CH Ar), 132.9 (CH Ar), 131.2 (CH Ar), 125.5 (CH Ar), 124.0 (C-4),

43.5 (C-1), 32.6 (C-2), 25.7 (CH_2 Et), 13.7 (CH_3 Et). **HRMS** (ESI): calculated for $C_{12}H_{16}N_2O_4SNa$ $[M+Na]^+$ requires *m/z* 307.0728, found *m/z* 307.0723. **IR** (film) ν_{max}: 3297, 3980, 1536, 1440, 1361, 1161 cm^{-1}.

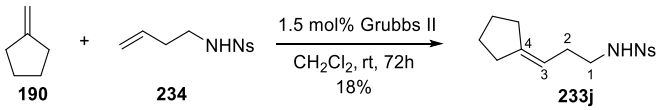
5.7.21 *N*-(4-methylpent-3-en-1-yl)-2-nitrobenzenesulfonamide (*E*-233i)



To a r.b.f. charged with a magnetic stir bar was added bromide **261** (0.500 g, 3.01 mmol, 1.1 equiv.), 2-nitrobenzenesulfonamide (0.553 g, 2.74 mmol, 1.0 equiv.), K_2CO_3 (0.755 g, 5.47 mmol, 2.0 equiv.) and acetone (3 mL). The reaction mixture was heat at 60 °C for 16 hours. The reaction mixture was filtered through a plug of Celite and washed with EtOAc, the filtrate was then concentrated under reduced pressure, which was purified (FCC: gradient elution: 10% → 15% EtOAc - pentane) to yield ***E*-233i** as a yellow oil (0.107 g, 14%).

Data for ***E*-233i**: $\mathbf{R_f}$ 0.40 (30% EtOAc - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 8.11-8.15 (1H, m, Ar), 7.84-7.89 (1H, m, Ar), 7.70-7.77 (2H, m, Ar), 5.28 (1H, t, *J* = 6.6 Hz, NH), 4.94 (1H, tp, *J* = 7.4, 1.5 Hz, 3-H), 3.10 (2H, q, *J* = 6.6 Hz, 1-H_2), 2.22 (2H, q, *J* = 7.0 Hz, 2-H_2), 1.66 (3H, s, Me), 1.56 (3H, s, Me). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 148.2 (C Ar), 136.2 (C-4), 134.0 (C Ar), 133.6 (CH Ar), 132.9 (CH Ar), 131.2 (CH Ar), 125.5 (CH Ar), 119.5 (C-3), 43.8 (C-1), 28.2 (C-2), 25.9 (Me), 18.0 (Me). **HRMS** (ESI): calculated for $C_{12}H_{16}N_2O_4SNa$ $[M+Na]^+$ requires *m/z* 307.0728, found *m/z* 307.0722. **IR** (film) ν_{max}: 3341, 2980, 1538, 1408, 1338, 1162 cm^{-1}.

5.7.22 *N*-(3-cyclopentylidenepropyl)-2-nitrobenzenesulfonamide (233j)

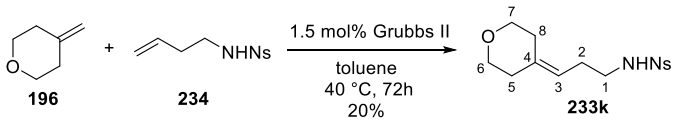


190 **234** **233j**

Methylenecyclopentane **190** (1.00 g, 12.2 mmol), sulfonamide **234** (0.625 g, 2.44 mmol) and Grubbs II (31.0 mg, 0.0366 mmol) were subjected to the general procedure **B** except conducting the reaction for 72 hours (FCC: gradient elution: 10% → 15% EtOAc - pentane) to yield **233j** (0.134 g, 18%) as a colorless oil.

Data for **233j**: $\mathbf{R_f}$ 0.40 (30% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.10-8.15 (1H, m, Ar), 7.83-7.88 (1H, m, Ar), 7.70-7.76 (2H, m, Ar), 5.30 (1H, t, *J* = 6.4 Hz, NH), 5.05 (1H, tt, *J* = 7.3, 2.3 Hz, 3-H), 3.11 (2H, q, *J* = 6.4 Hz, 1-H_2), 2.06-2.24 (7H, m, 2-H_2, CH cyclopentyl and 2 x CH_2 cyclopentyl), 1.51-1.68 (5H, m, CH cyclopentyl and 2 x CH_2 cyclopentyl). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 148.2 (C Ar), 134.0 (C Ar), 133.6 (CH Ar), 132.9 (CH Ar), 131.3 (C-4), 131.2 (CH Ar), 125.5 (CH Ar), 114.9 (C-3), 43.7 (C-1), 33.8 (CH_2 cyclopentyl), 29.8 (CH_2 cyclopentyl), 29.0 (CH_2 cyclopentyl), 26.4 and 26.3 (CH_2 cyclopentyl and C-2). **HRMS** (ESI): calculated for $C_{16}H_{15}N_2O_4SBrNa$ $[M+Na]^+$ requires *m/z* 432.9834, found *m/z* 432.9828. **IR** (film) ν_{max}: 3341, 2980, 2888, 1538, 1340, 1163 cm^{-1}.

5.7.23 2-Nitro-*N*-[3-(tetrahydro-4H-pyran-4-ylidene)propyl]benzenesulfonamide (233k)



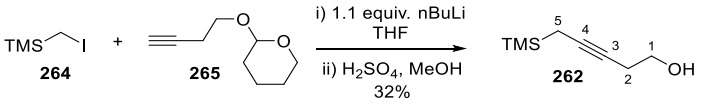
196 **234** **233k**

4-Methylenetetrahydro-2*H*-pyran **196** (0.156 g, 0.796 mmol), sulfonamide **234** (0.102 g, 0.398 mmol) and Grubbs II (5.1 mg, 0.0060 mmol) were subjected to the

general procedure **B** except conducting the reaction in toluene at 40 °C for 72 hours (FCC: gradient elution: 15% → 40% EtOAc - pentane) to yield **233k** (0.134 g, 20%) as a colorless oil.

Data for **233k**: $\mathbf{R_f}$ 0.40 (50% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.11-8.16 (1H, m, Ar), 7.83-7.88 (1H, m, Ar), 7.70-7.76 (2H, m, Ar), 5.31 (1H, t, *J* = 6.6 Hz, NH), 5.05 (1H, t, *J* = 7.5 Hz, 3-H), 3.66 and 3.63 (6H, t, *J* = 5.5 Hz, 6-H_2 and 7-H_2), 3.11 (2H, q, *J* = 6.6 Hz, 1-H_2), 2.28 (2H, q, *J* = 7.0 Hz, 2-H_2), 2.22 and 2.18 (6H, t, *J* = 5.5 Hz, 5-H_2 and 8-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 139.0 (C Ar), 133.9 (C Ar), 133.7 (CH Ar), 132.9 (CH Ar), 131.3 (CH Ar and C-4), 125.6 (CH Ar), 118.1 (C-3), 69.6 and 68.8 (C-6 and C-7), 43.7 (C-1), 37.1 and 29.9 (C-5 and C-8), 27.3 (C-2). **IR** (film) ν_{max}: 3199, 2980, 2888, 2360, 1382, 1251 cm^{-1}.

5.7.24 5-(Trimethylsilyl)pent-3-yn-1-ol (262)



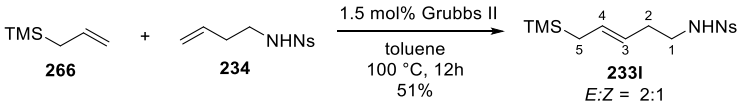
To a solution of THP ether protected propargyl alcohol **264** (1.476 g, 9.584 mmol, 1.0 equiv.) in dry THF (4.0 mL) at –30 °C under argon was added dropwisely a solution of *n*-BuLi (2.5 M in hexane, 4.2 mL, 10.54 mmol, 1.1 equiv.). The mixture was stirred for 15 min. at –30 °C and another 15 min. at 0 °C, iodomethyltrimethylsilane **265** (2.193 g, 10.26 mmol, 1.07 equiv.) was added slowly. Next, the reaction flask was wrapped with aluminum foil and was left overnight at 60 °C. After cooling to rt, the mixture was diluted with diethyl ether/pentane mixture (1:1, 20 mL). It was washed with water and

brine dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude mixture was dissolved in methanol (17.0 mL), added with 0.001 mL conc. H_2SO_4 and the solution was stirred at room temperature overnight. The mixture was then dissolved in diethyl ether/pentane mixture (1:1, 20 mL) and washed successively with saturated $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. FCC (gradient elution: 20% → 50% Et_2O - pentane) addorded **262** as a colorless oil (0.130 g, 43%). Spectroscopic properties matched those previously reported.[42]

Data for **262**: $\mathbf{R_f}$ 0.45 (50% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 3.66 (2H, q, *J* = 6.2 Hz, 1-H_2), 2.43 (2H, tt, *J* = 6.2, 2.7 Hz, 2-H_2), 1.75 (1H, t, *J* = 6.2 Hz, OH), 1.45 (2H, t, *J* = 2.7 Hz, 5-H_2), 0.09 (9H, s, 3 x Me TMS). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 80.3 and 75.0 (C-3 and C-4), 61.8 (C-1), 23.5 (C-2), 7.1 (C-5), -1.95 (3 x Me TMS).

5.7.25 (3*E*)-2-nitro-*N*-[5-(trimethylsilyl)pent-3-en-1-yl]benzenesulfonamide (*E*-233l)

(3*Z*)-2-nitro-*N*-[5-(trimethylsilyl)pent-3-en-1-yl]benzenesulfonamide (*Z*-233l)



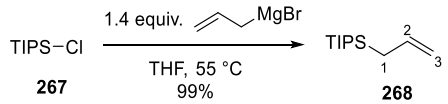
Allyltrimethylsliane **266** (1.179 g, 10.35 mmol), sulfonamide **234** (0.530 g, 2.07 mmol) and Grubbs II (26.3 mg, 0.0311 mmol) were subjected to the general procedure **B** except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 10% → 15% EtOAc - pentane) to yield an inseparable 2:1 mixture of ***E*-233l** and ***E*-233l** as a yellow oil (0.361 g, 51%).

Data for ***E*-233l** (from the mixture): $\mathbf{R_f}$ 0.40 (30% EtOAc - pentane). **^{1}H NMR (400**

MHz, $CDCl_3$) δ 8.11-8.16 (1H, m, Ar), 7.83-7.88 (1H, m, Ar), 7.70-7.76 (2H, m, Ar), 5.45 (1H, dtt, *J* = 15.1, 8.1, 1.3 Hz, 4-H), 5.30 (1H, t, *J* = 6.5 Hz, NH), 5.03-5.12 (1H, m, 3-H), 3.07-3.14 (2H, m, 1-H_2), 2.15-2.25 (2H, m, 2-H_2), 1.34-1.45(2H, m, 5-H_2), -0.04 (9H, m, 3 x Me TMS). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 148.3 (C Ar), 134.0 (C Ar), 133.59 (CH Ar), 132.87 (CH Ar), 131.24 (CH Ar), 131.23 (C-4), 125.5 (CH Ar), 123.3 (C-3), 43.9 (C-1), 32.9 (C-2), 23.1 (C-5), -1.88 (3 x Me TMS). **HRMS** (ESI): calculated for $C_{14}H_{22}N_2O_4SSiNa$ $[M+Na]^+$ requires *m/z* 365.0967, found *m/z* 365.0963. **IR** (film) ν_{max}: 3345, 2980, 2889, 1539, 1342, 1164 cm^{-1}.

Data for ***Z*-233l** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.11-8.16 (1H, m, Ar), 7.83-7.88 (1H, m, Ar), 7.70-7.76 (2H, m, Ar), 5.50-5.58 (1H, m, 4-H), 5.32 (1H, t, *J* = 6.5 Hz, NH), 5.03-5.12 (1H, m, 3-H), 3.07-3.14 (2H, m, 1-H_2), 2.15-2.25 (2H, m, 2-H_2), 1.34-1.45(2H, m, 5-H_2), -0.03 (9H, m, 3 x Me TMS). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 141.4 (C Ar), 135.1 (C Ar), 133.61 (CH Ar), 132.91 (CH Ar), 131.3 (CH Ar), 130.1 (C-4), 125.6 (CH Ar), 121.8 (C-3), 43.8 (C-1) , 27.3 (C-2), 19.0 (C-5), -1.70 (3 x Me TMS).

5.7.26 Allyltriisopropylsilane (268)



267 **268**

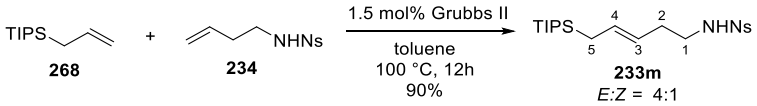
Triisopropylsilyl chloride **267** (1.10 mL, 5.21 mmol), allylmagnesium bromide (1M, 7.30 mL, 7.30 mmol) and THF (1.5 mL) were subjected to the general procedure **G** except using 1.4 equivalents of allylmagnesium bromide and conducting the reaction at 55 °C (FCC: gradient elution: 0% → 5% Et_2O - pentane) to yield **268** as a colorless oil

(1.020 g, 99%). Spectroscopic properties matched those previously reported.[43]

Data for **268**: **R_f** 0.40 (2% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 5.88 (1H, ddt, *J* = 16.9, 10.0, 8.1 Hz, 2-H), 4.76-4.97 (2H, m, 3-H_2), 1.64 (2H, d, *J* = 8.1 Hz, 1-H_2), 1.06 (18H, s, 6 x Me TIPS), 1.03-1.08 (3H, m, 3 x CH TIPS). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 136.4 (C-2), 112.9 (C-3), 18.8 (6 x Me TIPS), 11.2 (3 x $CH(Me)_2$ TIPS).

5.7.27 (3*E*)-2-nitro-*N*-[5-(triisopropylsilyl)pent-3-en-1-yl]benzenesulfonamide (*E*-233m)

(3*Z*)-2-nitro-*N*-[5-(triisopropylsilyl)pent-3-en-1-yl]benzenesulfonamide (*Z*-233m)



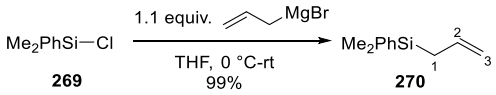
Allyltriisopropylsilane **268** (0.790 g, 4.00 mmol), sulfonamide **234** (0.511 g, 2.00 mmol) and Grubbs II (25.4 mg, 0.0300 mmol) were subjected to the general procedure **B** except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 10% → 15% Et_2O - pentane) to yield an inseparable 4:1 mixture of ***E*-233m** and ***E*-233m** as a yellow oil (0.770 g, 90%).

Data for ***E*-233m** (from the mixture): **R_f** 0.30 (45% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.11-8.16 (1H, m, Ar), 7.83-7.88 (1H, m, Ar), 7.70-7.76 (2H, m, Ar), 5.51 (1H, dtt, *J* = 15.3, 8.1, 1.3 Hz, 4-H), 5.29 (1H, t, *J* = 5.9 Hz, NH), 5.13 (1H, dtt, *J* = 15.3, 6.9, 1.3 Hz, 3-H), 3.10 (2H, td, *J* = 6.9, 5.9 Hz, 1-H_2), 2.18 (2H, qd, *J* = 6.9, 1.2 Hz, 2-H_2), 1.52 (2H, dd, *J* = 8.1, 1.3 Hz, 5-H_2), 1.01 (18H, s, 6 x Me TIPS), 0.97-1.04 (3H, m, 3 x CH TIPS).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3 (C Ar), 134.1 (C Ar), 133.58 (CH Ar), 132.8 (CH Ar), 132.0 (C-4), 131.2 (CH Ar), 125.47 (CH Ar), 123.3 (C-3), 43.84 (C-1), 33.0 (C-2), 18.8 (6 x Me TIPS), 15.7 (C-5), 11.1 (3 x $CH(Me)_2$ TIPS). **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max}: 3347, 2980, 2888, 1540, 1382, 1164 cm^{-1}.

Data for ***Z*-233m** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.11-8.16 (1H, m, Ar), 7.83-7.88 (1H, m, Ar), 7.70-7.76 (2H, m, Ar), 5.50-5.58 (1H, m, 3-H), 5.63 (1H, dtt, *J* = 10.2, 8.6, 1.6 Hz, 4-H), 5.34 (1H, d, *J* = 5.9 Hz, NH), 5.00-5.08 (1H, m, 3-H), 3.14 (1H, td, *J* = 6.9, 5.9 Hz, 1-H_2), 2.29 (2H, qd, *J* = 6.9, 1.6 Hz, 2-H_2), 1.52 (2H, dd, *J* = 8.6, 1.3 Hz, 5-H_2), 1.01 (18H, s, 6 x Me TIPS), 0.97-1.04 (3H, m, 3 x CH TIPS). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 148.3 (C Ar), 134.1 (C Ar), 133.61 (CH Ar), 132.9 (CH Ar), 131.3 (CH Ar), 130.9 (C-4), 125.51 (CH Ar), 121.7 (C-3), 43.8 (C-1), 27.4 (C-2), 18.8 (6 x Me TIPS), 11.2 (C-5 and 3 x $CH(Me)_2$ TIPS).

5.7.28 Allyldimethyl(phenyl)silane (270)



269 **270**

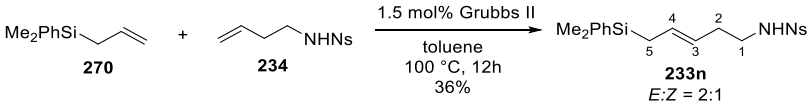
Chloro(dimethyl)phenylsilane **269** (1.00 mL, 5.98 mmol), allylmagnesium bromide (1M, 7.2 mL, 7.20 mmol) and THF (1.5 mL) were subjected to the general procedure **G** except using 1.2 equivalents of Allylmagnesium bromide (FCC: gradient elution: 0% → 5% Et_2O - pentane) to yield **270** as a colorless oil (1.052 g, 99%). Spectroscopic properties matched those previously reported.[44]

Data for **270**: **R_f** 0.40 (2% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.50-7.55

(2H, m, Ar), 7.34-7.39 (3H, m, Ar), 5.79 (1H, ddt, *J* = 16.9, 10.2, 8.1 Hz, 2-H), 4.83-4.91 (2H, m, 3-H_2), 1.77 (2H, dt, *J* = 8.1, 1.2 Hz, 1-H_2), 0.30 (6H, s, 2 x Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 138.8 (C Ar), 134.8 (C-2), 133.8 (2 x CH Ar), 129.1 (CH Ar), 127.9 (2 x CH Ar), 113.5 (C-3), 23.8 (C-1), -3.4 (2 x Me).

5.7.29 (3*E*)-2-nitro-*N*-{5-[dimethyl(phenyl)silyl]pent-3-en-1-yl}benzenesulfonamide (*E*-233n)

(3*Z*)-2-nitro-*N*-{5-[dimethyl(phenyl)silyl]pent-3-en-1-yl}benzenesulfonamide (*Z*-233n)



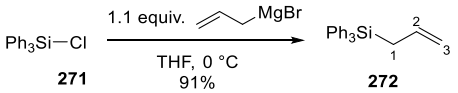
Allyldimethyl(phenyl)silane **270** (0.260 g, 1.48 mmol), sulfonamide **234** (0.207 g, 0.809 mmol) and Grubbs II (10.3 mg, 0.0121 mmol) were subjected to the general procedure **B** except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 15% → 20% Et_2O - pentane) to yield an inseparable 2:1 mixture of ***E*-233n** and ***E*-233n** as a yellow oil (0.188 g, 36%).

Data for ***E*-233n** (from the mixture): **R_f** 0.40 (60% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.06-8.13 (1H, m, Ar), 7.80-7.86 (1H, m, Ar), 7.68-7.74 (2H, m, Ar), 7.41-7.49 (2H, m, Ar), 7.30-7.39 (3H, m, Ar), 5.58 (1H, dtt, *J* = 15.3, 8.4, 1.4 Hz, 4-H), 5.25 (1H, t, *J* = 6.5 Hz, NH), 5.11-5.20 (1H, m, 3-H), 3.06 (2H, q, *J* = 6.5 Hz, 1-H_2), 2.05-2.10 (2H, m, 2-H_2), 1.54-1.68 (2H, m, 5-H_2), 0.22 (6H, s, 2 x Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 138.0 (C Ar), 134.1 (C Ar), 133.9 (C Ar), 133.6 (CH Ar), 133.5 (2 x CH Ar), 133.4 (CH Ar),

132.7 (C-4), 131.1 (CH Ar), 129.2 (CH Ar), 127.8 (CH Ar), 127.77 (CH Ar), 125.3 (CH Ar), 122.7 (C-3), 43.7 (C-1), 32.8 (C-2), 21.95 (C-5), -3.47 (2 x Me). **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max}: 3350, 2980, 2888, 1538, 1382, 1072 cm^{-1}.

Data for ***Z*-233n** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.06-8.13 (1H, m, Ar), 7.80-7.86 (1H, m, Ar), 7.68-7.74 (2H, m, Ar), 7.41-7.49 (2H, m, Ar), 7.30-7.39 (3H, m, Ar), 5.36-5.46 (1H, m, 4-H), 5.25 (1H, t, *J* = 6.5 Hz, NH), 5.03-5.10 (1H, m, 3-H), 2.99 (2H, q, *J* = 6.8 Hz, 1-H_2), 2.05-2.10 (2H, m, 2-H_2), 1.54-1.68 (2H, m, 5-H_2), 0.24 (6H, s, 2 x Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 138.0 (C Ar), 134.1 (C Ar), 133.9 (C Ar), 133.6 (CH Ar), 133.5 (2 x CH Ar), 133.4 (CH Ar), 131.06 (CH Ar), 130.3 (C-4), 129.0 (CH Ar), 127.9 (CH Ar), 127.77 (CH Ar), 125.3 (CH Ar), 124.1 (C-3), 43.5 (C-1), 27.2 (C-2), 22.03 (C-5), -3.43 (2 x Me).

5.7.30 Allyltriphenylsilane (272)



271 **272**

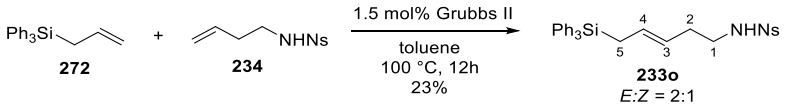
Chlorotriphenylsilane **271** (1.000 g, 3.401 mmol), allylmagnesium bromide (1M, 3.70 mL, 3.70 mmol) and THF (1.8 mL) were subjected to the general procedure **G** (FCC: gradient elution: 0% → 5% Et_2O - pentane) to yield **272** as a colorless oil (0.928 g, 91%). Spectroscopic properties matched those previously reported.[45]

Data for **272**: **R_f** 0.40 (2% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.50-7.56 (5H, m, Ar), 7.32-7.44 (10H, m, Ar), 5.88 (1H, ddt, *J* = 17.0, 10.1, 7.9 Hz, 2-H), 4.85-5.00 (2H, m, 3-H_2), 2.41 (2H, dt, *J* = 7.8, 1.4 Hz, 1-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 135.9 (6 x

CH Ar), 134.8 (3 x C Ar), 134.0 (C-2), 129.7 (3 x CH Ar), 128.0 (6 x CH Ar), 115.2 (C-3), 21.4 (C-1).

5.7.31 (3*E*)-2-nitro-*N*-[5-(triphenylsilyl)pent-3-en-1-yl]benzenesulfonamide (*E*-233o)

(3*Z*)- 2-nitro-*N*-[5-(triphenylsilyl)pent-3-en-1-yl]benzenesulfonamide (*Z*-233o)

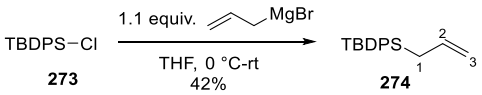


Allyltriphenylsilane **272** (0.260 g, 1.48 mmol), sulfonamide **234** (0.207 g, 0.809 mmol) and Grubbs II (10.3 mg, 0.0121 mmol) were subjected to the general procedure **B** except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 15% → 20% Et_2O - pentane) to yield an inseparable 2:1 mixture of ***E*-233o** and ***E*-233o** as a yellow oil (0.160 g, 23%).

Data for ***E*-233o** (from the mixture): $\mathbf{R_f}$ 0.40 (60% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.91-8.01 (1H, m, Ar), 7.64-7.74 (1H, m, Ar), 7.52-7.61 (2H, m, Ar), 7.33-7.43 (6H, m, Ar), 7.20-7.32 (9H, m, Ar), 5.33-5.34 (1H, m 4-H), 5.50 (1H, t, *J* = 6.6 Hz, NH), 4.95-5.04 (1H, m 3-H), 2.87 (2H, q, *J* = 6.6 Hz, 1-H_2), 2.12-2.20 (1H, m 5-H_2), 1.94-2.02 (1H, m 2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 148.0 (C Ar), 135.9 (C Ar), 135.71 (4 x CH Ar), 135.70 (2 x CH Ar), 135.0 (C Ar), 134.1 (C Ar), 133.8 (C Ar), 133.59 (CH Ar), 132.75 (CH Ar), 130.99 (CH Ar), 129.73 (CH Ar), 129.66 (2 x CH Ar), 129.2 (C-4), 127.94 (2 x CH Ar), 127.93 (4 x CH Ar), 125.8 (C-3), 125.3 (CH Ar), 43.6 (C-1), 32.9 (C-2), 19.6 (C-5). **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max}: 3346, 2980, 2888, 1538, 1381, 1163 cm^{-1}.

Data for ***Z*-233o** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.91-8.01 (1H, m, Ar), 7.64-7.74 (1H, m, Ar), 7.52-7.61 (2H, m, Ar), 7.33-7.43 (6H, m, Ar), 7.20-7.32 (9H, m, Ar), 5.45-5.50 (1H, m 4-H), 5.50 (1H, t, *J* = 6.6 Hz, NH), 4.95-5.04 (1H, m 3-H), 2.74 (2H, q, *J* = 6.6 Hz, 1-H_2), 2.12-2.20 (1H, m 5-H_2), 1.82-1.88 (1H, m 2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 148.0 (C Ar), 135.9 (C Ar), 135.65 (4 x CH Ar), 135.63 (2 x CH Ar), 135.0 (C Ar), 134.1 (C Ar), 133.8 (C Ar), 133.63 (CH Ar), 132.81 (CH Ar), 131.03 (CH Ar), 130.4 (C-4), 130.1 (CH Ar), 129.8 (2 x CH Ar), 128.1 (2 x CH Ar), 128.0 (4 x CH Ar), 125.2 (CH Ar), 124.0 (C-3), 43.3 (C-1), 27.3 (C-2), 15.5 (C-5).

5.7.32 Allyl(*tert*-butyl)diphenylsilane (274)



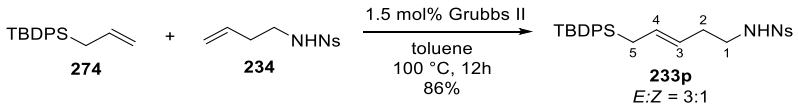
273 **274**

tert-Butylchlorodiphenylsilane **273** (1.00 mL, 3.91 mmol), allylmagnesium bromide (1M, 4.30 mL, 4.30 mmol) and THF (2.3 mL) were subjected to the general procedure G (FCC: gradient elution: 0% → 5% Et_2O - pentane) to yield **274** as a colorless oil (0.458 g, 42%). Spectroscopic properties matched those previously reported.[46]

Data for **274**: **R_f** 0.40 (2% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.59-7.65 (4H, m, Ar), 7.32-7.43 (6H, m, Ar), 5.79 (1H, ddt, *J* = 17.0, 10.0, 7.9 Hz, 2-H), 4.92 (1H, dq, *J* = 17.0, 1.6 Hz, 3-H_A), 4.81 (1H, ddt, *J* = 10.0, 2.1, 1.2 Hz, 3-H_B), 2.20 (2H, dt, *J* = 7.9, 1.3 Hz, 1-H_2), 1.08 (9H, s, 3 x Me ^{t}Bu). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 136.2 (4 x CH Ar), 134.8 (2 x C Ar), 134.6 (C-2), 129.2 (2 x CH Ar), 127.7 (4 x CH Ar), 114.6 (C-3), 28.0 (C-1), 18.9 (3 x Me ^{t}Bu), 18.6 (CMe_3 ^{t}Bu).

5.7.33 (3*E*)-2-nitro-*N*-[5-(*tert*-butyldiphenylsilyl)pent-3-en-1-yl]benzenesulfonamide (*E*-233p)

(3*Z*)-2-nitro-*N*-[5-(*tert*-butyldiphenylsilyl)pent-3-en-1-yl]benzenesulfonamide (*Z*-233p)

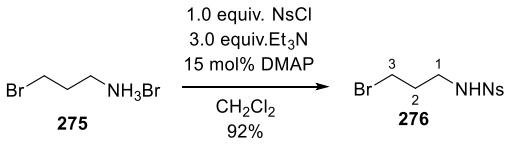


Allyl(*tert*-butyl)diphenylsilane **274** (0.387 g, 1.38 mmol), sulfonamide **234** (0.177 g, 0.691 mmol) and Grubbs II (8.8 mg, 0.0104 mmol) were subjected to the general procedure B except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 15% → 25% Et_2O - pentane) to yield a 3:1 mixture of ***E*-233p** and ***E*-233p**, which was partially separable into 2 fractions: first fraction of 16:1 of diastereomers ***E*-233p** and ***Z*-233p** (0.018 g, 1%) as a yellow oil, and second fraction of 3:1 of diastereomers ***E*-233p** and ***Z*-233p** as a yellow oil (0.285 g, 85%).

Data for ***E*-233p**: $\mathbf{R_f}$ 0.50 (60% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.03-8.08 (1H, m, Ar), 7.78-7.82 (1H, m, Ar), 7.65-7.71 (2H, m, Ar), 7.52-7.58 (4H, m, Ar), 7.30-7.41 (6H, m, Ar), 5.37 (1H, dt, *J* = 15.4, 7.8 Hz, 4-H), 5.10 (1H, t, *J* = 6.5 Hz, NH), 5.05 (1H, dt, *J* = 15.4, 7.0 Hz, 3-H), 2.93 (2H, q, *J* = 6.5 Hz, 1-H_2), 2.07 (2H, d, *J* = 7.8 Hz, 5-H_2), 2.01 (2H, q, *J* = 7.0 Hz, 2-H_2), 1.02 (9H, s, 3 x Me ^{t}Bu). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 136.1 (4 x CH Ar), 134.4 (3 x C Ar), 133.9 (C Ar), 133.5 (CH Ar), 132.8 (CH Ar), 131.2 (CH Ar), 130.3 (C-4), 129.3 (2 x CH Ar), 127.7 (4 x CH Ar), 125.4 (CH Ar), 125.2 (C-3), 45.8 (C-1), 32.9 (C-2), 28.0 (3 x Me ^{t}Bu), 18.5 (CMe_3 ^{t}Bu), 17.1 (C-5). **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max}: 3347, 2980, 2888, 1539, 1426, 1163 cm^{-1}.

Data for ***Z*-233p** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.06-8.09 (1H, m, Ar), 7.82-7.86 (1H, m, Ar), 7.70-7.75 (2H, m, Ar), 7.52-7.58 (4H, m, Ar), 7.30-7.41 (6H, m, Ar), 5.51-5.61 (1H, m, 4-H), 5.13 (1H, t, *J* = 6.5 Hz, NH), 4.93-5.01 (1H, m, 3-H), 2.85 (2H, td, *J* = 7.0, 5.9 Hz, 1-H_2), 1.90-2.04 (4H, m, 2-H_2 and 5-H_2), 1.05 (9H, s, 3 x Me ^{t}Bu). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 136.2 (4 x CH Ar), 134.4 (3 x C Ar), 133.9 (C Ar), 133.5 (CH Ar), 132.8 (CH Ar), 131.2 (CH Ar), 129.4 (2 x CH Ar and C-4), 127.7 (4 x CH Ar), 125.4 (CH Ar), 123.3 (C-3), 43.5 (C-1), 27.95 (3 x Me ^{t}Bu), 27.4 (C-2), 18.5 (CMe_3 ^{t}Bu), 12.9 (C-5).

5.7.34 *N*-(3-bromopropyl)-2-nitrobenzenesulfonamide (276)

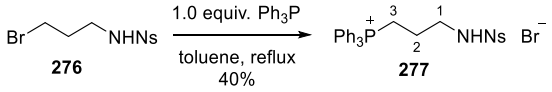


A r.b.f. was charged with 3-bromopropylamine hydrobromide **275** (1.000 g, 4.570 mmol, 1.0 equiv.), DMAP (0.083 g, 4.570 mmol, 0.15 equiv.) and 7 mL CH_2Cl_2. The mixture was cooled to 0 °C in an ice bath, and then *o*-nitrobenzenesulfonyl chloride (1.012 g, 4.570 mmol, 1.0 equiv.) and Et_3N (1.91 mL, 13.7 mmol, 3.0 equiv.) was slowly added. The mixture was stirred at room temperature for 8 h. The resulting yellow mixture was washed with 1N HCl twice, and the aqueous layer was extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4, which was concentrated under reduced pressure. The compound **276** was obtained (FCC: gradient elution: 15% → 25% Et_2O - pentane) as a yellow solid (2.700 g, 92%). Spectroscopic properties matched those previously reported.[47]

Data for **276**: **R_f** 0.50 (60% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.12-8.16

(1H, m, Ar), 7.84-7.88 (1H, m, Ar), 7.73-7.78 (2H, m, Ar), 5.46 (1H, t, *J* = 6.3 Hz, NH), 3.46 (2H, t, *J* = 6.3 Hz, 1-H_2), 3.27 (2H, q, *J* = 6.3 Hz, 3-H_2), 2.10 (2H, p, *J* = 6.3 Hz, 2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 148.1 (C Ar), 133.9 (CH Ar), 133.5 (C Ar), 133.1 (CH Ar), 131.2 (CH Ar), 125.6 (CH Ar), 42.1 (C-1), 32.5 (C-3), 30.1 (C-2).

5.7.35 {3-[(2-nitrophenyl)sulfonamido]propyl}triphenylphosphonium bromide (277)

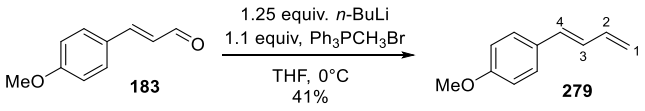


276 **277**

A r.b.f. was charged with *N*-(3-bromopropyl)-2-nitrobenzenesulfonamide **276** (1.000 g, 4.570 mmol, 1.0 equiv.) was added triphenylphosphine (1.000 g, 4.570 mmol, 1.0 equiv.) and toluene (1.000 mL). The reaction mixture was heat under reflux for 16 hours. It was then concentrated under reduced pressure to afford the **277** as a white solid.

Data for **277**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.63-7.90 (19H, m, Ar), 3.42-3.51 (2H, m, 1-H_2), 3.00 (2H, q, *J* = 6.6 Hz, 3-H_2), 1.55-1.62 (2H, m, 2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 137.4 (C Ar), 135.08 (CH Ar), 135.06 (CH Ar), 134.3 (C Ar), 134.2 (3 x C Ar), 133.6 (3 x CH Ar), 133.5 (3 x CH Ar), 132.8 (CH Ar), 130.4 (3 x CH Ar), 130.3 (3 x CH Ar), 42.7 (C-1), 22.6 (C-2), 17.9 (C-3). **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max}: 3247, 2980, 2889, 1537, 1426, 1263 cm^{-1}.

5.7.36 (3*E*)-1-(Buta-1,3-dien-1-yl)-4-methoxybenzene (279)

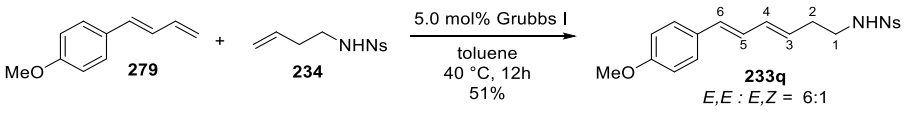


Methyltriphenylphosphonium bromide (4.753 g, 13.58 mmol), *n*-BuLi (2.5 M, 6.2 mL, 15.43 mmol), 4-methoxycinnamaldehyde **183** (2.000 g, 12.35 mmol) and THF (53 mL) were subjected to the general procedure **A** (FCC: gradient elution: 5% → 10% Et_2O - pentane) to yield **279** as a white solid (0.885 g, 41%). Spectroscopic properties matched those previously reported. [48]

Data for **279**: **R_f** 0.5 (20% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.34 (d, *J* = 8.8 Hz, Ar), 6.86 (d, *J* = 8.8 Hz, Ar), 6.61-6.71 (1H, m, 4-H), 6.42-6.54 (2H, m, 2-H and 3-H), 5.24-5.30 (1H, m, 1-H_A), 5.11 (1H, ddd, *J* = 10.7, 1.5, 0.7 Hz, 1-H_B), 3.81 (OMe). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.5 (C Ar), 137.5 (C-2), 132.6 (C-3), 130.1 (C Ar), 127.83 (C-4), 127.80 (2 x CH Ar), 116.6 (C-1), 114.2 (2 x CH Ar), 55.5 (OMe).

5.7.37 *N*-[(3*E*,5*E*)-6-(4-methoxyphenyl)hexa-3,5-dien-1-yl]-2-nitrobenzenesulfonamide (*E,E*-233q)

N-[(3*E*,5*Z*)-6-(4-methoxyphenyl)hexa-3,5-dien-1-yl]-2-nitrobenzenesulfonamide (*E,Z*-233q)



Diene **279** (0.118 g, 0.738 mmol), sulfonamide **234** (0.095 g, 0.37 mmol) and Grubbs I (15.2 mg, 0.0185 mmol) were subjected to the general procedure **B** except using 5 mol% of Grubbs I catalyst and conducting the reaction in toluene at 40 °C (FCC:

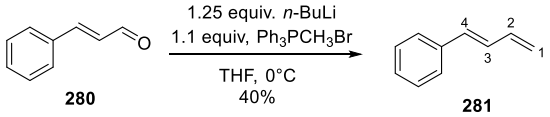
gradient elution: 20% → 35% EtOAc - pentane) to yield a 6:1 mixture of ***E,E*-233q** and ***E,Z*-233q**, which was partially separable into 2 fractions: first fraction of ***E,E*-233q** (15.4 mg, 15%) as a yellow oil, and second fraction of 4:1 of diastereomers ***E,E*-233q** and ***E,Z*-233q** as a yellow oil (38.6 mg, 36%).

Data for ***E,E*-233q**: R_f 0.50 (40% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.14 (1H, dd, *J* = 7.6, 1.6 Hz, Ar), 7.83 (1H, dd, *J* = 7.6, 1.6 Hz, Ar), 7.67-7.76 (2H, m, Ar), 7.28 (2H, d, *J* = 8.7 Hz, Ar), 6.85 (2H, d, *J* = 8.7 Hz, Ar), 6.47 (1H, dd, *J* = 15.6, 9.9 Hz, 5-H), 6.36 (1H, d, *J* = 15.6 Hz, 6-H), 6.14 (1H, ddt, *J* = 14.8, 9.9, 1.3 Hz, 4-H), 5.52 (1H, dt, *J* = 14.8, 6.8 Hz, 3-H), 5.37 (1H, t, *J* = 6.8 Hz, NH), 3.81 (3H, s, OMe), 3.23 (2H, q, *J* = 6.8 Hz, 1-H_2), 2.35 (2H, qd, *J* = 6.8, 1.3 Hz, 2-H_2). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.4 (C Ar), 134.3 (C-4), 134.2 (2 x C Ar), 133.6 (CH Ar), 132.9 (CH Ar), 131.6 (C-6), 131.1 (CH Ar), 130.1 (C Ar), 128.1 (C-3), 127.7 (2 x CH Ar), 126.4 (C-5), 125.6 (CH Ar), 114.2 (2 x CH Ar), 55.4 (OMe), 43.6 (C-1), 33.1 (C-2). **HRMS** (EI): calculated for $C_{19}H_{20}N_2O_5SNa$ $[M+Na]^+$ requires *m/z* 411.0991, found *m/z* 411.0986. **IR** (film) ν_{max}: 3349, 2980, 2888, 1541, 1428, 1163 cm^{-1}.

Data for ***E,Z*-233q**: **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.14 (1H, dd, *J* = 7.6, 1.6 Hz, Ar), 7.83 (1H, dd, *J* = 7.6, 1.6 Hz, Ar), 7.60-7.79 (2H, m, Ar), 7.30 (2H, d, *J* = 8.7 Hz, Ar), 6.85 (2H, d, *J* = 8.7 Hz, Ar), 6.69 (1H, ddd, *J* = 15.4, 11.1, 1.2 Hz, 5-H), 6.13 (1H, d, *J* = 15.4 Hz, 6-H), 6.15-6.23 (1H, m, 4-H), 5.43 (1H, d, *J* = 6.4 Hz, NH), 5.28 (1H, dt, *J* = 10.7, 7.7 Hz, 3-H), 3.82 (3H, s, OMe), 3.19-3.26 (2H, m, 1-H_2), 2.50 (2H, qd, *J* = 6.9, 1.5 Hz, 2-H_2). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.6 (C Ar), 148.1 (C Ar), 134.1 (C Ar), 133.71 (CH Ar), 133.66 (CH Ar), 132.5 (C-4), 131.6 (C-6), 131.07 (CH Ar), 130.0 (C Ar), 127.9 (2 x CH Ar), 125.6

(CH Ar), 125.5 (C-3), 121.4 (C-5), 114.2 (2 x CH Ar), 55.5 (OMe), 43.7 (C-1), 28.4 (C-2).

5.7.38 (3*E*)-Buta-1,3-dien-1-ylbenzene (281)



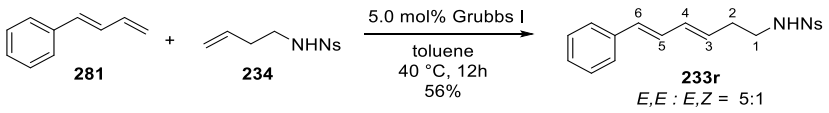
280 **281**

Methyltriphenylphosphonium bromide (6.125 g, 17.50 mmol), *n*-BuLi (2.5 M, 8.0 mL, 19.89 mmol), cinnamaldehyde **280** (2.0 mL, 15.91 mmol) and THF (53 mL) were subjected to the general procedure **A** (FCC: gradient elution: 0% → 5% Et_2O - pentane) to yield **281** as a white solid (0.817 g, 41%). Spectroscopic properties matched those previously reported.[49]

Data for **281**: **R_f** 0.5 (10% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.38-7.44 (2H, m, Ar), 7.29-7.36 (2H, m, Ar), 7.20-7.27 (1H, m, Ar), 6.80 (1H, dd, *J* = 15.7, 10.5 Hz, 3-H), 6.58 (1H, d, *J* = 15.7 Hz, 4-H), 6.52 (1H, dt, *J* = 16.9, 10.5 Hz, 2-H), 5.35 (1H, d, *J* = 16.9 Hz, 1-H_A), 5.19 (1H, d, *J* = 10.5 Hz, 1-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 137.32 (C-2), 137.27 (C Ar), 133.0 (C-4), 129.8 (C-3), 128.7 (2 x CH Ar), 127.8 (CH Ar), 126.6 (2 x CH Ar), 117.8 (C-1).

5.7.39 *N*-[(3*E*,5*E*)-6-(4-phenyl)hexa-3,5-dien-1-yl]-2-nitrobenzenesulfonamide (*E,E*-233r)

N-[(3*E*,5*Z*)-6-(4-phenyl)hexa-3,5-dien-1-yl]-2-nitrobenzenesulfonamide (*E,Z*-233r)



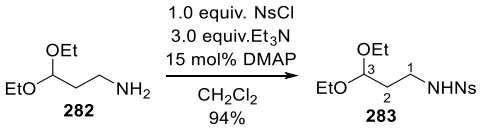
281 234 233r

E,E : *E,Z* = 5:1

Diene **281** (0.259 g, 1.94 mmol), sulfonamide **234** (0.248 g, 0.969 mmol) and Grubbs I (40.0 mg, 0.0484 mmol) were subjected to the general procedure **B** except using 5 mol% of Grubbs I catalyst and conducting the reaction in toluene at 40 °C (FCC: gradient elution: 10% → 35% EtOAc - pentane) to yield a 6:1 mixture of ***E,E*-233r** and ***E,Z*-233r**, which was partially separable into 2 fractions: first fraction of ***E,E*-233r** (44.5 mg, 13%) as a yellow oil, and second fraction of 3.6:1 of diastereomers ***E,E*-233r** and ***E,Z*-233r** as a yellow oil (147.2 mg, 43%).

Data for ***E,E*-233r**: $\mathbf{R_f}$ 0.40 (40% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.15 (1H, dd, *J* = 7.6, 1.7 Hz, Ar), 7.84 (1H, dd, *J* = 7.7, 1.6 Hz, Ar), 7.67-7.82 (2H, m, Ar), 7.28-7.38 (4H, m, Ar), 7.19-7.24 (1H, m, Ar), 6.60 (1H, dd, *J* = 15.7, 10.4 Hz, 5-H), 6.42 (1h, d, *J* = 15.7 Hz, 6-H), 6.17 (1H, ddt, *J* = 15.2, 10.4, 1.4 Hz, 4-H), 5.59 (1H, dt, *J* = 15.2, 6.4 Hz, 3-H), 5.36 (1H, t, *J* = 6.4 Hz, NH), 3.24 (q, *J* = 6.4 Hz, 1-H_2), 2.37 (2H, qd, *J* = 6.4, 1.4 Hz, 2-H_2). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 137.2 (C Ar), 134.1 (C Ar), 134.1 (C-4), 133.6 (CH Ar), 132.9 (CH Ar), 132.1 (C-6), 131.2 (CH Ar), 129.4 (C-3), 128.8 (2 x CH Ar), 128.3 (C-5), 127.7 (CH Ar), 126.5 (2 x CH Ar), 125.6 (CH Ar), 43.5 (C-1), 33.1 (C-2). **IR** (film) ν_{max}: 3304, 2980, 2888, 1382, 1251, 1158 cm^{-1}.

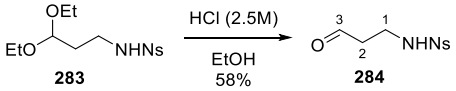
5.7.40 *N*-(3,3-diethoxypropyl)-2-nitrobenzenesulfonamide (283)



A r.b.f. was charged with 1-amino-3,3-diethoxypropane **282** (0.94 mL, 5.80 mmol, 1.0 equiv.), DMAP (0.106 g, 0.869 mmol, 0.15 equiv.) and 9.0 mL CH_2Cl_2. The mixture was cooled to 0 °C in an ice bath, and then *o*-nitrobenzenesulfonyl chloride (1.286 g, 5.795 mmol, 1.0 equiv.) and Et_3N (2.42 mL, 17.4 mmol, 3.0 equiv.) was slowly added. The mixture was stirred at room temperature for 8 h. The resulting yellow mixture was washed with 1N HCl twice, and the aqueous layer was extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4, which was concentrated under reduced pressure. The compound **283** was obtained (FCC: gradient elution: 25% → 30% EtOAc - pentane) as a yellow oil (1.729 g, 92%).

Data for **283**: $\mathbf{R_f}$ 0.50 (40% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.06-8.12 (1H, m, Ar), 7.80-7.85 (1H, m, Ar), 7.68-7.74 (2H, m, Ar), 5.97 (1H, t, *J* = 5.8 Hz, NH), 4.52 (1H, t, *J* = 5.9 Hz, 3-H), 3.54-3.65 (2H, m, CH_2 Et), 3.39-3.48 (2H, m, CH_2 Et), 3.20 (2H, q, *J* = 5.9 Hz, 1-H_2), 1.78-1.86 (2H, m, 2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 148.2 (C Ar), 133.8 (C Ar), 133.6 (CH Ar), 132.8 (CH Ar), 131.1 (CH Ar), 125.4 (CH Ar), 101.9 (C-3), 62.4 (2 x CH_2 Et), 39.8 (C-1), 33.1 (C-2), 15.3 (2 x CH_3 Et). **HRMS**: stable ion was not found in ESI, EI and CI.

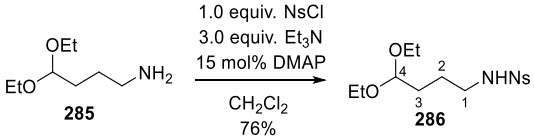
5.7.41 2-Nitro-*N*-(3-oxopropyl)benzenesulfonamide (284)



To a stirred solution of sulfonamide **283** (0.361 g, 1.08 mmol, 1.0 equiv.) in EtOH (0.65 mL) was added HCl solution (2.5M, 0.43 mL, 1.0 equiv.). The mixture was stirred for 12 hours and then quenched with saturated NH_4Cl solution. The crude mixture was extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4, which was concentrated under reduced pressure. The compound **284** was obtained (FCC: gradient elution: 25% → 30% EtOAc - pentane) as a yellow oil (0.126 g, 58%). Spectroscopic properties matched those previously reported.[50]

Data for **284**: **R_f** 0.50 (40% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 9.77 (1H, s, 3-H), 8.09-8.15 (1H, m, Ar), 7.84-7.90 (1H, m, Ar), 7.71-7.79 (2H, m, Ar), 5.80 (1H, t, *J* = 6.1 Hz, NH), 3.38 (2H, q, *J* = 6.1 Hz, 1-H_2), 2.83 (2H, t, *J* = 6.1 Hz, 2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 200.2 (C-3), 148.2 (C Ar), 133.9 (CH Ar), 133.6 (C Ar), 133.0 (CH Ar), 131.1 (CH Ar), 125.7 (CH Ar), 43.8 (C-1), 37.4 (C-2).

5.7.42 *N*-(4,4-diethoxybutyl)-2-nitrobenzenesulfonamide (286)

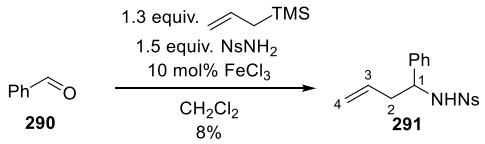


A r.b.f. was charged with 4,4-diethoxybutan-1-amine **285** (1.00 mL, 5.80 mmol, 1.0 equiv.), DMAP (0.106 g, 0.869 mmol, 0.15 equiv.) and 9.0 mL CH_2Cl_2. The mixture was cooled to 0 °C in an ice bath, and then *o*-nitrobenzenesulfonyl chloride (1.286 g, 5.795

mmol, 1.0 equiv.) and Et_3N (2.42 mL, 17.4 mmol, 3.0 equiv.) was slowly added. The mixture was stirred at room temperature for 8 h. The resulting yellow mixture was washed with 1N HCl twice, and the aqueous layer was extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4, which was concentrated under reduced pressure. The compound **286** was obtained (FCC: gradient elution: 25% → 30% EtOAc - pentane) as a yellow oil (1.523 g, 76%).

Data for **286**: $\mathbf{R_f}$ 0.50 (40% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.05-8.12 (1H, m, Ar), 7.80-7.85 (1H, m, Ar), 7.68-7.74 (2H, m, Ar), 5.48 (1H, t, *J* = 5.8 Hz, NH), 4.38-4.45 (1H, m, 4-H), 3.51-3.63 (2H, m, CH_2 Et), 3.37-3.47 (2H, m, CH_2 Et), 3.06-3.14 (2H, m, 1-H_2), 1.55-1.64 (4H, m, 2-H_2 and 3-H_2), 1.09-1.18 (6H, m, 2 x CH_3 Et). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 148.2 (C Ar), 133.9 (C Ar), 133.6 (CH Ar), 132.8 (CH Ar), 131.1 (CH Ar), 125.4 (CH Ar), 102.4 (C-4), 61.6 (2 x CH_2 Et), 43.7 (C-1), 30.7 and 24.8 (C-2 and C-3), 15.3 (2 x CH_3 Et). **HRMS**: stable ion was not found in ESI, EI and CI.

5.7.43 (±)-2-Nitro-*N*-(1-phenylbut-3-en-1-yl)benzenesulfonamide (291)

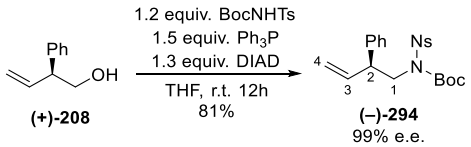


To a stirring solution of benzaldehyde **290** (0.29 mL, 2.83 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) were added *o*-nitrobenzenesulfonamide (0.858 g, 4.25 mmol, 1.5 equiv.) and $FeCl_3$ (0.046 g, 0.28 mmol, 0.1 equiv.). The resulting mixture was stirred at 40 °C for 1 h, then allyltrimethylsilane (0.58 mL, 3.68 mmol, 1.3 equiv.) was added. The mixture was further stirred at 40 °C for 16 hours. The reaction was then quenched by addition of

H_2O (3 mL). The aqueous layer was separated and extracted with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The compound **291** was obtained (FCC: gradient elution: 8% → 12% EtOAc - pentane) as a yellow oil (0.075 g, 8%).

Data for **291**: **R_f** 0.50 (30% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.72 (1H, dd, *J* = 7.9, 1.3 Hz, Ar), 7.63 (1H, dd, *J* = 7.8, 1.4 Hz, Ar), 7.50-7.54 (1H, m, Ar), 7.36-7.40 (1H, m, Ar), 7.03-7.09 (5H, m, Ar), 5.84 (1H, d, *J* = 8.4 Hz, NH), 5.62 (1H, ddt, *J* = 17.2, 10.2, 7.1 Hz, 3-H), 5.06-5.15 (2H, m, 4-H_2), 4.61 (1H, dt, *J* = 8.4, 6.9 Hz, 1-H), 2.48-2.64 (2H, m, 2-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 146.9 (C Ar), 139.7 (C Ar), 134.7 (C Ar), 133.0 (CH Ar), 132.8 (C-3), 132.5 (CH Ar), 130.8 (CH Ar), 128.5 (2 x CH Ar), 127.8 (CH Ar), 126.7 (2 x CH Ar), 125.0 (CH Ar), 119.5 (C-4), 58.8 (C-1), 41.8 (C-2). **HRMS** (ESI): calculated for $C_{16}H_{16}N_2O_4SNa$ $[M+Na]^+$ requires *m/z* 355.0728, found *m/z* 355.0723. **IR** (film) ν_{max}: 3341, 2980, 2888, 2360, 1537, 1456, 1167 cm^{-1}.

5.7.44 (–)-*tert*-Butyl (2*S*)-[(2-nitrophenyl)sulfonyl](2-phenylbut-3-en-1-yl)carbamate [(–)-294]

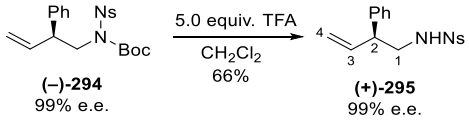


Alcohol **(+)-208** (0.652 g, 4.41 mmol), BocNHNs (1.597 g, 5.286 mmol), triphenylphosphine (1.731 g, 6.608 mmol) and DIAD (1.150 g, 5.727 mmol) were subjected to the general procedure **E** (FCC: gradient elution: 5% → 25% Et_2O - pentane) to yield **(–)-294** as a colorless oil (1.530 g, 81%).

Data for **(–)-294**: **R_f** 0.30 (50% Et_2O - pentane). $[\alpha]_D^{25}$ = –0.164 (*c* = 10.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 8.24-8.28 (1H, m, Ar), 7.68-7.75 (3H, m, Ar), 7.29-7.37 (4H, m, Ar), 7.23-7.27 (1H, m, Ar), 6.11 (1H, ddd, *J* = 17.1, 10.2, 8.7 Hz, 3-H), 5.18-5.27 (4H, m, 4-H_2), 4.10 (1H, dd, *J* = 14.6, 9.2 Hz, 1-H_A), 4.01 (1H, dd, *J* = 14.6, 6.6 Hz, 1-H_B), 3.78-3.86 (1H, m, 2-H), 1.32 (9H, s, 3 x Me Boc). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 150.4 (C=O Boc), 147.7 (C Ar), 140.9 (C Ar), 138.1 (C-3), 134.2 (CH Ar), 133.8 (CH Ar), 133.7 (C Ar), 131.8 (CH Ar), 128.8 (2 x CH Ar), 128.2 (2 x CH Ar), 127.2 (CH Ar), 124.5 (CH Ar), 117.7 (C-4), 85.1 (CMe_3 Boc), 52.7 (C-1), 50.8 (C-2), 27.9 (3 x Me Boc). **HRMS** (ESI): calculated for $C_{21}H_{24}N_2O_6SNa$ $[M+Na]^+$ requires *m/z* 455.1253, found *m/z* 455.1239. **IR** (film) ν_{max}: 2980, 2888, 2360, 1728, 1541, 1365 cm^{-1}.

Racemic **(±)-294** (81%) was made with the same procedure with racemic alcohol **(±)-208**.

5.7.45 (+)-(2*S*)-2-Nitro-*N*-(2-phenylbut-3-en-1-yl)benzenesulfonamide [(+)-295]



(–)-294
99% e.e.

(+)-295
99% e.e.

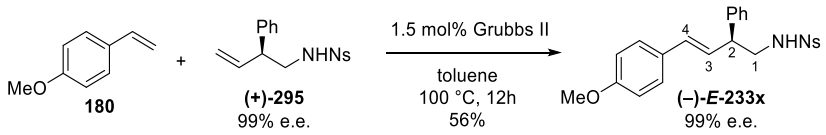
Carbamate **(–)-294** (0.320 g, 0.744 mmol) and TFA (0.29 mL, 3.72 mmol) were subjected to general procedure **F** to yield **(+)-295** as a colorless oil (0.240 g, 97%). Spectroscopic properties matched those previously reported.

Data for **(+)-295**: **R_f** 0.40 (70% Et_2O - pentane). $[\alpha]_D^{25}$ = 0.182 (*c* = 10.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 8.09-8.13 (1H, m, Ar), 7.81-7.86 (1H, m, Ar), 7.70-7.76 (2H, m, Ar), 7.19-7.28 (3H, m, Ar), 7.05-7.09 (2H, m, Ar), 5.89 (1H, ddd, *J* = 17.5, 10.3, 7.5 Hz,

3-H), 5.34 (1H, t, *J* = 6.5 Hz, NH), 5.06-5.20 (2H, m, 4-H_2), 3.49 (1H, q, *J* = 7.5 Hz, 2-H), 3.37-3.43 (2H, m, 1-H_2). **^{13}C NMR** (100 MHz, CDCl3) **δ** 148.1 (C Ar), 139.9 (C Ar), 137.7 (C-3), 133.9 (C Ar), 133.7 (CH Ar), 133.0 (CH Ar), 131.1 (CH Ar), 129.1 (2 x CH Ar), 127.7 (2 x CH Ar), 127.5 (CH Ar), 125.6 (CH Ar), 117.6 (C-4), 49.5 (C-1), 48.0 (C-2). **IR** (film) ν_{max}: 3360, 2980, 2888, 2360, 1738, 1545 cm^{-1}.

Racemic **(±)-295** (81%) was made with the same procedure with racemic carbamate **(±)-294**.

5.7.46 (–)-(2*S*,3*E*)-*N*-[4-(4-methoxyphenyl)-2-phenylbut-3-en-1-yl]-2-nitrobenzenesulfonamide [(–)-*E*-233x]



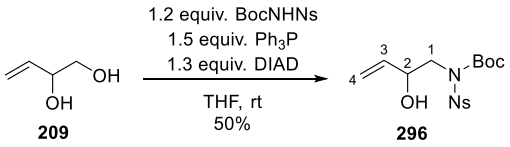
4-Methoxystyrene **180** (61.0 mg, 0.453 mmol), sulfonamide **(+)-295** (73.0 mg, 0.227 mmol) and Grubbs II (3.0 mg, 0.0034 mmol) were subjected to the general procedure **B** except conducting the reaction in toluene at 100 °C (FCC: gradient elution: 15% → 50% Et_2O - pentane) to yield **(–)-*E*-233x** as a yellow oil (55.4 mg, 56%).

Data for **(–)-*E*-233x**: **R_f** 0.50 (75% Et_2O - pentane). $[\alpha]_D^{25}$ = –0.153 (*c* = 10.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.10-8.14 (1H, m, Ar), 7.65-7.79 (3H, m, Ar), 7.24-7.30 (2H, m, Ar), 7.17-7.24 (3H, m, Ar), 7.11-7.16 (2H, m, Ar), 6.81 (2H, d, *J* = 8.7 Hz, Ar), 6.34 (1H, d, *J* = 15.8 Hz, 4-H), 6.05 (1H, dd, *J* = 15.9, 7.9 Hz, 3-H), 5.40 (1H, t, *J* = 5.9 Hz, NH), 3.80 (OMe), 3.63 (1H, q, *J* = 7.6 Hz, 2-H), 3.47-3.52 (1H, m, 1-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.5 (C Ar), 148.0 (C Ar), 140.4 (C Ar), 134.0 (C Ar), 133.5 (CH Ar), 132.9 (CH Ar), 132.1

(C-4), 131.0 (CH Ar), 129.4 (C Ar), 129.1 (2 x CH Ar), 127.7 (2 x CH Ar), 127.6 (2 x CH Ar), 127.5 (CH Ar), 126.8 (C-3), 125.6 (CH Ar), 114.1 (2 x CH Ar), 55.4 (OMe), 49.0 (C-2), 48.6 (C-1). **IR** (film) ν_{max}: 3344, 2980, 2888, 1576, 1510, 1163 cm^{-1}.

Racemic **(±)-*E*-233x** (56%) was made with the same procedure with racemic sulfonamide **(±)-295**.

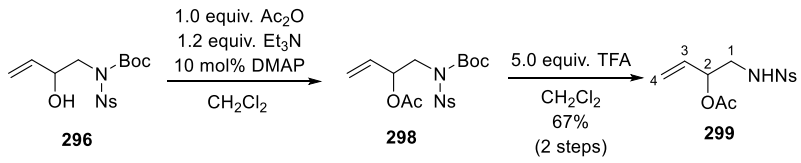
5.7.47 *tert*-Butyl (2-hydroxybut-3-en-1-yl)[(2-nitrophenyl)sulfonyl]carbamate (296)



Alcohol **209** (0.524 g, 5.95 mmol), BocNHNs (1.612 g, 5.949 mmol), triphenylphosphine (2.338 g, 8.924 mmol) and DIAD (1.52 mL, 7.73 mmol) were subjected to the general procedure **E** (FCC: gradient elution: 15% → 35% EtOAc - pentane) to yield **296** as a colorless oil (1.108 g, 50%).

Data for **296**: $\mathbf{R_f}$ 0.30 (40% EtOAc - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 8.34-8.37 (1H, m, Ar), 7.70-7.74 (3H, m, Ar), 6.11 (1H, ddd, *J* = 17.1, 10.5, 6.3 Hz, 3-H), 5.30-5.45 (4H, m, 4-H_2), 4.96 (1H, dtt, *J* = 7.6, 6.0, 1.5 Hz, 2-H), 4.06-4.15 (1H, m, 1-H_A), 3.98 (1H, m, 1-H_B), 2.30 (1H, d, *J* = 8.2 Hz, OH), 1.35 (9H, s, 3 x Me Boc). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 150.6 (C=O Boc), 148.0 (C Ar), 134.2 (CH Ar), 134.1 (C Ar), 133.3 (CH Ar), 132.9 (C-3), 132.1 (CH Ar), 124.6 (CH Ar), 119.1 (C-4), 85.9 (CMe_3 Boc), 63.8 (C-1), 62.8 (C-2), 27.9 (3 x Me Boc). **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max}: 3199, 2980, 2888, 1731, 1541, 1370 cm^{-1}.

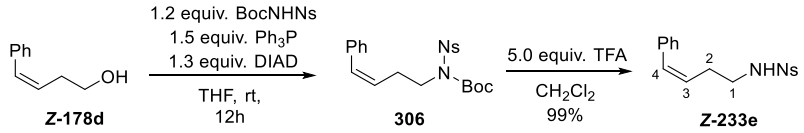
5.7.48 1-[(2-nitrophenyl)sulfonamido]but-3-en-2-yl acetate (299)



A r.b.f. was charged with alcohol **296** (0.231 g, 0.620 mmol, 1.0 equiv.), acetic anhydride (0.06 mL, 0.620 mmol, 1.0 equiv.), DMAP (0.0076 g, 0.062 mmol, 0.10 equiv.) and CH_2Cl_2 (1.2 mL). The mixture was cooled to 0 °C in an ice bath, and then Et_3N (0.11 mL, 0.744 mmol, 1.2 equiv.) was slowly added. The mixture was stirred at room temperature for 8 h. The resulting mixture was washed with 1N HCl twice, and the aqueous layer was extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4, which was concentrated under reduced pressure. The crude oil and TFA (0.29 mL, 3.72 mmol) were subjected to general procedure **F** to yield **299** (FCC: gradient elution: 20% → 30% EtOAc - pentane) as a colorless oil (0.131 g, 67%).

Data for **299**: $\mathbf{R_f}$ 0.50 (50% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 8.09-8.13 (1H, m, Ar), 7.85-7.90 (1H, m, Ar), 7.71-7.76 (2H, m, Ar), 5.63-5.71 (2H, m, 3-H and NH), 5.09-5.25 (2H, m, 4-H_2), 4.25-4.32 (1H, m, 2-H), 4.04-4.16 (2H, m, 1-H_2), 1.97 (3H, s, Me Ac). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 170.7 (C=O Ac), 147.9 (C Ar), 134.8 (C Ar), 133.7 (CH Ar), 133.4 (C-3), 133.0 (CH Ar), 131.0 (CH Ar), 125.5 (CH Ar), 118.7 (C-4), 65.6 (C-1), 56.0 (C-2), 20.7 (Me Ac). **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max}: 2980, 2888, 2360, 1739, 1539, 1382 cm^{-1}.

5.7.49 (3*Z*)-2-Nitro-N-(4-phenylbut-3-en-1-yl)benzenesulfonamide (*Z*-233e)

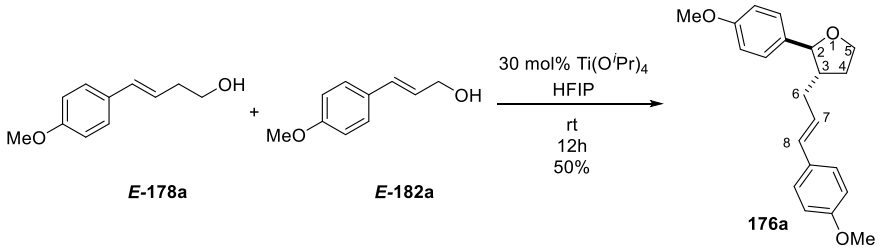


Acohol ***Z*-178d** (0.148 g, 1.00 mmol), BocNHNs (0.325 g, 1.20 mmol), triphenylphosphine (0.393 g, 1.50 mmol) and DIAD (0.26 mL, 1.30 mmol) were subjected to the general procedure **E** to yield a crude oil. The crude oil and TFA (0.70 mL, 9.13 mmol) were subjected to general procedure **F** except using 10 equivalents of TFA (FCC: gradient elution: 20% → 40% EtOAc - pentane) to yield ***Z*-233e** as a colorless oil (0.131 g, 67%).

Data for ***Z*-233e**: $\mathbf{R_f}$ 0.40 (60% EtOAc - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 8.06-8.10 (1H, m, Ar), 7.74-7.79 (1H, m, Ar), 7.63-7.68 (2H, m, Ar), 7.19-7.32 (3H, m, Ar), 7.12-7.17 (2H, m, Ar), 6.53 (1H, d, *J* = 11.6 Hz, 4-H), 5.52 (1H, dt, *J* = 11.6, 7.0 Hz, 3-H), 5.38 (1H, t, *J* = 7.0 Hz, NH), 3.25 (2H, q, *J* = 7.0 Hz, 1-H_2), 2.53 (2H, qd, *J* = 7.0, 1.8 Hz, 2-H_2). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 148.0 (C Ar), 136.8 (C Ar), 134.0 (C Ar), 133.6 (CH Ar), 132.9 (CH Ar), 132.5 (C-4), 131.0 (CH Ar), 128.7 (CH Ar), 128.4 (2 x CH Ar), 127.19 (2 x CH Ar), 127.17 (C-3), 125.6 (CH Ar), 43.9 (C-1), 28.8 (C-2). **HRMS** (EI): calculated for $C_{16}H_{16}N_2O_4SNa$ $[M+Na]^+$ requires *m/z* 355.0728, found *m/z* 355.0721. **IR** (film) ν_{max}: 3347, 2980, 2888, 1542, 1429, 1161 cm^{-1}.

5.8 Synthesis of THFs *via* Cyclization of Homoallylic Alcohols

5.8.1 (±)-(2*S*,3*S*)-2-(4-Methoxyphenyl)-3-[(2'*E*)-3'-(4-methoxyphenyl)allyl]tetrahydrofuran (176a)



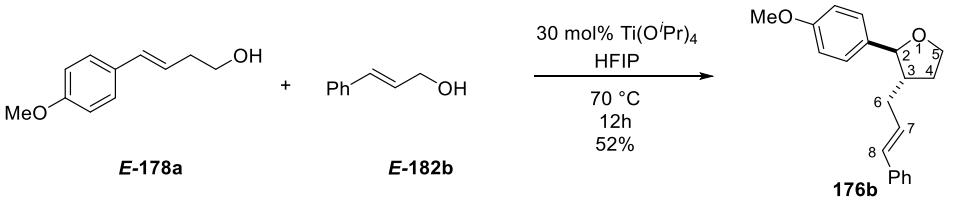
***E*-178a** ***E*-182a** **176a**

Alcohols ***E*-178a** (20.0 mg, 0.112 mmol) and ***E*-182a** (16.6 mg, 0.112 mmol) and Ti(O^{i}Pr)$_4$ (9.5 mg, 0.034 mmol) were subjected to the general procedure **H** except conducting the reaction at room temperature and using 2 equivalents of alcohol ***E*-182a** (FCC: gradient elution: 10% → 20% Et_2O - pentane) to yield **176a** as a colorless oil (18.1 mg, 50%).

Data for **176a**: **R_f** 0.50 (50% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.27 (2H, d, *J* = 8.6 Hz, Ar), 7.22 (2H, d, *J* = 8.8 Hz, Ar), 6.87 (2H, d, *J* = 8.7 Hz, Ar), 6.82 (2H, d, *J* = 8.8 Hz, Ar), 6.34 (1H, d, *J* = 15.8 Hz, 8-H), 5.97 (1H, dt, *J* = 15.8, 7.0 Hz, 7-H), 4.41 (1H, d, *J* = 7.2 Hz, 2-H), 4.10 (1H, q, *J* = 7.2 Hz, 5-H_A), 4.00 (1H, td, *J* = 8.3, 4.7 Hz, 5-H_B), 3.90 (6H, s, 2 x OMe), 2.37-2.44 (1H, m, 6-H_A), 2.13-2.26 (3H, m, 3-H, 4-H_A and 6-H_B), 1.75-1.84 (1H, m, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.1 (C Ar), 158.8 (C Ar), 134.3 (C Ar), 130.7 (C-8), 130.3 (C Ar), 127.6 (2 x CH Ar), 127.1 (2 x CH Ar), 126.2 (C-7), 113.9 (2 x CH Ar), 113.8 (2 x CH Ar), 85.8 (C-2), 67.8 (C-5), 55.3 (2 x OMe), 48.0 (C-3), 35.5 (C-6), 32.4 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H_A, between 2-H and 7-H. **HRMS** (EI): calculated for $C_{21}H_{24}O_3$ $[M]^+$ requires *m/z* 324.1725, found *m/z* 324.1720. **IR**

(film) ν_{max}: 2980, 1608, 1511, 1247, 1173, 1033 cm^{-1}.

5.8.2 (±)-(2*S*,3*S*)-3-Cinnamyl-2-(4-methoxyphenyl)tetrahydrofuran (176b)

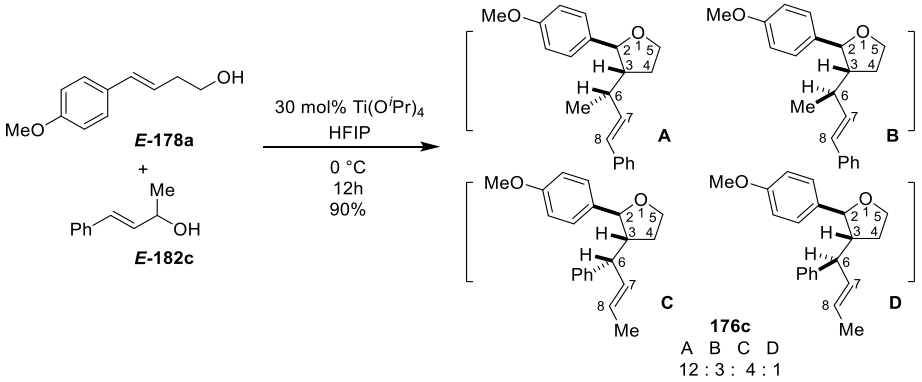


***E*-178a** ***E*-182b** **176b**

Alcohols ***E*-178a** (45.6 mg, 0.256 mmol), cinnamyl alcohol ***E*-182b** (31.8 mg, 0.256 mmol) and Ti(O^{i}Pr)$_4$ (21.8 mg, 0.0767 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 12% → 20% Et_2O - pentane) to yield **176b** as a colorless oil (39.0 mg, 52%).

Data for **176b**: $\mathbf{R_f}$ 0.50 (50% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.26-7.31 (6H, m, Ar), 7.18-7.23 (1H, m, Ar), 6.89 (2H, d, *J* = 8.7 Hz, Ar), 6.41 (1H, d, *J* = 15.7 Hz, 8-H), 6.14 (1H, dt, *J* = 15.8, 7.0 Hz, 7-H), 4.43 (1H, d, *J* = 7.2 Hz, 2-H), 4.12 (1H, q, *J* = 7.2 Hz, 5-H_A), 4.02 (1H, td, *J* = 8.3, 4.6 Hz, 5-H_B), 3.81 (3H, s, OMe), 2.40-2.48 (1H, m, 6-H_A), 2.22-2.29 (2H, m, 6-H_B and 4-H_A), 2.22-2.15 (1H, m, 3-H), 1.82 (1H, dq, *J* = 11.3, 7.7 Hz, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.2 (C Ar), 137.6 (C Ar), 134.3 (C Ar), 131.5 (C-8), 128.6 (2 x C-H Ar), 128.6 (C-7), 127.8 (2 x C-H Ar), 127.2 (C-H Ar), 126.1 (2 x C-H Ar), 113.9 (2 x C-H Ar), 86.0 (C-2), 68.0 (C-5), 55.4 (OMe), 48.0 (C-3), 35.6 (C-6), 32.5 (C-4). **HRMS** (ESI): calculated for $C_{20}H_{23}O_2$ $[M+H]^+$ requires *m/z* 295.16926, found *m/z* 295.16925. **IR** (film) ν_{max}: 2930, 1512, 1244, 1031, 827, 692 cm^{-1}

5.8.3 (±)-(2*S*, 3*S*)-2-(4-Methoxyphenyl)-3-[(1'*S*, 2'*E*)-4-phenylbut-3-en-2-yl] tetrahydrofuran, (±)-(2*S*, 3*R*)-2-(4-methoxyphenyl)-3-[(1'*R*,2'*E*)-4-phenylbut-3-en-2-yl]tetrahydrofuran; (±)-(2*S*,3*R*)-2-(4-methoxyphenyl)-3-[(1'*S*,2'*E*)-1-phenylbut-2-en-1-yl]tetrahydrofuran, (±)-(2*S*,3*R*)-2-(4-methoxyphenyl)-3-[(1'*R*, 2'*E*)-1-phenylbut-2-en-1-yl] tetrahydrofuran (176c)



Alcohols ***E*-178a** (33.9 mg, 0.190 mmol), ***E*-182c** (28.2 mg, 0.190 mmol) and $Ti(O^iPr)_4$ (16.2 mg, 0.0570 mmol) were subjected to the general procedure **H** except conducting the reaction at 0 °C (FCC: 10% Et_2O - pentane) to yield **3c** as a 12:3:4:1 mixture of **diastereomer A, B, C** and **D** (52.8 mg, 90%), which was partially separable into 2 clean fractions: first fraction of mixture of 13:1 **diastereomer A** and **B** (25.0 mg, 47%) as a colorless oil, and second fraction of mixture of 2:1 **diastereomer C** and **D** as a colorless oil (10.0 mg, 19%).

Data for **diastereomer A** of **176c** (from the mixture)**:** $\mathbf{R_f}$ 0.45 (40% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.23-7.28 (2H, m, Ar), 7.15-7.22 (5H, m, Ar), 6.79 (2H, d, *J* = 8.7 Hz, Ar), 6.34 (1H, d, *J* = 15.8 Hz, 8-H), 5.84 (1H, dd, *J* = 15.8, 8.6 Hz, 7-H), 4.57 (1H, d, *J* = 6.8 Hz, 2-H), 4.05-4.12 (1H, m, 5-H_A), 3.95 (1H, td, *J* = 8.2, 5.0 Hz, 5-H_B),

3.76 (3H, s, OMe), 2.36-2.45 (1H, m, 6-H), 2.17-2.25 (2H, m, 3-H and 4-H_A), 1.83-1.92 (1H, m, 4-H_B), 1.13 (3H, d, *J* = 6.8 Hz, Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.0 (C Ar), 137.58 (C Ar), 135.3 (C-8), 135.1 (C Ar), 129.0 (C-7), 128.5 (2 x CH Ar), 128.4 (CH Ar), 127.1 (2 x CH Ar), 126.2 (2 x CH Ar), 113.8 (2 x CH Ar), 84.6 (C-2), 68.1 (C-5), 55.40 (OMe), 53.3 (C-3), 40.6 (C-6), 31.1 (C-4), 19.2 (Me). **NOESY- 2D (400 MHz, $CDCl_3$)**: between 2-H and 6-H, between 2-H and Me, between 2-H and 7-H, between 2-H and 8-H. **HRMS** (Cl): calculated for $C_{21}H_{25}O_2$ $[M+H]^+$ requires *m/z* 309.18491, found *m/z* 309.18491. **IR** (film) ν_{max}: 2980, 2885, 2360, 1512, 1243, 964 cm^{-1}.

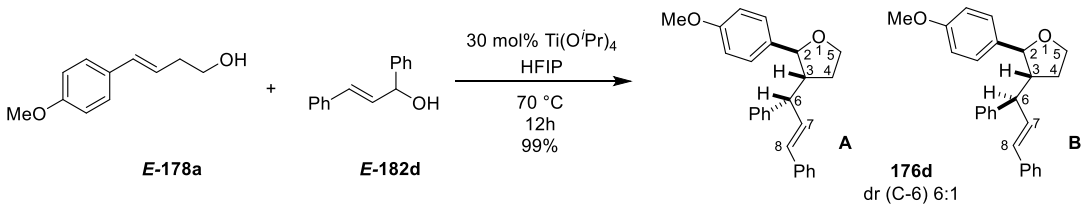
Data **diastereomer B** of **176c** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.14-7.38 (7H, m, Ar), 6.89 (2H, d, *J* = 8.6 Hz, Ar), 6.41 (1H, d, *J* = 15.8 Hz, 8-H), 6.16 (1H, dd, *J* = 15.8, 8.6 Hz, 7-H), 4.56 (1H, d, *J* = 7.4 Hz, 2-H), 4.05-4.12 (1H, m, 5-H_A), 3.95 (1H, td, *J* = 8.2, 5.0 Hz, 5-H_B), 3.81 (3H, s, OMe), 2.36-2.45 (1H, m, 6-H), 2.17-2.25 (2H, m, 3-H and 4-H_A), 1.83-1.92 (1H, m, 4-H_B), 1.08 (3H, d, *J* = 6.8 Hz, Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.2 (C Ar), 137.64 (C Ar), 134.9 (C Ar), 133.2 (C-8), 130.4 (C-7), 129.0 (2 x CH Ar), 128.7 (2 x CH Ar), 128.0 (2 x CH Ar), 127.3 (CH Ar), 114.0 (2 x CH Ar), 84.1 (C-2), 68.0 (C-5), 55.43 (OMe), 53.2 (C-3), 38.4 (C-6), 29.8 (C-4), 20.2 (Me).

Data for **diastereomer C** of **176c** (from the mixture)**: R_f** 0.50 (40% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.13-7.32 (7H, m, Ar), 6.87 (2H, d, *J* = 8.7 Hz, Ar), 5.52 (1H, dq, *J* = 15.2, 6.5 Hz, 8-H), 5.40 (1H, ddd, *J* = 15.1, 9.1, 1.5 Hz, 7-H), 4.72 (1H, d, *J* = 5.5 Hz, 2-H), 4.04 (1H, td, *J* = 8.2, 5.6 Hz, 5-H_A), 3.89 (1H, dt, *J* = 8.5, 7.2 Hz, 5-H_B), 3.81 (3H, s, OMe), 3.24-3.21 (1H, m, 6-H), 2.55 (1H, ddt, *J* = 10.7, 8.0, 5.6 Hz, 3-H), 1.91 (1H, dq, *J* = 12.7, 7.6 Hz, 4-H_A), 1.57-1.65 (1H, m, 4-H_B), 1.58 (3H, dd, *J* = 6.3, 1.6 Hz, Me). **^{13}C**

NMR (125 MHz, $CDCl_3$) δ 158.9 (C Ar), 144.1 (C Ar), 135.7 (C Ar), 134.3 (C-7), 128.7 (2 x CH Ar), 128.1 (3 x CH Ar), 127.0 (CH Ar), 125.42 (C-8), 126.1 (CH Ar), 113.7 (2 x CH Ar), 84.7 (C-2), 67.90 (C-5), 55.44 (OMe), 53.4 (C-6), 52.3 (C-3), 31.1 (C-4), 18.0 (Me). **HRMS** (Cl): calculated for $C_{21}H_{25}O_2$ $[M+H]^+$ requires *m/z* 309.18491, found *m/z* 309.18512. **IR** (film) ν_{max} : 2980, 2360, 1728, 1513, 1245, 1062 cm^{-1}.

Data **diastereomer D** of **176c** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.18-7.21 (3H, m, Ar), 7.08-7.11 (2H, m, Ar), 6.90 (2H, d, *J* = 9.1 Hz, Ar), 6.72 (2H, d, *J* = 8.7 Hz, Ar), 5.65 (1H, ddd, *J* = 15.1, 8.9, 1.6 Hz, 7-H), 5.52 (1H, dq, *J* = 15.2, 6.5 Hz, 8-H), 4.49 (1H, d, *J* = 5.9 Hz, 2-H), 4.10 (1H, td, *J* = 8.0, 5.7 Hz, 5-H_A), 3.96 (1H, dt, *J* = 8.5, 7.2 Hz, 5-H_B), 3.76 (3H, s, OMe), 3.24-3.27 (1H, m, 6-H), 2.45-2.51 (1H, m, 3-H), 2.09 (1H, dq, *J* = 12.5, 7.5 Hz, 4-H_A), 2.00 (1H, ddt, *J* = 12.0, 7.5, 5.8 Hz, 4-H_B), 1.69 (3H, dd, *J* = 6.3, 1.5 Hz, Me). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.7 (C Ar), 143.9 (C Ar), 135.4 (C Ar), 132.5 (C-7), 128.6 (2 x CH Ar), 127.9 (3 x CH Ar), 127.3 (2 x CH Ar), 125.39 (C-8), 113.6 (2 x CH Ar), 84.0 (C-2), 67.91 (C-5), 55.37 (OMe), 52.7 (C-3), 51.6 (C-6), 30.0 (C-4), 18.2 (Me).

5.8.4 (±)-(2*S*,*R*)-3-[(1'*S*,2'*E*)-1,3-Diphenylallyl]-2-(4-methoxyphenyl)tetrahydrofuran and (±)-(2*S*,3*S*)-3-[(1'*R*,2'*E*)-1,3-Diphenylallyl]-2-(4-methoxyphenyl) tetrahydrofuran (176d)



E-178a + *E*-182d → **176d** dr (C-6) 6:1

Alcohols ***E*-178a** (42.4 mg, 0.238 mmol), *trans*-1,3-diphenyl-2-propen-1-ol

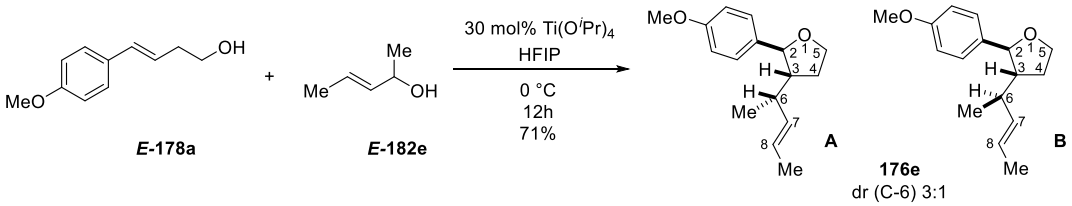
***E*-182d** (20.0 mg, 0.238 mmol) and $Ti(O^iPr)_4$ (20.0 mg, 0.0704 mmol) were subjected to the general procedure **H** (FCC: 15% Et_2O - pentane) to yield an inseparable 6:1 mixture of diastereomers **176d** as a colorless oil (87.1 mg, 99%).

Data for **major diastereomer A** of **176d** (from the mixture): $\mathbf{R_f}$ 0.40 (40% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.31-7.36 (2H, m, Ar), 7.15-7.29 (10H, m, Ar), 6.84 (2H, d, *J* = 8.7 Hz, Ar), 6.45 (1H, d, *J* = 15.7 Hz, 8-H), 6.12 (1H, dd, *J* = 15.7, 9.2 Hz, 7-H), 4.78 (1H, d, *J* = 6.0 Hz, 2-H), 4.11 (1H, td, *J* = 7.9, 5.8 Hz, 5-H_A), 3.96 (1H, dt, *J* = 8.4, 7.1 Hz, 5-H_B), 3.80 (3H, s, OMe), 3.49 (1H, t, *J* = 9.6 Hz, 6-H), 2.73 (1H, ddt, *J* = 10.3, 8.0, 6.1 Hz, 3-H), 1.96-2.08 (1H, m, 4-H_A), 1.72 (1H, ddt, *J* = 12.3, 7.6, 6.0 Hz, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.0 (C Ar), 143.4 (C Ar), 137.2 (C Ar), 135.20 (C Ar), 133.0 (C-7), 130.4 (C-8), 128.8 (2 x C-H Ar), 128.5 (2 x C-H Ar), 128.3 (2 x C-H Ar), 128.0 (2 x C-H Ar), 127.3 (C-H Ar), 126.7 (C-H Ar), 126.4 (2 x C-H Ar), 113.9 (2 x C-H Ar), 84.9 (C-2), 67.92 (C-5), 55.39 (OMe), 53.7 (C-6), 52.5 (C-3), 31.5 (C-4). **HRMS** (CI): calculated for $C_{26}H_{25}O_2$ $[M-H]^+$ requires *m/z* 369.18491, found *m/z* 369.18475. **IR** (film) ν_{max}: 2979, 1511, 1451, 1244, 1030, 694 cm^{-1}.

Data for **minor diastereomer B** of **176d** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.36-7.39 (2H, m, Ar), 7.15-7.29 (8H, m, Ar), 6.95 (2H, d, *J* = 8.7 Hz, Ar), 6.77 (2H, d, *J* = 8.7 Hz, Ar), 6.49 (1H, d, *J* = 15.8 Hz, 8-H), 6.42 (1H, dd, *J* = 15.7, 8.7 Hz, 7-H), 4.60 (1H, d, *J* = 5.7 Hz, 2-H), 4.17 (1H, td, *J* = 8.0, 5.5 Hz, 5-H_A), 4.03 (1H, dt, *J* = 8.6, 7.3 Hz, 5-H_B), 3.79 (3H, s, OMe), 3.49 (1H, t, *J* = 9.6 Hz, 6-H), 2.66-2.69 (1H, m, 3-H), 2.15-2.19 (1H, m, 4-H_A), 2.06-2.12 (1H, m, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.8 (C Ar), 143.0 (C Ar), 137.3 (C Ar), 135.15 (C Ar), 131.6 (C-7), 131.3 (C-8), 128.7 (2 x C-H Ar), 128.6 (2 x

C-H Ar), 128.3 (2 x C-H Ar), 128.2 (2 x C-H Ar), 127.5 (C-H Ar), 127.3 (C-H Ar), 126.3 (2 x C-H Ar), 113.7 (2 x C-H Ar), 84.1 (C-2), 67.87 (C-5), 55.36 (OMe), 53.9 (C-6), 52.0 (C-3), 30.2 (C-4).

5.8.5 (±)-(2*S*,3*S*)-2-(4-Methoxyphenyl)-3-[(1'*S*,2'*E*)-pent-3-en-2-yl]tetrahydrofuran and (±)-(2*S*,3*R*)-2-(4-methoxyphenyl)-3-[(1'*R*,2'*E*)-pent-3-en-2-yl] tetrahydrofuran (176e)



***E*-178a** ***E*-182e** **176e** dr (C-6) 3:1

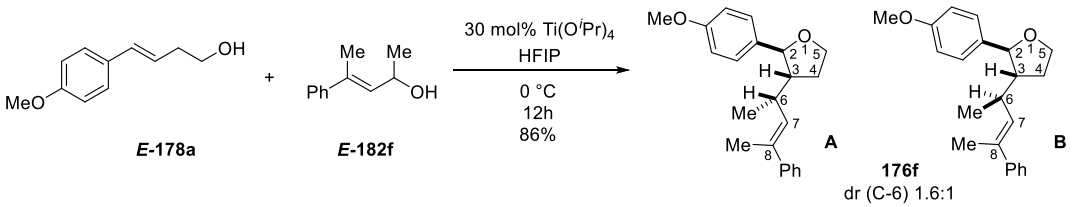
Alcohols ***E*-178a** (59.3 mg, 0.334 mmol) (*E*)-3-penten-2-ol ***E*-182e** (57.4 mg, 0.668 mmol) and Ti(O^{i}Pr)$_4$ (28.0 mg, 0.100 mmol) were subjected to the general procedure E except using 2 equivalents of ***E*-182e** and conducting the reaction at 0°C (FCC: gradient elution: 4% → 10% Et_2O - pentane) to yield an inseparable 3:1 mixture of diastereomer **176e** as a colorless oil (58.3 mg, 71%).

Data for **major diastereomer A** of **176e** (from the mixture): **R_f** 0.40 (25% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.20 (2H, d, *J* = 8.6 Hz, Ar), 6.85 (2H, d, *J* = 8.8 Hz, Ar), 5.33-5.43 (1H, m, 7-H), 5.12 (1H, dqd, *J* = 15.2, 8.4, 1.6 Hz, 8-H), 4.54 (1H, d, *J* = 6.7 Hz, 2-H), 4.05 (1H, q, *J* = 8.2 Hz, 5-H_A), 3.91 (1H, td, *J* = 8.0, 5.4 Hz, 5-H_B), 3.79 (3H, s, OMe), 2.14-2.23 (1H, m, 6-H), 2.07-2.14 (1H, m, 4-H_A), 1.99-2.07 (1H, m, 3-H), 1.75-1.85 (1H, m, 4-H_B), 1.57 (3H, dd, *J* = 4.7, 1.5 Hz, Me), 0.99 (3H, d, *J* = 6.7 Hz, Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.9 (C Ar), 136.2 (C-8), 133.8 (C Ar), 128.2 (2 x CH Ar), 124.2 (C-7),

113.7 (2 x CH Ar), 84.3 (C-2), 68.1 (C-5), 55.4 (OMe), 53.0 (C-3), 39.8 (C-6), 30.7 (C-4), 19.0 (Me), 17.9 (Me). **HRMS** (Cl): calculated for $C_{16}H_{23}O_2$ $[M+H]^+$ requires *m/z* 247.16926, found *m/z* 247.16933. **IR** (film) ν_{max}: 3657, 2980, 2888, 1512, 1381, 1245 cm^{-1}.

Data for **minor diastereomer B** of **176e** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.25 (2H, d, *J* = 8.7 Hz, Ar), 6.87 (2H, d, *J* = 8.8 Hz, Ar), 5.41-5.52 (1H, m, 7-H), 5.31-5.40 (1H, m, 8-H), 4.49 (1H, d, *J* = 7.3 Hz, 2-H), 4.03 (1H, q, J= 7.1 Hz, 5-H_A), 3.90 (1H, td, *J* = 8.2, 4.8 Hz, 5-H_B), 3.80 (3H, s, OMe), 2.14-2.23 (1H, m, 6-H), 2.07-2.14 (1H, m, 4-H_A), 1.99-2.07 (1H, m, 3-H), 1.75-1.85 (1H, m, 4-H_B), 1.69 (3H, dd, *J* = 6.2, 1.5 Hz, Me), 0.95 (3H, d, *J* = 6.9 Hz, Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.9 (C Ar), 135.2 (C Ar), 133.8 (C-8), 127.9 (2 x CH Ar), 125.7 (C-7), 133.9 (2 x CH Ar), 84.0 (C-2), 68.0 (C-5), 55.4 (OMe),53.2 (C-3), 37.7 (C-6), 29.2 (C-4), 20.5 (Me), 18.2 (Me).

5.8.6 (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-3-[(1'*S*,2'*E*)-4-phenylpent-3-en-2-yl]tetrahydrofuran and (±)-(2*S*,3*R*)-2-(4-methoxyphenyl)-3-[(1'*R*,2'*E*)-4-phenylpent-3-en-2-yl]tetrahydrofuran (176f)



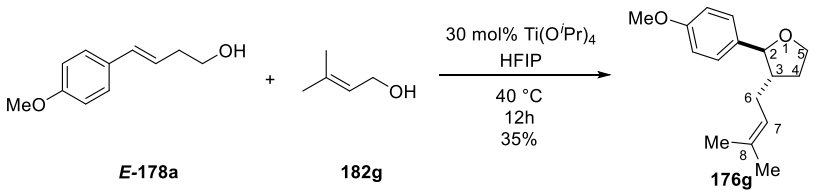
Alcohols ***E*-178a** (59.3 mg, 0.334 mmol) (*E*)-4-phenylpent-3-en-2-ol ***E*-182f** (54.1 mg, 0.334 mmol) and $Ti(O^iPr)_4$ (28.0 mg, 0.100 mmol) were subjected to the general procedure **H** except conducting the reaction at 0°C (FCC: gradient elution: 4% → 10%

Et_2O - pentane) to yield a separable 1.6:1 mixture of diastereomers **176f** as a colorless oil (92.5 mg, 86%).

Data for **major diastereomer A** of **176f:** **R_f** 0.40 (25% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.22-7.40 (7H, m, Ar), 6.89 (2H, d, *J* = 8.6 Hz, Ar), 5.67 (1H, dd, *J* = 10.0, 1.4 Hz, 7-H), 4.54 (1H, d, *J* = 7.4 Hz, 2-H), 4.08 (1H, dt, *J* = 8.3, 7.0 Hz, 5-H_A), 3.94 (1H, td, *J* = 8.3, 5.4 Hz, 5-H_B), 3.81 (3H, s, OMe), 2.68 (1H, dp, *J* = 10.0, 6.7 Hz, 6-H), 2.15-2.24 (1H, m, 3-H), 2.07-2.15 (1H, m, 4-H_A), 2.05 (3H, d, *J* = 1.4 Hz, Me), 1.88-1.97 (1H, m, 4-H_B), 1.02 (3H, d, *J* = 6.7 Hz, Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.2 (C Ar), 144.1 (C Ar), 135.0 (C Ar), 134.7 (C-8), 131.5 (C-7), 128.3 (2 x CH Ar), 128.1 (2 x CH Ar), 126.9 (C Ar), 125.9 (2 x CH Ar),113.9 (2 x CH Ar), 84.4 (C-2), 68.0 (C-5), 55.4 (OMe), 53.6 (C-3), 34.0 (C-6), 29.5 (C-4), 20.2 (Me), 16.5 (Me). **IR** (film) ν_{max}: 2972, 1381, 1245, 1153, 1071, 954 cm^{-1}.

Data for **major diastereomer B** of **176f:** **R_f** 0.35 (25% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.15-7.24 (5H, m, Ar), 7.06-7.11 (2H, m, Ar), 6.80 (2H, d, *J* = 8.7 Hz, Ar), 5.35 (1H, dd, *J* = 9.8, 1.5 Hz, 7-H), 4.51 (1H, d, *J* = 6.8 Hz, 2-H), 4.10 (1H, dt, *J* = 8.4, 7.1 Hz, 5-H_A), 3.98 (1H, td, *J* = 8.4, 5.0 Hz, 5-H_B), 3.77 (3H, s, OMe), 2.58-2.68 (1H, m, 6-H), 2.13-2.29 (1H, m, 3-H and 4-H_A), 2.02 (3H, d, *J* = 1.4 Hz, Me), 1.84-1.94 (1H, m, 4-H_B), 1.07 (3H, d, *J* = 6.7 Hz, Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.1 (C Ar), 143.7 (C Ar), 135.2 (C Ar), 133.4 (C-7), 133.3 (C-8), 128.3 (2 x CH Ar), 128.1 (2 x CH Ar), 126.7 (CH Ar), 125.8 (2 x CH Ar), 113.9 (2 x CH Ar), 85.1 (C-2), 68.0 (C-5), 55.4 (OMe), 53.5 (C-3), 36.3 (C-6), 31.2 (C-4), 19.4 (Me), 16.1 (Me). **IR** (film) ν_{max}: 2972, 1381, 1245, 1153, 1071, 954 cm^{-1}.

5.8.7 (±)-(2*S*,3*S*)-2-(4-Methoxyphenyl)-3-(3-methylbut-2-en-1-yl)tetrahydrofuran (176g)

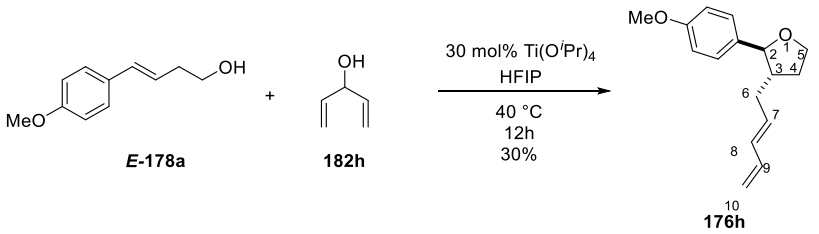


***E*-178a** **182g** **176g**

Alcohols ***E*-178a** (21.1 mg, 0.119 mmol), 3-methyl-2-buten-1-ol **182g** (0.03 mL, 0.3 mmol) and Ti(O^{i}Pr)$_4$ (10.1 mg, 0.0356 mmol) were subjected to the general procedure **H** except using 2.0 eq. of 3-methyl-2-buten-1-ol and conducting the reaction at 40 °C (FCC: gradient elution: 5% → 10% Et_2O - pentane) to yield **176g** as a colorless oil (10.3 mg, 35%).

Data for **176g**: **R_f** 0.40 (30% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.24 (2H, d, *J* = 8.6 Hz, Ar), 6.87 (2H, d, *J* = 8.7 Hz, Ar), 5.08 (1H, t, *J* = 7.1 Hz, 7-H), 4.37 (1H, d, *J* = 7.3 Hz, 2-H), 4.07 (1H, q, *J* = 8.3 Hz, 5-H_A), 3.98 (1H, td, *J* = 8.3, 5.0 Hz, 5-H_B), 3.80 (3H, s, OMe), 2.11-2.23 (2H, m, 4-H_A and 6-H_A), 1.98-2.10 (2H, m, 3-H and 6- H_B), 1.69-1.76 (1H, m, 4-H_B), 1.67 (3H, s, Me), 1.58 (3H, s, Me). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.1 (C Ar), 134.7 (C Ar), 132.9 (C-8), 127.6 (2 x C-H Ar), 122.4 (C-7), 113.8 (2 x C-H Ar), 85.8 (C-2), 68.0 (C-5), 55.4 (OMe), 48.4 (C-3), 32.5 (C-4), 30.4 (C-6), 25.9 (Me), 18.0 (Me). **HRMS** (ESI): calculated for $C_{16}H_{23}O_2$ $[M+H]^+$ requires *m/z* 247.16926, found *m/z* 247.16937. **IR** (film) ν_{max}: 2980, 2360, 2341, 1513, 1380, 1246 cm^{-1}.

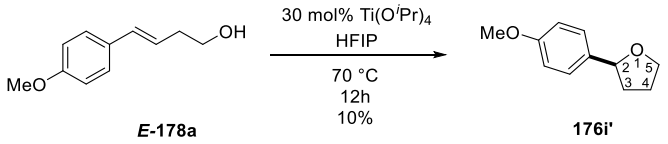
5.8.8 (±)-(2*S*,3*S*)-2-(4-Methoxyphenyl)-3-[(2'*E*,4'*E*)-penta-2,4-dien-1-yl]tetrahydrofuran (176h)



Alcohols ***E*-178a** (40.0 mg, 0.225 mmol), 1,4-pentadien-3-ol **182h** (0.05 mL, 0.6 mmol) and Ti(O^{i}Pr)$_4$ (19.1 mg, 0.0673 mmol) were subjected to the general procedure **H** except using 2 equivalents of 1,4-pentadien-3-ol **182h** and conducting the reaction at 40 °C (FCC: gradient elution: 7% → 10% Et_2O - pentane) to yield **176h** as a colorless oil (16.5 mg, 30%).

Data for **176h**: **R_f** 0.40 (30% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.24 (2H, d, *J* = 8.5 Hz, Ar), 6.88 (2H, d, *J* = 8.5 Hz, Ar), 6.27 (1H, dt, *J* = 16.9, 10.2 Hz, 9-H), 6.06 (1H, dd, *J* = 15.2, 10.4 Hz, 8-H), 5.62 (1H, dt, *J* = 14.3, 6.8 Hz, 7-H), 5.10 (1H, d, *J* = 17.0 Hz, 10-H_A), 4.98 (1H, d, *J* = 10.1 Hz, 10-H_B), 4.36 (1H, d, *J* = 6.7 Hz, 2-H), 4.08 (1H, q, *J* = 8.6 Hz, 5-H_A), 3.98 (1H, td, *J* = 8.2, 4.9 Hz, 5-H_B), 3.80 (3H, s, OMe), 2.26-2.35 (1H, m, 6-H_A), 2.14-2.24 (1H, m, 4-H_A), 2.05-2.14 (2H, m, 3-H and 6-H_B), 1.68-1.79 (1H, m, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.2 (C Ar), 137.1 (C-9), 134.3 (C Ar), 132.7 (C-7), 132.6 (C-8), 127.7 (2 x CH Ar), 115.6 (C-10), 113.9 (2 x CH Ar), 85.9 (C-2), 67.9 (C-5), 55.4 (OMe), 47.8 (C-3), 35.1 (C-6), 32.4 (C-4). **HRMS** (CI): calculated for $C_{16}H_{21}O_2Na$ $[M+H]^+$ requires *m/z* 245.15361, found *m/z* 245.15364. **IR** (film) ν_{max}: 2980, 2360, 1513, 1381, 1246, 1072 cm^{-1}.

5.8.9 (±)-(2*S*)-2-(4-Methoxyphenyl)tetrahydrofuran (176i')

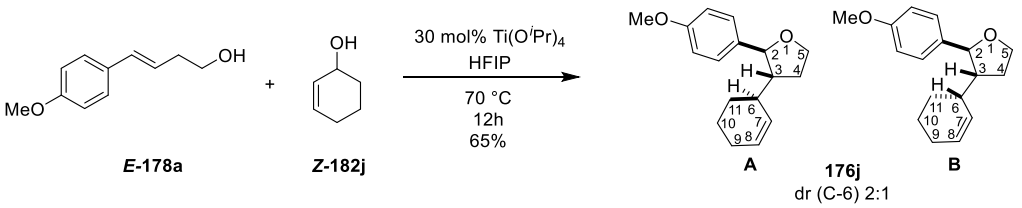


***E*-178a** **176i'**

Alcohol ***E*-178a** (40.0 mg, 0.225 mmol) was subjected to the general procedure **H** (FCC: gradient elution: 10% → 15% Et_2O - pentane) to yield **176i'** as a colorless oil (4.1 mg, 30%). Spectroscopic properties matched those previously reported.[51]

Data for **176i'**: **R_f** 0.40 (30% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.25 (2H, d, *J* = 3.6 Hz, Ar), 6.87 (2H, d, *J* = 8.6 Hz, Ar), 4.83 (1H, t, *J* = 7.2 Hz, 2-H), 4.08 (1H, dd, *J* = 14.7, 7.2 Hz, 5-H_A), 3.91 (1H, dd, *J* = 14.3, 7.9 Hz, 5-H_B), 3.80 (3H, s, OMe), 2.36-2.20 (1H, m, 3-H_A), 2.11-1.94 (2H, m, 4-H_A and 3-H_B), 1.85-1.71 (1H, m, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.8 (C Ar),, 135.3 (C Ar), 126.9 (2 x CH Ar), 113.7 (2 x CH Ar), 80.4 (C-2), 68.5 (C-5), 55.3 (OMe), 34.5 (C-3), 26.1 (C-4)

5.8.10 (±)-(2*S*,3*R*)-3-[(1'*R*)-Cyclohex-2-en-1-yl]-2-(4-methoxyphenyl)tetrahydrofuran and (±)-(2*S*,3*R*)-3-[(1'*S*)-cyclohex-2-en-1-yl]-2-(4-methoxyphenyl)tetrahydrofuran (176j)



***E*-178a** ***Z*-182j** **A** **176j** dr (C-6) 2:1 **B**

Alcohols ***E*-178a** (53.8 mg, 0.302 mmol) and ***Z*-182j** (29.6 mg, 0.302 mmol) and $Ti(O^iPr)_4$ (25.7 mg, 0.0905 mmol) were subjected to the general procedure **H** (FCC: 6%

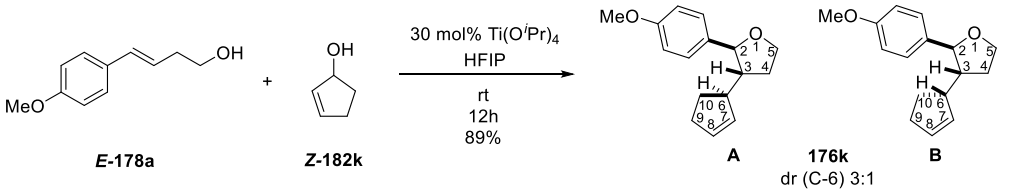
Et_2O - pentane) to yield a inseparable 2:1 mixture of diastereomer **176j** as a colorless oil (50.6 mg, 65%).

Data for **major diastereomer A** of **176j** (from the mixture): **R_f** 0.50 (30% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.26 (2H, d, *J* = 8.3 Hz, Ar), 6.87 (2H, d, *J* = 8.8 Hz, Ar), 5.76-5.82 (1H, m, 8-H), 5.66-5.71 (1H, m, 7-H), 4.56 (1H, d, *J* = 7.5 Hz, 2-H), 3.99-4.10 (1H, m, 5-H_A), 3.89-3.96 (1H, m, 5-H_B), 3.80 (3H, s, OMe), 2.21-2.28 (1H, m, 6-H), 2.13-2.20 (1H, m, 3-H), 2.05-2.13 (1H, m, 4-H_A), 1.92-1.99 (2H, m, CH_2 cyclohexenyl), 1.83-1.90 (1H, m, 4-H_B), 1.61-1.70 (2H, m, 2 x CH cyclohexenyl), 1.40-1.54 (1H, m, CH cyclohexenyl), 1.13-1.27 (1H, m, CH cyclohexenyl). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.10 (C Ar), 135.2 (C Ar), 129.3 (C-8), 128.7 (C-7), 128.06 (2 x CH Ar), 113.86 (2 x CH Ar), 83.9 (C-2), 68.1 (C-5), 55.4 (OMe), 52.2 (C-3), 36.8 (C-6), 29.8 (C-4), 29.1 (CH_2 cyclohexenyl), 25.44 (CH_2 cyclohexenyl), 21.96 (CH_2 cyclohexenyl). **HRMS** (CI): calculated for $C_{17}H_{23}O_2$ $[M+H]^+$ requires *m/z* 259.16926, found *m/z* 259.16922. **IR** (film) ν_{max}: 3657, 2980, 2888, 1512, 1382, 1244 cm^{-1}.

Data for **minor diastereomer B** of **176j** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.27 (2H, d, *J* = 8.5 Hz, Ar), 6.87 (2H, d, *J* = 8.8 Hz, Ar), 5.62-5.65 (1H, m, 8-H), 5.41-5.47 (1H, m, 7-H), 4.60 (1H, d, *J* = 7.3 Hz, 2-H), 3.99-4.10 (1H, m, 5-H_A), 3.89-3.96 (1H, m, 5-H_B), 3.80 (3H, s, OMe), 2.21-2.28 (1H, m, 6-H), 2.05-2.13 (2H, m, 3-H and 4-H_A), 1.92-1.99 (2H, m, CH_2 cyclohexenyl), 1.77-1.91 (2H, m, 4-H_B and CH cyclohexenyl), 1.72-1.76 (1H, m, CH cyclohexenyl), 1.40-1.54 (1H, m, CH cyclohexenyl), 1.28-1.35 (1H, m, CH cyclohexenyl). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.13 (C Ar), 135.0 (C Ar), 130.4 (C-7), 128.1 (C-8), 128.05 (2 x CH Ar), 113.90 (2 x CH Ar), 83.7 (C-2), 67.9 (C-5), 55.4 (OMe),

52.0 (C-3), 37.2 (C-6), 30.2 (C-4), 26.8 (CH_2 cyclohexenyl), 25.35 (CH_2 cyclohexenyl), 22.01 (CH_2 cyclohexenyl).

5.8.11 (±)-(2*S*,3*R*)-3-[(1'*R*)-Cyclopent-2-en-1-yl]-2-(4-methoxyphenyl)tetrahydrofuran and (±)-(2*S*,3*R*)-3-[(1'*S*)-cyclopent-2-en-1-yl]-2-(4-methoxyphenyl)tetrahydrofuran (176k)



***E*-178a** ***Z*-182k** **A** **176k** dr (C-6) 3:1 **B**

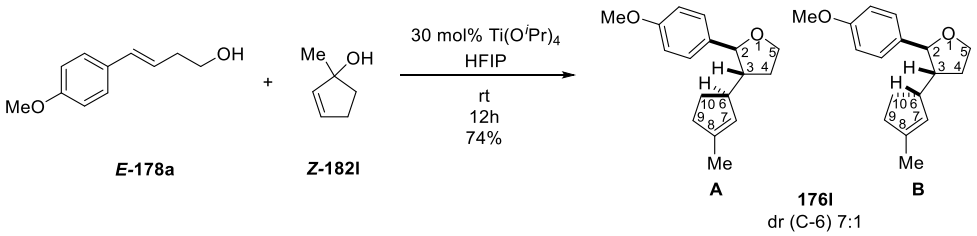
Alcohols ***E*-178a** (53.0 mg, 0.298 mmol) and ***Z*-182k** (50.0 mg, 0.596 mmol) and Ti(O^{i}Pr)$_4$ (25.4 mg, 0.0894 mmol) were subjected to the general procedure E except using 2 equivalents of the ***Z*-182k** and conducting the reaction at room temperature (FCC: 6% Et_2O - pentane) to yield an inseparable 3:1 mixture of diastereomer (3.5:1 dr shown in crude NMR) **176k** as a colorless oil (64.7 mg, 89%).

Data for **major diastereomer A** of **176k** (from the mixture): **R_f** 0.50 (30% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.26 (2H, d, *J* = 8.5 Hz, Ar), 6.87 (2H, d, *J* = 8.7 Hz, Ar), 5.79-5.83 (1H, m, 7-H), 5.69-5.74 (1H, m, 8-H), 4.48 (1H, d, *J* = 6.3 Hz, 2-H), 4.06 (1H, q, *J* = 7.2 Hz, 5-H_A), 3.95 (1H, td, *J* = 8.4, 4.7 Hz, 5-H_B), 3.80 (3H, s, OMe), 2.74-2.83 (1H, m, 6-H), 2.20-2.28 (2H, m, 9-H_2), 2.06-2.17 (2H, m, 3-H and 4-H_A), 1.87-1.97 (1H, m, 10-H_A), 1.75-1.86 (1H, m, 4-H_B), 1.25-1.36 (1H, m, 10-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.2 (C Ar), 134.9 (C Ar), 132.5 (C-7), 132.4 (C-8), 128.1 (2 x CH Ar), 113.8 (2 x CH Ar),

85.2 (C-2), 68.0 (C-5), 55.4 (OMe), 52.6 (C-3), 47.3 (C-6), 32.3 (C-9), 30.4 (C-4), 29.0 (C-10). **HRMS** (EI): calculated for $C_{16}H_{20}O_2$ $[M]^+$ requires *m/z* 244.1458, found *m/z* 244.1466. **IR** (film) ν_{max}: 3677, 2988, 2898, 1510, 1342, 1244 cm^{-1}.

Data for **minor diastereomer B** of **176k (from the mixture)**: **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.26 (2H, d, *J* = 8.5 Hz, Ar), 6.87 (2H, d, *J* = 8.7 Hz, Ar), 5.67-5.69 (1H, m, 7-H), 5.45-5.50 (1H, m, 8-H), 4.50 (1H, d, *J* = 7.5 Hz, 2-H), 4.07 (1H, q, *J* = 7.1 Hz, 5-H_A), 3.95 (1H, td, *J* = 8.4, 4.7 Hz, 5-H_B), 3.80 (3H, s, OMe), 2.74-2.83 (1H, m, 6-H), 2.28-2.34 (2H, m, 9-H_2), 2.06-2.17 (2H, m, 3-H and 4-H_A), 1.99-2.05 (1H, m, 10-H_A), 1.75-1.86 (1H, m, 4-H_B), 1.50-1.57 (1H, m, 10-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.2 (C Ar), 134.8 (C Ar), 133.5 (C-7), 131.4 (C-8), 128.0 (2 x CH Ar), 113.9 (2 x CH Ar), 84.9 (C-2), 67.9 (C-5), 55.4 (OMe), 52.2 (C-3), 47.3 (C-6), 32.2 (C-9), 30.6 (C-4), 29.0 (C-10).

5.8.12 (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-3-[(1'*S*)-3-methylcyclopent-2-en-1-yl]tetrahydrofuran and (±)-(2*S*,3*R*)-2-(4-methoxyphenyl)-3-[(1'*R*)-3-methylcyclopent-2-en-1-yl]tetrahydrofuran (176l)



Alcohols ***E*-178a** (20.7 mg, 0.116 mmol) and ***Z*-182l** (22.9 mg, 0.232 mmol) and $Ti(O^iPr)_4$ (9.9 mg, 0.035 mmol) were subjected to the general procedure E except using 2 equivalents of alcohol ***Z*-182l** and conducting reaction at room temperature (FCC:

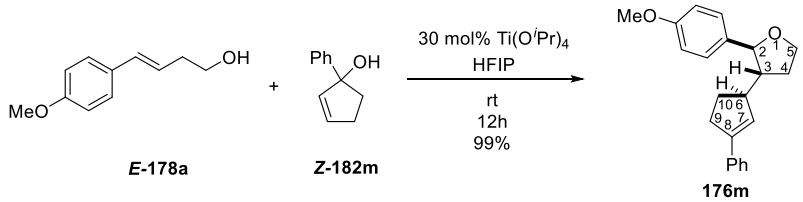
gradient elution: 6% → 12% Et_2O - pentane) to yield 2 clean fractions: first fraction of mixture of 10:1 **diastereomer A** and **B** (10.0 mg, 33%) as a colorless oil, and second fraction of mixture of 5.5:1 **diastereomer A** and **B** as a colorless oil (12.1 mg, 41%).

Data for **major diastereomer A** of **176l** (from the mixture)**: R_f** 0.40 (30% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.25 (2H, d, *J* = 8.9 Hz, Ar), 6.86 (2H, d, *J* = 8.7 Hz, Ar), 5.28-5.33 (1H, m, 7-H), 4.46 (1H, d, *J* = 7.3 Hz, 2-H), 4.06 (1H, q, *J* = 8.1 Hz, 5-H_A), 3.94 (1H, td, *J* = 8.3, 4.7 Hz, 5-H_B), 3.80 (3H, s, OMe), 2.72-2.81 (1H, m, 6-H), 2.12-2.20 (2H, m, 9-H_2), 2.03-2.11 (2H, m, 3-H and 4-H_A), 1.94 (1H, ddt, *J* = 13.2, 8.3, 6.7 Hz, 10-H_A), 1.77-1.86 (1H, m, 4-H_B), 1.72 (3H, s, Me), 1.35 (1H, dtd, *J* = 12.8, 8.1, 6.4 Hz, 10-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.1 (C Ar), 142.3 (C-8), 135.1 (C Ar), 128.03 (2 x C-H Ar), 126.2 (C-7), 113.8 (2 x C-H Ar), 85.2 (C-2), 68.0 (C-5), 55.4 (OMe), 53.0 (C-3), 47.5 (C-6), 36.6 (C-9), 30.4 (C-4), 29.9 (C-10), 16.9 (Me). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H, between 2-H and 7-H, between 2-H and 10-H_B. **HRMS** (ESI): calculated for $C_{17}H_{22}O_2Na$ $[M+Na]^+$ requires *m/z* 281.15120, found *m/z* 281.15128. **IR** (film) ν_{max}: 2930, 1611, 1512, 1245, 1031, 828 cm^{-1}.

Data for **minor diastereomer B** of **176l** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.25 (2H, d, *J* = 8.9 Hz, Ar), 6.86 (2H, d, *J* = 8.7 Hz, Ar), 5.08-5.11 (1H, m, 7-H), 4.49 (1H, d, *J* = 7.4 Hz, 2-H), 4.06 (1H, q, *J* = 8.1 Hz, 5-H_A), 3.94 (1H, td, *J* = 8.3, 4.7 Hz, 5-H_B), 3.80 (3H, s, OMe), 2.72-2.81 (1H, m, 6-H), 2.12-2.20 (2H, m, 9-H_2), 2.03-2.11 (2H, m, 3-H and 4-H_A), 1.94 (1H, ddt, *J* = 13.2, 8.3, 6.7 Hz, 10-H_A), 1.77-1.86 (1H, m, 4-H_B), 1.72 (3H, s, Me), 1.35 (1H, dtd, *J* = 12.8, 8.1, 6.4 Hz, 10-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.1 (C Ar), 141.2 (C-8), 135.1 (C Ar), 127.95 (2 x C-H Ar), 127.3 (C-7), 113.9 (2 x C-H Ar),

84.8 (C-2), 67.9 (C-5), 55.4 (OMe), 52.5 (C-3), 47.6 (C-6), 36.5 (C-9), 30.6 (C-4), 28.3 (C-10), 16.8 (Me).

5.8.13 (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-3-[(1'*S*)-3-phenylcyclopent-2-en-1-yl]tetrahydrofuran (176m)

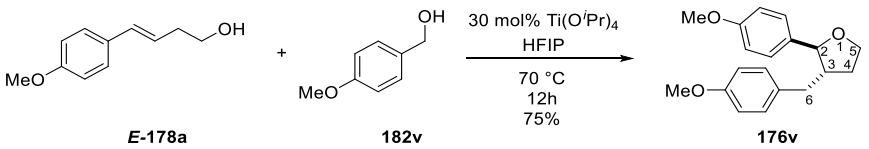


Alcohols ***E*-178a** (38.0 mg, 0.212 mmol) and ***Z*-182m** (34.0 mg, 0.212 mmol) and Ti(O^{i}Pr)$_4$ (18.0 mg, 0.0633 mmol) were subjected to the general procedure except E conducting reaction at room temperature (FCC: gradient elution: 7% → 15% Et_2O - pentane) to yield **176m** as a yellow oil (67.5 mg, 99%).

Data for **176m**: **R_f** 0.50 (40% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.43 (2H, d, *J* = 8.6 Hz, Ar), 7.21-7.36 (5H, m, Ar), 6.88 (2H, d, *J* = 8.7 Hz, Ar), 6.15 (1H, q, *J* = 2.0 Hz, 7-H), 4.56 (1H, d, *J* = 7.2 Hz, 2-H), 4.13 (1H, q, *J* = 7.1 Hz, 5-H_A), 3.98 (1H, td, *J* = 8.4, 4.7 Hz, 5-H_B), 3.81 (3H, s, OMe), 2.96-3.04 (1H, m, 6-H), 2.61-2.71 (2H, m, 9-H_2), 2.19-2.27 (2H, m, 3-H and 4-H_A), 2.11 (1H, dtd, *J* = 13.1, 8.3, 5.0 Hz, 10-H_A), 1.90 (1H, ddd, *J* = 8.3, 7.3, 3.8 Hz, 4-H_B), 1.54 (1H, ddt, *J* = 12.9, 9.0, 7.1 Hz, 10-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.2 (C Ar), 143.8 (C-8), 136.5 (C Ar), 134.9 (C Ar), 128.4 (2 x C-H Ar), 128.1 (2 x C-H Ar), 127.5 (C-7), 127.4 (C-H Ar), 125.8 (2 x C-H Ar), 113.9 (2 x C-H Ar), 85.1 (C-2), 68.1 (C-5), 55.4 (OMe), 52.7 (C-3), 47.9 (C-6), 32.9 (C-9), 30.6 (C-4), 29.2 (C-10). **NOESY- 2D (400 MHz, $CDCl_3$)**: between 2-H and 6-H, between 2-H and 7-H, between 2-H

and 10-H_B. **HRMS** (ESI): calculated for $C_{22}H_{24}O_2Na$ $[M+Na]^+$ requires *m/z* 343.16685, found *m/z* 343.16690. **IR** (film) ν_{max}: 2965, 1712, 1512, 1245, 1030, 827 cm^{-1}.

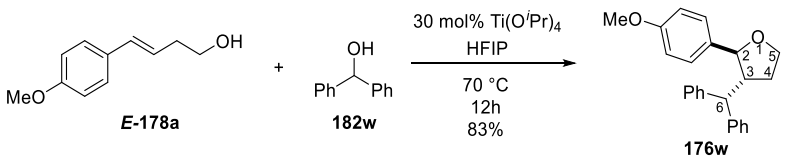
5.8.14 (±)-(2*S*,3*S*)-3-(4-Methoxybenzyl)-2-(4-methoxyphenyl)tetrahydrofuran (176v)



Alcohol ***E*-178a** (42.5 mg, 0.239 mmol), 4-methoxybenzyl alcohol **182v** (33.0 mg, 0.239 mmol) and $Ti(O^iPr)_4$ (20.3 mg, 0.0715 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 10% → 14% Et_2O - pentane) to yield **176v** as a yellow oil (53.4 mg, 75%).

Data for **176v**: $\mathbf{R_f}$ 0.50 (60% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.24 (2H, d, *J* = 8.9 Hz, Ar), 7.05 (2H, d, *J* = 8.6 Hz, Ar), 6.88 (2H, d, *J* = 8.8 Hz, Ar), 6.81 (2H, d, *J* = 8.6 Hz, Ar), 4.45 (1H, d, *J* = 7.6 Hz, 2-H), 4.06 (1H, q, *J* = 8.4 Hz, 5-H_A), 4.01 (1H, td, *J* = 8.6, 4.9 Hz, 5-H_B), 3.81 (3H, s, OMe), 3.78 (3H, s, OMe), 2.80 (1H, dd, *J* = 13.6, 5.1 Hz, 6-H_A), 2.51 (1H, dd, *J* = 13.6, 9.7 Hz, 6-H_B), 2.25-2.36 (1H, m, 3-H), 2.00-2.10 (1H, m, 4-H_A), 1.71-1.82 (1H, m, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.1 (C Ar), 158.0 (C Ar), 134.4 (C Ar), 132.6 (C Ar), 129.8 (2 x CH Ar), 127.6 (2 x CH Ar), 113.9 (2 x CH Ar), 113.8 (2 x CH Ar), 85.8 (C-2), 67.9 (C-5), 55.4 (OMe), 55.3 (OMe), 50.0 (C-3), 37.3 (C-6), 32.4 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H_A, between 2-H and 6-H_B. **HRMS** (ESI): calculated for $C_{19}H_{22}O_3Na$ $[M+Na]^+$ requires *m/z* 321.14612, found *m/z* 321.14609. **IR** (film) ν_{max}: 2916, 1611, 1510, 1241, 1030, 828 cm^{-1}.

5.8.15 (±)-(2*S*,3*R*)-3-Benzhydryl-2-(4-methoxyphenyl)tetrahydrofuran (176w)

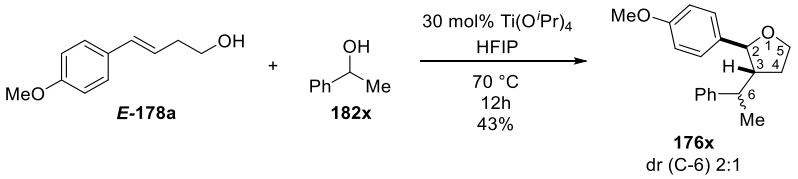


Alcohol ***E*-178a** (19.8 mg, 0.111 mmol), diphenylmethanol **182w** (20.5 mg, 0.111 mmol) and $Ti(O^iPr)_4$ (9.5 mg, 0.033 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 10% → 20% Et_2O - pentane) to yield **176w** as a yellow foam (31.2 mg, 83%).

Data for **176w**: $\mathbf{R_f}$ 0.50 (40% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.16-7.25 (4H, m, Ar), 7.06-7.15 (5H, m, Ar), 7.01-7.06 (1H, m, Ar), 6.79 (2H, d, *J* = 8.4 Hz, Ar), 6.63 (2H, d, *J* = 8.3 Hz, Ar), 4.55 (1H, d, *J* = 4.3 Hz, 2-H), 4.06 (1H, td, *J* = 8.3, 4.5 Hz, 5-H_A), 3.91 (1H, q, *J* = 7.9 Hz, 5-H_B), 3.84 (1H, d, *J* = 11.5 Hz, 6-H), 3.68 (3H, s, OMe), 3.03 (1H, ddt, *J* = 12.1, 8.4, 4.4 Hz, 3-H), 2.00-2.12 (1H, m, 4-H_A), 1.65 (1H, ddt, *J* = 11.8, 7.9, 4.5 Hz, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 144.1 (C Ar), 143.6 (C Ar), 135.7 (C Ar), 128.7 (2 x C-H Ar), 128.6 (2 x C-H Ar), 128.5 (2 x C-H Ar), 128.2 (2 x C-H Ar), 127.2 (2 x C-H Ar), 126.6 (CH Ar), 126.5 (CH Ar), 125.6 (C Ar), 113.6 (2 x C-H Ar), 84.7 (C-2), 67.8 (C-5), 55.7 (C-6), 55.4 (OMe), 51.6 (C-3), 31.2 (C-4). **HRMS** (Cl): calculated for $C_{24}H_{24}O_2Na$ $[M+Na]^+$ requires *m/z* 367.16685, found *m/z* 367.16638. **IR** (film) ν_{max}: 3656, 2980, 1492, 1239, 954, 750 cm^{-1}.

5.8.16 (±)-(2*S*,3*R*)-2-(4-methoxyphenyl)-3-[(1'*R*)-1-phenylethyl]tetrahydrofuran

(±)-(2*S*,3*R*)-2-(4-methoxyphenyl)-3-[(1'*S*)-1-phenylethyl]tetrahydrofuran (176x)



Alcohols ***E*-178a** (17.8 mg, 0.100 mmol), **182x** (12.2 mg, 0.100 mmol) and $Ti(O^iPr)_4$ (8.5 mg, 0.030 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 10% → 30% Et_2O - pentane) to yield an inseparable 2:1 mixture of diastereomers **176x** as a colorless oil (12.1 mg, 43%).

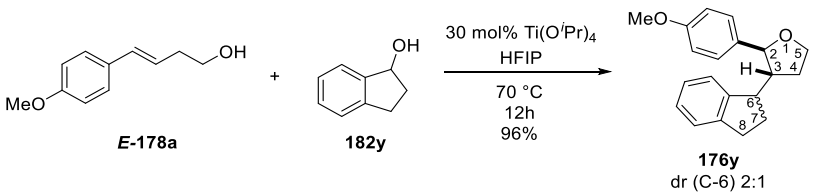
Data for **major diastereomer** of **176x** (from the mixture): $\mathbf{R_f}$ 0.40 (30% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.27-7.34 (3H, m, Ar), 7.15-7.22 (3H, m, Ar), 7.02-7.07 (1H, m, Ar), 6.90 (2H, d, *J* = 8.7 Hz, Ar), 4.60 (1H, d, *J* = 6.7 Hz, 2-H), 3.93-4.01 (1H, m, 5-H_A), 3.82-3.87 (1H, m, 5-H_B), 3.82 (3H, s, OMe), 2.69-2.81 (1H, m, 6-H), 2.39-2.48 (1H, m, 3-H), 1.84-1.93 (1H, m, 4-H_A), 1.59-1.67 (1H, m, 4-H_B), 1.19 (3H, d, *J* = 7.0 Hz, Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.2 (C Ar), 146.0 (C Ar), 135.3 (C Ar), 128.5 (2 x C-H Ar), 128.2 (2 x C-H Ar), 127.8 (2 x C-H Ar), 126.4 (C-H Ar), 113.9 (2 x C-H Ar), 84.9 (C-2), 68.0 (C-5), 55.42 (OMe), 53.7 (C-3), 42.8 (C-6), 31.4 (C-4), 21.7 (Me). **HRMS** (ESI): calculated for $C_{19}H_{22}O_2Na$ $[M+Na]^+$ requires *m/z* 305.1017, found *m/z* 305.1512. **IR** (film) ν_{max}: 2980, 1492, 1339, 1145, 954, 750 cm^{-1}.

Data for **minor diastereomer** of **176x** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.27-7.34 (3H, m, Ar), 7.15-7.22 (2H, m, Ar), 7.10-7.14 (1H, m, Ar), 6.84 (2H, d, *J* = 8.7 Hz, Ar), 6.68 (2H, d, *J* = 8.7 Hz, Ar), 4.45 (1H, d, *J* = 6.5 Hz, 2-H), 4.09 (1H, ddd, *J* =

8.4, 7.3, 6.6 Hz, 5-H_A), 3.93-4.01 (1H, m, 5-H_B), 3.75 (3H, s, OMe), 2.69-2.81 (1H, m, 6-H), 2.33-2.39 (1H, m, 3-H), 2.17 (1H, dtd, *J* = 12.4, 7.3, 5.9 Hz, 4-H_A), 1.93-2.01 (1H, m, 4-H_B), 1.31 (3H, d, *J* = 7.0 Hz, Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.6 (C Ar), 145.9 (C Ar), 135.3 (C Ar), 128.4 (2 x C-H Ar), 127.7 (2 x C-H Ar), 127.4 (2 x C-H Ar), 126.3 (C-H Ar), 113.5 (2 x C-H Ar), 84.6 (C-2), 67.7 (C-5), 55.36 (OMe), 54.4 (C-3), 42.4 (C-6), 30.6 (C-4), 19.9 (Me).

5.8.17 (±)-(2*S*,3*R*)-3-[(1'*R*)-2,3-dihydro-1*H*-inden-1-yl]-2-(4-methoxyphenyl)tetrahydrofuran

(±)-(2*S*,3*R*)-3-[(1'*S*)-2,3-dihydro-1*H*-inden-1-yl]-2-(4-methoxyphenyl)tetrahydrofuran (176y)



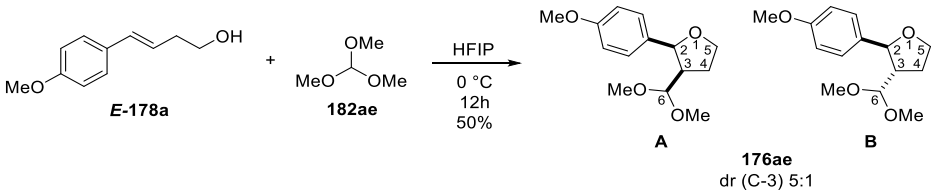
Alcohols ***E*-178a** (17.8 mg, 0.100 mmol), **182y** (13.4 mg, 0.100 mmol) and Ti(O^{i}Pr)$_4$ (8.5 mg, 0.030 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 10% → 30% Et_2O - pentane) to yield an inseparable 2:1 mixture of diastereomers **176y** as a colorless oil (28.2 mg, 96%).

Data for **major diastereomer** of **176y** (from the mixture): **R_f** 0.40 (30% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.08-7.28 (6H, m, Ar), 6.86 (2H, d, *J* = 8.7 Hz, Ar), 4.68 (1H, d, *J* = 7.5 Hz, 2-H), 4.04-4.14 (1H, m, 5-H_A), 3.92-4.00 (1H, m, 5-H_B), 3.81 (3H, s, OMe), 3.24-3.34 (1H, m, 6-H), 2.70-3.00 (2H, m, 8-H_2), 2.47 (1H, p, *J* = 7.7 Hz, 3-H),

2.08-2.29 (2H, m, 7-H_2), 1.84-1.96 (1H, m, 4-H_A), 1.68-1.80 (1H, m, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.2 (C Ar), 145.4 (C Ar), 144.9 (C Ar), 135.0 (C Ar), 128.1 (2 x C-H Ar), 126.8 (C-H Ar), 126.1 (C-H Ar), 125.0 (C-H Ar), 124.8 (C-H Ar), 113.9 (2 x C-H Ar), 84.6 (C-2), 68.0 (C-5), 55.42 (OMe), 51.3 (C-3), 47.0 (C-6), 31.5, 31.13 and 31.11 (C-4, C-7 and C-8). **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max}: 2980, 1692, 1439, 1245, 1154, 750 cm^{-1}.

Data for **minor diastereomer** of **176y** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.31 (2H, d, *J* = 8.7 Hz, Ar), 7.08-7.28 (4H, m, Ar), 6.91 (2H, d, *J* = 8.7 Hz, Ar), 4.04-4.14 (1H, m, 5-H_A), 3.92-4.00 (1H, m, 5-H_B), 3.82 (3H, s, OMe), 3.24-3.34 (1H, m, 6-H), 2.70-3.00 (2H, m, 8-H_2), 2.62-2.70 (1H, m, 3-H), 2.08-2.29 (2H, m, 7-H_A), 1.96-2.03 (2H, m, 7-H_B), 1.84-1.96 (1H, m, 4-H_A), 1.68-1.80 (1H, m, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.3 (C Ar), 145.9 (C Ar), 144.1 (C Ar), 134.2 (C Ar), 127.7 (2 x C-H Ar), 126.6 (C-H Ar), 126.3 (C-H Ar), 124.6 (C-H Ar), 123.7 (C-H Ar), 114.0 (2 x C-H Ar), 83.8 (C-2), 68.0 (C-5), 55.40 (OMe), 50.9 (C-3), 43.9 (C-6), 31.8 (C-8), 28.0 (C-4), 27.0 (C-7).

5.8.18 (±)-(2*S*,3*R*)-3-(Dimethoxymethyl)-2-(4-methoxyphenyl)tetrahydrofuran and (±)-(2*S*,3*S*)-3-(dimethoxymethyl)-2-(4-methoxyphenyl)tetrahydrofuran (176ae)



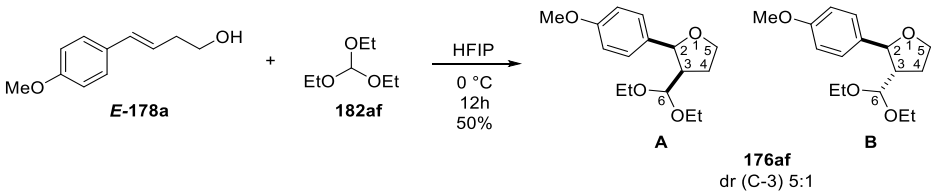
Alcohol ***E*-178a** (17.8 mg, 0.100 mmol) and trimethyl orthoformate **182ae** (53.0 mg, 0.500 mmol) were subjected to the general procedure **H** except conducting the

reaction at 0 °C, using 5 equivalents of paraformaldehyde **182ae** and using no additional additive (FCC: gradient elution: 10% → 30% Et_2O - pentane) to yield an inseparable 5:1 mixture of diastereomers **176ae** as a colorless oil (12.6 mg, 50%).

Data for **diastereomer A** of **176ae** (from the mixture): **R_f** 0.40 (50% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.24 (2H, d, *J* = 8.7 Hz, Ar), 6.88 (2H, d, *J* = 8.7 Hz, Ar), 5.02 (1H, d, *J* = 4.3 Hz, 2-H), 4.16 (1H, d, *J* = 10.1 Hz, 6-H), 3.94 (1H, ddd, *J* = 9.6, 8.2, 2.9 Hz, 5-H_A), 3.81 (3H, s, OMe), 3.76 (1H, q, *J* = 8.2 Hz, 5-H_B), 3.43 (3H, s, OMe), 3.14 (3H, s, OMe), 2.39 (1H, dddd, *J* = 12.4, 10.1, 8.4, 4.3 Hz, 3-H), 1.53-1.67 (1H, m, 4-H_A), 1.24-1.36 (1H, m, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.4 (C Ar), 133.3 (C Ar), 128.4 (2 x C-H Ar), 113.9 (2 x C-H Ar), 104.4 (C-2), 82.6 (C-6), 66.7 (C-5), 56.3 (OMe), 55.4 (OMe), 55.0 (OMe), 51.4 (C-3), 26.4 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 3-H. **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max}: 2980, 2888, 1615, 1515, 1482, 1246 cm^{-1}.

Data for **diastereomer B** of **176ae** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.20 (2H, d, *J* = 8.7 Hz, Ar), 6.89 (2H, d, *J* = 8.7 Hz, Ar), 5.09 (1H, d, *J* = 1.3 Hz, 2-H), 3.78-3.89 (2H, m, 5-H_2), 3.76 (1H, d, *J* = 8.5 Hz, 6-H), 3.81 (3H, s, OMe), 3.38 (3H, s, OMe), 3.13 (3H, s, OMe), 2.48 (1H, dddd, *J* = 10.1, 8.5, 5.7, 1.3 Hz, 3-H), 1.68-1.76 (1H, m, 4-H_A), 1.24-1.36 (1H, m, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.5 (C Ar), 132.1 (C Ar), 128.9 (2 x C-H Ar), 114.0 (2 x C-H Ar), 107.8 (C-2), 84.6 (C-6), 66.3 (C-5), 56.5 (OMe), 55.4 (OMe), 54.9 (OMe), 52.7 (C-3), 27.5 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H.

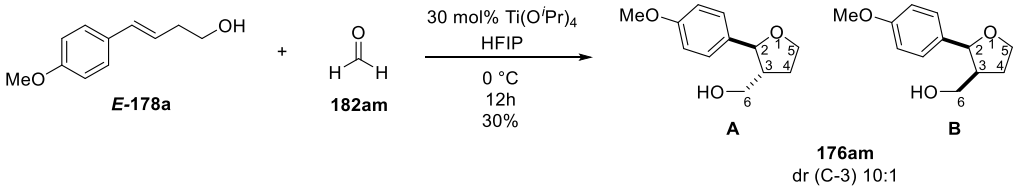
5.8.19 (±)-(2*S*,3*R*)-3-(Diethoxymethyl)-2-(4-methoxyphenyl)tetrahydrofuran and (±)-(2*S*,3*S*)-3-(diethoxymethyl)-2-(4-methoxyphenyl)tetrahydrofuran (176af)



Alcohol ***E*-178a** (17.8 mg, 0.100 mmol) and triethyl orthoformate **182af** (53.0 mg, 0.500 mmol) were subjected to the general procedure **H** except conducting the reaction at 0 °C, using 5 equivalents of paraformaldehyde **182af** and using no additional additive (FCC: gradient elution: 10% → 30% Et_2O - pentane) to yield **176af-A** (12.6 mg, 50%) as a colorless oil (dr was based on crude ^1H NMR).

Data for **diastereomer A** of **176ae**: **R_f** 0.40 (50% Et_2O - pentane). **^1H NMR (400 MHz, $CDCl_3$) δ** 7.25 (2H, d, *J* = 8.7 Hz, Ar), 6.87 (2H, d, *J* = 8.7 Hz, Ar), 5.15 (1H, d, *J* = 4.4 Hz, 2-H), 4.29 (1H, d, *J* = 10.2 Hz, 6-H), 3.96 (1H, ddd, *J* = 9.5, 8.1, 2.9 Hz, 5-H_A), 3.81 (3H, s, OMe), 3.69-3.81 (2H, m, CH Et and 5-H_B), 3.55 (1h, dq, *J* = 10.0, 7.1 Hz, CH Et), 3.20-3.38 (2H, m, CH_2 Et), 2.38 (1H, dddd, *J* = 12.4, 10.2, 8.3, 4.4 Hz, 3-H), 1.59-1.70 (1H, m, 4-H_A), 1.26-1.35 (1H, m, 4-H_B), 1.24 (3H, t, *J* = 7.1 Hz, CH_3 Et), 1.12 (3H, t, *J* = 7.1 Hz, CH_3 Et). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.2 (C Ar), 134.2 (C Ar), 128.3 (2 x C-H Ar), 113.8 (2 x C-H Ar), 103.2 (C-2), 80.8 (C-6), 66.8 (C-5), 63.8 (CH_2 Et), 63.3 (CH_2 Et), 55.4 (OMe), 51.4 (C-3), 26.5 (C-4), 15.47 (CH_3 Et), 15.45 (CH_3 Et). **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max}: 2980, 2888, 2360, 1473, 1382, 1251 cm^{-1}.

5.8.20 (±)-[(2*S*,3*R*)-2-(4-methoxyphenyl)tetrahydrofuran-3-yl]methanol and (±)-[(2*S*,3*S*)-2-(4-methoxyphenyl)tetrahydrofuran-3-yl]methanol (176am)



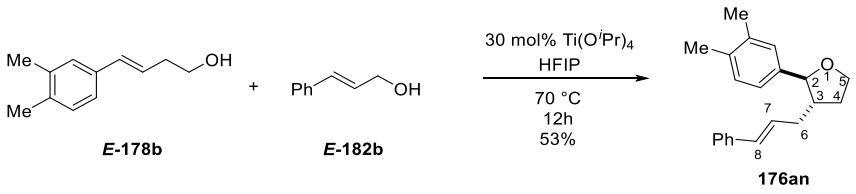
Alcohol ***E*-178a** (17.8 mg, 0.100 mmol), paraformaldehyde **182am** (60.0 mg, 2.00 mmol) and $Ti(O^iPr)_4$ (8.5 mg, 0.030 mmol) were subjected to the general procedure **H** except conducting the reaction at 0 °C and using 20 equivalents of paraformaldehyde **182am** (FCC: gradient elution: 20% → 50% acetone - pentane) to yield an inseparable 10:1 mixture of diastereomers **176am** as a colorless oil (6.2 mg, 30%).

Data for **diastereomer A** of **176am** (from the mixture): $\mathbf{R_f}$ 0.40 (50% acetone - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.30 (2H, d, *J* = 8.7 Hz, Ar), 6.90 (2H, d, *J* = 8.7 Hz, Ar), 4.59 (1H, d, *J* = 7.0 Hz, 2-H), 4.12 (1H, ddd, *J* = 8.5, 7.5, 6.5 Hz, 5-H_A), 3.98 (1H, td, *J* = 8.5, 5.8 Hz, 5-H_B), 3.82 (3H, s, OMe), 3.75 (1H, dd, *J* = 10.6, 6.2 Hz, 6-H_A), 3.69 (1H, dd, *J* = 10.6, 6.6 Hz, 6-H_B), 2.28-2.38 (1H, m, 3-H), 2.21 (1H, dtd, *J* = 12.4, 7.5, 5.8 Hz, 4-H_A), 1.83-1.93 (1H, m, 4-H_B), 1.53 (1H, br s, OH). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.2 (C Ar), 134.5 (C Ar), 127.5 (2 x C-H Ar), 114.0 (2 x C-H Ar), 83.1 (C-2), 68.0 (C-5), 64.1 (C-7), 55.42 (OMe), 50.1 (C-3), 29.8 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H_A, between 2-H and 6-H_B. **HRMS** (ESI): calculated for $C_{12}H_{16}O_3Na$ $[M+Na]^+$ requires *m/z* 231.0997, found *m/z* 231.0922. **IR** (film) ν_{max}: 3407, 2980, 2888, 1612, 1513, 1462, 1246 cm^{-1}.

Data for **diastereomer B** of **176am** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$)**

δ 7.24-7.34 (2H, m, Ar), 6.85-6.92 (2H, m, Ar), 4.99 (1H, d, *J* = 6.8 Hz, 2-H), 4.19-4.23 (1H, m, 5-H_A), 3.86-3.93 (1H, m, 5-H_B), 3.83 (3H, s, OMe), 3.32-3.37 (1H, m, 6-H_A), 3.23-3.29 (1H, m, 6-H_B), 2.57-2.64 (1H, m, 3-H), 1.53 (1H, br s, OH), 1.29-1.36 (1H, m, 4-H_A), 1.14-1.23 (1H, m, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.0 (C Ar), 131.6 (C Ar), 127.3 (2 x C-H Ar), 114.1 (2 x C-H Ar), 81.9 (C-2), 67.6 (C-5), 63.1 (C-7), 55.39 (OMe), 45.7 (C-3), 31.2 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 3-H_A.

5.8.21 (±)-(2*S*,3*S*)-3-Cinnamyl-2-(3,4-dimethylphenyl)tetrahydrofuran (176an)

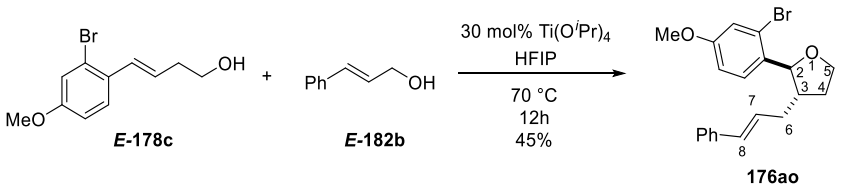


Alcohol ***E*-178b** (59.3 mg, 0.31 mmol), cinnamyl alcohol ***E*-182b** (41.6 mg, 0.310 mmol) and Ti(O^{i}Pr)$_4$ (26.4mg, 0.0930 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 6% → 20% Et_2O - pentane) to yield **176an** as a colorless oil (50.2 mg, 53%).

Data for **176an**: **R_f** 0.50 (25% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.27-7.31 (4H, m, Ar), 7.16-7.23 (1H, m, Ar), 7.05-7.13 (3H, m, Ar), 6.41 (1H, d, *J* = 15.8 Hz, 8-H), 6.14 (1H, dt, *J* = 15.8, 6.9 Hz, 7-H), 4.42 (1H, d, *J* = 6.3 Hz, 2-H), 4.12 (1H, dt, *J* = 8.4, 7.1 Hz, 5-H_A), 4.02 (1H, td, *J* = 8.3, 4.7 Hz, 5-H_B), 2.40-2.52 (1H, m, 6-H_A), 2.25 (6H, s, 2 x Me), 2.16-2.24 (3H, m, 3-H, 4-H_A and 6-H_B), 1.80 (1H, dddd, *J* = 13.4, 6.1, 3.9, 2.4 Hz, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 139.8 (C Ar), 137.6 (C Ar), 136.7 (C Ar), 135.9 (C Ar), 131.4 (C-8), 129.7 (CH Ar), 128.6 (2 x CH Ar and C-7), 127.7 (CH Ar), 127.2 (CH Ar), 126.1

(2 x CH Ar), 123.9 (CH Ar), 86.1 (C-2), 68.0 (C-5), 48.0 (C-3), 35.7 (C-6), 32.5 (C-4), 20.0 (Me), 19.6 (Me). **HRMS** (ESI): calculated for $C_{21}H_{25}O$ $[M+H]^+$ requires *m/z* 293.18999, found *m/z* 293.18997. **IR** (film) ν_{max} : 2971, 1497, 1449, 964, 743, 692 cm^{-1}

5.8.22 (±)-(2*S*,3*S*)-2-(2-Bromo-4-methoxyphenyl)-3-cinnamyltetrahydrofuran (176ao)

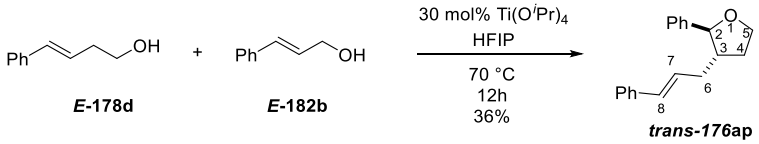


Alcohol ***E*-178c** (66.8 mg, 0.261 mmol), cinnamyl alcohol ***E*-182b** (35.0 mg, 0.261 mmol) and $Ti(O^iPr)_4$ (22.0 mg, 0.0774 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 8%→12% Et_2O - pentane) to yield **176ao** as a colorless oil (39.7 mg, 45%).

Data for **176ao**: **R_f** 0.45 (30% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.25-7.36 (5H, m, Ar), 7.17-7.22 (1H, m, Ar), 7.07 (1H, d, *J* = 2.6 Hz, Ar), 6.87 (1H, dd, *J* = 8.6, 2.6 Hz, Ar), 6.42 (1H, d, *J* = 15.8 Hz, 8-H), 6.18 (1H, dt, *J* = 15.8, 7.0 Hz, 7-H), 4.93 (1H, d, *J* = 5.6 Hz, 2-H), 4.19 (1H, td, *J* = 8.1, 5.6 Hz, 5-H_A), 4.01-4.08 (1H, m, 5-H_B), 3.78 (3H, s, OMe), 2.58 (1H, dddd, *J* = 13.0, 6.4, 4.6, 1.4 Hz, 6-H_A), 2.30-2.38 (1H, m, 6-H_B), 2.20-2.30 (1H, m, 3-H), 2.13 (1H, dq, *J* = 14.3, 7.3 Hz, 4-H_A), 1.77-1.88 (1H, m, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.3 (C Ar), 137.6 (C Ar), 134.0 (C Ar), 131.5 (C-8), 128.6 (3 x CH Ar), 128.5 (C-7), 127.2 (CH Ar), 126.1 (2 x CH Ar), 122.7 (C Ar), 117.7 (CH Ar), 114.0 (CH Ar), 84.4 (C-2), 68.2 (C-5), 55.7 (OMe), 47.8 (C-3), 35.9 (C-6), 31.0 (C-4). **HRMS** (CI): calculated for $C_{20}H_{22}BrO_2$ $[M+H]^+$ requires *m/z* 373.07977, found *m/z* 373.07950. **IR** (film)

ν_{max} : 3658, 2980, 1602, 1491, 1283, 964 cm^{-1}.

5.8.23 (±)-(2*S*,3*S*)-3-Cinnamyl-2-phenyltetrahydrofuran (*trans*-176ap)

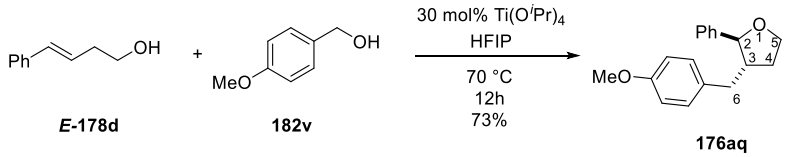


E-178d *E*-182b *trans*-176ap

Alcohol ***E*-178d** (64.3 mg, 0.434 mmol), cinnamyl alcohol ***E*-182b** (58.0 mg, 0.434 mmol) and Ti(O^{i}Pr)$_4$ (37.0 mg, 0.130 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 6% → 12% Et_2O - pentane) to yield ***trans*-176ap** as a colorless oil (40.9 mg, 36%).

Data for ***trans*-176ap**: **R_f** 0.40 (20% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.35 (4H, d, *J* = 4.3 Hz, Ar), 7.28-7.31 (5H, m, Ar), 7.17-7.24 (1H, m, Ar), 6.42 (1H, d, *J* = 15.8 Hz, 8-H), 6.14 (1H, dt, *J* = 15.8, 6.9 Hz, 7-H), 4.49 (1H, d, *J* = 6.8 Hz, 2-H), 4.14 (1H, dt, *J* = 8.4, 7.1 Hz, 5-H_A), 4.04 (1H, td, *J* = 8.3, 4.7 Hz, 5-H_B), 2.47 (1H, dddd, *J* = 11.1, 6.6, 4.3, 1.4 Hz, 6-H_A), 2.17-2.32 (3H, m, 3-H, 4-H_A and 6-H_B), 1.78-1.87 (1H, m, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 142.5 (C Ar), 137.5 (C Ar), 131.6 (C-8), 128.6 (2 x CH Ar), 128.5 (2 x CH Ar), 128.4 (C-7), 127.6 (CH Ar), 127.2 (CH Ar), 126.4 (2 x CH Ar), 126.1 (2 x CH Ar), 86.1 (C-2), 68.2 (C-5), 48.2 (C-3), 35.7 (C-6), 32.5 (C-4). **NOESY- 2D (400 MHz, $CDCl_3$)**: between 2-H and 6-H_A, between 2-H and 6-H_B. **HRMS** (ESI): calculated for $C_{19}H_{21}O$ $[M+H]^+$ requires *m/z* 265.15869, found *m/z* 265.15872. **IR** (film) ν_{max} : 3657, 2980, 1451, 1251, 1153, 964 cm^{-1}.

5.8.24 (±)-(2*S*,3*S*)-3-(4-Methoxybenzyl)-2-phenyltetrahydrofuran (176aq)

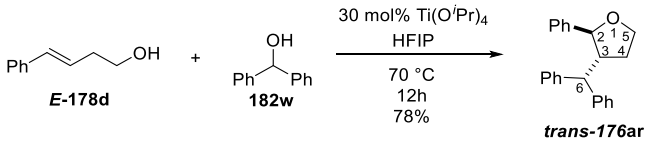


E-178d 182v 176aq

Alcohol ***E*-178d** (207.4 mg, 1.401 mmol), 4-methoxybenzylic alcohol **182v** (192.4 mg, 1.401 mmol) and Ti(O^{i}Pr)$_4$ (119.3 mg, 0.4201 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 7% → 15% Et_2O - pentane) to yield **176aq** as a colorless oil (274.0 mg, 73%).

Data for **176aq**: **R_f** 0.50 (40% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.24-7.37 (5H, m, Ar), 7.06 (2H, *J* = 8.6 Hz, Ar), 6.81 (2H, d, *J* = 8.6 Hz, Ar), 4.53 (1H, d, *J* = 7.2 Hz, 2-H), 4.09 (1H, q, *J* = 7.3 Hz, 5-H_A), 4.04 (1H, td, *J* = 8.2, 5.2 Hz, 5-H_B), 3.79 (3H, s, OMe), 2.84 (1H, dd, *J* = 13.6, 5.4 Hz, 6-H_A), 2.55 (1H, dd, *J* = 13.6, 9.5 Hz, 6-H_B), 2.34 (1H, dqd, *J* = 9.5, 7.5, 5.4 Hz, 3-H), 2.01-2.11 (1H, m, 4-H_A), 1.78 (1H, dq, *J* = 12.3, 7.8 Hz, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.1 (C Ar), 142.6 (C Ar), 132.6 (C Ar), 129.9 (2 x C-H Ar), 128.5 (2 x C-H Ar), 127.5 (C-H Ar), 126.2 (2 x C-H Ar), 113.9 (2 x C-H Ar), 85.6 (C-2), 68.1 (C-5), 55.4 (OMe), 50.2 (C-3), 37.5 (C-6), 32.4 (C-4). **HRMS** (ESI): calculated for $C_{18}H_{20}O_2Na$ $[M+Na]^+$ requires *m/z* 291.13555, found *m/z* 291.13568. **IR** (film) ν_{max}: 2980, 1510, 1243, 1177, 1034, 699 cm^{-1}.

5.8.25 (±)-(2*S*,3*R*)-3-Benzhydryl-2-phenyltetrahydrofuran (*trans*-176ar)



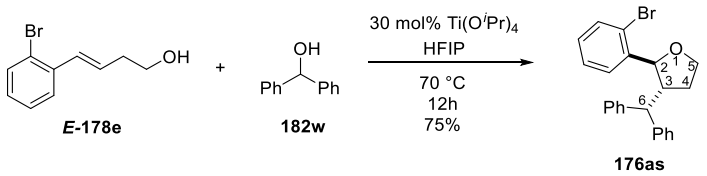
E-178d 182w *trans*-176ar

Alcohol ***E*-178d** (57.3 mg, 0.387 mmol), benzhydrol **182w** (71.2 mg, 0.387 mmol)

and $Ti(O^iPr)_4$ (33.0 mg, 0.116 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 7% → 10% Et_2O - pentane) to yield ***trans*-176ar** as a colorless oil (93.8 mg, 78%).

Data for ***trans*-176ar**: R_f 0.50 (30% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.14-7.39 (13H, m, Ar), 7.01 (2H, d, *J* = 7.6 Hz, Ar), 4.76 (1H, d, *J* = 4.0 Hz, 2-H), 4.21 (1H, dt, *J* = 8.3, 4.2 Hz, 5-H_A), 4.07 (1H, q, *J* = 8.0 Hz, 5-H_B), 3.99 (1H, d, *J* = 11.6 Hz, 6-H), 3.19 (1H, ddt, *J* = 11.6, 7.9, 4.0 Hz, 3-H), 2.12-2.23 (1H, m, 4-H_A), 1.72-1.82 (1H, m, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 144.0 (C Ar), 143.7 (C Ar), 143.6 (C Ar), 128.7 (2 x C-H Ar), 128.6 (2 x C-H Ar), 128.4 (2 x C-H Ar), 128.09 (2 x C-H Ar), 128.07 (2 x C-H Ar), 126.9 (C-H Ar), 126.5 (C-H Ar), 126.4 (C-H Ar), 125.8 (2 x C-H Ar), 84.8 (C-2), 67.9 (C-5), 55.6 (C-6), 51.7 (C-3), 30.9 (C-4). **HRMS** (ESI): calculated for $C_{23}H_{22}ONa$ $[M+Na]^+$ requires *m/z* 337.15629, found *m/z* 337.15631. **IR** (film) ν_{max}: 2980, 2360, 1493, 1451, 1382, 1058 cm^{-1}.

5.8.26 (±)-(2*S*,3*R*)-3-Benzhydryl-2-(2-bromophenyl)tetrahydrofuran (176as)

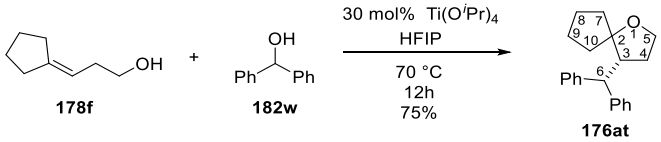


Alcohol ***E*-178e** (69.6 mg, 0.308 mmol), benzhydrol **182w** (56.7 mg, 0.308 mmol) and $Ti(O^iPr)_4$ (26.2 mg, 0.0923 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 5% → 7% Et_2O - pentane) to yield **176as** as a white foam (90.5 mg, 75%).

Data for **176as**: R_f 0.50 (30% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ**

7.25-7.39 (4H, m, Ar), 7.17-7.24 (4H, m, Ar), 6.98-7.12 (6H, m, Ar), 5.08 (1H, d, *J* = 5.1 Hz, 2-H), 4.21 (1H, td, *J* = 8.3, 5.0 Hz, 5-H_A), 4.02 (1H, q, *J* = 8.0 Hz, 5-H_B), 4.00 (1H, d, *J* = 10.6 Hz, 6-H), 3.29 (1H, ddt, *J* = 10.6, 7.4, 5.1 Hz, 3-H), 2.11-2.23 (1H, m, 4-H_A), 1.79-1.89 (1H, m, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 144.0 (C Ar), 142.8 (C Ar), 141.6 (C Ar), 132.9 (CH Ar), 132.8 (CH Ar), 128.72 (3 x CH Ar), 128.69 (3 x CH Ar), 128.2 (3 x CH Ar), 127.2 (CH Ar), 126.5 (CH Ar), 126.4 (CH Ar), 122.8 (C Ar), 84.4 (C-2), 68.0 (C-5), 55.2 (C-6), 50.1 (C-3), 31.3 (C-4). **HRMS** (ESI): calculated for $C_{23}H_{21}OBrNa$ $[M+Na]^+$ requires *m/z* 415.06680, found *m/z* 415.06686. **IR** (film) ν_{max} : 3649, 2980, 2887, 1450, 1521, 1037 cm^{-1}.

5.8.27 (±)-(3*R*)-4-Benzhydryl-1-oxaspiro[4.4]nonane (176at)

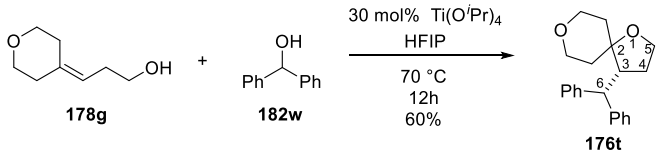


Alcohol **178f** (41.4 mg, 0.329 mmol), benzhydrol **182w** (60.4 mg, 0.329 mmol) and $Ti(O^iPr)_4$ (28.0 mg, 0.0986 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 5% → 7% Et_2O - pentane) to yield **176at** as a white foam (72.0 mg, 75%).

Data for **176at**: $\mathbf{R_f}$ 0.50 (30% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.33-7.37 (4H, m, Ar), 7.22-7.28 (4H, m, Ar), 7.11-7.16 (2H, m, Ar), 3.79 (1H, d, *J* = 11.7 Hz, 6-H), 3.72 (1H, dt, *J* = 8.8, 4.4 Hz, 5-H_A), 3.69 (1H, q, *J* = 8.3 Hz, 5-H_B), 3.10 (1H, ddd, *J* = 11.7, 10.0, 7.6 Hz, 3-H), 1.93 (1H, dtd, *J* = 12.7, 7.5, 4.0 Hz, 4-H_A), 1.46-1.64 (6H, m, 4-H_B, 7-H_A, 8-H_A, 9-H_A and 10-H_2), 1.37-1.45 (1H, m, 9-H_B), 1.05-1.16 (2H, m, 7-H_B and

8-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 145.3 (C Ar), 143.8 (C Ar), 128.73 (2 x C-H Ar), 128.65 (2 x C-H Ar), 128.2 (2 x C-H Ar), 127.8 (2 x C-H Ar), 126.5 (C-H Ar), 126.3 (C-H Ar), 93.2 (C-2), 63.6 (C-5), 54.8 (C-6), 47.6 (C-3), 37.8 (C-7), 33.6 (C-4), 31.6 (C-10), 23.7 (C-9), 23.1 (C-8). **HRMS** (EI): calculated for $C_{21}H_{24}O$ $[M]^+$ requires *m/z* 292.1822, found *m/z* 292.1818. **IR** (film) ν_{max}: 2980, 2888, 1493, 1451, 1153, 947 cm^{-1}.

5.8.28 (±)-(3*R*)-4-Benzhydryl-1,8-dioxaspiro[4.5]decane (176au)

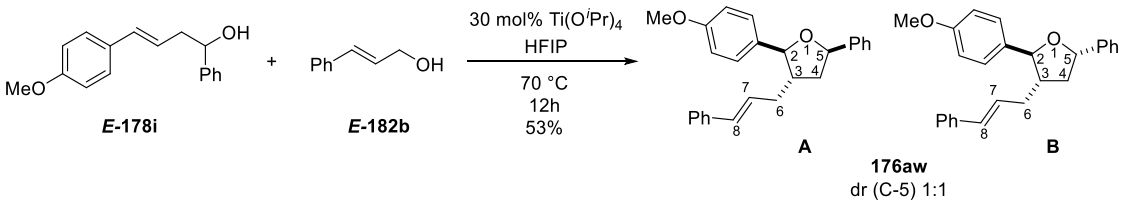


Alcohol **178g** (13.6 mg, 0.096 mmol), benzhydrol **182w** (17.7 mg, 0.096 mmol) and Ti(O^{i}Pr)$_4$ (8.2 mg, 0.029 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 12% → 16% Et_2O - pentane) to yield **176au** as a yellow foam (17.7 mg, 60%).

Data for **176au**: **R_f** 0.40 (60% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.31-7.39 (4H m, Ar), 7.22-7.32 (4H, m, Ar), 7.11-7.19 (2H, m, Ar), 3.61-3.82 (6H, m, 6-H, 5-H_2, CH_2 tetrahydropyranyl and CH tetrahydropyranyl), 3.55 (1H, ddd, *J* = 11.1, 4.6, 2.4 Hz, CH tetrahydropyranyl), 2.84 (1H, td, *J* = 11.4, 7.5 Hz, 3-H), 1.89 (1H, dtd, *J* = 12.8, 7.5, 3.2 Hz, 4-H_A), 1.59-1.75 (2H, m, 4-H_B and CH tetrahydropyranyl), 1.53 (1H, dd, *J* = 13.1, 2.2 Hz, CH tetrahydropyranyl), 1.14-1.23 (2H, m, CH_2 tetrahydropyranyl). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 145.1 (C Ar), 143.2 (C Ar), 128.9 (2 x C-H Ar), 128.8 (2 x C-H Ar), 128.1 (2 x C-H Ar), 127.7 (2 x C-H Ar), 126.4 (C-H Ar), 125.7 (C-H Ar), 80.2 (C-2), 65.0 (C-5), 64.0 (CH_2 tetrahydropyranyl), 63.9 (CH_2 tetrahydropyranyl), 53.5 (C-6), 51.8 (C-3), 37.8 (CH_2

tetrahydropyranyl), 32.7 (C-4), 31.2 (CH_2 tetrahydropyranyl). **HRMS** (ESI): calculated for $C_{21}H_{24}O_2Na$ $[M+Na]^+$ requires *m/z* 331.16685, found *m/z* 331.16690. **IR** (film) ν_{max}: 3657, 2980, 2888, 1382, 1251, 1151 cm^{-1}.

5.8.29 (±)-(2*R*,3*R*,5*R*)-3-Cinnamyl-2-(4-methoxyphenyl)-5-phenyltetrahydrofuran and (±)-(2*R*,3*R*,5*S*)-3-cinnamyl-2-(4-methoxyphenyl)-5-phenyltetrahydrofuran (176aw)



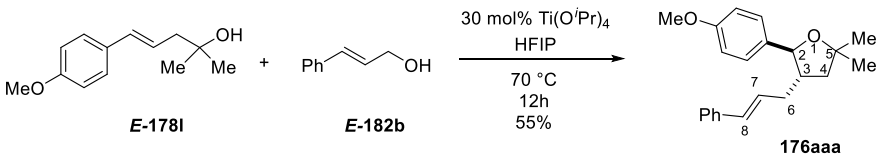
Alcohol ***E*-178i** (15.0 mg, 0.059 mmol), cinnamyl alcohol ***E*-182b** (7.9 mg, 0.059 mmol) and $Ti(O^iPr)_4$ (5.0 mg, 0.018 mmol) were subjected to general procedure **H** (FCC: 6% Et_2O - pentane) to yield a separable 1:1 mixtures of diastereomers **176aw** as a colorless oil (12.0 mg, 55%).

Data for **diastereomer A** of **176aw** (from the mixture): $\mathbf{R_f}$ 0.50 (30% Et_2O - pentane). **^{1}H NMR** (500 MHz, $CDCl_3$) **δ** 7.42-7.39 (2H, m, Ar), 7.38-7.32 (5H, m, Ar), 7.28-7.24 (4H, m, Ar), 7.21-7.17 (1H, m, Ar), 6.91 (2H, d, *J* = 8.7 Hz, Ar), 6.36 (1H, d, *J* = 15.7 Hz, 8-H), 6.10 (1H, dt, *J* = 15.7, 8.7 Hz, 7-H), 5.30 (1H, dd, *J* = 9.9, 5.9 Hz, 5-H), 4.73 (1H, d, J = 8.7 Hz, 2-H), 3.82 (3H, s, OMe), 2.69 (1H, dt, *J* = 12.2, 6.1 Hz, 4-H_A), 2.49-2.43 (1H, m, 6-H_A), 2.42-2.38 (1H, m, 3H), 2.27-2.20 (1H, m, 6-H_B), 1.80 (1H, ddd, *J* = 12.4, 11.0, 9.9 Hz, 4-H_B). **^{13}C NMR** (125 MHz, $CDCl_3$) **δ** 159.4 (C Ar), 143.8 (C Ar), 137.5 (C Ar), 134.2 (C Ar), 131.6 (C-8), 128.6 (2 x CH Ar), 128.5 (2 x CH Ar), 128.3 (C-7), 128.0 (2 x CH

Ar), 127.3 (CH Ar), 127.2 (CH Ar), 126.1 (2 x CH Ar), 125.6 (2 x CH Ar), 114.0 (2 x CH Ar), 86.9 (C-2), 80.9 (C-5), 55.5 (OMe), 49.6 (C-3), 42.7 (C-4), 35.1 (C-6). **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max}: 3667, 2985, 1451, 1231, 1159, 984 cm^{-1}.

Data for **diastereomer B** of **176aw** (from the mixture): $\mathbf{R_f}$ 0.45 (30% Et_2O - pentane). **^{1}H NMR** (500 MHz, $CDCl_3$) **δ** 7.46-7.43 (2H, m, Ar), 7.41-7.33 (5H, m, Ar), 7.29-7.24 (4H, m, Ar), 7.21-7.17 (1H, m, Ar), 7.21-7.17 (1H, m, Ar), 6.41 (1H, d, *J* = 15.8 Hz, 8-H), 6.10 (1H, dt, *J* = 15.8, 7.0 Hz, 7-H), 5.12 (1H, t, *J* = 7.3 Hz, 5-H), 4.59 (1H, d, *J* = 7.5 Hz, 2-H), 3.82 (3H, s, OMe), 2.50-2.43 (1H, m, 6-H_A), 2.39-2.33 (1H, m, 3-H), 2.33-2.28 (1H, m, 6-H_B), 2.28-2.20 (2H, m, 4-H_2). **^{13}C NMR** (125 MHz, $CDCl_3$) **δ** 159.4 (C Ar), 143.4 (C Ar), 137.5 (C Ar), 133.5 (C Ar), 131.6 (C-8), 128.6 (2 x CH Ar), 128.5 (2 x CH Ar), 128.4 (C-7), 128.3 (2 x CH Ar), 127.4 (CH Ar), 127.2 (CH Ar), 126.1 (2 x CH Ar), 126.0 (2 x CH Ar), 114.0 (2 x CH Ar), 86.9 (C-2), 79.7 (C-5), 55.5 (OMe), 47.3 (C-3), 40.8 (C-4), 35.9 (C-6).

5.8.30 (±)-(2*S*,3*S*)-3-Cinnamyl-2-(4-methoxyphenyl)-5,5-dimethyltetrahydrofuran (176aaa)

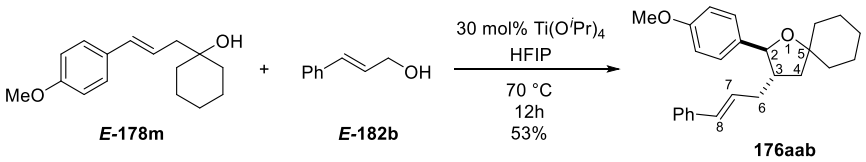


E-178l *E*-182b 176aaa

Alcohol ***E*-178l** (62.2 mg, 0.302 mmol), cinnamyl alcohol ***E*-182b** (40.5 mg, 0.302 mmol) and Ti(O^iPr)$_4$ (25.7 mg, 0.0905 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 20% → 35% Et_2O - pentane) to yield **176aaa** as a colorless oil (51.8 mg, 55%).

Data for **176aaa**: **R_f** 0.50 (35% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.23-7.33 (6H, m, Ar), 7.15-7.22 (1H, m, Ar), 6.88 (2H, d, *J* = 8.7 Hz, Ar), 6.34 (1H, d, *J* = 15.8 Hz, 8-H), 6.05 (1H, dt, *J* = 15.8, 6.7 Hz, 7-H), 4.46 (1H, d, *J* = 9.4 Hz, 2-H), 3.79 (3H, s, OMe), 2.35 (1H, dddd, *J* = 13.5, 6.6, 4.2, 1.5 Hz, 6-H_A), 2.25 (1H, dddd, *J* = 9.2, 7.9, 3.9, 2.2 Hz, 3-H), 2.09-2.18 (2H, m, 4-H_A and 6-H_B), 1.61-1.71 (1H, m, 4-H_B), 1.39 (3H, s, Me), 1.38 (3H, s, Me). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.3 (C Ar), 137.6 (C Ar), 133.6 (C Ar), 131.1 (C-8), 128.6 (C-7), 128.6 (2 x CH Ar), 128.2 (CH Ar), 127.1 (2 x CH Ar), 126.1 (2 x CH Ar), 113.9 (2 x CH Ar), 85.8 (C-2), 80.0 (C-5), 55.4 (OMe), 48.7 (C-3), 46.1 (C-4), 34.8 (C-6), 29.9 (Me), 29.6 (Me). **HRMS** (ESI): calculated for $C_{22}H_{27}O_2$ $[M+H]^+$ requires *m/z* 323.20056, found *m/z* 323.20053. **IR** (film) ν_{max} : 2980, 2889, 1512, 1461, 1245, 1153 cm^{-1}.

5.8.31 (±)-(2*R*,3*R*)-3-Cinnamyl-2-(4-methoxyphenyl)-1-oxaspiro[4.5]decane (176aab)

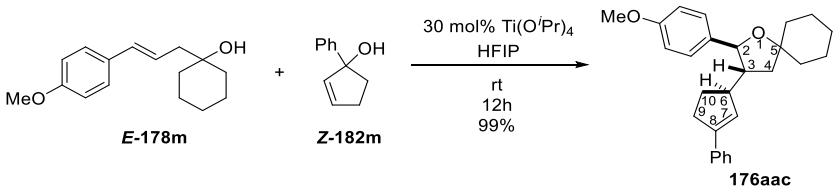


Alcohol ***E*-178m** (71.5 mg, 0.291 mmol), cinnamyl alcohol ***E*-182b** (39 mg, 0.291 mmol) and $Ti(O^iPr)_4$ (24.8 mg, 0.087 mmol) were subjected to general procedure E (FCC: gradient elution: 4% → 6% Et_2O - pentane) to yield **176aab** as a colorless oil (44.9 mg, 42%).

Data for **176aab**: **R_f** 0.50 (10% Et_2O - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 7.34-7.27 (6H, m, Ar), 7.25-7.16 (1H, m, Ar), 6.89 (2H, d, *J* = 8.8 Hz, Ar), 6.36 (1H, d, *J* = 15.8 Hz, 8-H), 6.08 (1H, dt, *J* = 15.8, 7.0 Hz, 7-H), 4.46 (1H, d, *J* = 8.5 Hz, 2-H), 3.81 (3H, s,

OMe), 2.40-2.32 (1H, m, 6-H_A), 2.23-2.08 (3H, m, 3-H, 6-H_B and CH cyclohexyl), 1.80-1.59 (6H, m, 3 x CH_2 cyclohexyl), 1.55-1.32 (5H, m, 4-H_2, CH_2 cyclohexyl and CH cyclohexyl). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 159.3 (C Ar), 137.6 (C Ar), 133.9 (C Ar), 131.1 (C-8), 128.7 (C-7), 128.6 (2 x CH Ar), 128.2 (2 x CH Ar), 127.1 (CH Ar), 126.1 (2 x CH Ar), 113.9 (2 x CH Ar), 85.2 (C-2), 82.1 (C-5), 55.4 (OMe), 48.4 (C-3), 43.7 (CH_2 cyclohexyl), 39.3 (CH_2 cyclohexyl), 38.7 (CH_2 cyclohexyl), 34.9 (C-6), 25.7 (CH_2 cyclohexyl), 24.1 (C-4), 23.8 (CH_2 cyclohexyl). **HRMS**: submitted for accurate mass service. **IR** (film) ν_{max} : 3657, 2979, 2888, 1381, 1521, 951 cm^{-1}.

5.8.32 (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-3-[(1'*S*)-3-phenylcyclopent-2-en-1-yl]-1-oxaspiro[4.5]decane (176aac)

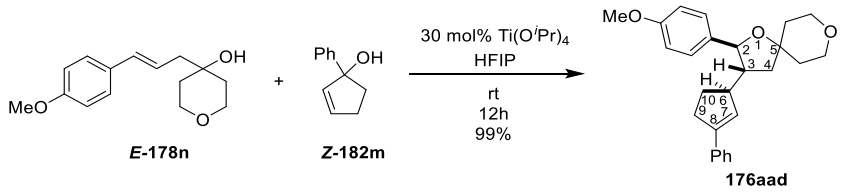


Alcohols ***E*-178m** (50.0 mg, 0.203 mmol) and ***Z*-182m** (32.5 mg, 0.203 mmol), and Ti(O^{i}Pr)$_4$ (17.3 mg, 0.0609 mmol) were subjected to the general procedure **H** except conducting the reaction at room temperature (FCC: gradient elution: 5% → 20% Et_2O - pentane) to yield **176aac** as a yellow foam (78.3 mg, 99%).

Data for **176aac**: **R_f** 0.40 (20% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.40-7.46 (2H, m, Ar), 7.29-7.36 (4H, m, Ar), 7.21-7.28 (1H, m, Ar), 6.88 (2H, d, *J* = 8.7 Hz, Ar), 6.13 (1H, q, *J* = 2.0 Hz, 7-H), 4.60 (1H, d, *J* = 9.6 Hz, 2-H), 3.81 (3H, s, OMe), 2.83-2.94 (1H, m, 6-H), 2.53-2.66 (2H, m, 9-H_2), 2.18-2.27 (1H, m, 3-H), 2.14 (1H, dd, *J* =

11.9, 7.5 Hz, 4-H_A), 1.96 (1H, dtd, *J* = 13.2, 8.3, 4.9 Hz, 10-H_A), 1.59-1.82 (7H, m, 4-H_B and 3 x CH_2 cyclohexyl), 1.31-1.50 (5H, m, 10-H_B and 2 x CH_2 cyclohexyl). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.3 (C Ar), 143.6 (C-8), 136.5 (C Ar), 134.4 (C Ar), 128.6 (2 x C-H Ar), 128.4 (2 x C-H Ar), 127.5 (C-7), 127.3 (C-H Ar), 125.7 (2 x C-H Ar), 113.8 (2 x C-H Ar), 84.4 (C-2), 81.8 (C-5), 55.4 (OMe), 52.9 (C-3), 47.1 (C-6), 41.3 (C-4), 39.2 (CH_2 cyclohexyl), 38.9 (CH_2 cyclohexyl), 32.9 (C-9), 29.4 (C-10), 25.8 (CH_2 cyclohexyl), 24.2 (CH_2 cyclohexyl), 23.8 (CH_2 cyclohexyl). **HRMS** (ESI): calculated for $C_{27}H_{33}O_2$ $[M+H]^+$ requires *m/z* 389.24751, found *m/z* 389.24783. **IR** (film) ν_{max}: 3656, 2980, 2929, 1512, 1244, 1072 cm^{-1}.

5.8.33 (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-3-[(1'*S*)-3-phenylcyclopent-2-en-1-yl]-1,8-dioxaspiro[4.5]decane (176aad)

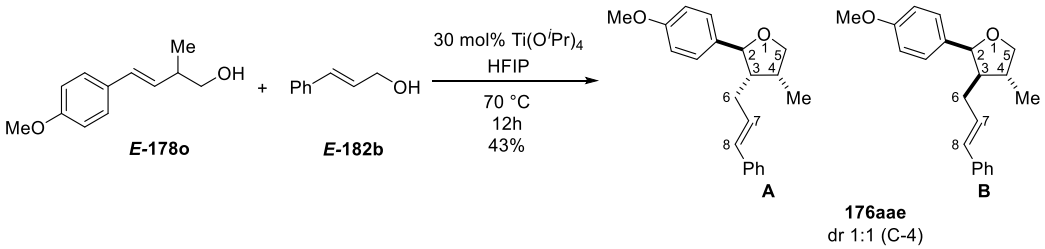


Alcohols ***E*-178n** (60.0 mg, 0.242 mmol) and ***Z*-182m** (38.7 mg, 0.242 mmol), and Ti(O^{i}Pr)$_4$ (20.6 mg, 0.0725 mmol) were subjected to the general procedure **H** except conducting the reaction at room temperature (FCC: gradient elution: 20% → 35% Et_2O - pentane) to yield **176aad** as a yellow solid (94.0 mg, 99%).

Data for **176aad**: **R_f** 0.30 (60% Et_2O - pentane). **M.p.**: 89 °C (10% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.43 (2H, d, *J* = 7.9 Hz, Ar), 7.23-7.36 (5H, m, Ar), 6.90 (2H, d, *J* = 7.9 Hz, Ar), 6.12 (1H, q, *J* = 2.0 Hz, 7-H), 4.62 (1H, d, *J* = 9.6 Hz, 2-H), 3.85-3.97 (2H, m, CH_2 tetrahydropyranyl), 3.68-3.75 (1H, m, CH tetrahydropyranyl),

3.59-3.68 (1H, m, CH tetrahydropyranyl), 2.86-2.95 (1H, m, 6-H), 2.55-2.68 (2H, m, 9-H_2), 2.22-2.31 (1H, m, 3-H), 2.15-2.21 (1H, m, 4-H_A), 1.99 (1H, dtd, *J* = 13.2, 8.2, 4.5 Hz, 10-H_A), 1.85-1.93 (1H, m, CH tetrahydropyranyl), 1.76-1.82 (3H, m, CH tetrahydropyranyl and CH_2 tetrahydropyranyl), 1.72 (1H, t, *J* = 11.6 Hz, 4-H_B), 1.38 (1H, dq, *J* = 15.2, 7.8 Hz, 10-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.4 (C Ar), 143.9 (C-8), 136.4 (C Ar), 133.8 (C Ar), 128.54 (2 x C-H Ar), 128.45 (2 x C-H Ar), 127.4 (C-H Ar), 127.1 (C-7), 125.8 (2 x C-H Ar), 113.9 (2 x C-H Ar), 84.6 (C-2), 78.5 (C-5), 65.6 (CH_2 tetrahydropyranyl), 65.5 (CH_2 tetrahydropyranyl), 55.4 (OMe), 52.6 (C-3), 46.9 (C-6), 41.9 (C-4), 39.4 (CH_2 tetrahydropyranyl), 39.0 (CH_2 tetrahydropyranyl), 32.9 (C-9), 29.4 (C-10). **HRMS** (ESI): calculated for $C_{26}H_{30}O_3Na$ $[M+Na]^+$ requires *m/z* 413.20872, found *m/z* 413.21051. **IR** (film) ν_{max}: 3657, 2980, 1461, 1248, 1152, 1073 cm^{-1}.

5.8.34 (±)-(2*R*,3*R*,4*R*)-3-Cinnamyl-2-(4-methoxyphenyl)-4-methyltetrahydrofuran and (±)-(2*R*,3*R*,4*S*)-3-cinnamyl-2-(4-methoxyphenyl)-4-methyltetrahydrofuran (176aae)

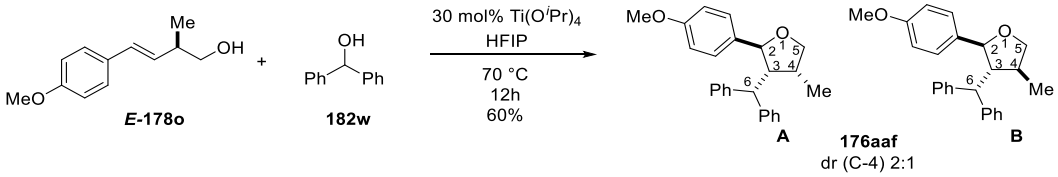


Alcohol ***E*-178o** (49.5 mg, 0.258 mmol), cinnamyl alcohol ***E*-182b** (34.5 mg, 0.258 mmol) and $Ti(O^iPr)_4$ (22 mg, 0.077 mmol) were subjected to general procedure E (FCC: gradient elution: 7% → 10% Et_2O - pentane) to yield an inseparable 1:1 mixture of diastereomers **176aae** as colorless oil and (37.8 mg, 43%).

Data for **diastereomer A** of **176aae** (from the mixture): $\mathbf{R_f}$ 0.45 (40% Et_2O - pentane). **^{1}H NMR** (500 MHz, $CDCl_3$) **δ** 7.31-7.23 (6H, m, Ar), 7.24-7.17 (1H, m, Ar), 6.87 (2H, d, *J* = 8.8 Hz, Ar), 6.41 (1H, d, *J* = 15.7 Hz, 7-H), 6.13-6.01 (1H, m, 8-H), 4.57 (1H, d, *J* = 7.8 Hz, 2-H), 4.26 (1H, dd, *J* = 8.3, 6.1 Hz, 4-H_A), 3.82 (3H, s, OMe), 3.70 (1H, dd, *J* = 8.3, 3.9 Hz, 4-H_B), 2.52 (1H, m, 3-H), 2.35-2.29 (1H, m, 5-H_A), 2.26-2.17 (2H, m, 5-H_B and 2-H), 1.10 (3H, d, *J* = 7.1 Hz, Me). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 159.15 (C Ar), 137.58 (C Ar), 134.4 (C Ar), 131.2 (C-7), 128.8 (C-6), 128.59 (2 x C-H Ar), 128.08 (C-H Ar), 127.15 (2 x C-H Ar), 126.08 (2 x C-H Ar), 113.88 (2 x C-H Ar), 84.3 (C-1), 75.6 (C-4), 55.4 (OMe), 51.3 (C-2), 25.9 (C-3), 30.4 (C-5), 13.6 (Me). **HRMS** (ESI): calculated for $C_{21}H_{25}O_2$ $[M+H]^+$ requires *m/z* 309.1855, found *m/z* 309.1845. **IR** (film) ν_{max}: 3657, 2980, 2888, 1511, 1381, 1245cm^{-1}.

Data for **diastereomer B** of **176aae** (from the mixture): **^{1}H NMR** (500 MHz, $CDCl_3$) **δ** 7.31-7.23 (6H, m, Ar), 7.24-7.17 (1H, m, Ar), 6.87 (2H, d, *J* = 8.8 Hz, Ar), 6.39 (1H, d, *J* = 15.7 Hz, 7-H), 6.13-6.01 (1H, m, 8-H), 4.49 (1H, d, *J* = 9.0 Hz, 2-H), 4.11 (1H, t, *J* = 8.0 Hz, 4-H_A), 3.82 (3H, s, OMe), 3.68 (1H, t, *J* = 8.2 Hz, 4-H_B), 2.43-2.33 (2H, m, 5-H_2), 2.26-2.17 (1H, m, 3-H), 1.79 (1H, tt, *J* = 9.0, 6.3 Hz, 2-H), 1.12 (3H, d, *J* = 6.6 Hz, Me). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 159.24 (C Ar), 137.64 (C Ar), 134.9 (C Ar), 131.6 (C-7), 128.61 (2 x C-H Ar), 128.19 (C-6), 128.08 (C-H Ar), 127.16 (2 x C-H Ar), 126.12 (2 x C-H Ar), 113.92 (2 x C-H Ar), 86.7 (C-1), 75.2 (C-4), 55.4 (OMe), 55.3 (C-2), 39.9 (C-3), 34.0 (C-5), 17.1 (Me).

5.8.35 (±)-(2*S*,3*S*,4*S*)-3-Benzhydryl-2-(4-methoxyphenyl)-4-methyltetrahydrofuran (±)-(2*S*,3*S*,4*R*)-3-benzhydryl-2-(4-methoxyphenyl)-4-methyltetrahydrofuran (176aaf)

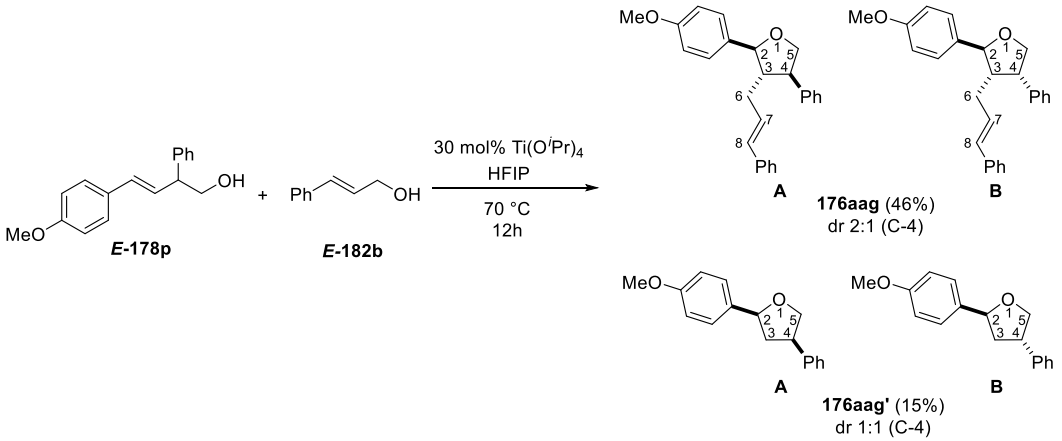


Alcohol ***E*-178o** (19.2 mg, 0.100 mmol), benzhydrol **182w** (18.4 mg, 0.100 mmol) and $Ti(O^iPr)_4$ (8.5 mg, 0.030 mmol) were subjected to the general procedure E (FCC: gradient elution: 6% → 20% Et_2O - pentane) to yield a separable 2:1 mixture of diastereomers **176aaf** as colorless oil (21.5 mg, 60%).

Data for **major diastereomer A** of **176aaf:** R_f 0.45 (40% Et_2O - pentane). **^{1}H NMR** (500 MHz, $CDCl_3$) **δ** 7.35-7.41 (2H, m, Ar), 7.23-7.29 (2H, m, Ar), 7.12-7.17 (1H, m, Ar), 6.86-6.98 (5H, m, Ar), 6.73 (2H, d, *J* = 8.7 Hz, Ar), 6.53 (2H, d, *J* = 8.7 Hz, Ar), 4.60 (1H, d, *J* = 8.4 Hz, 2-H), 4.29 (1H, dd, *J* = 8.2, 5.2 Hz, 5-H_A), 3.97 (1H, d, *J* = 11.9 Hz, 6-H), 4.29 (1H, dd, *J* = 8.2, 2.4 Hz, 5-H_B), 3.70 (3H, s, OMe), 3.32 (1H, ddd, *J* = 11.9, 8.7, 6.3 Hz, 3-H), 2.43-2.54 (1H, m, 4-H), 0.98 (3H, d, *J* = 7.1 Hz, Me). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 158.3 (C Ar), 144.3 (C Ar), 142.9 (C Ar), 135.9 (C Ar), 128.7 (2 x C-H Ar), 128.2 (2 x C-H Ar), 128.1 (2 x C-H Ar), 127.9 (2 x C-H Ar), 127.6 (2 x C-H Ar), 126.4 (C-H Ar), 126.2 (C-H Ar), 113.3 (2 x C-H Ar), 84.3 (C-2), 75.5 (C-5), 55.4 (OMe), 53.8 (C-3), 52.2 (C-6), 37.1 (C-4), 14.3 (Me). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H, between 2-H and Me, between 6-H and Me. **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max}: 3252, 2972, 2887, 1382, 1250, 1151 cm^{-1}.

Data for **minor diastereomer B** of **176aaf:** $\mathbf{R_f}$ 0.30 (40% Et_2O - pentane). **^{1}H NMR** (500 MHz, $CDCl_3$) **δ** 7.24-7.31 (5H, m, Ar), 7.05-7.20 (5H, m, Ar), 6.77 (2H, d, *J* = 8.7 Hz, Ar), 6.68 (2H, d, *J* = 8.7 Hz, Ar), 4.53 (1H, d, *J* = 5.6 Hz, 2-H), 4.02 (1H, dd, *J* = 8.8, 6.4 Hz, 5-H_A), 3.90 (1H, d, *J* = 11.6 Hz, 6-H), 3.76 (3H, s, OMe), 3.71 (1h, dd, *J* = 8.8, 3.8 Hz, 5-H_B), 2.76 (1H, ddd, *J* = 11.6, 5.6, 3.5 Hz, 3-H), 2.07-2.17 (1H, m, 4-H), 0.98 (3H, d, *J* = 6.9 Hz, Me). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 158.6 (C Ar), 144.1 (C Ar), 143.2 (C Ar), 135.1 (C Ar), 128.7 (2 x C-H Ar), 128.6 (2 x C-H Ar), 128.5 (2 x C-H Ar), 128.2 (2 x C-H Ar), 127.8 (2 x C-H Ar), 126.7 (C-H Ar), 126.5 (C-H Ar), 113.5 (2 x C-H Ar), 86.6 (C-2), 74.6 (C-5), 58.8 (C-3), 57.6 (C-6), 55.4 (OMe), 40.2 (C-4), 20.5 (Me). **HRMS**: submitted for accurate mass service. **IR** (film) ν_{max} : 3252, 2972, 2887, 1382, 1250, 1151 cm^{-1}.

5.8.36 (±)-(2*R*,3*R*,4*R*)-3-Cinnamyl-2-(4-methoxyphenyl)-4-phenyltetrahydrofuran (±)-(2*R*,3*R*,4*S*)-3-cinnamyl-2-(4-methoxyphenyl)-4-phenyltetrahydrofuran (176aag) and (±)-(2*S*,4*R*)-2-(4-methoxyphenyl)-4-phenyltetrahydrofuran (±)-(2*S*,4*S*)-2-(4-methoxyphenyl)-4-phenyltetrahydrofuran (176aag')



Alcohol ***E*-178p** (64.4 mg, 0.254 mmol), cinnamyl alcohol ***E*-182b** (34 mg, 0.254 mmol) and $Ti(O^iPr)_4$ (26.6 mg, 0.076 mmol) were subjected to general procedure **H** (FCC: gradient elution: 6% → 15% Et_2O - pentane) to yield an inseparable 2:1 mixture of diastereomer **176aag** as a colorless oil (43.2 mg, 46%) and a separable 1:1 mixture of diastereomer **176aag'** as a colorless oil (14.1 mg, 15%).

Data for **diastereomer A** of **176aag** (from the mixture): $\mathbf{R_f}$ 0.40 (30% Et_2O - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 7.43-7.17 (10H, m, Ar), 7.10 (2H, d, *J* = 7.7 Hz, Ar), 6.92 (2H, d, *J* = 8.0 Hz, Ar), 6.32 (1H, d, *J* = 15.7 Hz, 8-H), 5.89 (1H, dt, *J* = 15.9, 6.8 Hz, 7-H), 4.66 (1H, d, *J* = 8.2 Hz, 2-H), 4.34 (1H, t, *J* = 8.6 Hz, 5-H_A), 4.14 (1H, t, *J* = 8.3 Hz, 5-H_B), 3.82 (3H, s, OMe), 3.34 (1H, q, *J* = 8.3 Hz, 4-H), 2.45-2.35 (3H, m, 3-H and 6-H_2).

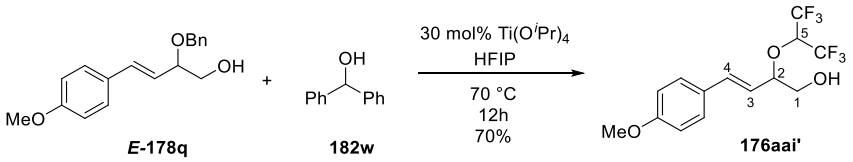
^{13}C NMR (100 MHz, $CDCl_3$) **δ** 159.4 (C Ar), 141.9 (C Ar), 137.5 (C Ar), 133.5 (C Ar), 131.7 (C-8), 128.85 (2 x CH Ar),128.56 (CH Ar), 128.46 (2 x CH Ar), 128.2 (2 x CH Ar), 127.93 (2 x CH Ar), 127.87 (C-7), 126.79 (CH Ar), 126.1 (2 x CH Ar), 114.01 (2 x CH Ar), 86.6 (C-2), 75.3 (C-5), 56.4 (C-3), 55.4 (OMe), 51.9 (C-4), 33.8 (C-6). **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max}: 3658, 2980, 1382, 1250, 1152, 1072 cm^{-1}.

Data for **diastereomer B** of **176aag** (from the mixture): **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 7.43-7.17 (10H, m, Ar), 7.10 (2H, d, *J* = 7.7 Hz, Ar), 6.92 (2H, d, *J* = 8.0 Hz, Ar), 6.17 (1H, d, *J* = 15.8 Hz, 8-H), 5.93 (1H, dt, *J* = 16.8, 6.7 Hz, 7-H), 4.74 (1H, d, *J* = 8.5 Hz, 2-H), 4.34 (1H, t, *J* = 8.6 Hz, 5-H_A), 4.04 (1H, t, *J* = 8.3 Hz, 5-H_B), 3.69-3.60 (1H, m, 4-H), 2.59-2.50 (1H, m, 3-H), 2.10-1.98 (1H, m, 6-H_A), 1.96-1.85 (1H, m, 6-H_B). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 159.2 (C Ar), 130.5 (C Ar), 137.6 (C Ar), 134.5 (C Ar), 131.4 (C-8), 128.91 (2 x CH Ar), 128.59 (CH Ar), 128.49 (2 x CH Ar), 127.81 (2 x CH Ar and C-7),127.1 (2 x CH Ar), 126.83 (CH Ar), 126.0 (2 x CH Ar), 113.95 (2 x CH Ar), 84.6 (C-2), 75.1 (C-5), 55.4 (OMe), 52.7 (C-3), 48.5 (C-4), 31.2 (C-6).

Data for **diastereomer A** of **176aag': R_f** 0.45 (30% Et_2O - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 7.16-7.35 (7H, m, Ar), 6.87 (2H, d, *J* = 8.3 Hz, Ar), 4.98 (1H, dd, *J* = 10.3, 5.6 Hz, 2-H), 4.31 (1H, t, *J* = 8.2 Hz, 5-H_A), 3.98 (1H, t, *J* = 8.4 Hz, 5-H_B), 3.78 (3H, s, OMe), 3.54-3.66 (1H, m, 4-H), 2.68 (1H, dt, *J* = 10.3, 5.6 Hz, 3-H_A), 1.98 (1H, q, *J* = 10.3 Hz, 3-H_B). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 159.2 (C Ar), 142.1 (C Ar), 134.7 (C Ar), 128.8 (2 x CH Ar), 127.4 (2 x CH Ar), 127.3 (2 x CH Ar), 126.8 (CH Ar), 114.0 (2 x CH Ar), 81.8 (C-2), 75.5 (C-5), 55.5 (OMe), 46.1 (C-4), 43.8 (C-3). **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max}: 3658, 2980, 1382, 1250, 1152, 1072 cm^{-1}.

Data for **diastereomer B** of **176aag': R_f** 0.45 (30% Et_2O - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 7.16-7.35 (7H, m, Ar), 6.87 (2H, d, *J* = 8.3 Hz, Ar), 6.87 (1H, d, *J* = 8.2 Hz, 2-H), 5.10 (1H, t, *J* = 6.8 Hz, 2-H), 4.42 (1H, t, *J* = 8.0 Hz, 5-H_A), 3.89 (1H, t, *J* = 8.1 Hz, 5-H_B), 3.78 (3H, s, OMe), 3.46-3.55 (1H, m, 4-H), 2.41 (1H, dt, *J* = 12.7, 7.6 Hz, 3-H_A), 2.23-2.33 (1H, m, 3-H_B). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 159.2 (C Ar), 142.1 (C Ar), 134.7 (C Ar), 128.8 (2 x CH Ar), 127.5 (2 x CH Ar), 127.0 (2 x CH Ar), 126.8 (CH Ar), 113.9 (2 x CH Ar), 80.6(C-2), 75.1 (C-5), 55.5 (OMe), 44.7 (C-4), 42.8 (C-3).

5.8.37 (+)-(3*E*)-2-[(1,1,1,3,3,3-hexafluoropropan-2-yl)oxy]-4-(4-methoxyphenyl)but-3-en-1-ol (176aai')



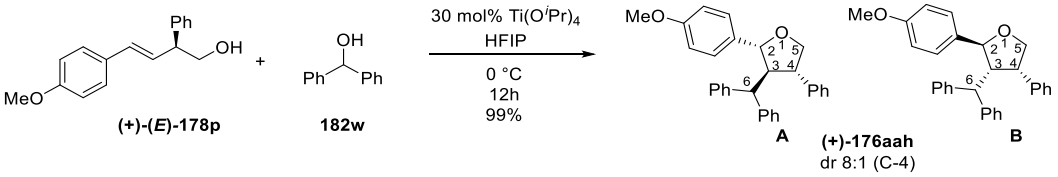
E-178q 182w 176aai'

Alcohol **(*E*)-178q** (28.4 mg, 0.100 mmol), benzhydrol **182w** (18.4 mg, 0.100 mmol) and Ti(O^{i}Pr)$_4$ (8.5 mg, 0.030 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 20% → 30% Et_2O - pentane) to yield **176aai'** as a colorless oil (23.4 mg, 70%).

Data for **176aai'**: **R_f** 0.30 (45% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.36 (2H, d, *J* = 7.8 Hz, Ar), 6.89 (2H, d, *J* = 7.8 Hz, Ar), 6.67 (1H, d, *J* = 16.0 Hz, 4-H), 5.91 (1H, dd, *J* = 16.0, 9.2 Hz, 3-H), 4.35-3.41 (1H, m, 2-H), 4.28-4.35 (1H, m, 5-H), 3.83 (3H, s, OMe), 3.72-3.83 (2H, m, 1-H_2), 2.07 (1H, t, *J* = 6.8 Hz, OH). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 160.3 (C Ar), 137.8 (C-4), 128.3 (2 x C-H Ar), 127.8 (C Ar), 119.9 (C-3), 114.2 (2 x C-H Ar), 85.8 (C-2), 72.21 (p, *J* = 32.3 Hz, C-5), 65.3 (C-1), 55.4 (OMe). **HRMS** (ESI): calculated for

$C_{14}H_{14}O_3F_6Na$ $[M+Na]^+$ requires *m/z* 367.0745, found *m/z* 367.0739. **IR** (film) ν_{max}: 2980, 1381, 1252, 1188, 1151, 1132 cm^{-1}.

5.8.38 (+)-(2*R*,3*R*,4*S*)-3-Benzhydryl-2-(4-methoxyphenyl)-4-phenyltetrahydrofuran and (+)-(2*S*,3*S*,4*S*)-3-benzhydryl-2-(4-methoxyphenyl)-4-phenyltetrahydrofuran [(+)-176aah]



Alcohol **(+)-(*E*)-178p** (22.7 mg, 0.0894 mmol), benzhydrol **182w** (16.4 mg, 0.0894 mmol) and $Ti(O^iPr)_4$ (7.6 mg, 0.027 mmol) were subjected to the general procedure **H** except conducting the reaction at 0 °C (FCC: gradient elution: 10% → 20% Et_2O - pentane) to yield an inseparable 8:1 mixture of diastereomers **(+)-176aah** as a white foam (37.4 mg, 99%, 99% ee).

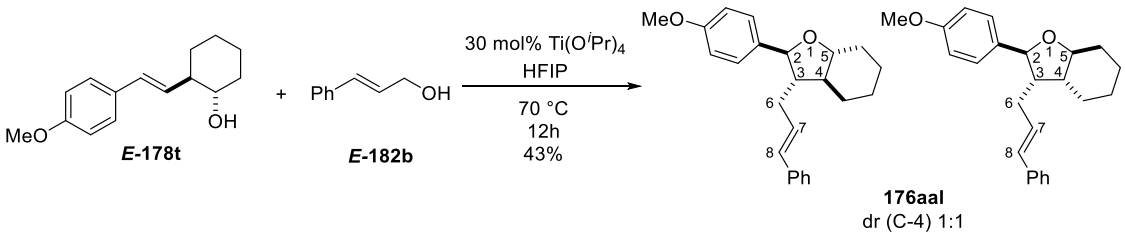
Data for **diastereomer A** of **(+)-176aah** (from the mixture): $\mathbf{R_f}$ 0.30 (25% Et_2O - pentane). $[\alpha]_D^{25}$ = +2.5 (*c* = 10.0, $CHCl_3$). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.00-7.23 (12H, m, Ar), 6.81-6.88 (5H, m, Ar), 6.67 (2H, d, *J* = 7.8 Hz, Ar), 4.64 (1H, d, *J* = 6.3 Hz, 2-H), 4.25 (1H, dd, *J* = 9.3, 7.3 Hz, 5-H_A), 4.17 (1H, dd, *J* = 9.3, 4.2 Hz, 5-H_B), 4.03 (1H, d, *J* = 11.3 Hz, 6-H), 3.76 (3H, s, OMe), 3.26 (1H, ddd, *J* = 11.1, 6.3, 4.5 Hz, 3-H), 3.19 (1H, dt, *J* = 7.2, 4.4 Hz, 4-H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.8 (C Ar), 145.3 (C Ar), 143.3 (C Ar), 142.8 (C Ar), 134.0 (C Ar), 128.7 (2 x C-H Ar), 128.5 (3 x C-H Ar), 128.44 (2 x C-H Ar), 128.40 (2 x C-H Ar), 128.3 (2 x C-H Ar), 128.1 (C-H Ar), 127.6 (2 x C-H Ar), 126.62 (C-H Ar), 126.56 (C-H

Ar), 126.1 (C-H Ar),113.6 (2 x C-H Ar), 87.4 (C-2), 75.1 (C-5), 60.8 (C-3), 58.7 (C-6), 55.4 (OMe), 52.1 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H, between 2-H and 4-H, between 4-H and 6-H. **HRMS** (ESI): calculated for $C_{30}H_{28}O_2Na$ $[M+Na]^+$ requires *m/z* 443.19815, found *m/z* 443.19785. **IR** (film) ν_{max}: 3649, 2980, 1513, 1453, 1302, 1248 cm^{-1}.

Data for **diastereomer B** of **(+)-176aah** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.00-7.23 (11H, m, Ar), 6.89-6.94 (2H, m, Ar), 6.78-6.81 (2H, m, Ar), 6.74 (2H, d, *J* = 8.7 Hz, Ar), 6.54 (2H, d, *J* = 8.7 Hz, Ar), 4.77 (1H, d, *J* = 9.0 Hz, 2-H), 4.60 (1H, dd, *J* = 8.7, 5.4 Hz, 5-H_A), 4.19-4.23 (1H, m, 5-H_B), 3.73 (3H, s, OMe), 3.64-3.71 (1H, m, 3-H), 3.56-3.62 (1H, m, 4-H), 3.39 (1H, d, *J* = 11.8 Hz, 6-H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.4 (C Ar), 143.6 (C Ar), 142.7 (C Ar), 141.1 (C Ar), 135.6 (C Ar), 129.1 (C-H Ar), 128.5 (3 x C-H Ar), 128.44 (2 x C-H Ar), 128.40 (2 x C-H Ar), 128.2 (2 x C-H Ar), 128.00 (2 x C-H Ar), 127.98 (2 x C-H Ar), 126.7 (C-H Ar), 126.3 (C-H Ar), 126.2 (C-H Ar), 113.4 (2 x C-H Ar), 84.6 (C-2), 75.2 (C-5), 55.5 (C-3), 55.4 (OMe), 52.8 (C-6), 49.7 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H.

Racemic **(±)-176aai** (99%, 8:1 dr) was made with the same procedure with racemic alcohol **(±)-(*E*)-178p**.

5.8.39 (±)-(2*R*,3*R*,4*S*,5*R*)-3-Cinnamyl-2-(4-methoxyphenyl)octahydrobenzofuran and (±)-(2*R*,3*R*,4*R*,5*S*)-3-cinnamyl-2-(4-methoxyphenyl)octahydrobenzofuran (176aal)



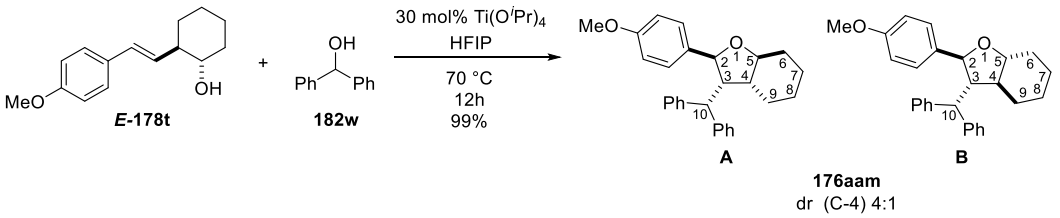
Alcohol ***E*-178t** (63.3 mg, 0.273 mmol), cinnamyl alcohol ***E*-182b** (36.6 mg, 0.273 mmol) and Ti(O^{i}Pr)$_4$ (23.2 mg, 0.082 mmol) were subjected to general procedure **H** (FCC: gradient elution: 6% → 20% Et_2O - pentane) to yield an inseparable 1:1 diastereomers **176aal** as a colorless oil (40.8 mg, 43%).

Data for **diastereomer A** of **176aal** (from the mixture): $\mathbf{R_f}$ 0.45 (25% Et_2O - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 7.29-7.20 (5H, m, Ar), 7.15 (2H, d, *J* = 8.3 Hz, Ar), 6.76 (2H, d, *J* = 8.3 Hz, Ar), 6.41 (1H, d, *J* = 15.8 Hz, 8-H), 6.08 (1H, dt, *J* = 16.0, 7.3 Hz, 7-H), 4.64 (1H, d, *J* = 2.7 Hz, 2-H), 3.71 (3H, s, OMe), 3.40 (1H, td, *J* = 10.7, 3.9 Hz, 5-H), 2.45-2.37 (1H, m, 6-H_A), 2.25-2.16 (3H, m, 3-H, CH Cy and 6-H_B), 1.85-1.71 (3H, m, 3 x CH Cy), 1.51-1.39 (1H, m, CH Cy), 1.31-1.06 (3H, m, 3 x CH Cy). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 158.8 (C Ar), 137.6 (C Ar), 136.4 (C Ar), 131.8 (C-8), 129.1 (C-7), 128.7 (2 x CH Ar), 127.8 (2 x CH Ar), 127.2 (CH Ar), 126.1 (2 x CH Ar), 113.8 (2 x CH Ar), 85.4 (C-2), 81.5 (C-5), 55.4 (OMe), 49.5 (C-3), 47.9 (C-4), 34.0 (C-6), 32.2 (CH_2 Cy), 29.1 (CH_2 Cy), 25.9 (CH_2 Cy), 24.5 (CH_2 Cy). **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max}: 3688, 2987, 1392, 1270, 1112, 1062 cm^{-1}.

Data for **diastereomer B** of **176aal** (from the mixture): $\mathbf{R_f}$ 0.40 (25% Et_2O -

pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 7.33-7.17 (7H, m, Ar), 6.86 (2H, d, *J* = 8.5 Hz, Ar), 6.39 (1H, d, *J* = 15.8 Hz, 8-H), 6.07 (1H, dt, *J* = 15.3, 7.3 Hz, 7-H), 4.60 (1H, d, *J* = 8.7 Hz, 2-H), 3.80 (3H, s, OMe), 3.60 (1H, td, *J* = 10.5, 3.7 Hz, 5-H), 2.49-2.36 (2H, m, 6-H_2), 2.19-2.13 (1H, m, CH Cy), 2.07-1.96 (2H, m, 4-H and CH Cy), 1.88-1.80 (1H, m, CH Cy), 1.78-1.70 (1H, m, CH Cy), 1.46-1.37 (2H, m, 4-H and CH Cy), 1.35-1.08 (3H, m, 3 x CH Cy). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 129.1 (C Ar), 137.6 (C Ar), 135.9 (C Ar), 131.4 (C-8), 128.6 (2 x CH Ar), 128.5 (C-7), 128.0 (2 x CH Ar), 127.1 (CH Ar), 126.1 (2 x CH Ar), 113.9 (2 x CH Ar), 85.6 (C-2), 84.3 (C-5), 55.4 (OMe), 52.8 (C-3), 51.8 (C-4), 34.5 (C-6), 32.0 (CH_2 Cy). 28.5 (CH_2 Cy). 25.8 (CH_2 Cy). 24.4 (CH_2 Cy). **HRMS**: submitted for accurate mass service. **IR** (film) ν_{max} : 3690, 2988, 1392, 1271, 1112, 1062 cm^{-1}.

5.8.40 (±)-(2*S*,3*S*,4*R*,5*S*)-3-Benzhydryl-2-(4-methoxyphenyl)octahydrobenzofuran (±)-(2*S*,3*S*,4*S*,5*R*)-3-benzhydryl-2-(4-methoxyphenyl)octahydrobenzofuran (176aam)



Alcohol ***E*-178t** (23.2 mg, 0.100 mmol), benzhydrol **182w** (18.4 mg, 0.100 mmol) and $Ti(O^iPr)_4$ (8.5 mg, 0.030 mmol) were subjected to general procedure **H** (FCC: gradient elution: 6% → 20% Et_2O - pentane) to yield a separable 1:1 diastereomers **176aam** as a colorless oil (39.7 mg, 99%).

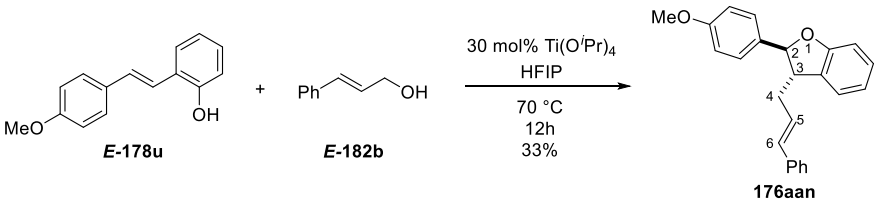
Data for **diastereomer A** of **176aam:** R_f 0.45 (25% Et_2O - pentane). **^{1}H NMR** (400

MHz, $CDCl_3$) **δ** 7.31-7.36 (2H, m, Ar), 7.19-7.27 (6H, m, Ar), 7.10-7.18 (2H, m, Ar), 6.69-6.76 (4H, m, Ar), 4.57 (1H, d, *J* = 3.3 Hz, 2-H), 4.04 (1H, d, *J* = 12.5 Hz, 10-H), 3.77 (3H, s, OMe), 3.64 (1H, td, *J* = 10.7, 4.0 Hz, 5-H), 3.19 (1H, ddd, *J* = 12.5, 7.9, 3.3 Hz, 3-H), 2.23-2.31 (1H, m, 6-H_A), 1.81-1.91 (1H, m, 4-H), 1.72-1.81 (1H, m, 7-H_A), 1.51-1.61 (1H, m, 8-H_A), 1.42-1.51 (1H, m, 6-H_B), 1.16-1.25 (1H, m, 7-H_B), 1.06-1.14 (1H, m, 9-H_A), 0.96-1.06 (1H, m, 8-H_B), 0.75-0.88 (1H, m, 9-H_B). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 158.7 (C Ar), 144.7 (C Ar), 144.2 (C Ar), 136.4 (C Ar), 129.0 (2 x CH Ar), 128.7 (2 x CH Ar), 128.5 (2 x CH Ar), 127.8 (2 x CH Ar), 127.5 (2 x CH Ar), 126.5 (CH Ar), 126.3 (CH Ar), 113.4 (2 x CH Ar), 84.3 (C-2), 81.6 (C-5), 55.3 (OMe), 53.3 (C-10), 52.7 (C-3), 48.5 (C-4), 32.3 (C-6), 27.8 (C-9), 26.5 (C-8), 24.1 (C-7). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 5-H, between 2-H and 10-H, between 10-H and 9-H_B, between 10-H and 5-H. **HRMS** (ESI): calculated for $C_{28}H_{30}O_2Na$ $[M+Na]^+$ requires *m/z* 421.2143, found *m/z* 421.2134. **IR** (film) ν_{max}: 2980, 2888, 1509, 1461, 1382, 1250 cm^{-1}.

Data for **diastereomer B** of **176aam: R_f** 0.40 (25% Et_2O - pentane). **^{1}H NMR** (400 MHz, $CDCl_3$) **δ** 7.28-7.34 (2H, m, Ar), 7.22-7.28 (2H, m, Ar), 7.13-7.20 (1H, m, Ar), 6.96-7.05 (5H, m, Ar), 6.80 (2H, d, *J* = 8.7 Hz, Ar), 6.64 (2H, d, *J* = 8.7 Hz, Ar), 4.55 (1H, d, *J* = 7.5 Hz, 2-H), 3.88 (1H, d, *J* = 10.3 Hz, 10-H), 3.75 (3H, s, OMe), 3.66 (1H, td, *J* = 10.5, 3.8 Hz, 5-H), 2.99 (1H, td, *J* = 10.3, 7.5 Hz, 3-H), 2.05-2.14 (1H, m, 6-H_A), 1.69-1.79 (1H, m, 7-H_A), 1.46-1.54 (1H, m, 8-H_A), 1.38-1.46 (1H, m, 4-H), 1.27-1.38 (1H, m, 6-H_B), 1.14-1.27 (1H, m, 7-H_B), 0.95-1.03 (1H, m, 8-H_B), 0.78-0.95 (2H, m, 9-H_2). **^{13}C NMR** (100 MHz, $CDCl_3$) **δ** 158.6 (C Ar), 143.9 (C Ar), 143.2 (C Ar), 136.7 (C Ar), 128.6 (2 x CH Ar), 128.4 (2 x CH Ar), 128.3 (2 x CH Ar), 128.23 (2 x CH Ar), 128.19 (2 x CH Ar), 126.7 (CH Ar), 126.3 (CH

Ar), 113.6 (2 x CH Ar), 86.1 (C-2), 84.0 (C-5), 58.1 (C-10), 55.6(C-3), 55.4 (OMe), 53.0 (C-4), 32.0 (C-6), 29.6 (C-9), 26.0 (C-8), 24.3 (C-7). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 10-H, between 2-H and 4-H, between 3-H and 5-H. **HRMS** (ESI): calculated for $C_{28}H_{30}O_2Na$ $[M+Na]^+$ requires *m/z* 421.2143, found *m/z* 421.2134. **IR** (film) ν_{max}: 2980, 2888, 1509, 1461, 1382, 1250 cm^{-1}.

5.8.41 (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-3-[(1'*S*)-3-phenylcyclopent-2-en-1-yl]-1,8-dioxaspiro[4.5]decane (176aan)

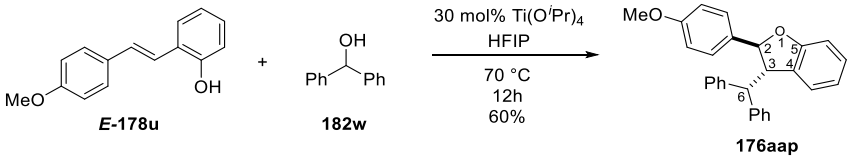


Alcohol ***E*-178u** (69.2 mg, 0.306 mmol), cinnamyl alcohol ***E*-182b** (41.0 mg, 0.306 mmol) and $Ti(O^iPr)_4$ (26.0 mg, 0.0915 mmol) were subjected to the general procedure **H** (FCC: 3% Et_2O - pentane) to yield **176aan** as a colorless oil (30.8 mg, 33%).

Data for **176aan**: R_f 0.30 (10% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.25-7.34 (6H, m, Ar), 7.16-7.24 (3H, m, Ar), 6.84-6.94 (4H, m, Ar), 6.50 (1H, d, *J* = 16.0 Hz, 6-H), 6.17 (1H, dt, *J* = 14.4, 7.2 Hz, 5-H), 5.35 (1H, d, *J* = 7.1 Hz, 2-H), 3.79 (3H, s, OMe), 3.58 (1H, q, *J* = 7.2 Hz, 3-H), 2.61-2.81 (2H, m, 4-H_2). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.62 (C Ar), 159.59 (C Ar), 137.3 (C Ar), 133.6 (C Ar), 132.7 (C-6), 127.0 (C Ar), 128.7 (3 x CH Ar), 127.7 (2 x CH Ar), 127.4 (CH Ar), 127.2 (C-5), 126.3 (2 x CH Ar), 124.5 (CH Ar), 120.8 (CH Ar), 114.1 (2 x CH Ar), 109.7 (CH Ar), 89.4 (C-2), 55.4 (OMe), 50.5 (C-3), 38.1 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 4-H_2, between 2-H and 5-H,

between 2-H and 6-H. **HRMS** (ESI): calculated for $C_{24}H_{23}O_2$ $[M+H]^+$ requires *m/z* 343.16926, found *m/z* 343.16937. **IR** (film) ν_{max}: 3658, 2980, 1513, 1247, 956, 826 cm^{-1}.

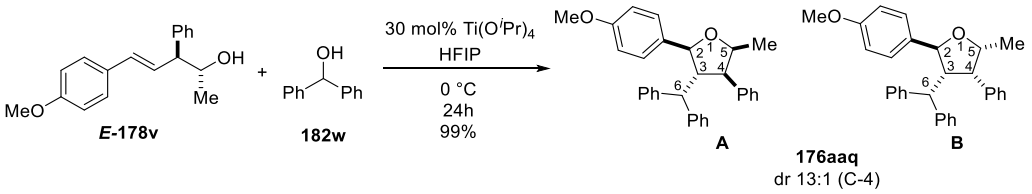
5.8.42 (±)-(2*S*,3*S*)-3-Benzhydryl-2-(4-methoxyphenyl)-2,3-dihydrobenzofuran (176aap)



Alcohol ***E*-178u** (20.2 mg, 0.0891 mmol), benzhydrol **182w** (16.4 mg, 0.0891 mmol) and $Ti(O^iPr)_4$ (7.6 mg, 0.027 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 4% → 10% Et_2O - pentane) to yield **176aap** as a white foam (20.7 mg, 60%).

Data for **176aap**: $\mathbf{R_f}$ 0.40 (15% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.19 -7.32 (10H, m, Ar), 7.13 (1H, t, *J* = 7.7 Hz, Ar), 6.83-6.89 (3H, m, Ar), 6.75 (2H, d, *J* = 8.7 Hz, Ar), 6.59 (1H, t, *J* = 7.6 Hz, Ar), 6.14 (1H, d, *J* = 7.6 Hz, Ar), 5.30 (1H, d, *J* = 4.1 Hz, 2-H), 4.26 (1H, dd, *J* = 11.5, 4.1 Hz, 3-H), 4.09 (1H, d, *J* = 11.5 Hz, 6-H), 3.77 (3H, s, OMe). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 160.0 (C-4), 159.4 (C-5), 142.7 (C Ar), 142.6 (C Ar), 134.5 (C Ar), 128.82 (5 x C-H Ar), 128.78 (2 x C-H Ar), 128.7 (C Ar), 128.5 (2 x C-H Ar), 127.2 (2 x C-H Ar), 126.96 (C-H Ar), 126.95 (C-H Ar), 126.3 (C-H Ar), 120.0 (C-H Ar), 113.9 (2 x C-H Ar), 109.4 (C-H Ar), 88.2 (C-2), 58.1 (C-6), 55.4 (OMe), 55.0 (C-3). **HRMS** (ESI): calculated for $C_{28}H_{24}O_2Na$ $[M+Na]^+$ requires *m/z* 415.16685, found *m/z* 415.16687. **IR** (film) ν_{max}: 2980, 2887, 2360, 1457, 1302, 1022 cm^{-1}.

5.8.43 (±)-(2*S*,3*S*,4*R*,5*S*)-3-Benzhydryl-2-(4-methoxyphenyl)-5-methyl-4-phenyltetrahydrofuran and (±)-(2*S*,3*S*,4*S*,5*R*)-3-benzhydryl-2-(4-methoxyphenyl)-5-methyl-4-phenyltetrahydrofuran (176aaq)



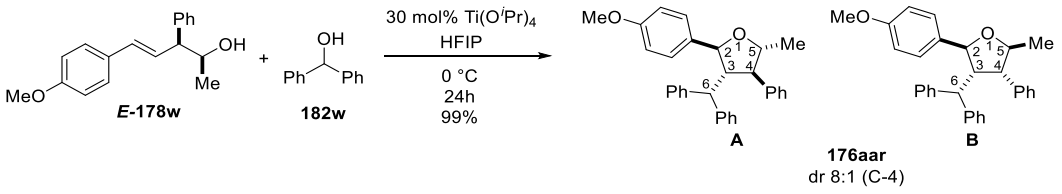
Alcohol ***E*-178v** (23.9 mg, 0.0864 mmol), benzhydrol **182w** (15.9 mg, 0.0864 mmol) and $Ti(O^iPr)_4$ (7.3 mg, 0.026 mmol) were subjected to the general procedure **H** except conducting the reaction at 0 °C for 24 hours (FCC: gradient elution: 5% → 6% Et_2O - pentane) to yield an inseparable 13:1 mixture of diastereomers **176aaq** as a colorless oil (37.7 mg, 99%).

Data for **diastereomer A** of **176aaq** (from the mixture): $\mathbf{R_f}$ 0.50 (30% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.17-7.27 (3H, m, Ar), 7.07-7.15 (5H, m, Ar), 6.96-7.06 (7H, m, Ar), 6.86 (2H, d, *J* = 8.7 Hz, Ar), 6.64 (2H, d, *J* = 8.8 Hz, Ar), 4.58 (1H, d, *J* = 7.5 Hz, 2-H), 4.32 (1H, quint, *J* = 6.3 Hz, 5-H), 4.09 (1H, d, *J* = 11.4 Hz, 6-H), 3.75 (3H, s, OMe), 3.35 (1H, ddd, *J* = 11.2, 7.5, 3.5 Hz, 3-H), 3.01 (1H, dd, *J* = 6.4, 3.4 Hz, 4-H), 0.98 (3H, d, *J* = 6.3 Hz, Me). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.8 (C Ar), 143.6 (C Ar), 143.3 (C Ar), 142.7 (C Ar), 133.1 (C Ar), 129.2 (2 x C-H Ar), 128.59 (2 x C-H Ar), 128.57 (2 x C-H Ar), 128.51 (2 x C-H Ar), 128.41 (2 x C-H Ar), 128.37 (2 x C-H Ar), 128.07 (2 x C-H Ar), 126.5 (C-H Ar), 126.4 (C-H Ar), 126.1 (C-H Ar), 113.46 (2 x C-H Ar), 86.6 (C-2), 77.8 (C-5), 60.9 (C-3), 58.3 (C-6), 56.5 (C-4), 55.38 (OMe), 16.7 (Me). **NOESY- 2D (500 MHz, $CDCl_3$)**:

between 2-H and 4-H, between 2-H and 5-H, between 2-H and 6-H, between 4-H and 6-H. **HRMS** (ESI): calculated for $C_{31}H_{30}O_2Na$ $[M+Na]^+$ requires *m/z* 457.21380, found *m/z* 457.21353. **IR** (film) ν_{max}: 2980, 2888, 1382, 1248, 1152, 954 cm^{-1}.

Data for **diastereomer B** of **176aaq** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.31-7.42 (3H, m, Ar), 7.07-7.15 (5H, m, Ar), 6.96-7.06 (7H, m, Ar), 6.77 (2H, d, *J* = 8.6 Hz, Ar), 6.56 (2H, d, *J* = 8.6 Hz, Ar), 4.85-4.89 (1H, m, 5-H), 4.84 (1H, d, *J* = 7.5 Hz, 2-H), 3.80-3.87 (1H, m, 3-H), 3.73 (3H, s, OMe), 3.52 (1H, d, *J* = 11.9 Hz, 6-H), 3.31-3.34 (1H, m, 4-H), 1.02 (3H, d, *J* = 6.3 Hz, Me). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.4 (C Ar), 143.5 (C Ar), 137.2 (C Ar), 136.6 (C Ar), 128.63 (C Ar), 128.59 (2 x C-H Ar), 128.46 (2 x C-H Ar), 128.23 (2 x C-H Ar), 128.22 (2 x C-H Ar), 128.12 (2 x C-H Ar), 127.92 (2 x C-H Ar), 127.85 (2 x C-H Ar), 126.7 (C-H Ar), 126.6 (C-H Ar), 126.3 (C-H Ar), 113.48 (2 x C-H Ar), 84.8 (C-2), 78.9 (C-5), 57.3 (C-3), 55.41 (OMe), 54.8 (C-4), 53.1 (C-6), 16.9 (Me). **NOESY-2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H, between 3-H and 5-H.

5.8.44 (±)-(2*S*,3*S*,4*R*,5*R*)-3-Benzhydryl-2-(4-methoxyphenyl)-5-methyl-4-phenyltetrahydrofuran and (±)-(2*S*,3*S*,4*S*,5*S*)-3-benzhydryl-2-(4-methoxyphenyl)-5-methyl-4-phenyltetrahydrofuran (176aar)



Alcohol ***E*-178w** (5.0 mg, 0.019 mmol), benzhydrol **182w** (3.5 mg, 0.019 mmol)

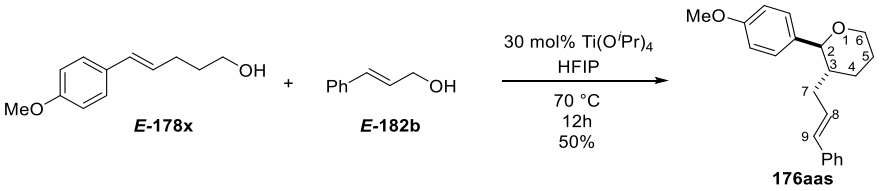
and $Ti(O^iPr)_4$ (1.7 mg, 0.0057 mmol) were subjected to the general procedure **H** except conducting the reaction at 0 °C for 24 hours (FCC: gradient elution: 5% → 10% Et_2O - pentane) to yield an inseparable 8:1 mixture of diastereomers **176aar** as a colorless oil (8.0 mg, 99%).

Data for **diastereomer A** of **176aar** (from the mixture): $\mathbf{R_f}$ 0.50 (30% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.23 (2H, d, *J* = 8.1 Hz, Ar), 7.15 (2H, t, *J* = 7.5 Hz, Ar), 6.95-7.11 (11H, m, Ar), 6.76 (2H, d, *J* = 8.7 Hz, Ar), 6.65-6.68 (2H, m, Ar), 4.95 (1H, d, *J* = 4.6 Hz, 2-H), 4.26 (1H, dq, *J* = 8.7, 5.9 Hz, 5-H), 4.06 (1H, d, *J* = 11.1 Hz, 6-H), 3.79 (3H, s, OMe), 3.47 (1H, ddd, *J* = 11.4, 7.1, 4.7 Hz, 3-H), 2.64 (1H, dd, *J* = 8.8, 7.1 Hz, 4-H), 1.24 (3H, d, *J* = 6.0 Hz, Me). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.6 (C Ar), 143.6 (C Ar), 142.5 (C Ar), 142.1 (C Ar), 135.7 (C Ar), 128.7 (2 x C-H Ar), 128.63 (2 x C-H Ar), 128.46 (2 x C-H Ar), 128.3 (2 x C-H Ar), 128.13 (2 x C-H Ar), 128.10 (2 x C-H Ar), 127.4 (2 x C-H Ar), 126.6 (C-H Ar), 126.3 (C-H Ar), 126.04 (C-H Ar), 113.8 (2 x C-H Ar), 84.6 (C-2), 83.4 (C-5), 61.3 (C-4), 60.9 (C-3), 59.5 (C-6), 55.4 (OMe), 19.5 (Me). **NOESY-2D (500 MHz, $CDCl_3$)**: between 2-H and Me, between 2-H and 6-H, between 2-H and 4-H, between 3-H and 5-H. **HRMS** (ESI): calculated for $C_{31}H_{30}O_2Na$ $[M+ Na]^+$ requires *m/z* 457.21380, found *m/z* 457.21353. **IR** (film) ν_{max}: 2980, 2888, 1382, 1248, 1152, 954 cm^{-1}.

Data for **diastereomer B** of **176aar** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.23 (2H, d, *J* = 8.1 Hz, Ar), 6.95-7.17 (13H, m, Ar), 6.80 (2H, d, *J* = 8.4 Hz, Ar), 6.53 (2H, d, *J* = 8.7 Hz, Ar), 4.77 (1H, d, *J* = 9.3 Hz, 2-H), 4.39-4.44 (1H, m, 5-H), 3.72 (3H, s, OMe), 3.62-3.68 (1H, m, 3-H), 3.49 (1H, d, *J* = 12.4 Hz, 6-H), 3.26 (1H, dd, *J* = 8.3, 4.1 Hz, 4-H), 1.49 (3H, d, *J* = 6.2 Hz, Me). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.6 (C Ar), 143.7 (C Ar), 142.1

(C Ar), 140.6 (C Ar), 129.1 (C Ar), 128.57 (2 x C-H Ar), 128.53 (2 x C-H Ar), 128.4 (2 x C-H Ar), 128.0 (2 x C-H Ar), 127.9 (2 x C-H Ar), 127.8 (2 x C-H Ar), 127.4 (2 x C-H Ar), 126.5 (C-H Ar), 126.1 (C-H Ar), 125.95 (C-H Ar), 113.4 (2 x C-H Ar), 85.9 (C-2), 81.3 (C-5), 56.2 (C-4), 55.4 (OMe), 53.3 (C-3), 52.3 (C-6), 22.7 (Me). **NOESY-2D (500 MHz, $CDCl_3$)**: between 2-H and 5-H, between 2-H and 6-H.

5.8.45 (±)-(2*S*,3*R*)-3-Cinnamyl-2-(4-methoxyphenyl)tetrahydro-2H-pyran (176aas)

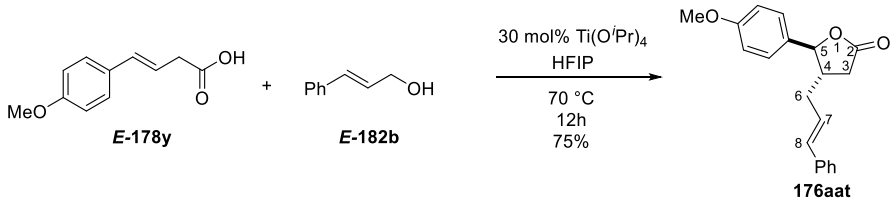


Alcohol ***E*-178x** (50.5 mg, 0.263 mmol), cinnamyl alcohol ***E*-182b** (35.2 mg, 0.263 mmol) and Ti(O^{i}Pr)$_4$ (22.4 mg, 0.0789 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 7% → 12% Et_2O - pentane) to yield **176aas** as a colorless oil (40.0 mg, 50%).

Data for **176aas**: R_f 0.50 (30% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.24-7.33 (6H, m, Ar), 7.15-7.23 (1H, m, Ar), 6.90 (2H, d, *J* = 8.7 Hz, Ar), 6.22 (1H, d, *J* = 15.7 Hz, 9-H), 6.00 (1H, dt, *J* = 14.9, 7.2 Hz, 8-H), 4.09 (1H, dt, *J* = 11.6, 4.1 Hz, 6-H_A), 3.94 (1H, d, *J* = 9.1 Hz, 2-H), 3.81 (3H, s, OMe), 3.54 (1H, td, *J* = 11.5, 2.6 Hz, 6-H_B), 2.04-2.12 (1H, m, 4-H_A), 1.96-2.04 (1H, m, 7-H_A), 1.72-1.87 (3H, m, 3-H, 5-H_A and 7-H_B), 1.62-1.70 (1H, m, 5-H_B), 1.34 (1H, qd, *J* = 13.0, 4.1 Hz, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.4 (C Ar), 137.7 (C Ar), 133.6 (C Ar), 131.5 (C-9), 128.8 (2 x C-H Ar), 128.6 (2 x C-H Ar), 128.2 (C-8), 127.0 (C-H Ar), 126.0 (2 x C-H Ar), 113.9 (2 x C-H Ar), 85.6 (C-2), 69.0 (C-6), 55.4

(OMe), 42.2 (C-3), 36.0 (C-7), 30.0 (C-4), 26.7 (C-5). **HRMS** (ESI): calculated for $C_{21}H_{25}O_2$ $[M+H]^+$ requires *m/z* 309.18491, found *m/z* 309.18488. **IR** (film) ν_{max}: 3658, 2980, 2933, 1512, 1241, 1075 cm^{-1}.

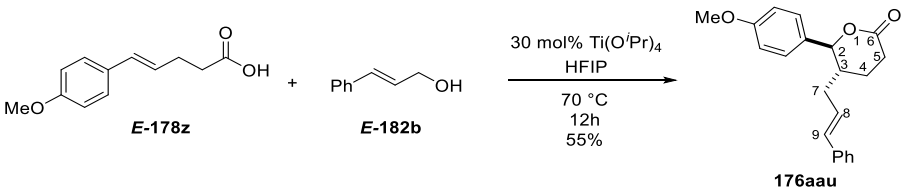
5.8.46 (±)-(4*S*,5*S*)-4-Cinnamyl-5-(4-methoxyphenyl)dihydrofuran-2(3H)-one (176aat)



Carboxylic acid ***E*-178y** (45.6 mg, 0.238 mmol), cinnamyl alcohol ***E*-182b** (31.8 mg, 0.238 mmol) and $Ti(O^iPr)_4$ (20.0 mg, 0.0704 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 15% → 45% Et_2O - pentane) to yield **176aat** as a colorless oil (55.0 mg, 75%).

Data for **176aat**: $\mathbf{R_f}$ 0.50 (40% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.19-7.34 (7H, m, Ar), 6.92 (2H, d, *J* = 8.7 Hz, Ar), 6.45 (1H, d, *J* = 15.9 Hz, 8-H), 6.04 (1H, dt, *J* = 15.8, 7.1 Hz, 7-H), 5.08 (1H, d, *J* = 7.6 Hz, 5-H), 3.82 (3H, s, OMe), 2.81 (1H, dd, *J* = 17.2, 7.9 Hz, 3-H_A), 2.54-2.68 (1H, m, 4-H), 2.46-2.54 (1H, m, 6-H_A), 2.42 (1H, dd, *J* = 17.2, 7.9 Hz, 3-H_B), 2.31-2.39 (1H, m, 6-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 176.0 (C=O), 160.0 (C Ar), 136.9 (C Ar), 133.0 (C-8), 130.1 (C Ar), 128.7 (2 x C-H Ar), 127.7 (2 x C-H Ar), 127.6 (C-H Ar), 126.2 (2 x C-H Ar), 125.9 (C-7), 114.2 (2 x C-H Ar), 86.1 (C-5), 55.4 (OMe), 44.5 (C-4), 35.4 (C-6), 35.0 (C-3). **HRMS** (CI): calculated for $C_{20}H_{21}O_3$ $[M+H]^+$ requires *m/z* 309.14852, found *m/z* 309.14856. **IR** (film) ν_{max} : 2980, 1774, 1514, 1248, 1144, 1029 cm^{-1}.

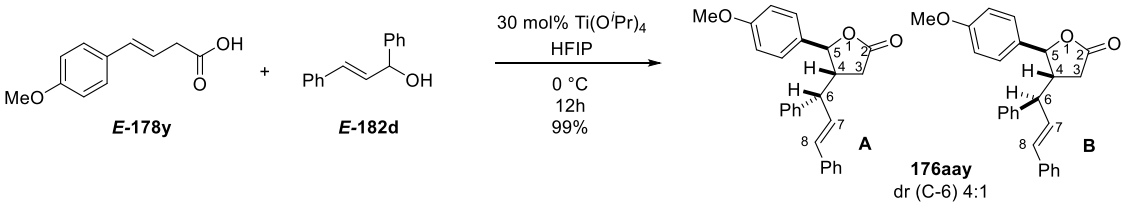
5.8.47 (±)-(5*R*,6*S*)-5-Cinnamyl-6-(4-methoxyphenyl)tetrahydro-2H-pyran-2-one (176aau)



Carboxylic acid ***E*-178z** (45.9 mg, 0.224 mmol), cinnamyl alcohol ***E*-182b** (30.0 mg, 0.224 mmol) and $Ti(O^iPr)_4$ (19.0 mg, 0.0669 mmol) were subjected to the general procedure E (FCC: gradient elution: 18% → 25% Et_2O - pentane) to yield **176aau** as a colorless oil (38.9 mg, 55%).

Data for **176aau**: $\mathbf{R_f}$ 0.50 (50% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.24-7.31 (6H, m, Ar), 7.17-7.26 (1H, m, Ar), 6.92 (2H, d, *J* = 8.7 Hz, Ar), 6.32 (1H, d, *J* = 15.8 Hz, 9-H), 6.00 (1H, ddd, *J* = 15.6, 8.2, 6.3 Hz, 8-H), 4.97 (1H, d, *J* = 9.4 Hz, 2-H), 3.81 (3H, s, OMe), 2.75 (1H, ddd, *J* = 17.9, 7.1, 4.6 Hz, 5-H_A), 2.61 (1H, ddd, *J* = 17.8, 9.5, 6.8 Hz, 5-H_B), 2.15-2.23 (1H, m, 7-H_A), 2.04-2.14 (2H, m, 3-H and 4-H_A), 1.91-2.04 (1H, m, 7-H_B), 1.74 (1H, dddd, *J* = 15.0, 11.3, 6.8, 4.7 Hz, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 171.1 (C-6), 159.7 (C Ar), 136.8 (C Ar), 132.6 (C-9), 130.1 (C Ar), 128.4 (2 x C-H Ar), 128.3 (2 x C-H Ar), 127.2 (C-H Ar), 125.9 (C-8), 125.8 (2 x C-H Ar), 113.8 (2 x C-H Ar), 86.1 (C-2), 55.1 (OMe), 39.4 (C-3), 34.7 (C-7), 29.3 (C-5), 24.3 (C-4). **HRMS** (Cl): calculated for $C_{21}H_{22}O_3$ $[M+H]^+$ requires *m/z* 323.16417, found *m/z* 323.16418. **IR** (film) ν_{max}: 2980, 1727, 1514, 1246, 1072, 966 cm^{-1}.

5.8.48 (±)-(4*R*,5*S*)-4-[(1'*R*,2'*E*)-1,3-diphenylallyl]-5-(4-methoxyphenyl)dihydrofuran-2(3*H*)-one and (±)-(4*R*,5*S*)-4-[(1'*S*,2'*E*)-1,3-diphenylallyl]-5-(4-methoxyphenyl)dihydrofuran-2(3*H*)- one (176aay)



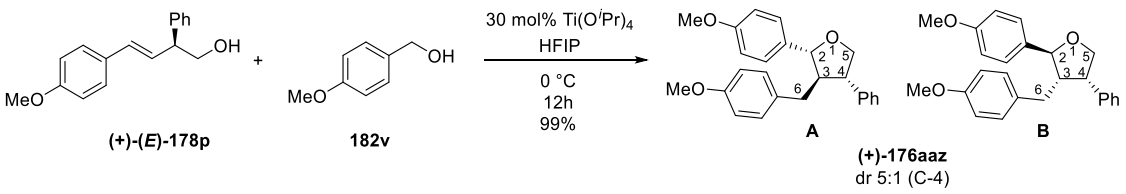
Carboxylic acid ***E*-178y** (200.0 mg, 1.031 mmol), *trans*-1,3-diphenyl-2-propen-1-ol ***E*-182d** (219.0 mg, 1.031 mmol) and Ti(O^{i}Pr)$_4$ (88.6 mg, 0.312 mmol) were subjected to the general procedure **H** except conducting the reaction at 0 °C (FCC: gradient elution: 15% → 30% Et_2O - pentane) to yield a separable 4:1 mixture of diastereomers **176aay** as a colorless oil (399.0 mg, 99%).

Data for **diastereomer A** of **176aay:** **R_f** 0.40 (70% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.32-7.37 (2H, m, Ar), 7.17-7.30 (10H, m, Ar), 6.86 (2H, d, *J* = 8.7 Hz, Ar), 6.51 (1H, d, *J* = 15.7 Hz, 8-H), 6.10 (1H, dd, *J* = 15.7, 9.2 Hz, 7-H), 5.37 (1H, d, *J* = 5.7 Hz, 5-H), 3.79 (3H, s, OMe), 3.54 (1H, t, *J* = 9.5 Hz, 6-H), 2.96-3.06 (1H, m, 4-H), 2.64 (1H, dd, *J* = 18.0, 8.7 Hz, 3-H_A), 2.35 (1H, dd, *J* = 18.0, 7.1 Hz, 3-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 176.0 (C=O), 159.8 (C Ar), 141.3 (C Ar), 136.6 (C Ar), 132.0 (C-8), 131.1 (C Ar), 130.6 (C-7), 129.2 (2 x C-H Ar), 128.6 (2 x C-H Ar), 128.0 (2 x C-H Ar), 127.79 (2 x C-H Ar), 127.75 (C-H Ar), 127.3 (C-H Ar), 126.4 (2 x C-H Ar), 114.3 (2 x C-H Ar), 84.9 (C-5), 55.4 (OMe), 52.6 (C-6), 48.6 (C-4), 33.6 (C-3). **HRMS** (ESI): calculated for $C_{26}H_{24}O_3Na$ $[M+ Na]^+$ requires *m/z* 407.16177, found *m/z* 407.16190. **IR** (film) ν_{max}: 2982, 1764, 1524, 1278, 1124,

1019 cm^{-1}.

Data for **diastereomer B** of **176aay:** R_f 0.50 (70% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.28-7.35 (6H, m, Ar), 7.17-7.26 (4H, m, Ar), 6.91 (2H, d, *J* = 8.7 Hz, Ar), 6.79 (2H, d, *J* = 8.8 Hz, Ar), 6.50 (1H, d, *J* = 15.7 Hz, 8-H), 6.27 (1H, dd, *J* = 15.7, 9.0 Hz, 7-H), 5.17 (1H, d, *J* = 4.8 Hz, 5-H), 3.78 (3H, s, OMe), 3.49 (1H, t, *J* = 9.2 Hz, 6-H), 2.90-2.97 (1H, m, 4-H), 2.81 (1H, dd, *J* = 17.9, 8.6 Hz, 3-H_A), 2.66 (1H, dd, *J* = 17.9, 5.9 Hz, 3-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 176.4 (C=O), 159.6 (C Ar), 141.3 (C Ar), 136.6 (C Ar), 132.7 (C-8), 131.2 (C Ar), 129.5 (C-7), 129.2 (2 x C-H Ar), 128.8 (2 x C-H Ar), 128.1 (2 x C-H Ar), 128.0 (C-H Ar), 127.4 (C-H Ar), 126.9 (2 x C-H Ar), 126.5 (2 x C-H Ar), 114.2 (2 x C-H Ar), 84.2 (C-5), 55.5 (OMe), 52.6 (C-6), 48.6 (C-4), 32.7 (C-3). **HRMS** (ESI): calculated for $C_{26}H_{24}O_3Na$ $[M+ Na]^+$ requires *m/z* 407.16177, found *m/z* 407.16190. **IR** (film) ν_{max}: 2982, 1764, 1524, 1278, 1124, 1019 cm^{-1}.

5.8.49 (+)-(2*R*,3*R*,4*S*)-3-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-4-phenyltetrahydrofuran and (+)-(2*S*,3*S*,4*S*)-3-(4-methoxybenzyl)-2-(4-methoxyphenyl)-4-phenyltetrahydrofuran [(+)-176aaz]



Alcohol **(+)-(*E*)-178p** (30.0 mg, 0.118 mmol), 4-methoxybenzylic alcohol **182v** (15.7 mg, 0.118 mmol) and $Ti(O^iPr)_4$ (9.7 mg, 0.034 mmol) were subjected to the

general procedure **H** except conducting the reaction at 0 °C (FCC: gradient elution: 10% → 15% Et_2O - pentane) to yield inseparable 5:1 mixture of diastereomers **(+)-176aaz** as a colorless oil (43.8 mg, 99%, 99% ee).

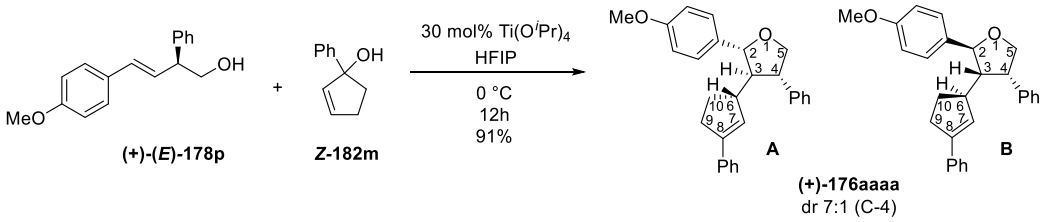
Data for **diastereomer A** of **(+)-176aaz** (from the mixture): $\mathbf{R_f}$ 0.50 (50% Et_2O - pentane). $[\alpha]_D^{25}$ = +39.6 (*c* = 6.75, $CHCl_3$). **^{1}H (500 MHz, $CDCl_3$) δ** 7.23-7.31 (4H, m, Ar), 7.14-7.22 (4H, m, Ar), 6.82-6.90 (3H, m, Ar), 6.68 (2H, d, *J* = 8.7 Hz, Ar), 4.61 (1H, d, *J* = 8.8 Hz, 2-H), 4.24 (1H, t, *J* = 8.4 Hz, 5-H_A), 4.06 (1H, t, *J* = 8.1 Hz, 5-H_B), 3.81 (3H, s, OMe), 3.75 (3H, s, OMe), 3.24 (1H, q, *J* = 8.2 Hz, 4-H), 2.66-2.79 (2H, m, 6-H_2), 2.59 (1H, m, 3-H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.3 (C Ar), 158.0 (C Ar), 142.1 (C Ar), 133.6 (C Ar), 130.9 (C Ar), 130.5 (2 x C-H Ar), 128.7 (2 x C-H Ar), 128.1 (2 x C-H Ar), 127.7 (2 x C-H Ar), 126.5 (C-H Ar), 113.93 (2 x C-H Ar), 113.6 (2 x C-H Ar), 86.2 (C-2), 75.3 (C-5), 57.0 (C-3), 55.40 (OMe), 55.38 (OMe), 51.3 (C-4), 35.7 (C-6). **HRMS** (ESI): calculated for $C_{25}H_{26}O_3Na$ $[M+Na]^+$ requires *m/z* 397.17742, found *m/z* 397.17747. **IR** (film) ν_{max}: 2980, 2889, 1510, 1381, 1243, 1031 cm^{-1}.

Data for **diastereomer B** of **(+)-176aaz** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.32-7.37 (2H, m, Ar), 7.14-7.22 (4H, m, Ar), 6.82-6.90 (5H, m, Ar), 6.76 (2H, d, *J* = 8.7 Hz, Ar), 4.77 (1H, d, *J* = 7.7 Hz, 2-H), 5.50-5.56 (1H, m, 5-H_A), 4.30 (1H, dd, *J* = 8.6, 4.3 Hz, 5-H_B), 3.81 (3H, s, OMe), 3.78 (3H, s, OMe), 3.56 (1H, q, *J* = 6.1 Hz, 4-H), 2.66-2.79 (1H, m, 3-H), 2.43 (1H, dd, *J* = 14.6, 6.4 Hz, 6-H_A), 2.19 (1H, dd, *J* = 14.4, 8.8 Hz, 6-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.0 (C Ar), 157.9 (C Ar), 140.3 (C Ar), 134.8 (C Ar), 132.1 (C Ar), 129.9 (2 x C-H Ar), 129.0 (2 x C-H Ar), 128.4 (2 x C-H Ar), 127.5 (2 x C-H Ar), 126.6 (C-H Ar), 113.87 (2 x C-H Ar), 113.7 (2 x C-H Ar), 84.4 (C-2), 74.0 (C-5), 55.38

(OMe), 55.34 (OMe), 54.2 (C-3), 47.7 (C-4), 32.4 (C-6).

Racemic **(±)-176aaz** (99%, 5:1 dr) was made with the same procedure with racemic alcohol **(±)-(*E*)-178p**.

5.8.50 (+)-(2*R*,3*R*,4*S*)-2-(4-Methoxyphenyl)-4-phenyl-3-[(1'*S*)-3-phenylcyclopent-2-en-1-yl]tetrahydrofuran and (+)-(2*S*,3*S*,4*S*)-2-(4-methoxyphenyl)-4-phenyl-3-[(1'R)-3-phenylcyclopent-2-en-1-yl]tetrahydrofuran [(+)-176aaab]



Alcohols **(+)-(*E*)-178p** (30.0 mg, 0.114 mmol) and **(*E*)-182m** (18.2 mg, 0.114 mmol), and $Ti(O^iPr)_4$ (9.7 mg, 0.034 mmol) were subjected to the general procedure **H** except conducting the reaction at 0 °C (FCC: gradient elution: 10% → 15% Et_2O - pentane) to yield inseparable 7:1 mixture of diastereomers **(+)-176aaab** as a yellow oil (41.7 mg, 91%, 99% ee).

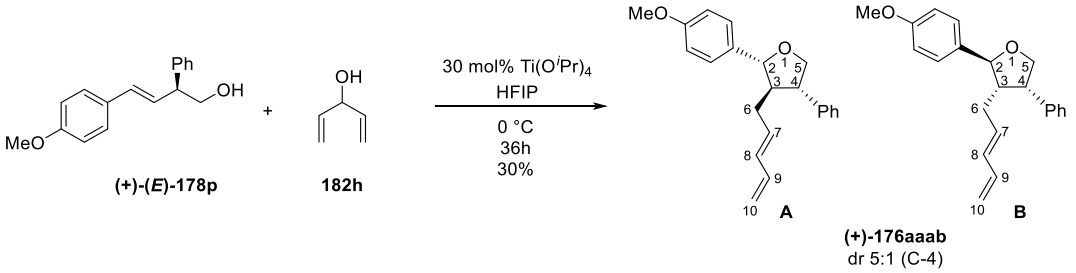
Data for **diastereomer A** of **(+)-176aaaa** (from the mixture): **R_f** 0.40 (30% Et_2O - pentane). $[\alpha]_D^{25}$ = +57.2 (*c* = 10.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.19-7.44 (12H, m, Ar), 6.89 (2H, d, *J* = 8.7 Hz, Ar), 5.95 (1H, q, *J* = 2.0 Hz, 7-H), 4.73 (1H, d, *J* = 8.9 Hz, 2-H), 4.27 (1H, t, *J* = 8.5 Hz, 5-H_A), 4.10 (dd, J = 8.8, 7.3 Hz, 5-H_B), 3.82 (3H, s, OMe), 3.37 (1H, td, *J* = 8.4, 7.3 Hz, 4-H), 3.11 (1H, dtd, *J* = 11.7, 6.5, 6.0, 2.2 Hz, 6-H), 2.51-2.65 (3H, m, 3-H and 9-H_2), 1.97-2.08 (1H, m, 10-H_A), 1.48-1.56 (1H, m, 10-H_B). **^{13}C NMR (100 MHz,**

$CDCl_3$) δ 159.4 (C Ar), 143.5 (C-8), 143.4 (C Ar), 136.4 (C Ar), 134.4 (C Ar),128.9 (2 x C-H Ar), 128.5 (2 x C-H Ar), 128.39 (2 x C-H Ar), 127.8 (2 x C-H Ar), 127.6 (C-H Ar), 127.3 (C-7), 126.7 (C-H Ar), 125.8 (2 x C-H Ar),114.0 (2 x C-H Ar), 85.6 (C-2), 76.0 (C-5), 60.1 (C-3), 55.4 (OMe), 50.3 (C-4), 47.1 (C-6), 32.8 (C-9), 27.7 (C-10). **HRMS** (ESI): calculated for $C_{28}H_{28}O_2Na$ $[M+Na]^+$ requires *m/z* 419.19815, found *m/z* 419.19800. **IR** (film) ν_{max}: 2980, 1611, 1512, 1381, 1247, 1172 cm^{-1}.

Data for **diastereomer B** of **(+)-176aaaa** (from the mixture): **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.19-7.44 (12H, m, Ar), 6.89 (2H, d, *J* = 8.7 Hz, Ar), 5.93 (1H, q, *J* = 2.1 Hz, 7-H), 4.90 (1H, d, *J* = 7.8 Hz, 2-H), 4.50 (1H, dd, J = 8.6, 6.0 Hz, 5-H_A), 4.22 (1H, dd, *J* = 8.6, 3.3 Hz, 5-H_B), 3.82 (3H, s, OMe), 3.73 (1H, td, *J* = 6.1, 3.2 Hz, 4-H), 2.51-2.65 (2H, m, 3-H and 6-H), 2.39-2.49 (2H, m, 9-H_2), 1.97-2.08 (1H, m, 10-H_A), 1.48-1.56 (1H, m, 10-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.3 (C Ar), 142.9 (C-8), 141.4 (C Ar), 136.5 (C Ar), 135.6 (C Ar),129.01 (2 x C-H Ar), 128.95 (2 x C-H Ar), 128.7 (C-7), 128.6 (2 x C-H Ar), 128.35 (2 x C-H Ar), 127.2 (C-H Ar), 126.8 (C-H Ar), 125.7 (2 x C-H Ar), 113.9 (2 x C-H Ar), 84.2 (C-2), 74.6 (C-5), 57.1 (C-3), 55.4 (OMe), 49.7 (C-4), 45.8 (C-6), 33.0 (C-9), 29.2 (C-10).

Racemic **(±)-176aaaa** (91%, 7:1 dr) was made with the same procedure with racemic alcohol **(±)-(*E*)-178p**.

5.8.51 (+)-(2*R*,3*R*,4*S*)-2-(4-Methoxyphenyl)-3-[(2'*E*)-penta-2,4-dien-1-yl]-4-phenyltetra hydrofuran and (+)-(2*S*,3*S*,4*S*)-2-(4-methoxyphenyl)-3-[(2'*E*)-penta-2,4-dien-1-yl]-4-phenyltetra hydrofuran [(+)-176aaab]



Alcohol **(+)-(*E*)-178p** (30.0 mg, 0.118 mmol), bis-allyl alcohol **182h** (15.7 mg, 0.118 mmol) and $Ti(O^iPr)_4$ (9.7 mg, 0.034 mmol) were subjected to the general procedure **H** except conducting the reaction at 0 °C for 36 hours (FCC: gradient elution: 7% → 9% Et_2O - pentane) to yield an inseparable 5:1 mixture of diastereomers **(+)-176aaab** as a colorless oil (11.3 mg, 30%, 99% ee).

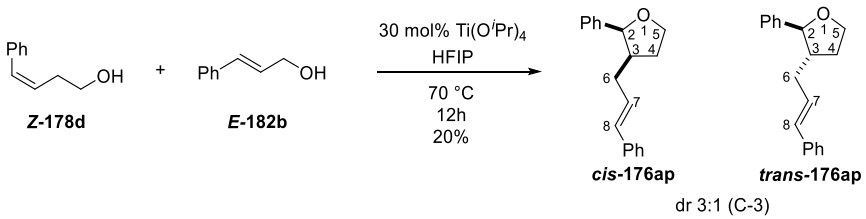
Data for **diastereomer A** of **(+)-176aaab** (from the mixture): **R_f** 0.50 (25% Et_2O - pentane). $[\alpha]_D^{25}$ = +20.0 (*c* = 1.35, $CHCl_3$). **^{1}H (500 MHz, $CDCl_3$) δ** 7.19-7.37 (7H, m, Ar), 6.90 (2H, d, *J* = 8.7 Hz, Ar), 6.12 (1H, dt, *J* = 16.9, 10.2 Hz, 9-H), 5.97 (1H, dd, *J* = 15.1, 10.4 Hz, 8-H), 5.38-5.48 (1H, m, 7-H), 5.05 (1H, dd, *J* = 16.8, 1.7 Hz, 10-H_A), 4.94 (1H, dd, *J* = 10.0, 1.8 Hz, 10-H_B), 4.58 (1H, d, *J* = 8.9 Hz, 2-H), 4.28 (1H, t, *J* = 8.5 Hz, 5-H_A), 4.09 (1H, dd, *J* = 8.7, 7.8 Hz, 5-H_B), 3.82 (3H, s, OMe), 3.26 (1H, q, *J* = 8.3 Hz, 4-H), 2.27-2.34 (1H, m, 3-H), 2.20-2.27 (2H, m, 6-H_2). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.4 (C Ar), 142.0 (C Ar), 136.9 (C-9), 133.5 (C Ar), 133.3 (C-8), 131.5 (C-7), 128.8 (2 x C-H Ar), 128.1 (2 x C-H Ar), 127.9 (2 x C-H Ar), 126.8 (C-H Ar), 115.6 (C-10), 114.00 (2 x C-H Ar), 86.4 (C-2), 75.3

(C-5), 56.2 (C-3), 55.5 (OMe), 51.6 (C-4), 33.1 (C-6). **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max}: 2980, 2888, 1461, 1382, 1252, 1152 cm^{-1}.

Partial data for **diastereomer B** of **(+)-176aaab** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.19-7.37 (7H, m, Ar), 6.90 (2H, d, *J* = 8.7 Hz, Ar), 6.21 (1H, dt, *J* = 17.0, 10.3 Hz, 9-H), 5.84 (1H, dd, *J* = 15.3, 10.4 Hz, 8-H), 5.38-5.48 (1H, m, 7-H), 5.03 (1H, dd, *J* = 16.8, 1.7 Hz, 10-H_A), 4.94 (1H, dd, *J* = 10.0, 1.8 Hz, 10-H_B), 4.66 (1H, d, *J* = 8.5 Hz, 2-H), 4.51 (1H, dd, *J* = 8.7, 6.2 Hz, 5-H_A), 4.26 (1H, dd, *J* = 8.6, 3.7 Hz, 5-H_B), 3.81 (3H, s, OMe), 3.61 (1H, ddd, *J* = 10.3, 6.8, 3.4 Hz, 4-H), 2.42 (1H, qd, *J* = 8.6, 6.2 Hz, 3-H), 1.85-1.96 (1H, m, 6-H_A), 1.66-1.77 (1H, m, 6-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.3 (C Ar), 140.4 (C Ar), 137.1 (C-9), 134.5 (C Ar), 132.7 (C-7), 132.6 (C-8), 128.9 (2 x C-H Ar), 128.5 (2 x C-H Ar), 127.8 (2 x C-H Ar), 126.8 (C-H Ar), 115.4 (C-10), 113.95 (2 x C-H Ar), 84.5 (C-2), 74.3 (C-5), 55.5 (OMe), 52.6 (C-3), 48.3 (C-4), 30.6 (C-6).

Racemic **(±)- 176aaab** (30%, 5:1 dr) was made with the same procedure with racemic alcohol **(±)-(*E*)-178p**.

5.8.52 (±)-(2*S*,3*R*)-3-cinnamyl-2-phenyltetrahydrofuran and (±)-(2*S*,3*S*)-3-Cinnamyl-2-phenyltetrahydrofuran (*cis*-176ap and *trans*-176ap)



Alcohol ***Z*-178d** (53.5 mg, 0.361 mmol), cinnamyl alcohol ***E*-182b** (48.4 mg, 0.361 mmol) and $Ti(O^iPr)_4$ (30.1 mg, 0.106 mmol) were subjected to the general procedure **H**

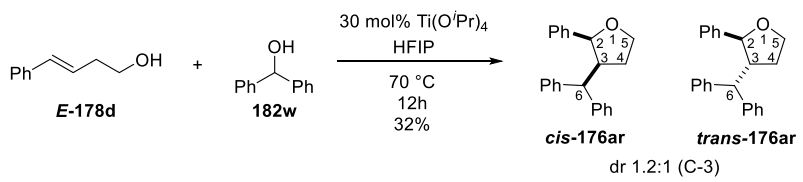
(FCC: gradient elution: 6% → 12% Et_2O - pentane) to yield ***cis*-176ap**: ***trans*-176ap** as a 3:1 dr mixture (19.7 mg, 20%), which was partially separable into 2 fractions: first fraction of ***cis*-176ap** (7.4 mg, 8%) as a colorless oil, and second fraction of 1.5:1 of diastereomers ***cis*-176ap** : ***trans*-176ap** as a colorless oil (12.3 mg, 12%).

Data for ***cis*-176ap**: R_f 0.40 (20% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.23-7.38 (8H, m, Ar), 7.17-7.23 (2H, m, Ar), 6.25 (1H, d, *J* = 15.8 Hz, 8-H), 6.01 (1H, ddd, *J* = 15.8, 7.9, 6.3 Hz, 7-H), 5.06 (1H, d, *J* = 6.7 Hz, 2-H), 4.22 (1H, td, *J* = 8.1, 5.1 Hz, 5-H_A), 3.95 (1H, q, *J* = 7.7 Hz, 5-H_B), 2.56 (1H, dqd, *J* = 11.2, 6.6, 4.7 Hz, 3-H), 2.17-2.22 (1H, m, 4-H_A), 1.85-1.97 (2H, m, 4-H_B and 6-H_A), 1.54-1.74 (1H, m, 6-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 140.6 (C Ar), 137.7 (C Ar), 131.2 (C-8), 129.2 (C-7), 128.6 (2 x CH Ar), 128.2 (2 x CH Ar), 127.2 (CH Ar), 127.1 (CH Ar), 126.6 (2 x CH Ar), 126.0 (2 x CH Ar), 83.4 (C-2), 67.6 (C-5), 43.5 (C-3), 33.7 (C-6), 31.1 (C-4). **NOESY- 2D (400 MHz, $CDCl_3$)**: between 2-H and 3-H. **HRMS** (ESI): calculated for $C_{19}H_{21}O$ $[M+H]^+$ requires *m/z* 265.15869, found *m/z* 265.15875. **IR** (film) ν_{max}: 3657, 2980, 2888, 1382, 1152, 954 cm^{-1}.

Data for ***trans*-176ap** matched those previously reported.

5.8.53 (±)-(2*S*,3*S*)-3-Benzhydryl-2-phenyltetrahydrofuran

(±)-(2*S*,3*R*)-3-benzhydryl-2-phenyltetrahydrofuran (*cis*-176ar and *trans*-176ar)



Alcohol ***Z*-178d** (53.5 mg, 0.361 mmol), benzhydrol **182w** (66.4 mg, 0.361 mmol)

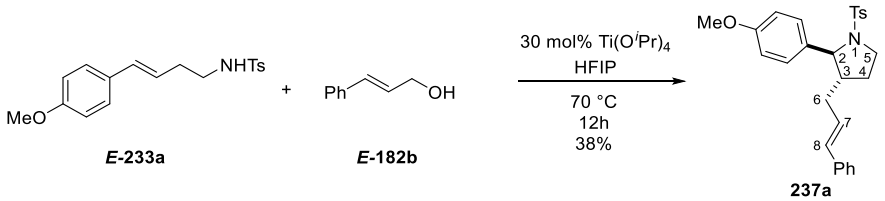
and $Ti(O^iPr)_4$ (30.1 mg, 0.106 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 5% → 15% Et_2O - pentane) to yield a inseparable 1.2:1 mixtures of ***cis*-176ar** and ***trans*-176ar** as a colorless oil (13.1 mg, 32%).

Data for ***cis*-176ar** (from the mixture): $\mathbf{R_f}$ 0.40 (20% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 6.99-7.26 (13H, m, Ar), 6.63-6.67 (2H, m, Ar), 5.08 (1H, d, *J* = 7.8 Hz, 2-H), 4.21 (1H, td, *J* = 8.4, 1.2 Hz, 5-H_A), 3.79-3.86 (1H, m, 5-H_B), 3.40 (1H, tdd, *J* = 11.8, 7.8, 6.3 Hz, 3-H), 3.09 (1H, d, *J* = 11.8 Hz, 6-H), 1.83 (1H, tdd, *J* = 12.4, 11.1, 7.8 Hz, 4-H_A), 1.56 (1H, dtd, *J* = 12.3, 6.3, 1.2 Hz, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 145.1 (C Ar), 143.1 (C Ar), 141.0 (C Ar), 128.6 (2 x CH Ar), 128.5 (2 x CH Ar), 128.2 (2 x CH Ar), 127.8 (2 x CH Ar), 127.59 (2 x CH Ar), 127.57 (2 x CH Ar), 127.3 (CH Ar), 126.44 (CH Ar), 126.35 (CH Ar), 82.4 (C-2), 68.6 (C-5), 52.8 (C-6), 48.3 (C-3), 31.0 (C-4). **HRMS** (ESI): calculated for $C_{23}H_{22}ONa$ $[M+Na]^+$ requires *m/z* 337.1568, found *m/z* 337.1563. **IR** (film) ν_{max} : 3026, 2980, 2360, 1493, 1451, 1382 cm^{-1}.

Data for ***trans*-176ar** matched those previously reported.

5.9 Synthesis of Pyrrolidines *via* Cyclization of Homoallylic Amines

5.9.1 (±)-(2*S*,3*S*)-3-Cinnamyl-2-(4-methoxyphenyl)-1-tosylpyrrolidine (237a)

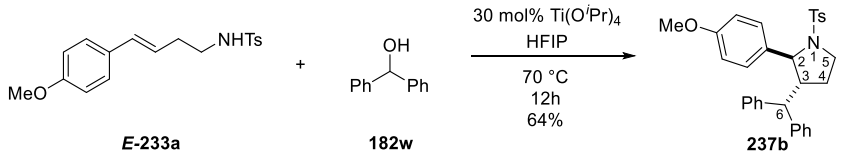


Amine ***E*-233a** (24.9 mg, 0.0752 mmol), cinnamyl alcohol ***E*-182b** (10.1 mg,

0.0752 mmol) and $Ti(O^iPr)_4$ (6.4 mg, 0.023 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 20% → 30% Et_2O - pentane) to yield pyrrolidines **237a** as a colorless oil (12.8 mg, 38%).

Data for **237a**: **R_f** 0.50 (60% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.63 (2H, d, *J* = 8.3 Hz, Ar), 7.20-7.32 (7H, m, Ar), 7.19 (2H, d, *J* = 8.7 Hz, Ar), 6.83 (2H, d, *J* = 8.7 Hz, Ar), 6.18 (1H, d, *J* = 15.8 Hz, 8-H), 5.95 (1H, dt, *J* = 15.8, 7.1 Hz, 7-H), 4.29 (1H, d, *J* = 5.4 Hz, 2-H), 3.80 (3H, s, OMe), 3.57-3.65 (2H, m, 5-H_2), 2.42 (3H, s, Me Ts), 2.13-2.20 (1H, m, 3-H), 1.98-2.07 (2H, m, 4-H_A and 6-H_A), 1.88-1.96 (1H, m, 6-H_B), 1.39-1.49 (1H, m, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.9 (C Ar), 143.3 (C Ar), 137.3 (C Ar), 135.5 (C Ar), 134.6 (C Ar), 132.4 (C-8), 129.6 (2 x C-H Ar), 128.7 (2 x C-H Ar), 127.9 (2 x C-H Ar), 127.6 (2 x C-H Ar), 127.4 (C-H Ar), 127.3 (C-7), 126.1 (2 x C-H Ar), 113.9 (2 x C-H Ar), 68.0 (C-2), 55.4 (OMe), 49.6 (C-3), 48.5 (C-5), 35.5 (C-6), 29.5 (C-4), 21.7 (Me Ts). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H_B, between 2-H and 7-H. **HRMS** (ESI): calculated for $C_{27}H_{29}NO_3SNa$ $[M+Na]^+$ requires *m/z* 470.1766, found *m/z* 470.1761. **IR** (film) ν_{max}: 3648, 2980, 2360, 1612, 1382, 1095 cm^{-1}.

5.9.2 (±)-(2*S*,3*R*)-3-Benzhydryl-2-(4-methoxyphenyl)-1-tosylpyrrolidine (237b)



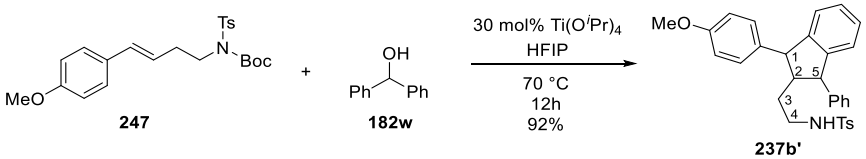
***E*-233a** **182w** **237b**

Amine ***E*-233a** (27.0 mg, 0.0816 mmol), benzhydrol **182w** (15.0 mg, 0.0816 mmol) and $Ti(O^iPr)_4$ (6.9 mg, 0.024 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 20% → 25% Et_2O - pentane) to yield pyrrolidines **237b** as a colorless oil

(26.2 mg, 64%).

Data for **237b**: **R_f** 0.50 (60% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.67 (2H, d, *J* = 8.3 Hz, Ar), 7.35 (2H, d, *J* = 8.3 Hz, Ar), 7.23-7.27 (2H, m, Ar), 717-7.22 (3H, m, Ar), 7.07-7.14 (1H, m, Ar), 7.05 (2H, d, *J* = 8.4 Hz, Ar), 6.98 (2H, d, *J* = 8.4 Hz, Ar), 6.95 (2H, d, *J* = 8.7 Hz, Ar), 6.77 (2H, d, *J* = 8.7 Hz, Ar), 4.47 (1H, d, *J* = 2.0 Hz, 2-H), 3.78 (3H, s, OMe), 3.67-3.73 (1H, m, 5-H_A), 3.52 (1H, td, *J* = 10.0, 6.7 Hz, 5-H_B), 3.20 (1H, d, *J* = 12.1 Hz, 6-H), 2.93 (1H, ddt, *J* = 12.1, 6.6, 2.0 Hz, 3-H), 2.52 (3H, s, Me Ts), 2.03-2.12 (1H, m, 4-H_A), 1.52 (1H, ddt, *J* = 13.2, 6.7, 2.3 Hz, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.6 (C Ar), 143.4 (C Ar), 143.0 (C Ar), 142.8 (C Ar), 135.7 (C Ar), 135.6 (C Ar), 129.8 (2 x C-H Ar), 128.82 (2 x C-H Ar), 128.75 (2 x C-H Ar), 128.5 (2 x C-H Ar), 127.8 (4 x C-H Ar), 127.1 (2 x C-H Ar), 126.9 (C-H Ar), 126.7 (C-H Ar), 113.8 (2 x C-H Ar), 66.4 (C-2), 55.4 (OMe), 54.0 (C-6), 52.9 (C-3), 47.5 (C-5), 26.9 (C-4), 21.7 (Me Ts). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H. **HRMS** (ESI): calculated for $C_{31}H_{32}NO_3S$ $[M+H]^+$ requires *m/z* 498.2103, found *m/z* 498.2097. **IR** (film) ν_{max}: 3649, 2980, 2888, 1611, 1511, 1159 cm^{-1}.

5.9.3 (±)-*N*-{2-[1-(4-methoxyphenyl)-3-phenyl-2,3-dihydro-1H-inden-2-yl]ethyl}-4-methylbenzenesulfonamide (237b')

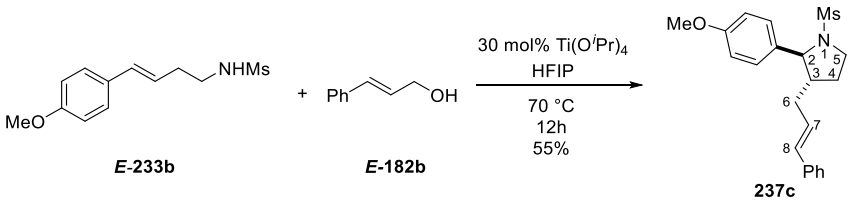


Boc-protected amine **247** (43.5 mg, 0.101 mmol), benzhydrol **182w** (18.6 mg, 0.101 mmol) and $Ti(O^iPr)_4$ (8.5 mg, 0.30 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 30% → 35% Et_2O - pentane) to yield **237b'** as a colorless oil

(37.2 mg, 92%).

Data for **237b'**: **R_f** 0.50 (70% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.40 (2H, d, *J* = 8.3 Hz, Ar), 7.32-7.36 (2H, m, Ar), 7.27-7.31 (1H, m, Ar), 7.20-7.24 (2H, m, Ar), 7.16-7.18 (2H, m, Ar), 7.15 (2H, d, *J* = 8.7 Hz, Ar), 7.10-7.12 (1H, m, Ar), 6.89 (2H, d, *J* = 8.7 Hz, Ar), 6.75-6.80 (2H, m, Ar), 3.92 (1H, d, *J* = 11.1 Hz, 5-H), 3.90 (1H, d, *J* = 10.8 Hz, 1-H), 3.85 (3H, s, OMe), 3.83 (1H, t, *J* = 6.8 Hz, NH), 2.63 (2H, qd, *J* = 7.0, 2.3 Hz, 4-H_2), 2.42-2.48 (1H, m, 2-H), 2.41 (3H, s, Me Ts). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.7 (C Ar), 146.7 (C Ar), 146.3 (C Ar), 143.4 (C Ar), 143.2 (C Ar), 136.7 (C Ar), 135.4 (C Ar), 129.9 (2 x C-H Ar), 129.6 (2 x C-H Ar), 129.0 (2 x C-H Ar), 128.9 (2 x C-H Ar), 127.2 (C-H Ar), 127.12 (C-H Ar), 127.10 (C-H Ar), 127.06 (2 x C-H Ar), 124.49 (C-H Ar), 124.46 (C-H Ar), 114.4 (2 x C-H Ar), 58.3 (C-2), 57.0 (C-5), 56.3 (C-1), 55.4 (OMe), 42.0 (C-4), 33.1 (C-3), 21.7 (Me Ts). **HRMS** (ESI): calculated for $C_{31}H_{31}NO_3SNa$ $[M+Na]^+$ requires *m/z* 520.1922, found *m/z* 520.1917. **IR** (film) ν_{max}: 3282, 2980, 2360, 1611, 1510, 1158 cm^{-1}.

5.9.4 (±)-(2*S*,3*S*)-3-cinnamyl-2-(4-methoxyphenyl)-1-(methylsulfonyl)pyrrolidine (237c)



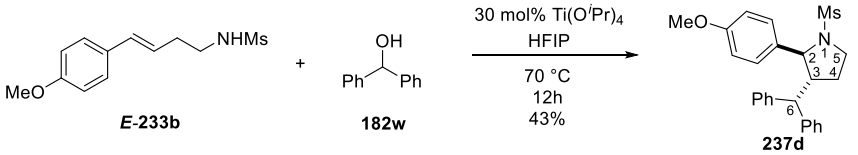
***E*-233b** ***E*-182b** **237c**

Amine ***E*-233b** (28.0 mg, 0.110 mmol), cinnamyl alcohol ***E*-182b** (14.7 mg, 0.110 mmol) and Ti(O^{i}Pr)$_4$ (9.4 mg, 0.033 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 30% → 40% Et_2O - pentane) to yield pyrrolidines **237c** as a

colorless oil (22.6 mg, 55%).

Data for **237c**: $\mathbf{R_f}$ 0.30 (80% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.26-7.30 (4H, m, Ar), 7.23-7.36 (2H, m, Ar), 7.19-7.23 (1H, m, Ar), 6.89 (2H, d, *J* = 8.7 Hz, Ar), 6.42 (1H, d, *J* = 15.8 Hz, 8-H), 6.08 (1H, dt, *J* = 15.8, 7.1 Hz, 7-H), 4.42 (1H, d, *J* = 6.3 Hz, 2-H), 3.83-3.92 (1H, m, 5-H_A), 3.80 (3H, s, OMe), 3.54 (1H, ddd, *J* = 10.3, 8.2, 6.7 Hz, 5-H_B), 2.58 (3H, s, Me Ms), 2.38-2.46 (1H, m, 6-H_A), 2.29-2.36 (1H, m, 3-H), 2.21-2.29 (1H, m, 6-H_B), 2.13-2.21 (1H, m, 4-H_A), 1.76 (1H, dd, *J* = 12.5, 8.0 Hz, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.2 (C Ar), 137.3 (C Ar), 133.7 (C Ar), 132.3 (C-8), 128.7 (2 x C-H Ar), 128.4 (2 x C-H Ar), 127.4 (C-7), 127.4 (C-H Ar), 126.2 (2 x C-H Ar), 114.2 (2 x C-H Ar), 68.2 (C-2), 55.4 (OMe), 49.9 (C-3), 48.1 (C-5), 39.7 (Me Ms), 35.9 (C-6), 30.4 (C-4). **HRMS** (ESI): calculated for $C_{21}H_{25}NO_3SNa$ $[M+Na]^+$ requires *m/z* 394.1453, found *m/z* 394.1447. **IR** (film) ν_{max}: 2980, 1511, 1462, 1381, 1246, 1147 cm^{-1}.

5.9.5 (±)-(2*S*,3*R*)-3-Benzhydryl-2-(4-methoxyphenyl)-1-(methylsulfonyl)pyrrolidine (237d)

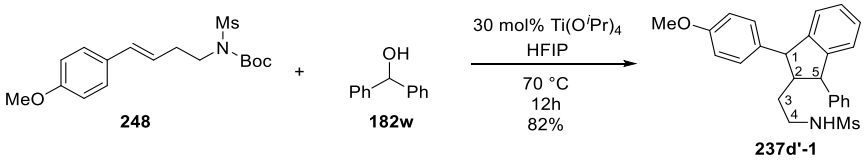


Amine ***E*-233b** (22.0 mg, 0.0863 mmol), benzhydrol **182w** (15.9 mg, 0.0863 mmol) and $Ti(O^iPr)_4$ (7.4 mg, 0.026 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 40% → 45% Et_2O - pentane) to yield pyrrolidines **237d** as a colorless oil (19.4 mg, 43%).

Data for **237d**: $\mathbf{R_f}$ 0.30 (80% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ**

7.15-7.32 (10H, m, Ar), 6.94 (2H, d, *J* = 8.7 Hz, Ar), 6.78 (2H, d, *J* = 8.7 Hz, Ar), 4.61 (1H, d, *J* = 2.4 Hz, 2-H), 3.87 (1H, d, *J* = 11.9 Hz, 6-H), 3.74-3.81 (1H, m, 5-H_A), 3.78 (3H, s, OMe), 3.61 (1H, ddd, *J* = 9.6, 8.0, 3.6 Hz, 5-H_B), 3.06 (1H, ddt, *J* = 11.9, 6.5, 3.0 Hz, 3-H), 2.62 (3H, s, Me Ms), 1.10-1.21 (1H, m, 4-H_A), 1.75 (1H, ddt, *J* = 13.5, 6.5, 3.5 Hz, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.8 (C Ar),143.1 (C Ar), 143.0 (C Ar), 135.0 (C Ar), 129.0 (2 x C-H Ar), 128.9 (2 x C-H Ar), 128.4 (2 x C-H Ar), 128.0 (2 x C-H Ar), 127.4 (2 x C-H Ar), 127.0 (C-H Ar), 126.8 (C-H Ar), 114.0 (2 x C-H Ar), 66.2 (C-2), 55.4 (OMe), 54.7 (C-6), 53.1 (C-3), 47.3 (C-5), 39.3 (Me Ms), 27.9 (C-4). **HRMS** (ESI): calculated for $C_{25}H_{27}NO_3SNa$ $[M+Na]^+$ requires *m/z* 444.1609, found *m/z* 444.1602. **IR** (film) ν_{max}: 2980, 1511, 1493, 1452, 1247, 1175 cm^{-1}.

5.9.6 (±)-*N*-{2-[1-(4-methoxyphenyl)-3-phenyl-2,3-dihydro-1H-inden-2-yl]ethyl}methanesulfonamide (237d'-1)

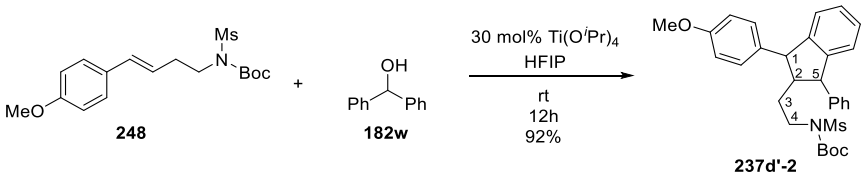


Boc-protected amine **248** (47.2 mg, 0.133 mmol), benzhydrol **182w** (24.5 mg, 0.133 mmol) and Ti(O^{i}Pr)$_4$ (11.3 mg, 0.0398 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 50% → 60% Et_2O - pentane) to yield **237d'-1** as a colorless oil (45.7 mg, 82%).

Data for **237d'-1**: **R_f** 0.40 (80% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.36-7.40 (2H, m, Ar), 7.27-7.33 (2H, m, Ar), 7.24 (2H, d, *J* = 8.6 Hz, Ar), 7.12-7.15 (2H, m, Ar), 6.93 (2H, d, *J* = 8.6 Hz, Ar), 6.79-6.84 (2H, m, Ar), 4.01 (1H, d, *J* = 10.2 Hz, 5-H), 3.98

(1H, d, *J* = 10.2 Hz, 1-H), 3.83 (3H, s, OMe), 3.75 (1H, t, *J* = 6.2 Hz, NH), 2.86 (2H, q, *J* = 6.9 Hz, 4-H_2), 2.53 (1H, tt, *J* = 10.2, 6.7 Hz, 2-H), 2.47 (3H, s, Me Ms), 1.96 (2H, q, *J* = 6.9 Hz, 3-H_2). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.8 (C Ar), 146.6 (C Ar), 146.3 (C Ar), 143.7 (C Ar), 135.5 (C Ar), 129.9 (2 x C-H Ar), 129.00 (2 x C-H Ar), 128.97 (2 x C-H Ar), 127.21 (2 x C-H Ar), 127.18 (C-H Ar), 124.50 (C-H Ar), 124.49 (C-H Ar), 114.4 (2 x C-H Ar), 58.0 (C-2), 57.2 (C-5), 56.5 (C-1), 55.4 (OMe), 41.6 (C-4), 39.9 (Me Ms), 33.4 (C-3). **HRMS** (ESI): calculated for $C_{25}H_{27}NO_3SNa$ $[M+Na]^+$ requires *m/z* 444.1609, found *m/z* 444.1595. **IR** (film) ν_{max}: 3294, 2980, 1510, 1318, 1176, 1149 cm^{-1}.

5.9.7 (±)-*tert*-Butyl{2-[1-(4-methoxyphenyl)-3-phenyl-2,3-dihydro-1H-inden-2-yl]ethyl}(methylsulfonyl)carbamate (237d'-2)

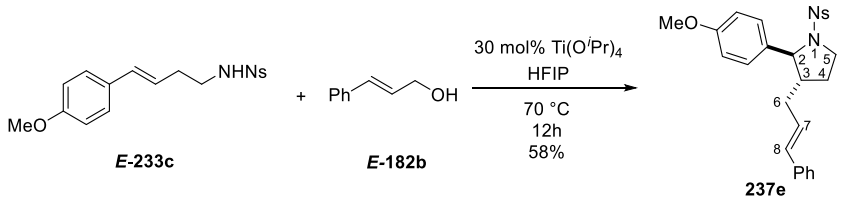


Boc-protected amine **248** (21.7 mg, 0.0611 mmol), benzhydrol **182w** (11.2 mg, 0.0611 mmol) and Ti(O^{i}Pr)$_4$ (5.2 mg, 0.018 mmol) were subjected to the general procedure **H** except conducting the reaction at room temperature (FCC: gradient elution: 20% → 30% Et_2O - pentane) to yield **237d'-2** as a colorless oil (29.3 mg, 92%).

Data for **237d'-2**: **R_f** 0.50 (60% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.34-7.39 (2H, m, Ar), 7.27-7.33 (3H, m, Ar), 7.24 (2H, d, *J* = 8.6 Hz, Ar), 7.11-7.15 (2H, m, Ar), 6.91 (2H, d, *J* = 8.6 Hz, Ar), 6.80-6.85 (2H, m, Ar), 4.03 (1H, d, *J* = 9.6 Hz, 5-H), 4.01 (1H, d, *J* = 9.4 Hz, 1-H), 3.83 (3H, s, OMe), 3.26-3.39 (2H, m, 4-H_2), 3.17 (3H, s, Me Ms),

2.43 (1H, tt, *J* = 10.2, 6.4 Hz, 2-H), 1.97-2.04 (2H, m, 3-H_2), 1.36 (9H, s, 3 x Me Boc). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.6 (C=O Boc), 151.5 (C Ar), 146.8 (C Ar), 146.4 (C Ar), 143.8 (C Ar), 135.8 (C Ar), 130.0 (2 x C-H Ar), 129.1 (2 x C-H Ar), 128.8 (2 x C-H Ar), 127.10 (C-H Ar), 127.06 (C-H Ar), 127.0 (C-H Ar), 124.59 (C-H Ar), 124.57 (C-H Ar), 114.2 (2 x C-H Ar), 84.3 (CMe_3 Boc), 59.2 (C-2), 56.8 (C-5), 56.1 (C-1), 55.4 (OMe), 45.5 (C-4), 42.3 (Me Ms), 33.3 (C-3), 28.0 (3 x Me Boc). **HRMS** (ESI): calculated for $C_{30}H_{35}NO_5SNa$ $[M+Na]^+$ requires *m/z* 544.2134, found *m/z* 544.2128. **IR** (film) ν_{max}: 2980, 2880, 1510, 1318, 1176, 1149 cm^{-1}.

5.9.8 (±)-(2*S*,3*S*)-3-Cinnamyl-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]pyrrolidine (237e)

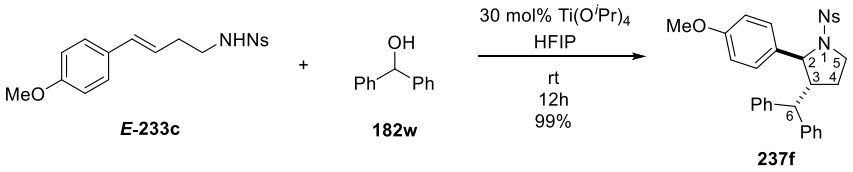


Amine ***E*-233c** (30.0 mg, 0.0829 mmol), cinnamyl alcohol ***E*-182b** (11.1 mg, 0.0829 mmol) and $Ti(O^iPr)_4$ (7.1 mg, 0.025 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 10% → 25% EtOAc - pentane) to yield pyrrolidines **237e** as a colorless oil (23.1 mg, 58%).

Data for **237e**: **R_f** 0.30 (30% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.51 (1H, dd, *J* = 7.9, 1.4 Hz, Ar), 7.43-7.48 (1H, m, Ar), 7.23-7.29 (5H, m, Ar), 7.16-7.22 (2H, m, Ar), 7.05 (2H, d, *J* = 8.7 Hz, Ar), 6.60(2H, d, *J* = 8.7 Hz, Ar), 6.35 (1H, d, *J* = 15.8 Hz, 8-H), 6.03 (1H, dt, *J* = 15.8, 7.1 Hz, 7-H), 4.49 (1H, d, *J* = 7.5 Hz, 2-H), 4.08 (1H, ddd, *J* =

10.9, 7.9, 3.1 Hz, 5-H_A), 3.75-3.82 (1H, m, 5-H_B), 3.72 (3H, s, OMe), 2.32-2.39 (1H, m, 6-H_A), 2.26-2.32 (1H, m, 3-H), 2.14-2.23 (2H, m, 4-H_A and 6-H_B), 1.75 (1H, dtd, *J* = 12.3, 9.5, 7.9 Hz, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.2 (C Ar), 147.5 (C Ar), 137.3 (C Ar), 134.1 (C Ar), 132.6 (C-H Ar), 132.3 (C-H Ar and C-8), 132.1 (C Ar), 131.1 (C-H Ar), 130.9 (C-H Ar), 128.9 (2 x C-H Ar), 128.6 (2 x C-H Ar), 127.4 (C-7), 126.2 (2 x C-H Ar), 123.6 (C-H Ar), 113.8 (2 x C-H Ar), 68.7 (C-2), 55.4 (OMe), 50.4 (C-3), 49.6 (C-5), 35.3 (C-4), 30.6 (C-6). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H_B, between 2-H and 7-H. **HRMS** (ESI): calculated for $C_{26}H_{27}N_2O_5S$ $[M+H]^+$ requires *m/z* 479.1641, found *m/z* 479.1636. **IR** (film) ν_{max}: 2980, 1541, 1511, 1371, 1289, 1159 cm^{-1}.

5.9.9 (±)-(2*S*,3*R*)-3-Benzhydryl-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]pyrrolidine (237f)



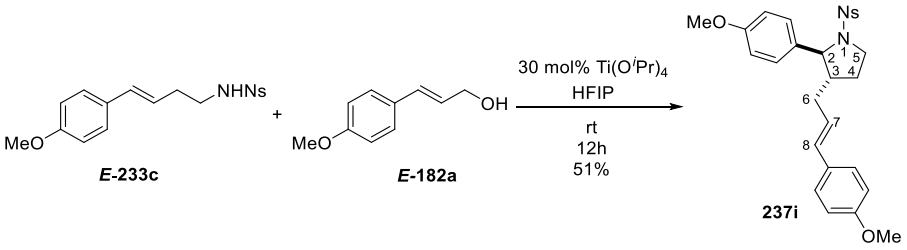
E-233c + 182w → 237f

Amine ***E*-233c** (40.0 mg, 0.110 mmol), benzhydrol **182w** (20.3 mg, 0.110 mmol) and Ti(O^{i}Pr)$_4$ (9.4 mg, 0.033 mmol) were subjected to the general procedure **H** except conducting the reaction at room temperature (FCC: gradient elution: 15% → 25% Et_2O - pentane) to yield pyrrolidines **237f** as a colorless oil (58.0 mg, 99%).

Data for **237f**: **R_f** 0.30 (50% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.47-7.55 (2H, m, Ar), 7.34 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.19-7.28 (6H, m, Ar), 7.06-7.18 (6H, m, Ar), 6.74 (2H, d, *J* = 8.7 Hz, Ar), 6.52 (2H, d, *J* = 8.7 Hz, Ar), 4.65 (1H, d, *J* = 3.6 Hz,

2-H), 3.97 (1H, dt, *J* = 10.2, 7.4 Hz, 5-H_A), 3.88 (1H, ddd, *J* = 10.2, 7.7, 5.0 Hz, 5-H_B), 3.79 (1H, d, *J* = 11.5 Hz, 6-H), 3.70 (3H, s, OMe), 3.05 (1H, m, 3-H), 3.01-3.09 (1H, m, 4-H_A), 1.72 (1h, ddt, *J* = 12.3, 7.2, 5.0 Hz, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.7 (C Ar), 147.7 (C Ar), 143.0 (C Ar), 142.9 (C Ar), 133.8 (C Ar), 133.6 (C Ar), 132.8 (C-H Ar), 131.2 (C-H Ar), 131.1 (C-H Ar), 128.9 (2 x C-H Ar),128.8 (2 x C-H Ar), 128.3 (2 x C-H Ar), 127.9 (2 x C-H Ar), 127.7 (2 x C-H Ar), 126.82 (C-H Ar), 126.81 (C-H Ar), 123.6 (C-H Ar), 113.6 (2 x C-H Ar), 67.0 (C-2). 55.4 (OMe), 54.9 (C-6), 53.6 (C-3), 48.6 (C-5), 28.3 (C-4). **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max}: 2980, 1542, 1511, 1493, 1371, 1161 cm^{-1}.

5.9.10 (±)-(2*S*,3*S*)-2-(4-Methoxyphenyl)-3-[(*E*)-3-(4-methoxyphenyl)allyl]-1-[(2-nitrophenyl)sulfonyl]pyrrolidine (237i)



Amine ***E*-233c** (40.0 mg, 0.110 mmol), alcohol ***E*-182a** (18.1 mg, 0.110 mmol) and $Ti(O^iPr)_4$ (9.4 mg, 0.033 mmol) were subjected to the general procedure **H** except conducting the reaction at room temperature (FCC: gradient elution: 20% → 23% EtOAc - pentane) to yield a 1:1.5 inseparable mixture of pyrrolidines **237i** and amine ***E*-233c** as a white solid (44.2 mg, 51%) (calculated yield based on **^{1}H NMR**).

Data for **237i** (from the mixture): **R_f** 0.50 (40% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.63-7.73 (1H, m, Ar), 7.48-7.51 (1H, m, Ar), 7.42-7.48 (1H, m, Ar),

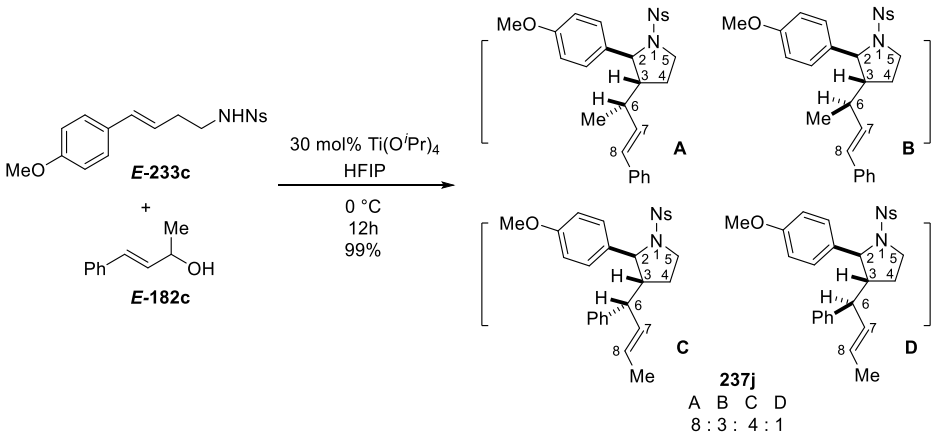
7.23-7.26 (1H, m, Ar), 7.12-7.21 (2H, m, Ar), 7.05 (2H, d, *J* = 8.6 Hz, Ar), 7.67-7.83 (2H, m, Ar), 6.60 (2H, d, *J* = 8.6 Hz, Ar), 6.28 (1H, d, *J* = 15.8 Hz, 8-H), 5.88 (1H, dt, *J* = 15.4, 7.0 Hz, 7-H), 4.49 (1H, d, *J* = 7.4 Hz, 2-H), 4.06 (1H, ddd, *J* = 10.7, 7.9, 3.2 Hz, 5-H_A), 3.79 (3H, s, OMe), 3.75-3.81 (1H, m, 5-H_A), 3.72 (3H, s, OMe), 2.30-2.35 (1H, m, 6-H_A), 2.24-2.30 (1H, m, 3-H), 2.11-2.20 (2H, m, 4-H_A and 6-H_B), 1.74 (1H, dq, *J* = 12.5, 9.0 Hz, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.2 (C Ar), 159.1 (C Ar), 148.1 (C Ar), 147.5 (C Ar), 134.11 (C Ar), 134.07 (C Ar), 132.9 (C-H Ar), 131.6 (C-8), 130.9 (C-H Ar), 129.7 (C-H Ar), 128.9 (2 x C-H Ar), 127.3 (2 x C-H Ar), 123.6 (C-H Ar), 114.1 (2 x C-H Ar), 113.7 (2 x C-H Ar), 68.7 (C-2), 55.4 (2 x OMe), 50.5 (C-3), 49.6 (C-5), 35.3 (C-4), 30.6 (C-6). **HRMS** (ESI): calculated for $C_{27}H_{29}N_2O_6S$ $[M+H]^+$ requires *m/z* 509.1746, found *m/z* 509.1744. **IR** (film) ν_{max}: 2980, 1545, 1521, 1371, 1389, 1259 cm^{-1}.

5.9.11 (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-3-[(1'*S*,2'*E*)-4-phenylbut-3-en-2-yl]pyrrolidine

(±)-(2*S*,3*R*)-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-3-[(1'*R*,2'*E*)-4-phenylbut-3-en-2-yl]pyrrolidine

(±)-(2*S*,3*R*)-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-3-[(1'*S*,2'*E*)-1-phenylbut-2-en-1-yl]pyrrolidine

(±)-(2*S*,3*R*)-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-3-[(1'*R*,2'*E*)-1-phenylbut-2-en-1-yl]pyrrolidine (237j)



Amine ***E*-233c** (40.0 mg, 0.110 mmol), alcohol ***E*-182c** (16.4 mg, 0.110 mmol) and $Ti(O^iPr)_4$ (9.4 mg, 0.033 mmol) were subjected to the general procedure **H** except conducting the reaction at 0 °C (FCC: gradient elution: 15% → 25% EtOAc - pentane) to yield an inseparable 8:3:4:1 mixture of diastereomers **A, B, C** and **D** as a colorless oil. (52.8 mg, 99%).

Data for **diastereomer A** of **237j** (from the mixture)**:** $\mathbf{R_f}$ 0.5 (40% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.00-7.52 (9H, m, Ar), 6.97 (2H, d, *J* = 8.7 Hz, Ar), 6.49 (2H, d, *J* = 8.7 Hz, Ar), 6.30 (1H, d, *J* = 15.8 Hz, 8-H), 5.72 (1H, dd, *J* = 15.8, 8.8 Hz,

7-H), 4.66 (1H, d, *J* = 7.3 Hz, 2-H), 4.00-4.10 (1H, m, 5-H_A), 3.75-3.84 (1H, m, 5-H_B), 3.68 (3H, s, OMe), 2.29-2.41 (1H, m, 6-H), 2.20-2.29 (1H, m, 3-H), 2.10-2.20 (1H, m, 4-H_A), 1.75-1.85 (1H, m, 4-H_B), 1.08 (3H, d, *J* = 6.7 Hz, Me). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.84 (C Ar), 137.2 (C Ar), 134.6 (C-7), 134.2 (C Ar), 130.05 (C Ar), 132.70 (C Ar), 132.4 (CH Ar), 130.95 (CH Ar), 130.87 (CH Ar), 129.51 (C-8), 129.45 (2 x CH Ar), 128.83 (CH Ar), 12877 (CH Ar), 128.5 (2 x CH Ar), 126.2 (2 x CH Ar), 123.45 (CH Ar), 113.6 (2 x CH Ar), 67.3 (C-2), 55.8 (C-3), 55.35 (OMe), 49.7 (C-5), 40.8 (C-6), 29.2 (C-4), 19.90 (Me). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H, between 2-H and 7-H, between 2-H and Me. **HRMS** (ESI): calculated for $C_{27}H_{29}N_2O_5S$ $[M+H]^+$ requires *m/z* 493.1797, found *m/z* 493.1792. **IR** (film) ν_{max}: 2980, 2888, 1541, 1511, 1372, 1247 cm^{-1}.

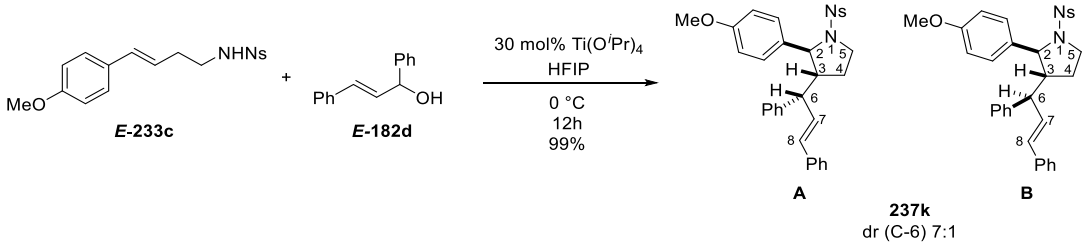
Data for **diastereomer B** of **237j** (from the mixture)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.00-7.52 (13H, m, Ar), 6.36 (1H, d, *J* = 15.8 Hz, 8-H), 6.02 (1H, dd, *J* = 15.8, 8.8 Hz, 7-H), 4.60 (1H, d, *J* = 8.0 Hz, 2-H), 3.99-4.05 (1H, m, 5-H_A), 3.75-3.84 (1H, m, 5-H_B), 3.74 (3H, s, OMe), 2.29-2.41 (1H, m, 6-H), 2.20-2.29 (1H, m, 3-H), 2.00-2.09 (1H, m, 4-H_A), 1.75-1.85 (1H, m, 4-H_B), 1.06 (3H, d, *J* = 6.7 Hz, Me). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.2 (C Ar), 147.6 (C Ar), 143.2 (C Ar), 133.9 (C Ar), 133.77 (C Ar), 131.7 (C-7), 131.1 (C-8), 128.65 (2 x CH Ar), 128.5 (CH Ar), 127.5 (CH Ar), 127.2 (2 x CH Ar), 126.7 (CH Ar), 126.3 (2 x CH Ar), 126.2 (CH Ar), 123.53 (CH Ar), 113.8 (2 x CH Ar), 66.8 (C-2), 55.7 (C-3), 55.39 (OMe), 49.5 (C-5), 37.8 (C-6), 27.2 (C-4), 19.92 (Me). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H, between 2-H and 7-H, between 2-H and Me.

Data for **diastereomer C** of **237j** (from the mixture)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.00-7.52 (11H, m, Ar), 6.65 (2H, d, *J* = 8.7 Hz, Ar), 5.30-5.44 (2H, m, 7-H and 8-H), 4.80

(1H, d, *J* = 5.1 Hz, 2-H), 3.74-3.97 (2H, m, 5-H_2), 3.74 (3H, s, OMe), 3.08-3.16 (1H, m, 6-H), 2.43-2.53 (1H, m, 3-H), 1.86-1.92 (1H, m, 4-H_A), 1.57 (4H, m, Me and 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.83 (C Ar), 147.4 (C Ar), 143.0 (C Ar), 133.65 (C Ar), 133.5 (C-7), 132.73 (CH Ar), 132.55 (C Ar), 131.4 (C-7), 131.03 (2 x CH Ar), 130.87 (CH Ar), 130.87 (CH Ar), 130.85 (2 x CH Ar), 128.9 (2 x CH Ar), 128.66 (CH Ar), 127.8 (CH Ar), 127.63 (2 x CH Ar), 126.8 (C-8), 123.50 (CH Ar), 66.9 (C-2), 55.39 (OMe), 54.7 (C-3), 52.8 (C-6), 49.0 (C-5), 28.5 (C-4), 17.9 (Me). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H, between 2-H and 7-H.

Data **diastereomer D** of **237j** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.00-7.52 (9H, m, Ar), 6.97 (2H, d, *J* = 8.7 Hz, Ar), 6.73 (2H, d, *J* = 8.7 Hz, Ar), 5.47-5.60 (2H, m, 7-H and 8-H), 4.52 (1H, d, *J* = 5.5 Hz, 2-H), 3.74-3.97 (2H, m, 5-H_2), 3.69 (3H, s, OMe), 3.08-3.16 (1H, m, 6-H), 2.43-2.53 (1H, m, 3-H), 1.94-2.00 (1H, m, 4-H_A), 1.75-1.85 (1H, m, 4-H_B), 1.68 (3H, d, *J* = 4.8 Hz, Me). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.7 (C Ar), 147.5 (C Ar), 143.2 (C Ar), 133.80 (C Ar), 133.08 (CH Ar), 132.65 (CH Ar), 132.55 (C Ar), 131.2 (2 x CH Ar), 128.70 (CH Ar), 128.1 (2 x CH Ar), 127.9 (C-8), 127.63 (2 x CH Ar), 127.61 (CH Ar), 126.6 (CH Ar), 123.53 (CH Ar), 113.5 (2 x CH Ar), 66.5 (C-2), 55.33 (OMe), 54.9 (C-3), 51.0 (C-6), 48.9 (C-5), 27.5 (C-4), 18.1 (Me). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H, between 2-H and 7-H.

5.9.12 (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-3-[(1'*S*,2'*E*)-4-phenylbut-3-en-2-yl]pyrrolidine and (±)-(2*S*,3*R*)-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-3-[(1'*R*,2'*E*)-4-phenylbut-3-en-2-yl]pyrrolidine (237k)



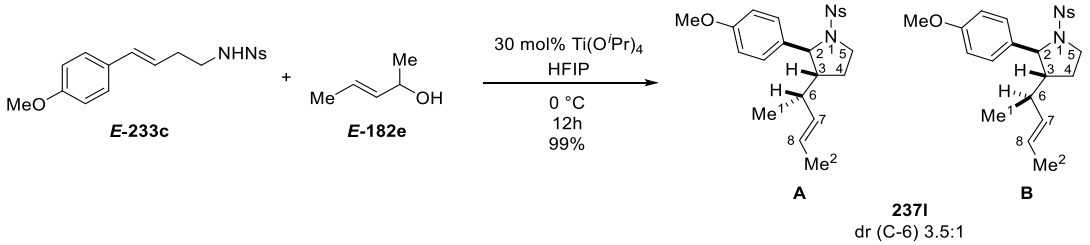
Amine ***E*-233c** (40.0 mg, 0.110 mmol), alcohol ***E*-182d** (23.2 mg, 0.110 mmol) and $Ti(O^iPr)_4$ (9.4 mg, 0.033 mmol) were subjected to the general procedure **H** except conducting the reaction at 0 °C (FCC: gradient elution: 25% → 30% EtOAc - pentane) to yield an inseparable 7:1 mixture of diastereomers **237k** as a colorless oil (60.8 mg, 99%).

Data for **diastereomer A** of **237k** (from the mixture)**:** $\mathbf{R_f}$ 0.5 (35% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.43-7.52 (2H, m, Ar), 7.13-7.33 (12H, m, Ar), 7.02 (2H, d, *J* = 8.7 Hz, Ar), 6.55 (2H, d, *J* = 8.7 Hz, Ar), 6.37 (1H, d, *J* = 15.8 Hz, 8-H), 6.04 (1H, dd, *J* = 15.8, 9.3 Hz, 7-H), 4.84 (1H, d, *J* = 5.7 Hz, 2-H), 3.97 (1H, ddd, *J* = 10.3, 7.5, 5.2 Hz, 5-H_A), 3.81 (1H, dt, *J* = 10.3, 7.5 Hz, 5-H_B), 3.70 (3H, s, OMe), 3.39 (1H, t, *J* = 9.8 Hz, 6-H), 2.64-2.71 (1H, m, 3-H), 1.89-1.97 (1H, m, 4-H_A), 1.67 (1H, dq, *J* = 12.7, 7.5 Hz, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.9 (C Ar), 147.5 (C Ar), 142.4 (C Ar), 137.0 (C Ar), 133.9 (C Ar), 133.2 (C Ar), 132.6 (CH Ar), 132.2 (C-7), 131.06 (C-8), 130.97 (2 x CH Ar), 129.1 (2 x CH Ar), 129.0 (2 x CH Ar), 128.5 (2 x CH Ar), 127.7 (2 x CH Ar), 127.5 (CH Ar), 126.94 (CH Ar), 126.42 (2 x CH Ar), 123.5 (CH Ar), 113.7 (2 x CH Ar), 67.2 (C-2), 55.39 (OMe), 55.0 (C-3), 53.5 (C-6), 49.2 (C-5), 29.1 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**:

between 2-H and 6-H, between 2-H and 7-H, between 2-H and 8-H. **HRMS** (ESI): calculated for $C_{32}H_{30}N_2O_5SNa$ $[M+Na]^+$ requires *m/z* 577.1773, found *m/z* 577.1764. **IR** (film) ν_{max}: 2980, 2888, 1541, 1511, 1372, 1159 cm^{-1}.

Data for **diastereomer B** of **237k** (from the mixture)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.43-7.52 (2H, m, Ar), 7.13-7.33 (10H, m, Ar), 7.07 (2H, d, *J* = 6.9 Hz, Ar), 6.76 (2H, d, *J* = 8.7 Hz, Ar), 6.53(2H, d, *J* = 8.7 Hz, Ar), 6.45 (1H, d, *J* = 15.7 Hz, 8-H), 6.29 (1H, dd, *J* = 15.7, 9.3 Hz, 7-H), 4.59 (1H, d, *J* = 5.3 Hz, 2-H), 4.04 (1H, ddd, *J* = 10.2, 7.4, 6.0 Hz, 5-H_A), 3.83-3.89 (1H, m, 5-H_B), 3.70 (3H, s, OMe), 3.38 (1H, d, *J* = 6.0 Hz, 6-H), 2.60-2.65 (1H, m, 3-H), 2.12-2.20 (1H, m, 4-H_A), 1.99-2.07 (1H, m, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.8 (C Ar), 147.6 (C Ar), 142.4 (C Ar), 137.0 (C Ar), 133.7 (C Ar), 133.1 (C Ar), 132.7 (CH Ar), 132.0 (C-8), 131.09 (CH Ar), 130.3 (C-7), 128.8 (2 x CH Ar), 128.7 (2 x CH Ar), 128.03 (2 x CH Ar), 128.01 (2 x CH Ar), 127.64 (CH Ar), 126.87 (CH Ar), 126.42 (CH Ar), 126.39 (2 x CH Ar), 123.5 (CH Ar), 113.6 (2 x CH Ar), 66.5 (C-2), 55.36 (OMe), 54.8 (C-3), 51.5 (C-6), 48.9 (C-5), 27.7 (C-4).

5.9.13 (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-3-[(1'*S*,2'*E*)-pent-3-en-2-yl]pyrrolidine and (±)-(2*S*,3*R*)-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-3-[(1'*R*,2'*E*)-pent-3-en-2-yl]pyrrolidine (237l)



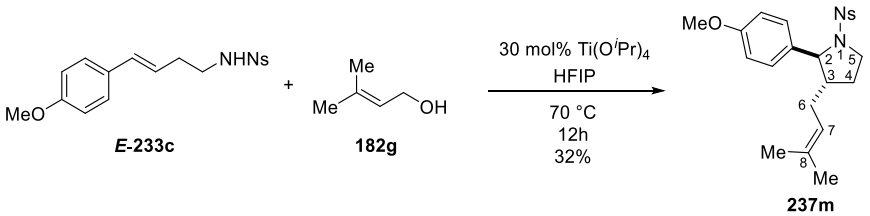
Amine ***E*-233c** (40.0 mg, 0.110 mmol), alcohol ***E*-182e** (19.1 mg, 0.220 mmol) and $Ti(O^iPr)_4$ (9.4 mg, 0.033 mmol) were subjected to the general procedure **H** except using 2 equivalents of alcohol ***E*-182e** and conducting the reaction at 0 °C (FCC: gradient elution: 10% → 15% EtOAc - pentane) to yield an inseparable 3.5:1 mixture of diastereomers **237l** as a colorless oil (47.2 mg, 99%).

Data for **diastereomer A** of **237l** (from the mixture)**:** $\mathbf{R_f}$ 0.4 (30% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.42-7.51 (2H, m, Ar), 7.16-7.24 (2H, m, Ar), 6.99 (2H, d, *J* = 8.7 Hz, Ar), 6.57 (2H, d, *J* = 8.7 Hz, Ar), 5.32 (1H, dq, *J* = 15.1, 6.3 Hz, 8-H), 4.98-5.05 (1H, m, 7-H), 4.61 (1H, d, *J* = 5.8 Hz, 2-H), 3.98 (1H, ddd, *J* = 10.6, 7.6, 3.3 Hz, 5-H_A), 3.76 (1H, ddd, *J* = 10.3, 9.2, 6.1 Hz, 5-H_B), 3.71 (3H, s, OMe), 2.04-2.14 (3H, m, 3-H, 4-H_A and 6-H), 1.71-1.81(1H, m, 4-H_B), 1.53 (3H, dd, *J* = 6.4, 1.7 Hz, Me^2), 0.93 (3H, d, *J* = 6.3 Hz, Me^1). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.8 (C Ar), 147.4 (C Ar), 135.5 (C-7), 134.15 (C Ar), 133.5 (C Ar), 132.43 (CH Ar), 130.9 (CH Ar), 130.87 (CH Ar), 129.2 (2 x CH Ar), 124.9 (C-8), 123.46 (CH Ar), 113.4 (2 x CH Ar), 67.0 (C-2), 55.5 (C-3), 55.4 (OMe), 49.6 (C-5), 39.7 (C-6), 28.6 (C-4), 18.6 (Me^1), 17.8 (Me^2). **NOESY- 2D (500 MHz, $CDCl_3$)**:

between 2-H and Me^1, between 2-H and 7-H, between 2-H and 8-H. **HRMS** (ESI): calculated for $C_{22}H_{27}N_2O_5S$ $[M+H]^+$ requires *m/z* 431.1641, found *m/z* 431.1637. **IR** (film) ν_{max}: 2980, 2888, 1541, 1511, 1372, 1159 cm^{-1}.

Data for **diastereomer B** of **237l** (from the mixture)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.42-7.51 (2H, m, Ar), 7.16-7.24 (2H, m, Ar), 7.04 (2H, d, *J* = 8.7 Hz, Ar), 6.59 (2H, d, *J* = 8.7 Hz, Ar), 5.43 (1H, dq, *J* = 15.2, 6.3 Hz, 8-H), 5.23-5.28 (1H, m, 7-H), 4.54 (1H, d, *J* = 7.8 Hz, 2-H), 3.95-4.02 (1H, m, 5-H_A), 3.73-3.79 (1H, m, 5-H_B), 3.72 (3H, s, OMe), 2.04-2.14 (2H, m, 3-H, and 6-H), 1.97 (1H, dtd, *J* = 12.1, 6.0, 2.9 Hz, 4-H_A), 1.71-1.81(1H, m, 4-H_B), 1.67 (3H, dd, *J* = 6.3, 1.6 Hz, Me^2), 0.92 (3H, d, *J* = 6.4 Hz, Me^1). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.8 (C Ar), 134.17 (C Ar), 134.15 (C Ar), 132.7 (C-7), 132.5 (C Ar), 132.47 (CH Ar), 130.89 (CH Ar), 130.85 (CH Ar), 129.0 (2 x CH Ar), 126.7 (C-8), 123.50 (CH Ar), 113.7 (2 x CH Ar), 66.8 (C-2), 55.6 (OMe), 55.4 (C-3), 49.5 (C-5), 37.0 (C-6), 26.8 (C-4), 20.2 (Me^1), 18.2 (Me^2). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and Me^1, between 2-H and 7-H, between 2-H and 8-H.

5.9.14 (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-3-[(1'*S*,2'*E*)-pent-3-en-2-yl]pyrrolidine (237m)

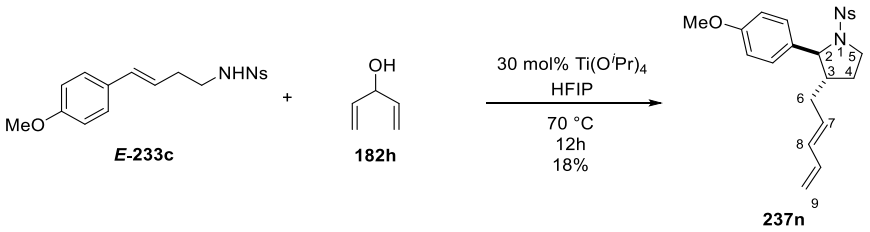


Amine ***E*-233c** (40.0 mg, 0.110 mmol), alcohol **182g** (19.0 mg, 0.220 mmol) and $Ti(O^iPr)_4$ (9.4 mg, 0.033 mmol) were subjected to the general procedure **H** except using

2 equivalents of alcohol **182g** (FCC: gradient elution: 10% → 15% EtOAc - pentane) to yield pyrrolidines **237m** as a colorless oil (15.0 mg, 32%).

Data for **237m: R_f** 0.5 (35% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.50 (1H, dd, *J* = 8.0, 1.5 Hz, Ar), 7.43-7.48 (1H, m, Ar), 7.24 (1H, dd, *J* = 8.0, 1.5 Hz, Ar), 7.16-7.20 (1H, m, Ar), 7.03 (2H, d, *J* = 8.7 Hz, Ar), 6.59 (2H, d, *J* = 8.7 Hz, Ar), 5.00 (1H, t, *J* = 7.2 Hz, 7-H), 4.42 (1H, d, *J* = 7.6 Hz, 2-H), 4.04 (1H, ddd, *J* = 10.6, 7.9, 3.1 Hz, 5-H_A), 3.72-3.80 (1H, m, 5-H_B), 3.72 (3H, s, OMe), 2.13-2.19 (1H, m, 3-H), 2.05-2.13 (2H, m, 4-H_A and 6-H_A), 1.95 (1H, dt, *J* = 15.0, 7.9 Hz, 6-H_B), 1.65-1.72 (1H, m, 4-H_B), 1.64 (3H, s, Me), 1.51 (3H, s, Me). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.1 (C Ar), 147.5 (C Ar), 134.2 (C Ar), 133.8 (C Ar), 132.5 (CH Ar), 132.4 (C-8), 131.0 (CH Ar), 130.9 (CH Ar), 128.8 (2 x CH Ar), 123.6 (CH Ar), 131.3 (C-7), 113.6 (2 x CH Ar), 68.8 (C-2), 55.4 (OMe), 50.8 (C-3), 49.6 (C-5), 30.4 (C-4), 29.9 (C-6), 25.9 (Me), 18.0 (Me). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H_B, between 2-H and 7-H. **HRMS** (ESI): calculated for $C_{22}H_{27}N_2O_5S$ $[M+H]^+$ requires *m/z* 431.1641, found *m/z* 431.1634. **IR** (film) ν_{max}: 2980, 2888, 2360, 1541, 1462, 1159, 1127 cm^{-1}.

5.9.15 (±)-(2*S*,3*S*)-2-(4-Methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-3-[(2'*E*,4'*E*)-penta-2,4-dien-1-yl]pyrrolidine (237n)

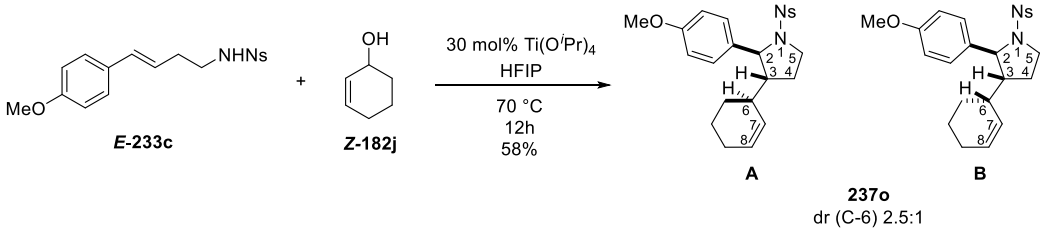


Amine ***E*-233c** (30.0 mg, 0.0828 mmol), alcohol **182h** (13.9 mg, 0.166 mmol) and

$Ti(O^iPr)_4$ (7.1 mg, 0.025 mmol) were subjected to the general procedure **H** except using 2 equivalents of alcohol **182h** (FCC: gradient elution: 10% → 15% EtOAc - pentane) to yield pyrrolidines **237n** as a colorless oil (9.8 mg, 18%).

Data for **237n:** $\mathbf{R_f}$ 0.5 (35% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.44-7.53 (2H, m, Ar), 7.17-7.25 (2H, m, Ar), 7.03 (2H, d, *J* = 8.7 Hz, Ar), 6.60 (2H, d, *J* = 8.7 Hz, Ar), 6.23 (1H, dt, *J* = 16.9, 10.3 Hz, 9-H), 6.00 (1H, dd, *J* = 15.1, 10.3 Hz, 8-H), 5.54 (1H, dt, *J* = 15.1, 7.1 Hz, 7-H), 5.09 (1H, dd, *J* = 17.0, 2.0 Hz, 10-H_A), 4.99 (1H, dd, *J* = 10.3, 2.0 Hz, 10-H_B), 4.43 (1H, d, *J* = 7.3 Hz, 2-H), 4.05 (1H, ddd, *J* = 10.8, 7.9, 3.2 Hz, 5-H_A), 3.74-3.80 (1H, m, 5-H_B), 3.73 (3H, s, OMe), 2.17-2.26 (2H, m, 3-H and 6-H_A), 2.10-2.16 (1H, m, 4-H_A), 2.00-2.09 (1H, m, 6-H_B), 1.69 (1H, dtd, *J* = 11.0, 9.4, 7.9 Hz, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.2 (C Ar), 147.5 (C Ar), 136.8 (C-9), 134.2 (C Ar), 133.4 (C-8), 132.6 (CH Ar), 132.1 (C Ar), 131.5 (C-7), 131.1 (CH Ar), 130.9 (CH Ar), 128.9 (2 x CH Ar), 123.6 (CH Ar), 116.1 (C-10), 113.7 (2 x CH Ar), 68.7 (C-2), 55.4 (OMe), 50.3 (C-3), 49.5 (C-5), 34.7 (C-6), 30.5 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H_B, between 2-H and 7-H, between 2-H and 8-H. **HRMS** (ESI): calculated for $C_{22}H_{25}N_2O_5S$ $[M+H]^+$ requires *m/z* 429.1484, found *m/z* 429.1479. **IR** (film) ν_{max}: 2980, 2889, 1542, 1374, 1249, 1161 cm^{-1}.

5.9.16 (±)-(2*S*,3*R*)-3-[(1'*R*)-cyclohex-2-en-1-yl]-2-(4-methoxyphenyl)-1-[(2-nitrophenyl) sulfonyl]pyrrolidine and (±)-(2*S*,3*R*)-3-[(1'*S*)-cyclohex-2-en-1-yl]-2-(4-methoxyphenyl)-1-[(2-nitrophenyl) sulfonyl]pyrrolidine (237o)



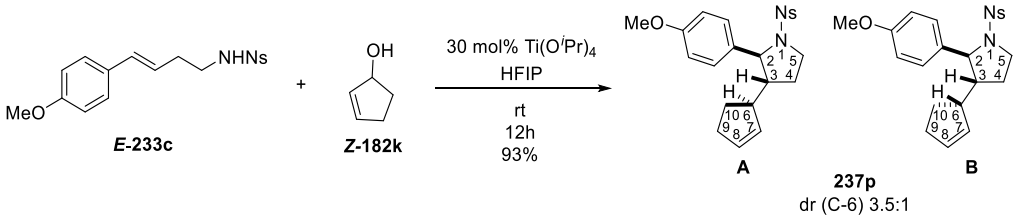
Amine ***E*-233c** (30.0 mg, 0.0828 mmol), alcohol ***Z*-182j** (8.1 mg, 0.0828 mmol) and Ti(O^{i}Pr)$_4$ (7.1 mg, 0.025 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 10% → 15% EtOAc - pentane) to yield pyrrolidine an inseparable 2.5:1 mixture of diastereomers **237o** as a colorless oil (21.4 mg, 58%).

Data for **diastereomer A** of **237o** (from the mixture)**: R_f** 0.4 (35% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.42-7.51 (2H, m, Ar), 7.14-7.23 (2H, m, Ar), 7.05 (2H, d, *J* = 8.7 Hz, Ar), 6.58 (2H, d, *J* = 8.7 Hz, Ar), 5.74-5.80 (1H, m, 8-H), 5.60 (1H, dd, *J* = 10.5, 2.3 Hz, 7-H), 4.65 (1H, d, *J* = 8.1 Hz, 2-H), 4.00-4.08 (1H, m, 5-H_A), 3.72-.379 (1H, m, 5-H_B), 3.72 (3H, s, OMe), 2.17-2.25 (1H, m, 3-H), 2.10-2.17 (1H, m, 6-H), 2.06 (1H, dtd, *J* = 12.6, 6.3, 2.7 Hz, 4-H_A), 1.88-1.96 (2H, m, CH_2 cyclohexenyl), 1.76-1.86 (1H, m, 4-H_B), 1.59-1.65 (1H, m, CH cyclohexenyl), 1.36-1.48 (2H, m, CH_2 cyclohexenyl), 1.15-1.29 (1H, m, CH cyclohexenyl). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.1 (C Ar), 147.4 (C Ar), 134.3 (C Ar), 133.01 (C Ar), 132.4 (CH Ar), 131.1 (CH Ar), 130.88 (CH Ar), 129.8 (C-8), 129.13 (2 x CH Ar), 127.6 (C-7), 123.5 (CH Ar), 113.66 (2 x CH Ar), 66.51 (C-2), 55.4 (OMe), 54.9 (C-3), 49.8 (C-5), 36.1 (C-6), 28.6 (CH_2 cyclohexenyl), 27.9 (C-4), 25.3 (CH_2 cyclohexenyl), 21.8

(CH_2 cyclohexenyl). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 7-H. **HRMS** (ESI): calculated for $C_{23}H_{27}N_2O_5S$ $[M+H]^+$ requires *m/z* 443.1641, found *m/z* 443.1635. **IR** (film) ν_{max}: 2980, 1541, 1512, 1370, 1159 cm^{-1}.

Data for **diastereomer B** of **237o** (from the mixture)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.42-7.51 (2H, m, Ar), 7.16-7.23 (2H, m, Ar), 7.06 (2H, d, *J* = 8.7 Hz, Ar), 6.59 (2H, d, *J* = 8.7 Hz, Ar), 5.62-5.66 (1H, m, 8-H), 5.39 (1H, dd, *J* = 10.2, 2.3 Hz, 7-H), 4.67 (1H, d, *J* = 8.4 Hz, 2-H), 4.00-4.08 (1H, m, 5-H_A), 3.72-.379 (1H, m, 5-H_B), 3.72 (3H, s, OMe), 2.17-2.25 (1H, m, 3-H), 2.10-2.17 (1H, m, 6-H), 2.00 (1H, dtd, *J* = 12.4, 6.6, 3.2 Hz, 4-H_A), 1.88-1.96 (2H, m, CH_2 cyclohexenyl), 1.76-1.86 (1H, m, 4-H_B), 1.68-1.76 (2H, m, 2 x CH cyclohexenyl), 1.59-1.65 (1H, m, CH cyclohexenyl), 1.15-1.29 (1H, m, CH cyclohexenyl). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.1 (C Ar), 147.4 (C Ar), 134.3 (C Ar), 133.03 (C Ar), 132.4 (CH Ar), 130.93 (CH Ar), 130.90 (CH Ar), 129.6 (C-7), 129.05 (2 x CH Ar), 128.7 (C-8), 123.5 (CH Ar), 113.72 (2 x CH Ar), 66.49 (C-2), 55.4 (OMe), 54.8 (C-3), 49.5 (C-5), 36.3 (C-6), 27.8 (C-4), 25.8 (CH_2 cyclohexenyl), 25.2 (CH_2 cyclohexenyl), 21.9 (CH_2 cyclohexenyl). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 7-H.

5.9.17 (±)-(2*S*,3*R*)-3-[(1'*R*)-cyclopent-2-en-1-yl]-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]pyrrolidine and (±)-(2*S*,3*R*)-3-[(1'*S*)-cyclopent-2-en-1-yl]-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]pyrrolidine (237p)



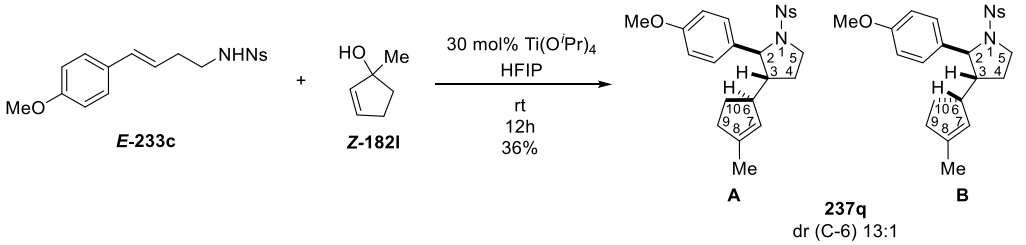
Amine ***E*-233c** (30.0 mg, 0.0828 mmol), alcohol ***Z*-182k** (13.9 mg, 0.166 mmol) and $Ti(O^iPr)_4$ (7.1 mg, 0.025 mmol) were subjected to the general procedure **H** except using 2 equivalents of alcohol ***Z*-182k** and conducting the reaction at room temperature (FCC: gradient elution: 15% → 20% EtOAc - pentane) to yield an inseparable 3.5:1 mixture of diastereomers **237p** as a colorless oil (32.9 mg, 93%).

Data for **diastereomer A** of **237p** (from the mixture)**:** $\mathbf{R_f}$ 0.4 (35% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.49 (1H, dd, *J* = 7.9, 1.4 Hz, Ar), 7.42-7.46 (1H, m, Ar), 7.15-7.23 (2H, m, Ar), 7.05 (2H, d, *J* = 8.7 Hz, Ar), 6.59 (2H, d, *J* = 8.7 Hz, Ar), 5.77-5.81 (1H, m, 8-H), 5.61-5.64 (1H, m, 7-H), 4.57 (1H, d, *J* = 7.9 Hz, 2-H), 4.03 (1H, ddd, *J* = 10.6, 7.9, 3.0 Hz, 5-H_A), 3.72-3.79 (1H, m, 5-H_B), 3.72 (3H, s, OMe), 2.66-2.74 (1H, m, 3-H), 2.14-2.28 (3H, m, 6-H and 9-H_2), 2.02-2.10 (1H, m, 4-H_A), 1.83-1.91(1H, m, 10-H_A), 1.71-1.81 (1H, m, 4-H_B), 1.23-1.33 (1H, m, 10-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.1 (C Ar), 147.4 (C Ar), 134.2 (C Ar), 132.9 (C-8), 132.84 (C Ar), 132.49 (CH Ar), 131.5 (C-7), 130.93 (CH Ar), 130.90 (CH Ar), 129.03 (2 x CH Ar), 123.53 (CH Ar), 113.6 (2 x CH Ar), 67.9 (C-2), 55.4 (OMe), 55.0 (C-6), 49.6 (C-5), 47.0 (C-3), 32.2 (C-9), 28.7 (C-10),

28.51 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 7-H. **HRMS** (ESI): calculated for $C_{22}H_{25}N_2O_5S$ $[M+H]^+$ requires *m/z* 429.1484, found *m/z* 429.1476. **IR** (film) ν_{max}: 2980, 2890, 1541, 1511, 1371, 1159 cm^{-1}.

Data for **diastereomer B** of **237p** (from the mixture)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.49 (1H, dd, *J* = 7.9, 1.4 Hz, Ar), 7.42-7.46 (1H, m, Ar), 7.15-7.23 (2H, m, Ar), 7.06 (2H, d, *J* = 8.7 Hz, Ar), 6.59 (2H, d, *J* = 8.7 Hz, Ar), 5.65-5.69 (1H, m, 8-H), 5.41-5.45 (1H, m, 7-H), 4.58 (1H, d, *J* = 8.1 Hz, 2-H), 3.99-4.05 (1H, m, 5-H_A), 3.72-3.79 (1H, m, 5-H_B), 3.72 (3H, s, OMe), 2.66-2.74 (1H, m, 3-H), 2.14-2.28 (3H, m, 6-H and 9-H_2), 2.02-2.10 (1H, m, 4-H_A), 1.94-2.01 (1H, m, 10-H_A), 1.71-1.81 (1H, m, 4-H_B), 1.48 (1H, ddt, *J* = 13.2, 8.9, 6.8 Hz, 10-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.2 (C Ar), 147.4 (C Ar), 132.84 (C Ar), 132.77 (C Ar), 132.53 (C-7), 132.49 (CH Ar), 132.0 (C-8), 130.93 (CH Ar), 130.90 (CH Ar), 129.0 (2 x CH Ar), 123.55 (CH Ar), 113.7 (2 x CH Ar), 67.7 (C-2), 55.4 (OMe), 54.7 (C-6), 49.4 (C-5), 46.8 (C-3), 32.1 (C-9), 28.47 (C-4), 26.8 (C-10). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 7-H.

5.9.18 (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-3-[(1'*R*)-3-methylcyclopent-2-en-1-yl]-1-[(2-nitrophenyl)sulfonyl]pyrrolidine and (±)-(2*S*,3*R*)-2-(4-methoxyphenyl)-3-[(1'*S*)-3-methylcyclopent-2-en-1-yl]-1-[(2-nitrophenyl)sulfonyl]pyrrolidine (237q)



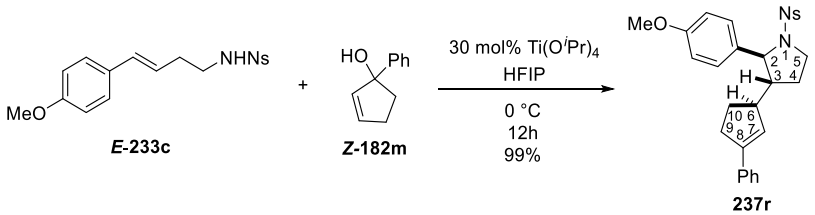
Amine ***E*-233c** (30.0 mg, 0.0828 mmol), alcohol ***Z*-182l** (16.2 mg, 0.166 mmol) and Ti(O^{i}Pr)$_4$ (7.1 mg, 0.025 mmol) were subjected to the general procedure **H** except using 2 equivalents of alcohol ***Z*-182l** and conducting the reaction at room temperature (FCC: gradient elution: 10% → 20% EtOAc - pentane) to yield an inseparable 13:1 mixture of diastereomers **237q** as a colorless oil (13.1 mg, 36%).

Data for **diastereomer A** of **237q** (from the mixture)**:** $\mathbf{R_f}$ 0.5 (25% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.42-7.51 (2H, m, Ar), 7.16-7.23 (2H, m, Ar), 7.04 (2H, d, *J* = 8.7 Hz, Ar), 6.58 (2H, d, *J* = 8.7 Hz, Ar), 5.20-5.24 (1H, m, 7-H), 4.54 (1H, d, *J* = 7.9 Hz, 2-H), 4.03 (1H, ddd, *J* = 10.7, 8.0, 3.0 Hz, 5-H_A), 3.73-3.79 (1H, m, 5-H_B), 3.72 (3H, s, OMe), 2.62-2.72 (1H, m, 6-H), 2.10-2.20 (3H, m, 3-H and 9-H_2), 2.05 (1H, dtd, *J* = 12.5, 6.2, 3.1 Hz, 4-H_A), 1.86-1.94 (1H, m, 10-H_A), 1.76 (dtd, J = 12.3, 9.8, 8.0 Hz, 4-H_B), 1.69 (1H, s, Me), 1.29-1.37 (1H, m, 10-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.1 (C Ar), 147.5 (C Ar), 142.8 (C Ar), 134.3 (C Ar), 133.0 (C-8), 132.4 (CH Ar), 131.0 (CH Ar), 130.9 (CH Ar), 129.1 (2 x CH Ar), 125.3 (C-7), 123.5 (CH Ar), 113.6 (2 x CH Ar), 67.6 (C-2), 55.4 (C-3 and OMe), 49.7 (C-5), 47.1 (C-6), 36.6 (C-9), 29.5 (C-10), 28.5 (C-4), 16.8 (Me). **NOESY- 2D**

(500 MHz, $CDCl_3$): between 2-H and 6-H, between 2-H and 7-H, between 2-H and 10-H_B. **HRMS** (ESI): calculated for $C_{23}H_{27}N_2O_5S$ $[M+H]^+$ requires *m/z* 443.1641, found *m/z* 443.1635. **IR** (film) ν_{max}: 2980, 2889, 1543, 1512, 1374, 1249 cm^{-1}.

Data for **diastereomer B** of **237q** (from the mixture)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.42-7.51 (2H, m, Ar), 7.16-7.23 (2H, m, Ar), 7.04 (2H, d, *J* = 8.7 Hz, Ar), 6.59 (2H, d, *J* = 8.7 Hz, Ar), 5.03-5.07 (1H, m, 7-H), 4.57 (1H, d, *J* = 7.9 Hz, 2-H), 4.00-4.05 (1H, m, 5-H_A), 3.73-3.79 (1H, m, 5-H_B), 3.72 (3H, s, OMe), 2.62-2.72 (1H, m, 6-H), 2.10-2.20 (3H, m, 3-H and 9-H_2), 2.02-2.08 (1H, m, 4-H_A), 1.97-2.00 (1H, m, 10-H_A), 1.72-1.81 (1H, m, 4-H_B), 1.64 (1H, s, Me), 1.29-1.37 (1H, m, 10-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.1 (C Ar), 147.5 (C Ar), 141.9 (C Ar), 134.3 (C Ar), 133.0 (C-8), 132.4 (CH Ar), 131.0 (CH Ar), 130.9 (CH Ar), 129.0 (2 x CH Ar), 126.3 (C-7), 123.5 (CH Ar), 113.7 (2 x CH Ar), 67.7 (C-2), 55.0 (C-3 and OMe), 49.4 (C-5), 46.9 (C-6), 36.4 (C-9), 28.4 (C-10), 27.7 (C-4), 16.8 (Me). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 7-H.

5.9.19 (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl)-3-[(1'*R*)-3-phenylcyclopent-2-en-1-yl]pyrrolidine (237r)

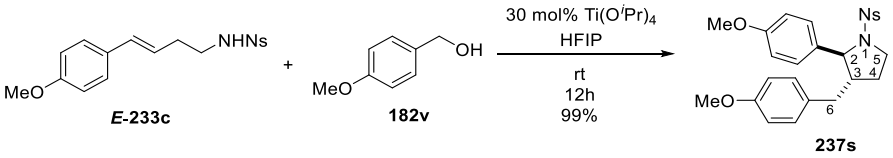


Amine ***E*-233c** (31.0 mg, 0.0856 mmol), alcohol ***Z*-182m** (13.7 mg, 0.0856 mmol) and $Ti(O^iPr)_4$ (7.3 mg, 0.026 mmol) were subjected to the general procedure **H** except conducting the reaction at 0 °C (FCC: gradient elution: 15% → 20% EtOAc - pentane) to

yield pyrrolidines **237r** as a colorless oil (43.1 mg, 99%).

Data for **237r:** $\mathbf{R_f}$ 0.4 (35% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.53 (1H, dd, *J* = 7.9, 1.4 Hz, Ar), 7.45-7.50 (1H, m, Ar), 7.38-7.42 (2H, m, Ar), 7.31-7.36 (2H, m, Ar), 7.24-7.28 (2H, m, Ar), 7.19-7.23 (1H, m, Ar), 7.10 (2H, d, *J* = 8.7 Hz, Ar), 6.62 (2H, d, *J* = 8.7 Hz, Ar), 6.07 (1H, q, *J* = 2.0 Hz, 7-H), 4.67 (1H, d, *J* = 8.0 Hz, 2-H), 4.09 (1H, ddd, *J* = 10.7, 8.0, 2.9 Hz, 5-H_A), 3.79-3.85 (1H, m, 5-H_B), 3.75 (3H, s, OMe), 2.93-3.00 (1H, m, 6-H), 2.61-2.72 (2H, m, 9-H_2), 2.35 (1H, ddt, *J* = 10.1, 8.0, 6.5 Hz, 3-H), 2.13-2.19 (1H, m, 4-H_A), 2.09 (1H, ddt, *J* = 13.2, 8.4, 4.2 Hz, 10-H_A), 1.82-1.91 (1H, m, 4-H_B), 1.54 (1H, ddt, *J* = 13.3, 8.6, 6.9 Hz, 10-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.2 (C Ar), 147.4 (C Ar), 144.2 (C Ar), 136.2 (C Ar), 134.2 (C Ar), 132.9 (C-8), 132.5 (CH Ar), 131.0 (CH Ar), 130.9 (CH Ar), 129.1 (2 x CH Ar), 128.4 (CH Ar), 127.5 (C-7), 126.5 (2 x CH Ar), 125.8 (CH Ar), 123.6 (2 x CH Ar), 113.7 (2 x CH Ar), 67.8 (C-2), 55.4 (OMe), 55.1 (C-3), 49.7 (C-5), 47.6 (C-6), 32.9 (C-9), 22.8 (C-10), 28.7 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H, between 2-H and 7-H, between 2-H and 10-H_A, between 2-H and 10-H_B. **HRMS** (ESI): calculated for $C_{28}H_{29}N_2O_5S$ $[M+H]^+$ requires *m/z* 505.1797, found *m/z* 505.1792. **IR** (film) ν_{max}: 2980, 2889, 1729, 1514, 1369, 1150 cm^{-1}.

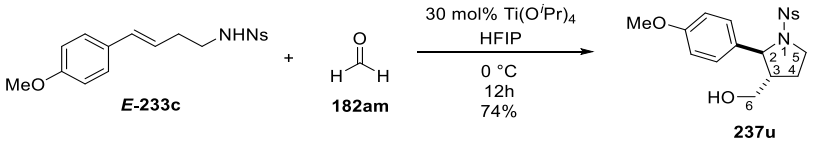
5.9.20 (±)-(2*S*,3*R*)-2-(4-Methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl)-3-[(1'*R*)-3-phenylcyclopent-2-en-1-yl]pyrrolidine (237s)



Amine ***E*-233c** (40.0 mg, 0.110 mmol), alcohol **182v** (15.0 mg, 0.110 mmol) and Ti(O^{i}Pr)$_4$ (9.4 mg, 0.033 mmol) were subjected to the general procedure **H** except conducting the reaction at room temperature (FCC: gradient elution: 15% → 25% EtOAc - pentane) to yield pyrrolidines **237s** as a colorless oil (53.0 mg, 99%).

Data for **237s:** **R_f** 0.45 (40% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.45-7.53 (2H, m, Ar), 7.24-7.27 (1H, m, Ar), 7.18-7.23 (1H, m, Ar), 7.00 (2H, d, *J* = 8.6 Hz, Ar), 6.95 (2H, d, *J* = 8.6 Hz, Ar), 6.78 (2H, d, *J* = 8.6 Hz, Ar), 6.60 (2H, d, *J* = 8.6 Hz, Ar), 4.48 (1H, d, *J* = 7.4 Hz, 2-H), 4.05 (1H, ddd, *J* = 11.9, 8.9, 3.5 Hz, 5-H_A), 3.77 (3H, s, OMe), 3.71-3.76 (1H, m, 5-H_B), 3.73 (3H, s, OMe), 2.69 (1H, dd, *J* = 13.4, 5.2 Hz, 6-H_A), 2.45 (1H, dd, *J* = 13.5, 9.2 Hz, 6-H_B), 2.32-2.41 (1H, m, 3-H), 2.00 (1H, dtd, *J* = 12.2, 6.1, 3.6 Hz, 4-H_A), 1.71 (1H, dq, *J* = 12.3, 8.9 Hz, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.2 (C Ar), 158.2 (C Ar), 147.5 (C Ar), 134.1 (C Ar), 132.6 (CH Ar), 132.1 (C Ar), 131.5 (C Ar), 131.0 (CH Ar), 130.9 (CH Ar), 129.9 (2 x CH Ar), 128.7 (2 x CH Ar), 123.6 (CH Ar), 114.0 (2 x CH Ar), 113.7 (2 x CH Ar), 68.5 (C-2), 55.40 (OMe), 55.37 (OMe), 52.3 (C-3), 49.4 (C-5), 37.0 (C-6), 30.3 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H_A, between 2-H and 6-H_B. **HRMS** (ESI): calculated for $C_{25}H_{27}N_2O_5S$ $[M+H]^+$ requires *m/z* 483.1590, found *m/z* 483.1585. **IR** (film) ν_{max}: 2980, 2890, 1514, 1510, 1244 cm^{-1}.

5.9.21 (±)-{(2*S*,3*S*)-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]pyrrolidin-3-yl}methanol (237u)



Amine ***E*-233c** (25.8 mg, 0.0713 mmol), paraformaldehyde **182am** (43.2 mg, 1.43 mmol) and $Ti(O^iPr)_4$ (6.1 mg, 0.021 mmol) were subjected to the general procedure **H** except using 20 equivalents of paraformaldehyde **182am** and conducting the reaction at 0 °C (FCC: gradient elution: 20% → 30% EtOAc - pentane) to yield pyrrolidines **237u** as a colorless oil (20.4 mg, 74%).

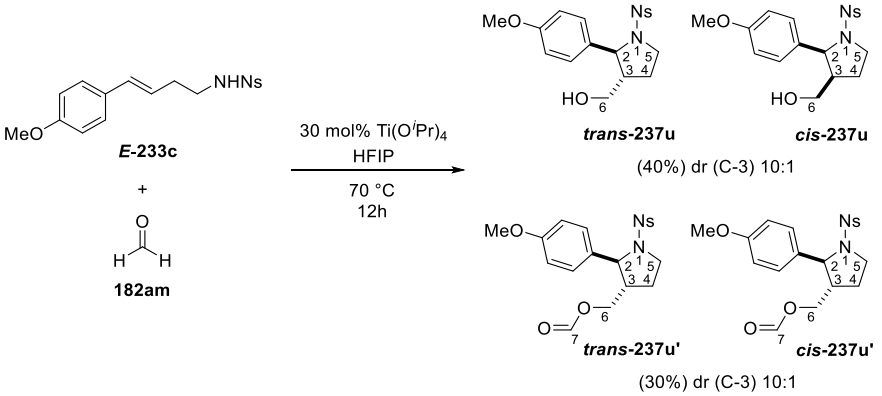
Data for **237u:** $\mathbf{R_f}$ 0.20 (30% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.46-7.53 (2H, m, Ar), 7.34 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.22-7.27 (1H, m, Ar), 7.07 (2H, d, *J* = 8.7 Hz, Ar), 6.62 (2H, d, *J* = 8.7 Hz, Ar), 4.70 (1H, d, *J* = 6.9 Hz, 2-H), 3.99 (1H, ddd, *J* = 10.3, 8.0, 4.2 Hz, 5-H_A), 3.76-3.84 (1H, m, 5-H_B), 3.72 (3H, s, OMe), 3.59-3.64 (1H, m, 6-H_A), 3.53-3.59 (1H, m, 6-H_B), 2.33-2.41 (1H, m, 3-H), 2.10-2.19 (1H, m, 4-H_A), 1.85 (1H, dq, *J* = 12.5, 8.4 Hz, 4-H_B), 1.60 (1H, br s, OH). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.2 (C Ar), 147.5 (C Ar), 133.8 (C Ar), 132.8 (CH Ar), 132.6 (C Ar), 131.07 (CH Ar), 131.05 (CH Ar), 128.5 (2 x CH Ar), 123.7 (CH Ar), 113.8 (2 x CH Ar), 65.7 (C-2), 63.0 (C-6), 55.4 (OMe), 52.3 (C-3), 49.4 (C-5), 27.7 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H_A, between 2-H and 6-H_B. **HRMS** (ESI): calculated for $C_{18}H_{20}N_2O_6SNa$ $[M+Na]^+$ requires *m/z* 415.0940, found *m/z* 415.0925. **IR** (film) ν_{max}: 3649, 2980, 2888, 2360, 1382, 1154 cm^{-1}.

5.9.22 (±)-{(2*S*,3*S*)-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]pyrrolidin-3-yl}methanol (*trans*-237u)

(±)-{(2*S*,3*R*)-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]pyrrolidin-3-yl}methanol (*cis*-237u)

(±)-{(2*S*,3*S*)-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]pyrrolidin-3-yl}methyl formate (*trans*-237u')

(±)-{(2*S*,3*S*)-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]pyrrolidin-3-yl}methyl formate (*cis*-237u')



Amine ***E*-233c** (20.0 mg, 0.0552 mmol), paraformaldehyde **182am** (33.5 mg, 1.10 mmol) and Ti(O^{i}Pr)$_4$ (4.7 mg, 0.017 mmol) were subjected to the general procedure **H** except using 20 equivalents of paraformaldehyde **182am** (FCC: gradient elution: 20% → 30% EtOAc - pentane) to yield pyrrolidines **237u** (8.4 mg, 30%, *trans*:*cis* = 10:1) and **7u'** (8.6 mg, 40%, *trans*:*cis* = 10:1) as colorless oil.

Data for ***trans*-237u** matched those previously reported.

Data for ***cis*-237u** (from the mixture)**: R_f** 0.20 (30% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.45-7.58 (2H, m, Ar), 7.22-7.27 (2H, m, Ar), 7.02-7.04 (2H, m, Ar),

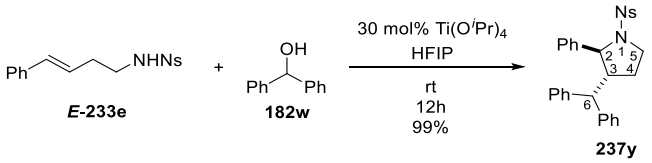
6.67 (2H, d, *J* = 8.7 Hz, Ar), 5.14 (1H, d, *J* = 8.2 Hz, 2-H), 3.95-4.04 (1H, m, 5-H_A), 3.76-3.84 (1H, m, 5-H_B), 3.72 (3H, s, OMe), 3.24-3.31 (1H, m, 6-H_A), 3.15-3.22 (1H, m, 6-H_B), 2.64-2.73 (1H, m, 3-H), 2.08 (1H, dt, *J* = 13.5, 6.8 Hz, 4-H_A), 1.87-1.93 (1H, m, 4-H_B), 1.48 (1H, br s, OH). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.2 (C Ar), 147.6 (C Ar), 133.1 (C Ar), 131.3 (CH Ar), 131.1 (2 x CH Ar), 130.2 (C Ar), 128.7 (2 x CH Ar), 123.6 (CH Ar), 113.80 (2 x CH Ar), 64.4 (C-2), 62.2 (C-6), 55.39 (OMe), 48.5 (C-5), 47.1 (C-3), 26.4 (C-4). **NOESY-2D (500 MHz, $CDCl_3$)**: between 2-H and 3-H. **HRMS** (ESI): calculated for $C_{18}H_{20}N_2O_6SNa$ $[M+Na]^+$ requires *m/z* 415.0940, found *m/z* 415.0925.

Data for ***trans*-237u'** (from the mixture)**: R_f** 0.40 (30% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.00 (1H, s, 7-H), 7.46-7.53 (2H, m, Ar), 7.29 (1H, dd, *J* = 8.0, 1.4 Hz, Ar), 7.20-7.25 (1H, m, Ar), 7.06 (2H, d, *J* = 8.7 Hz, Ar), 6.62 (2H, d, *J* = 8.7 Hz, Ar), 4.67 (1H, d, *J* = 7.6 Hz, 2-H), 4.08-4.16 (2H, m, 6-H_2), 4.05 (1H, ddd, *J* = 10.5, 8.0, 3.6 Hz, 5-H_A), 3.83 (1H, ddd, *J* = 10.3, 9.0, 6.5 Hz, 5-H_B), 3.73 (3H, s, OMe), 2.49-2.58 (1H, m, 3-H), 2.13-2.21 (1H, m, 4-H_A), 1.88 (1H, dtd, *J* = 12.5, 9.0, 8.0 Hz, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 160.75 (C=O), 159.5 (C Ar), 147.5 (C Ar), 133.8 (C Ar), 132.9 (CH Ar), 131.5 (C Ar), 131.09 (CH Ar), 131.05 (CH Ar), 128.6 (2 x CH Ar), 123.8 (CH Ar), 113.9 (2 x CH Ar), 65.7 (C-2), 63.2 (C-6), 55.45 (OMe), 49.3 and 49.1 (C-3 and C-5), 28.0 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H_A, between 2-H and 6-H_B. **HRMS**: stable ion was not found in ESI, EI and CI. **IR** (film) ν_{max}: 2980, 2889, 1723, 1542, 1375, 1161 cm^{-1}.

Data for ***cis*-237u'** (from the mixture)**: R_f** 0.40 (30% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.00 (1H, s, 7-H), 7.46-7.53 (2H, m, Ar), 7.27-7.30 (1H, m Ar), 7.20-7.25 (1H, m, Ar), 7.02-7.07 (2H, m, Ar), 6.59-6.64 (2H, m, Ar), 4.69(1H, d, *J* = 7.2 Hz,

2-H), 4.02-4.07 (1H, m, 5-H_A), 3.79-3.86 (1H, m, 5-H_B), 3.73 (3H, s, OMe), 3.40-3.50 (2H, m, 6-H_2), 2.38-2.46 (1H, m, 3-H), 2.13-2.21 (1H, m, 4-H_A), 1.82-1.93 (1H, m, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 160.75 (C=O), 159.5 (C Ar), 147.5 (C Ar), 133.8 (C Ar), 132.7 (CH Ar), 131.5 (C Ar), 131.05 (CH Ar), 130.6 (CH Ar), 128.6 (2 x CH Ar), 123.6 (CH Ar),113.8 (2 x CH Ar), 67.5 (C-6), 65.7 (C-2), 55.48 (OMe), 50.3 (C-3), 49.5 (C-5), 28.2 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 3-H.

5.9.23 (±)-(2*S*,3*R*)-3-Benzhydryl-1-[(2-nitrophenyl)sulfonyl]-2-phenylpyrrolidine (237y)

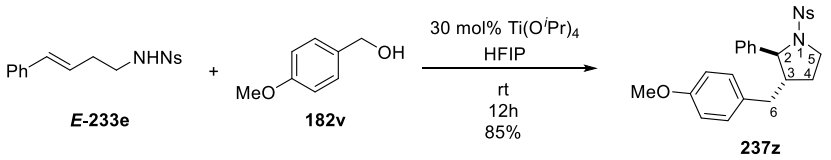


Amine ***E*-233e** (41.2 mg, 0.124 mmol), alcohol **182w** (23.6 mg, 0.124 mmol) and $Ti(O^iPr)_4$ (10.9 mg, 0.037 mmol) were subjected to the general procedure **H** except conducting the reaction at room temperature (FCC: gradient elution: 8% → 16% EtOAc - pentane) to yield pyrrolidines **237y** as a colorless oil (61.2 mg, 99%).

Data for **237y: R_f** 0.50 (30% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.46-7.53 (2H, m, Ar), 7.34 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.22-7.27 (4H, m, Ar), 7.08-7.21 (7H, m, Ar), 6.97-7.04 (3H, m, Ar), 6.80-6.84 (2H, m, Ar), 4.71 (1H, d, *J* = 3.2 Hz, 2-H), 3.99 (1H, dt, *J* = 10.1, 7.6 Hz, 5-H_A), 3.91 (1H, ddd, *J* = 10.1, 7.8, 4.7 Hz, 5-H_B), 3.80 (1H, d, *J* = 11.7 Hz, 6-H), 3.04-3.12 (1H, m, 3-H), 2.08-2.17 (1H, m, 4-H_A), 1.73 (1H, m, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 147.7 (C Ar), 142.92 (C Ar), 142.86 (C Ar), 141.6 (C Ar), 133.3 (C Ar), 133.0 (CH Ar), 131.14 (CH Ar), 131.07 (CH Ar), 128.9 (2 x CH Ar), 128.8 (2 x CH Ar), 128.3 (2 x CH Ar), 128.2 (2 x CH Ar), 127.9 (2 x CH Ar), 127.1 (CH Ar), 126.83 (CH Ar),

126.79 (CH Ar), 126.4 (2 x CH Ar), 123.6 (CH Ar), 67.3 (C-2), 54.8 (C-6), 53.6 (C-3), 48.6 (C-5), 28.0 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H. **HRMS** (ESI): calculated for $C_{29}H_{27}N_2O_4S$ $[M+H]^+$ requires *m/z* 499.1692, found *m/z* 499.1684. **IR** (film) ν_{max}: 2980, 2890, 2360, 1710, 1542, 1164 cm^{-1}.

5.9.24 (±)-(2*S*,3*S*)-3-(4-Methoxybenzyl)-1-[(2-nitrophenyl)sulfonyl]-2-phenylpyrrolidine (237z)

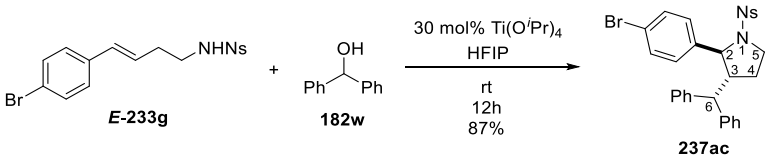


Amine ***E*-233e** (72.0 mg, 0.224 mmol), alcohol **182v** (30.9 mg, 0.224 mmol) and $Ti(O^iPr)_4$ (19.1 mg, 0.067 mmol) were subjected to the general procedure E except conducting the reaction at room temperature (FCC: gradient elution: 10% → 20% EtOAc - pentane) to yield pyrrolidines **237z** as a colorless oil (86.1 mg, 85%).

Data for **237z: R_f** 0.50 (35% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.51 (1H, dd, *J* = 8.0, 1.5 Hz, Ar), 7.43-7.48 (1H, m, Ar), 7.26 (1H, dd, *J* = 8.0, 1.5 Hz, Ar) 7.14-7.20 (1H, m, Ar), 7.04-7.10 (5H, m, Ar), 6.96 (2H, d, *J* = 8.7 Hz, Ar), 6.78 (2H, d, *J* = 8.7 Hz, Ar), 4.56 (1H, d, *J* = 6.8 Hz, 2-H), 4.06 (1H, ddd, *J* = 10.3, 7.7, 4.1 Hz, 5-H_A), 3.77-3.82 (1H, m, 5-H_B), 3.77 (OMe), 2.71 (1H, dd, *J* = 13.3, 5.5 Hz, 6-H_A), 2.48 (1H, dd, *J* = 13.3, 9.0 Hz, 6-H_B), 2.35-2.43 (1H, m, 3-H), 1.97-2.06 (1H, m, 4-H_A), 1.72 (1H, dq, *J* = 12.3, 7.7 Hz, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 158.2 (C Ar), 147.5 (C Ar), 140.4 (C Ar), 133.8 (C Ar), 132.8 (CH Ar), 131.4 (C Ar), 131.0 (CH Ar), 130.9 (CH Ar), 129.9 (2 x CH Ar), 128.3 (2 x CH Ar), 127.6 (CH Ar), 127.3 (2 x CH Ar), 123.6 (CH Ar), 114.0 (2 x CH Ar), 68.8

(C-2), 55.3 (OMe), 52.4 (C-3), 49.5 (C-5), 37.1 (C-6), 30.2 (C-4). **HRMS** (ESI): calculated for $C_{24}H_{24}N_2O_5SNa$ $[M+Na]^+$ requires *m/z* 475.1304, found *m/z* 475.1295. **IR** (film) ν_{max}: 3029, 2918, 1710, 1542, 1359, 1161 cm^{-1}.

5.9.25 (±)-(2*S*,3*R*)-3-Benzhydryl-2-(4-bromophenyl)-1-[(2-nitrophenyl)sulfonyl]pyrrolidine (237ac)

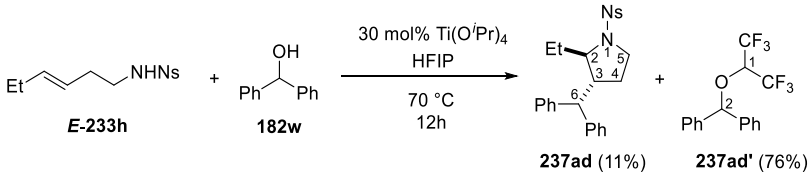


Amine ***E*-233g** (15.5 mg, 0.0378 mmol), alcohol **182w** (7.0 mg, 0.038 mmol) and $Ti(O^iPr)_4$ (3.3 mg, 0.011 mmol) were subjected to the general procedure **H** except conducting the reaction at room temperature (FCC: gradient elution: 10% → 20% EtOAc - pentane) to yield pyrrolidines **237ac** as a colorless oil (19.0 mg, 87%).

Data for **237ac:** $\mathbf{R_f}$ 0.40 (25% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.52-7.58 (2H, m, Ar), 7.33-7.37 (1H, m, Ar), 7.21-7.29 (5H, m, Ar), 7.12-7.19 (4H, m, Ar), 7.05-7.10 (4H, m, Ar), 6.67 (2H, d, *J* = 8.4 Hz, Ar), 4.64 (1H, d, *J* = 3.8 Hz, 2-H), 3.98 (1H, dt, *J* = 10.2, 7.4 Hz, 5-H_A), 3.88 (1H, ddd, *J* = 10.2, 7.6, 5.2 Hz, 5-H_B), 3.79 (1H, d, *J* = 11.7 Hz, 6-H), 3.02-3.09 (1H, m, 3-H), 2.05-2.14 (1H, m, 4-H_A), 1.74 (1H, ddt, *J* = 12.6, 7.2, 5.4 Hz, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 147.7 (C Ar), 142.74 (C Ar), 142.67 (C Ar), 140.8 (C Ar), 133.3 (C Ar), 133.1 (CH Ar), 131.3 (CH Ar), 131.2 (2 x CH Ar), 131.1 (CH Ar), 129.0 (2 x CH Ar),128.8 (2 x CH Ar), 128.4 (2 x CH Ar), 128.3 (2 x CH Ar), 127.8 (2 x CH Ar), 127.0 (CH Ar), 126.9 (CH Ar), 123.7 (CH Ar), 121.0 (C Ar), 67.0 (C-2), 55.2 (C-6), 53.8 (C-3), 48.9 (C-5), 28.6 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H. **HRMS** (ESI):

calculated for $C_{29}H_{26}N_2O_4S$ $[M+H]^+$ requires *m/z* 577.0797, found *m/z* 577.0791. **IR** (film) ν_{max}: 2922, 1709, 1543, 1359, 1163, 1221 cm^{-1}.

5.9.26 (±)-(2*R*,3*R*)-3-Benzhydryl-2-ethyl-1-[(2-nitrophenyl)sulfonyl]pyrrolidine (237ad) and {[(1,1,1,3,3,3-hexafluoropropan-2-yl)oxy]methylene}dibenzene (237ad')



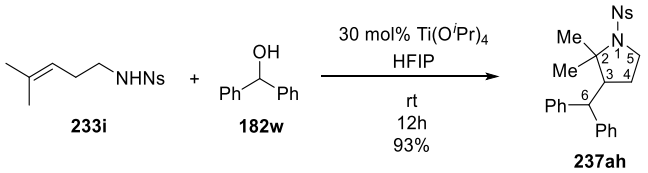
Amine ***E*-233h** (40.5 mg, 0.142 mmol), alcohol **182w** (26.2 mg, 0.142 mmol) and $Ti(O^iPr)_4$ (12.2 mg, 0.0428 mmol) were subjected to the general procedure E (FCC: gradient elution: 3% → 5% EtOAc - pentane) to yield two products: an inseparable 9:1 mixture of pyrrolidines **237ad** and amine starting material ***E*-233h** (7.0 mg, 11%), and side product **237ad'** (37.1 mg, 76%)

Data for **237ad** (from the mixture)**: R_f** 0.30 (5% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.94 (1H, dd, *J* = 8.1, 1.3 Hz, Ar), 7.83-7.87 (1H, m, Ar), 7.61-7.67 (2H, m, Ar), 7.09-7.33 (8H, m, Ar), 6.91-6.96 (2H, m, Ar), 3.65-6.69 (1H, m, 5-H_A), 3.54 (1H, ddd, *J* = 9.0, 4.0, 1.5 Hz, 2-H), 3.49 (1H, ddd, *J* = 10.2, 8.4, 3.5 Hz, 5-H_B), 3.40 (1H, d, *J* = 12.1 Hz, 6-H), 2.84-2.91 (1H, m, 3-H), 1.99-2.05 (1H, m, 4-H_A), 1.53-1.57 (1H, m, 4-H_A), 1.42-1.57 (2H, m, CH_2 Et), 0.74 (3H, t, *J* = 7.5 Hz, CH_3 Et). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 148.5 (C Ar), 143.2 (C Ar), 143.0 (C Ar), 133.9 (C Ar), 133.5 (CH Ar), 131.6 (CH Ar), 131.2 (CH Ar), 128.8 (2 x CH Ar), 128.7 (2 x CH Ar), 128.1 (2 x CH Ar), 128.0 (2 x CH Ar), 126.72 (CH Ar), 126.69 (CH Ar), 124.0 (CH Ar), 65.3 (C-2), 54.0 (C-6), 47.3 (C-5), 46.8 (C-3), 28.3 (CH_2 Et),

27.8 (C-4), 10.5 (CH_3 Et).

Data for **237ad': R_f** 0.50 (5% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.27-7.46 (10H, m, Ar), 5.83 (1H, s, 2-H), 4.17 (1H, hept, *J* = 5.9 Hz, 1-H). **HRMS** (EI): calculated for $C_{16}H_{16}F_6O$ $[M]^+$ requires *m/z* 334.0787, found *m/z* 334.0792. Spectroscopic properties matched those previously reported.[52]

5.9.27 (±)-3-Benzhydryl-2,2-dimethyl-1-[(2-nitrophenyl)sulfonyl]pyrrolidine (237ah)



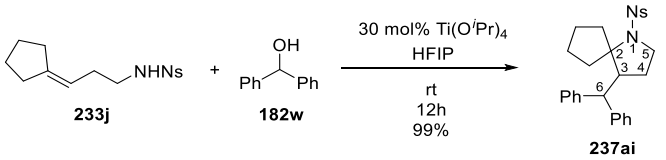
233i **182w** **237ah**

Amine **233i** (29.1 mg, 0.102 mmol), alcohol **182w** (18.9 mg, 0.102 mmol) and Ti(O^{i}Pr)$_4$ (8.7 mg, 0.031 mmol) were subjected to the general procedure **H** except conducting the reaction at room temperature (FCC: gradient elution: 15% → 20% EtOAc - pentane) to yield pyrrolidines **237ah** as a colorless oil (42.7 mg, 93%).

Data for **237ah: R_f** 0.30 (35% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.01 (1H, dd, *J* = 7.6, 1.7 Hz, Ar), 7.59-7.67 (2H, m, Ar), 7.57 (1H, dd, *J* = 7.1, 2.1 Hz, Ar), 7.30-7.35 (4H, m, Ar), 7.20-7.29 (4H, m, Ar), 7.10-7.17 (2H, m, Ar), 3.74 (1H, d, *J* = 11.5 Hz, 6-H), 3.56 (1H, td, *J* = 9.6, 2.1 Hz, 5-H_A), 3.33 (td, *J* = 9.6, 7.7 Hz, 5-H_B), 2.94 (1H, td, *J* = 11.5, 6.5 Hz, 3-H), 1.71-1.79 (1H, m, 4-H_A), 1.55 (3H, s, Me), 1.48-1.58 (1H, m, 4-H_B), 1.40 (3H, s, Me). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 148.3 (C Ar), 144.1 (C Ar), 142.8 (C Ar), 135.8 (C Ar), 133.3 (CH Ar), 131.5 (CH Ar), 130.4 (CH Ar), 128.9 (2 x CH Ar), 128.8 (2 x CH Ar), 128.3 (2 x CH Ar), 127.8 (2 x CH Ar), 126.9 (CH Ar), 126.7 (CH Ar), 123.9 (CH Ar), 68.6

(C-2), 53.9 (C-6), 53.4 (C-3), 47.0 (C-5), 28.5 (C-4), 27.5 (Me), 22.2 (Me). **HRMS** (ESI): calculated for $C_{25}H_{26}N_2O_4SNa$ $[M+Na]^+$ requires *m/z* 473.1511, found *m/z* 473.1506. **IR** (film) ν_{max}: 2980, 1542, 1370, 1337, 1216, 1159 cm^{-1}.

5.9.28 (±)- 4-Benzhydryl-1-[(2-nitrophenyl)sulfonyl]-1-azaspiro[4.4]nonane (237ai)

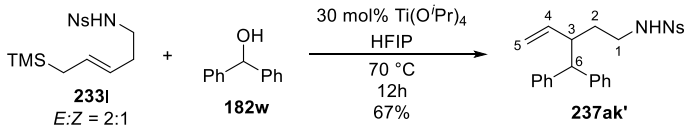


Amine **233j** (32.4 mg, 0.105 mmol), alcohol **182w** (19.2 mg, 0.105 mmol) and $Ti(O^iPr)_4$ (8.9 mg, 0.032 mmol) were subjected to the general procedure **H** except conducting the reaction at room temperature (FCC: gradient elution: 15% → 25% EtOAc - pentane) to yield pyrrolidines **237ai** as a colorless oil (49.8 mg, 99%).

Data for **237ai:** $\mathbf{R_f}$ 0.30 (30% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.00-8.05 (1H, m, Ar), 7.62-7.70 (3H, m, Ar), 7.33-7.37 (2H, m, Ar), 7.19-7.28 (6H, m, Ar), 7.09-7.16 (2H, m, Ar), 3.87 (1H, d, *J* = 10.5 Hz, 6-H), 3.41 (1H, ddd, *J* = 9.9, 8.8, 5.3 Hz, 5-H_A), 3.34 (1H, ddd, *J* = 9.9, 8.3, 6.7 Hz, 5-H_B), 3.07 (1H, ddd, *J* = 10.5, 8.5, 6.3 Hz, 3-H), 2.00-2.11 (2H, m, 2 x CH cyclopentyl), 1.90 (1H, ddd, *J* = 13.5, 8.3, 5.3 Hz, 4-H_A), 1.74-1.84 (1H, m, CH cyclopentyl), 1.65-1.74 (1H, m, CH cyclopentyl), 1.51-1.64 (3H, m, 3 x CH cyclopentyl), 1.42-1.50 (1H, m, 4-H_B), 1.17-1.29 (1H, m, CH cyclopentyl), 1.00-1.10 (1H, m, CH cyclopentyl). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 149.7 (C Ar), 144.6 (C Ar), 144.1 (C Ar), 135.4 (C Ar), 133.4 (CH Ar), 131.7 (CH Ar), 130.3 (CH Ar), 128.83 (2 x CH Ar), 128.77 (2 x CH Ar), 128.04 (2 x CH Ar), 128.02 (2 x CH Ar), 126.6 (CH Ar), 126.5 (CH Ar), 124.3 (CH Ar), 80.1 (C-2), 52.7 (C-6), 51.5 (C-3), 47.1 (C-5), 36.6 (CH_2 cyclopentyl), 33.3 (CH_2

cyclopentyl), 28.2 (C-4), 25.0 (CH_2 cyclopentyl), 24.3 (CH_2 cyclopentyl). **HRMS** (ESI): calculated for $C_{27}H_{28}N_2O_4SNa$ $[M+Na]^+$ requires *m/z* 499.1667, found *m/z* 499.1660. **IR** (film) ν_{max}: 2980, 2888, 1710, 1541, 1371, 1159 cm^{-1}.

5.9.29 *N*-(3-benzhydrylpent-4-en-1-yl)-2-nitrobenzenesulfonamide (237ak')

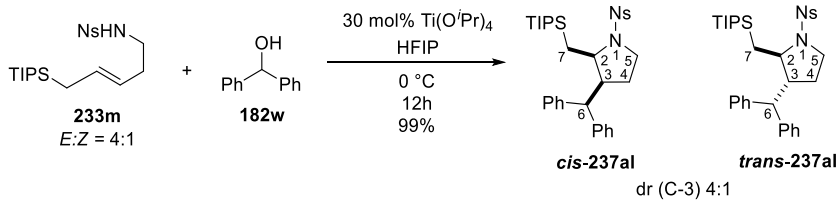


Amine **233l** (40.0 mg, 0.117 mmol), alcohol **182w** (21.5 mg, 0.117 mmol) and $Ti(O^iPr)_4$ (10.0 mg, 0.0351 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 10% → 20% EtOAc - pentane) to yield **237ak'** as a colorless oil (39.6 mg, 67%).

Data for **237ak': R_f** 0.30 (30% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.99-8.03 (1H, m, Ar), 7.80-7.84 (1H, m, Ar), 7.62-7.71 (2H, m, Ar), 7.08-7.29 (10H, m, Ar), 5.41 (1H, ddd, *J* = 16.9, 10.5, 9.1 Hz, 4-H), 5.19 (1H, t, *J* = 6.1 Hz, NH), 4.88-4.96 (2H, m, 5-H_2), 3.67 (1H, d, *J* = 10.7 Hz, 6-H), 3.03-3.15 (2H, m, 1-H_2), 2.91-3.03 (1H, m, 3-H), 1.63 (1H, dtd, *J* = 13.8, 8.0, 3.0 Hz, 2-H_A), 1.33 (1H, dddd, *J* = 13.8, 10.6, 6.7, 5.1 Hz, 2-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 148.2 (C Ar), 143.24 (C Ar), 143.21 (C Ar), 139.7 (C-4), 134.0 (C Ar), 133.5 (CH Ar), 132.9 (CH Ar), 131.1 (CH Ar), 128.9 (2 x CH Ar), 128.48 (2 x CH Ar), 128.45 (2 x CH Ar), 128.1 (2 x CH Ar), 126.6 (CH Ar), 126.4 (CH Ar), 125.4 (CH Ar), 117.8 (C-5), 57.3 (C-6), 45.5 (C-3), 42.0 (C-1), 32.8 (C-2). **HRMS** (ESI): calculated for $C_{24}H_{24}N_2O_4SNa$ $[M+Na]^+$ requires *m/z* 459.1354, found *m/z* 459.1354. **IR** (film) ν_{max}: 2980, 2888, 1710, 1541, 1371, 1159 cm^{-1}.

5.9.30 (±)-(2*S*,3*S*)-3-Benzhydryl-1-[(2-nitrophenyl)sulfonyl]-2-[(triisopropylsilyl)methyl]pyrrolidine (*cis*-237al)

(±)-(2*S*,3*R*)-3-benzhydryl-1-[(2-nitrophenyl)sulfonyl]-2-[(triisopropylsilyl)methyl]pyrrolidine (*trans*-237al)



Amine **233m** (22.2 mg, 0.0521 mmol), alcohol **182w** (9.6 mg, 0.052 mmol) and $Ti(O^iPr)_4$ (4.5 mg, 0.016 mmol) were subjected to the general procedure **H** except conducting the reaction at 0 °C (FCC: gradient elution: 10% → 20% EtOAc - pentane) to yield a separable 4:1 mixture of ***cis*-237al** and ***trans*-237al** as colorless oil (30.8 mg, 99%).

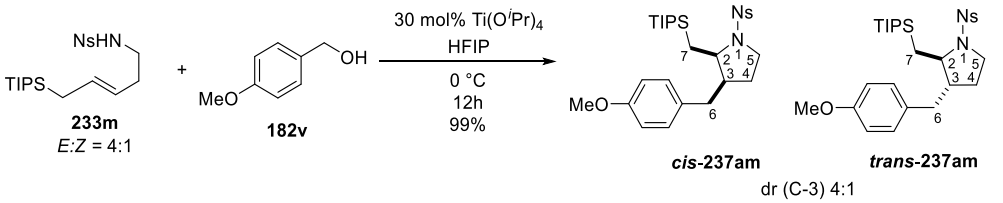
Data for ***cis*-237al: R_f** 0.4 (50% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.02 (1H, dd, *J* = 7.7, 1.6 Hz, Ar), 7.73-7.82 (2H, m, Ar), 7.68 (1H, dd, *J* = 7.7, 1.6 Hz, Ar), 7.24-7.29 (2H, m, Ar), 7.14-7.20 (5H, m, Ar), 7.05-7.12 (3H, m, Ar), 4.22 (1H, ddd, *J* = 12.6, 5.8, 2.0 Hz, 2-H), 3.71-3.77 (1H, m, 5-H_A), 3.70 (1H, d, *J* = 11.7 Hz, 6-H), 3.52 (1H, ddd, *J* = 12.9, 8.7, 4.7 Hz, 5-H_B), 2.43-2.52 (1H, m, 3-H), 1.68-1.78 (2H, m, 4-H_2), 1.11 (3H, hept, *J* = 7.5 Hz, 3 x CH ^{i}Pr), 0.95 (9H, d, *J* = 7.4 Hz, 3 x CH_3 ^{i}Pr), 0.82 (9H, d, *J* = 7.4 Hz, 3 x CH_3 ^{i}Pr), 0.76-0.80 (1H, m, 7-H_A), 0.69 (1H, dd, *J* = 14.8, 2.0 Hz, 7-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 148.8 (C Ar), 143.6 (C Ar), 142.6 (C Ar), 133.7 (CH Ar), 132.7 (C Ar), 131.6 (CH Ar), 131.3 (CH Ar), 129.1 (2 x CH Ar), 128.8 (2 x CH Ar), 127.9 (2 x CH Ar), 127.4 (2 x CH Ar), 127.0 (CH Ar), 126.6 (CH Ar), 124.1 (CH Ar), 60.4 (C-2), 53.7 (C-6), 49.0 (C-3), 46.6

(C-5), 28.3 (C-4), 19.3 (3 x CH_3 ^{i}Pr), 19.0 (3 x CH_3 ^{i}Pr), 11.6 (3 x CH ^{i}Pr), 7.6 (C-7). **NOESY-2D (500 MHz, $CDCl_3$)**: between 2-H and 3-H, between 6-H and 7-H_A, between 6-H and 7-H_B. **HRMS** (ESI): calculated for $C_{33}H_{44}N_2O_4SSiNa$ $[M+Na]^+$ requires *m/z* 615.2689, found *m/z* 615.2678. **IR** (film) ν_{max}: 2980, 2889, 1544, 1371, 1163, 1127 cm^{-1}.

Data for ***trans*-237al: R_f** 0.50 (50% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.09 (1H, dd, *J* = 7.8, 1.4 Hz, Ar), 7.65-7.77 (2H, m, Ar), 7.25-7.30 (3H, m, Ar), 7.21-7.24 (2H, m, Ar), 7.15-7.20 (1H, m, Ar), 7.05-7.14 (3H, m, Ar), 6.92-6.96 (2H, m, Ar), 3.97 (1H, dd, *J* = 12.1, 2.8 Hz, 2-H), 3.63-3.69 (1H, m, 5-H_A), 3.62 (1H, d, *J* = 11.8 Hz, 6-H), 3.51 (td, *J* = 9.6, 1.9 Hz, 5-H_B), 2.71 (1H, dd, *J* = 11.9, 6.2 Hz, 3-H), 2.16-2.27 (1H, m, 4-H_A), 1.77-1.85 (1H, m, 4-H_B), 1.06 (1H, dd, *J* = 15.0, 2.8 Hz, 7-H_A), 0.96-1.03 (1H, m, 7-H_B), 0.94 (9H, d, *J* = 7.4 Hz, 3 x CH_3 ^{i}Pr), 0.82 (9H, d, *J* = 7.4 Hz, 3 x CH_3 ^{i}Pr), 0.64 (3H, hept, *J* = 7.5 Hz, 3 x CH ^{i}Pr). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 148.4 (C Ar), 143.2 (C Ar), 143.0 (C Ar), 134.5 (C Ar), 133.4 (CH Ar), 131.7 (CH Ar), 131.5 (CH Ar), 128.9 (2 x CH Ar), 128.7 (2 x CH Ar), 128.6 (2 x CH Ar), 128.4 (2 x CH Ar), 126.71 (CH Ar), 126.67 (CH Ar), 124.3 (CH Ar), 61.6 (C-2), 53.0 (C-6), 49.7 (C-3), 45.6 (C-5), 27.2 (C-4), 19.2 (3 x CH_3 ^{i}Pr), 18.9 (3 x CH_3 ^{i}Pr), 16.7 (C-7), 11.5 (3 x CH ^{i}Pr). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H. **HRMS** (ESI): calculated for $C_{33}H_{44}N_2O_4SSiNa$ $[M+Na]^+$ requires *m/z* 615.2689, found *m/z* 615.2677. **IR** (film) ν_{max}: 2980, 2889, 1544, 1371, 1163, 1127 cm^{-1}.

5.9.31 (±)-(2*S*,3*R*)-3-(4-Methoxybenzyl)-1-[(2-nitrophenyl)sulfonyl]-2-[(triisopropylsilyl)methyl]pyrrolidine (*cis*-237am)

(±)-(2*S*,3*S*)-3-(4-methoxybenzyl)-1-[(2-nitrophenyl)sulfonyl]-2-[(triisopropylsilyl)methyl]pyrrolidine (*trans*-237am)



Amine **233m** (27.0 mg, 0.0634 mmol), alcohol **182v** (8.8 mg, 0.063 mmol) and $Ti(O^iPr)_4$ (5.4 mg, 0.019 mmol) were subjected to the general procedure E except conducting the reaction at 0 °C (FCC: gradient elution: 20% → 35% EtOAc - pentane) to yield a separable 4:1 mixture of ***cis*-237am** and ***trans*-237am** as colorless oil (34.5 mg, 99%).

Data for ***cis*-237am: R_f** 0.50 (60% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.99 (1H, dd, *J* = 7.7, 1.6 Hz, Ar), 7.62-7.71 (2H, m, Ar), 7.60 (1H, dd, *J* = 7.6, 1.6 Hz, Ar), 6.95 (2H, d, *J* = 8.7 Hz, Ar), 6.80 (2H, d, *J* = 8.7 Hz, Ar), 4.24 (1H, dt, *J* = 8.6, 5.9 Hz, 2-H), 3.78 (OMe), 3.68 (1H, ddd, *J* = 11.7, 9.0, 5.9 Hz, 5-H_A), 3.47 (1H, ddd, *J* = 11.7, 8.6, 5.8 Hz, 5-H_B), 2.65 (1H, dd, *J* = 14.0, 6.2 Hz, 6-H_A), 2.46 (1H, dd, *J* = 14.0, 6.9 Hz, 6-H_B), 2.02-2.10 (1H, m, 3-H), 1.75-1.84 (1H, m, 4-H_A), 1.69 (1H, dtd, *J* = 12.7, 8.6, 5.8 Hz, 4-H_B), 1.17 (3H, hept, *J* = 7.5 Hz, 3 x CH ^{i}Pr), 1.05 (9H, d, *J* = 7.4 Hz, 3 x CH_3 ^{i}Pr), 1.02 (9H, d, *J* = 7.4 Hz, 3 x CH_3 ^{i}Pr), 0.87 (1H, dd, *J* = 14.8, 8.6 Hz, 7-H_A), 0.75 (1H, dd, *J* = 14.8, 5.9 Hz, 7-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.2 (C Ar), 148.5 (C Ar), 133.6 (C Ar), 133.5 (CH Ar), 131.9 (C Ar), 131.4 (CH Ar), 131.1 (CH Ar), 129.6 (2 x CH Ar), 124.1 (CH Ar), 114.1 (2 x CH Ar), 62.0

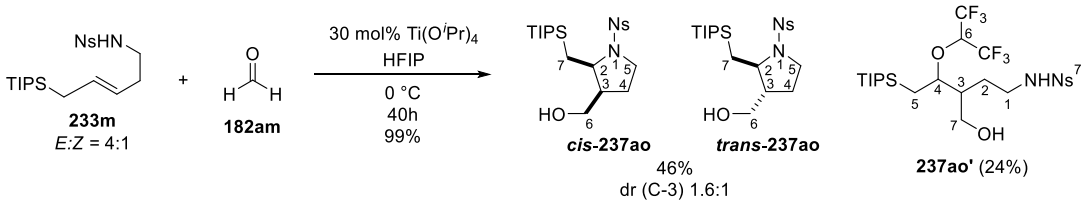
(C-2), 55.4 (OMe), 46.5 (C-5), 45.5 (C-3), 34.2 (C-6), 28.1 (C-4), 19.2 (3 x CH_3 ^{i}Pr), 19.1 (3 x CH_3 ^{i}Pr), 11.7 (3 x CH ^{i}Pr), 9.2 (C-7). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H, between 3-H_A and 7-H_B, between 6-H_B and 7-H_B. **HRMS** (ESI): calculated for $C_{28}H_{43}N_2O_5SSi$ $[M+H]^+$ requires *m/z* 547.2662, found *m/z* 547.2654. **IR** (film) ν_{max}: 2980, 2866, 1544, 1545, 1512, 1372 cm^{-1}.

Data for ***trans*-237am: R_f** 0.45 (60% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.07-8.11 (1H, m, Ar), 7.66-7.71 (2H, m, Ar), 7.60-7.64 (1H, m, Ar), 6.88 (2H, d, *J* = 8.7 Hz, Ar), 6.78 (2H, d, *J* = 8.7 Hz, Ar), 4.05 (1H, dd, *J* = 12.7, 2.5 Hz, 2-H), 3.77 (OMe), 3.53-3.59 (2H, m, 5-H_2), 2.45-2.51 (1H, m, 6-H_A), 2.06-2.17 (3H, m, 3-H, 4-H_A and 6-H_B), 1.69-1.76 (1H, m, 4-H_B), 1.04-1.13 (2H, m, 7-H_2), 0.99 (9H, d, *J* = 7.4 Hz, 3 x CH_3 ^{i}Pr), 0.97 (9H, d, *J* = 7.4 Hz, 3 x CH_3 ^{i}Pr), 0.86 (3H, hept, *J* = 7.5 Hz, 3 x CH ^{i}Pr). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.3 (C Ar), 148.4 (C Ar), 133.44 (CH Ar), 133.42 (C Ar), 131.7 (C Ar),131.4 (CH Ar), 131.0 (CH Ar), 130.1 (2 x CH Ar), 124.2 (CH Ar), 114.0 (2 x CH Ar), 63.8 (C-2), 55.4 (OMe), 46.8 (C-3), 45.7 (C-5), 37.8 (C-6), 27.6 (C-4), 19.0 (3 x CH_3 ^{i}Pr), 18.9 (3 x CH_3 ^{i}Pr), 18.0 (C-7), 11.4 (3 x CH ^{i}Pr). **HRMS** (ESI): calculated for $C_{28}H_{43}N_2O_5SSi$ $[M+H]^+$ requires *m/z* 547.2662, found *m/z* 547.2654. **IR** (film) ν_{max}: 2980, 2866, 1544, 1545, 1512, 1372 cm^{-1}.

5.9.32 (±)-[(2*S*,3*R*)-1-[(2-Nitrophenyl)sulfonyl]-2-[(triisopropylsilyl)methyl]pyrrolidin-3-yl)methanol (*cis*-237ao)

(±)-[(2*S*,3*S*)-1-[(2-nitrophenyl)sulfonyl]-2-[(triisopropylsilyl)methyl]pyrrolidin-3-yl)methanol (*trans*-237ao)

N-{4-[(1,1,1,3,3,3-hexafluoropropan-2-yl)oxy]-3-(hydroxymethyl)-5-(triisopropylsilyl)pentyl}-2-nitrobenzenesulfonamide (237ao')



Amine **233m** (28.1 mg, 0.0660 mmol), paraformaldehyde **182am** (40.0 mg, 1.32 mmol) and $Ti(O^iPr)_4$ (5.7 mg, 0.020 mmol) were subjected to the general procedure **H** except using 20 equivalents of paraformaldehyde **182am** and conducting the reaction at 0 °C for 40 hours (FCC: gradient elution: 10% → 25% EtOAc - pentane) to yield a separable 1.6:1 mixture of ***cis*-237ao** and ***trans*-237ao** as colorless oil (16.3 mg, 42%) and side product **237ao'** as a colorless oil (12.2 mg, 24%).

Data for ***cis*-237ao: R_f** 0.40 (25% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.01-8.05 (1H, m, Ar), 7.64-7.70 (2H, m, Ar), 7.56-7.59 (1H, m, Ar), 4.38 (1H, dt, *J* = 8.7, 6.0 Hz, 2-H), 3.75 (1H, ddd, *J* = 11.9, 9.2, 5.6 Hz, 5-H_A), 3.66 (1H, dd, *J* = 10.6, 7.0 Hz, 6-H_A), 3.58 (1H, dd, *J* = 10.6, 7.6 Hz, 6-H_B), 3.48 (ddd, *J* = 11.9, 8.8, 6.2 Hz, 5-H_B), 2.00-2.10 (1H, m, 3-H), 1.86-1.94 (1H, m, 4-H_A), 1.76-1.85 (1H, m, 4-H_B), 1.49 (1H, br s, OH), 1.17 (3H, hept, *J* = 7.5 Hz, 3 x CH ^{i}Pr), 1.05 (9H, d, *J* = 7.4 Hz, 3 x CH_3 ^{i}Pr), 1.04 (9H, d, *J* = 7.4 Hz, 3 x CH_3 ^{i}Pr), 0.82 (1H, dd, *J* = 14.8, 8.7 Hz, 7-H_A), 0.65 (1H, dd, *J* = 14.8, 6.0 Hz,

7-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 148.5 (C Ar), 135.6 (C Ar and CH Ar), 131.6 (CH Ar), 131.0 (CH Ar), 124.2 (CH Ar), 61.8 (C-6), 60.8 (C-2), 46.5 (C-5), 46.1 (C-3), 25.9 (C-4), 19.2 (3 x CH_3 ^{i}Pr), 19.1 (3 x CH_3 ^{i}Pr), 11.7 (3 x CH ^{i}Pr), 9.3 (C-7). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 3-H, between 6-H_A and 7-H_A, between 6-H_A and 7-H_B. **HRMS** (ESI): calculated for $C_{21}H_{36}N_2O_5SSiNa$ $[M+Na]^+$ requires *m/z* 479.2012, found *m/z* 479.2003. **IR** (film) ν_{max}: 3320, 2970, 2867, 1543, 1366, 1164 cm^{-1}.

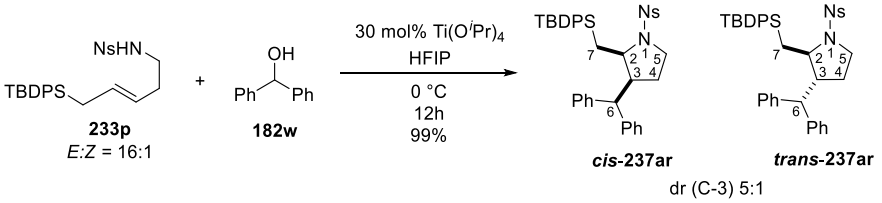
Data for ***trans*-237ao: R_f** 0.40 (25% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.02-8.05 (1H, m, Ar), 7.64-7.69 (2H, m, Ar), 7.57-7.60 (1H, m, Ar), 4.23 (1H, dd, *J* = 12.5, 2.7 Hz, 2-H), 3.55 (1H, td, *J* = 9.5, 2.3 Hz, 5-H_A), 3.36 (1H, td, *J* = 9.6, 8.0 Hz, 5-H_B), 3.22-3.29 (2H, m, 6-H_2), 2.12-2.18 (1H, m, 3-H), 2.18-2.26 (1H, m, 4-H_A), 1.82-1.89 (1H, m, 4-H_B), 1.62 (1H, br s, OH), 1.14 (3H, hept, *J* = 7.5 Hz, 3 x CH ^{i}Pr), 0.99-1.12 (20H, m, 6 x CH_3 ^{i}Pr and 7-H_2). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 148.2 (C Ar), 133.5 (CH Ar), 132.8 (C Ar), 131.5 (CH Ar), 131.1 (CH Ar), 124.1 (CH Ar), 63.4 (C-6), 61.3 (C-2), 46.8 (C-3), 45.3 (C-5), 25.7 (C-4), 18.94 (3 x CH_3 ^{i}Pr), 18.91 (3 x CH_3 ^{i}Pr), 18.5 (C-7), 11.4 (3 x CH ^{i}Pr). **HRMS** (ESI): calculated for $C_{21}H_{36}N_2O_5SSiNa$ $[M+Na]^+$ requires *m/z* 479.2012, found *m/z* 479.2003. **IR** (film) ν_{max}: 3320, 2970, 2867, 1543, 1366, 1164 cm^{-1}.

Data for **237ao': R_f** 0.45 (25% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.09-8.14 (1H, m, Ar), 7.82-7.87 (1H, m, Ar), 7.70-7.76 (2H, m, Ar), 4.03-4.12 (2H, m, 4-H and 7-H), 3.91 (1H, dd, *J* = 11.6, 4.3 Hz, 6-H_A), 3.74 (1H, dd, *J* = 11.6, 4.3 Hz, 6-H_B), 3.15-3.29 (2H, m, 1-H_2), 1.94-2.02 (1H, m, 2-H_A), 1.82-1.89 (1H, m, 3-H), 1.64-1.72 (1H, m, 2-H_B), 1.62 (1H, br s, OH), 1.14 (3H, hept, *J* = 7.5 Hz, 3 x CH ^{i}Pr), 0.99-1.12 (20H, m, 6 x CH_3 ^{i}Pr and 5-H_2). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 148.2 (C Ar), 133.9 (C Ar), 133.7 (CH Ar),

132.9 (CH Ar), 131.3 (CH Ar), 125.5 (CH Ar), 86.0 (C-7), 72.9 (p, *J* = 31.9 Hz, 2 x CF_3), 60.7 (C-6), 42.0 (C-1), 41.5 (C-3), 29.8 (C-2), 18.91 (3 x CH_3 ^{i}Pr), 18.86 (3 x CH_3 ^{i}Pr), 12.2 (C-5), 11.5 (3 x CH ^{i}Pr). **HRMS** (ESI): calculated for $C_{24}H_{38}N_2F_3O_6SSiNa$ $[M+Na]^+$ requires *m/z* 647.2022, found *m/z* 647.2010. **IR** (film) ν_{max}: 3320, 2970, 2867, 1543, 1366, 1164 cm^{-1}.

5.9.33 (±)-(2*S*,3*S*)-3-Benzhydryl-2-[(*tert*-butyldiphenylsilyl)methyl]-1-[(2-nitrophenyl)sulfonyl]pyrrolidine (*cis*-237ar)

(±)-(2*S*,3*R*)-3-Benzhydryl-2-[(*tert*-butyldiphenylsilyl)methyl]-1-[(2-nitrophenyl)sulfonyl]pyrrolidine (*trans*-237ar)



Amine **233p** (114.4 mg, 0.2252 mmol), alcohol **182w** (41.5 mg, 0.225 mmol) and $Ti(O^{i}Pr)_4$ (19.2 mg, 0.0676 mmol) were subjected to the general procedure E except conducting the reaction at 0 °C (FCC: gradient elution: 6% → 10% EtOAc - pentane) to yield a separable 5:1 mixture of ***cis*-237ar** and ***trans*-237ar** as colorless oil (149.5 mg, 99%).

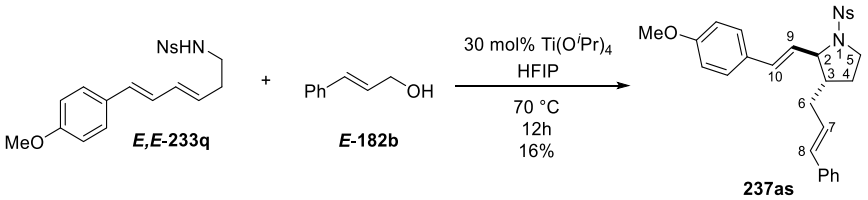
Data for ***cis*-237ar: R_f** 0.45 (30% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.51-7.60 (3H, m, Ar), 7.45-7.48 (1H, m, Ar), 7.15-7.40 (17H, m, Ar), 6.94-6.98 (2H, m, Ar), 6.65-6.68 (1H, m, Ar), 4.11 (1H, ddd, *J* = 12.2, 5.9, 2.0 Hz, 2-H), 3.86 (1H, d, *J* = 12.0 Hz, 6-H), 3.81-3.89 (1H, m, 5-H_A), 3.52 (1H, ddd, *J* = 13.0, 9.4, 3.8 Hz, 5-H_B), 2.65-2.76 (1H, m, 3-H), 1.78-1.93 (1H, m,4-H_2), 1.45 (1H, dd, *J* = 15.1, 12.2 Hz, 7-H_A), 1.34 (1H, dd, *J*

= 15.2, 2.1 Hz, 7-H_B). 0.83 (9H, s, 3 x CH_3 ^{t}Bu). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 147.2 (C Ar), 143.4 (C Ar), 142.9 (C Ar), 136.03 (2 x CH Ar), 136.02 (C Ar), 135.9 (2 x CH Ar), 133.5 (C Ar), 132.9 (C Ar), 132.7 (CH Ar), 131.9 (CH Ar), 131.3 (CH Ar), 129.3 (2 x CH Ar), 129.0 (CH Ar), 128.9 (2 x CH Ar), 128.7 (CH Ar), 128.0 (2 x CH Ar), 127.8 (2 x CH Ar), 127.4 (2 x CH Ar), 127.3 (2 x CH Ar), 127.0 (CH Ar), 126.8 (CH Ar), 123.9 (CH Ar), 59.5 (C-2), 53.7 (C-6), 49.5 (C-3), 46.9 (C-5), 28.3 (C-4), 27.5 (3 x CH_3 ^{t}Bu), 18.6 (CCH_3 ^{t}Bu), 7.0 (C-7). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 3-H, between 6-H and 7-H_A, between 6-H and 7-H_B. **HRMS** (ESI): calculated for $C_{40}H_{42}N_2O_4SSiNa$ $[M+Na]^+$ requires *m/z* 697.2532, found *m/z* 697.2521. **IR** (film) ν_{max}: 2980, 2360, 1543, 1372, 1164, 1126 cm^{-1}.

Data for ***trans*-237ar: R_f** 0.50 (30% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.11-7.15 (2H, m, Ar), 7.61-7.67 (2H, m, Ar), 7.48-7.56 (3H, m, Ar), 7.35-7.45 (4H, m, Ar), 7.22-7.31 (3H, m, Ar), 7.07-7.13 (2H, m, Ar), 7.02-7.07 (1H, m, Ar), 6.80-6.86 (1H, m, Ar), 6.74-6.79 (2H, m, Ar), 6.58-6.64 (2H, m, Ar), 6.01-6.06 (2H, m, Ar), 3.71-3.74 (1H, m, 2-H), 3.67-3.71 (1H, m, 5-H_A), 3.58 (1H, td, *J* = 9.6, 1.6 Hz, 5-H_B), 3.19 (1H, d, *J* = 12.0 Hz, 6-H), 2.64 (1H, dd, *J* = 12.1, 6.0 Hz, 3-H), 2.07-2.19 (1H, m, 4-H_A), 1.87 (1H, dd, *J* = 15.1, 2.2 Hz, 7-H_A), 1.61 (1H, dd, *J* = 15.1, 11.9 Hz, 7-H_B), 1.49-1.56 (1H, m, 4-H_B), 0.93 (9H, s, 3 x CH_3 ^{t}Bu). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 148.1 (C Ar), 143.5 (C Ar), 142.5 (C Ar), 136.42 (CH Ar), 136.35 (CH Ar), 134.9 (C Ar), 133.6 (C Ar), 133.0 (CH Ar), 132.8 (C Ar), 131.8 (CH Ar), 131.6 (CH Ar), 129.7 (CH Ar), 129.1 (CH Ar), 128.6 (2 x CH Ar), 128.3 (2 x CH Ar), 128.0 (2 x CH Ar), 127.9 (2 x CH Ar), 127.74 (2 x CH Ar), 127.70 (2 x CH Ar), 126.4 (CH Ar), 126.0 (CH Ar), 123.8 (CH Ar), 60.7 (C-2), 52.8 (C-6), 48.3 (C-3), 45.5 (C-5), 27.6 (3 x CH_3 ^{t}Bu), 26.6 (C-4), 18.4 (C-7), 18.2 (CCH_3 ^{t}Bu). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H

and 6-H. **HRMS** (ESI): calculated for $C_{40}H_{42}N_2O_4SSiNa$ $[M+Na]^+$ requires *m/z* 697.2532, found *m/z* 697.2521. **IR** (film) ν_{max}: 2980, 2360, 1543, 1372, 1164, 1126 cm^{-1}.

5.9.34 (±)-(2*S*,3*S*)-3-Cinnamyl-2-[(1'*E*)-4-methoxystyryl]-1-[(2-nitrophenyl)sulfonyl]pyrrolidine (237as)



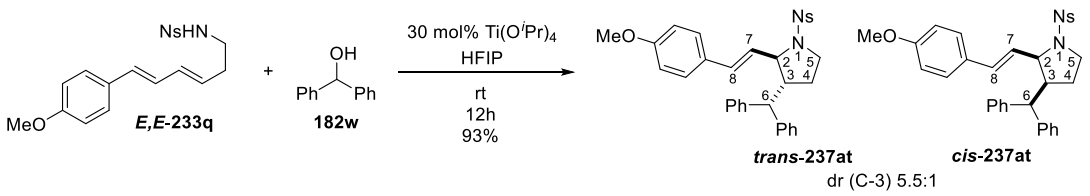
Amine ***E,E*-233q** (15.0 mg, 0.387 mmol), alcohol ***E*-182b** (5.2 mg, 0.39 mmol) and $Ti(O^iPr)_4$ (3.3 mg, 0.012 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 10% → 35% EtOAc - pentane) to yield pyrrolidines **237as** as a colorless oil (3.1 mg, 16%).

Data for **237as:** $\mathbf{R_f}$ 0.50 (35% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.91 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.56 (1H, dd, *J* = 7.9, 1.3 Hz, Ar), 7.45-7.51 (1H, m, Ar), 7.32-7.36 (1H, m, Ar), 7.25-7.31 (4H, m, Ar), 7.17-7.23 (1H, m, Ar), 7.05 (2H, d, *J* = 8.7 Hz, Ar), 6.78 (2H, d, *J* = 8.7 Hz, Ar), 6.40 (1H, d, *J* = 15.8 Hz, 10-H), 6.38 (1H, d, *J* = 15.8 Hz, 8-H), 6.12 (1H, dt, *J* = 15.8, 7.0 Hz, 7-H), 5.60 (1H, dd, *J* = 15.8, 8.6 Hz, 9-H), 4.10 (1H, dd, *J* = 8.6, 6.1 Hz, 2-H), 3.95 (1H, ddd, *J* = 10.8, 8.1, 3.1 Hz, 5-H_A), 3.81 (OMe), 3.49-3.60 (1H, m, 5-H_B), 2.36-2.45 (1H, m, 6-H_A), 2.08-2.20 (3H, m, 3-H, 4-H_A and 6-H_B), 1.64-1.74 (1H, m, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.6 (C Ar), 148.0 (C Ar), 137.3 (C Ar), 134.8 (C Ar), 133.4 (C-10), 133.0 (CH Ar), 132.3 (C-8), 131.7 (CH Ar), 131.4 (CH Ar), 128.9 (C Ar), 128.7 (2 x CH Ar), 127.8 (2 x CH Ar), 127.4 (C-7 and CH Ar), 126.2 (2 x CH Ar), 125.6 (C-9),

123.8 (CH Ar), 114.0 (2 x CH Ar), 67.9 (C-2), 55.4 (OMe), 48.8 (C-5), 47.0 (C-3), 35.3 (C-6), 30.3 (C-4). **HRMS** (ESI): calculated for $C_{28}H_{29}N_2O_5S$ $[M+H]^+$ requires *m/z* 505.1797, found *m/z* 505.1790. **IR** (film) ν_{max}: 2980, 2888, 2360, 1542, 1511, 1379 cm^{-1}.

5.9.35 (±)-(2*R*,3*R*)-3-Benzhydryl-2-[(1'*E*)-4-methoxystyryl]-1-[(2-nitrophenyl)sulfonyl]pyrrolidine (*trans*-237at)

(±)-(2*R*,3*S*)-3-benzhydryl-2-[(1'*E*)-4-methoxystyryl]-1-[(2-nitrophenyl)sulfonyl]pyrrolidine (*cis*-237at)



Amine ***E,E*-233q** (15.1 mg, 0.0389 mmol), alcohol **182w** (7.2 mg, 0.039 mmol) and $Ti(O^iPr)_4$ (3.3 mg, 0.012 mmol) were subjected to the general procedure **H** except conducting the reaction at room temperature (FCC: gradient elution: 10% → 20% EtOAc - pentane) to yield ***trans*-237at** and ***cis*-237at** as a separable 5.5:1 mixture of diastereomers (19.7 mg, 93%), which was partially separable into 2 fractions: first fraction of ***trans*-237at** (3.2 mg, 15%) as a colorless oil, and second fraction of 4.5:1 of diastereomers ***trans*-237at** : ***cis*-237at** as a colorless oil (16.9 mg, 78%).

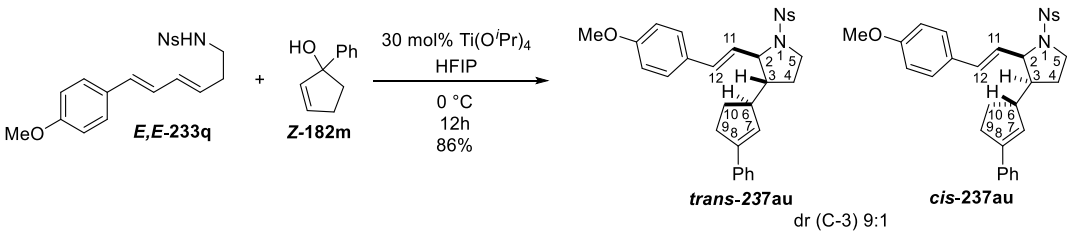
Data for ***trans*-237at: R_f** 0.45 (30% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.83 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.55 (1H, dd, *J* = 8.0, 1.4 Hz, Ar), 7.47-7.52 (1H, m, Ar), 7.31-7.36 (1H, m, Ar), 7.22-7.29 (4H, m, Ar), 7.14-7.21 (5H, m, Ar), 7.06-7.11 (1H, m, Ar), 6.94 (2H, d, *J* = 8.7 Hz, Ar), 6.74 (2H, d, *J* = 8.7 Hz, Ar), 5.92 (1H, d, *J* = 15.7 Hz, 8-H), 5.57

(1H, dd, *J* = 15.7, 7.8 Hz, 7-H), 4.27 (1H, dd, *J* = 7.8, 3.6 Hz, 2-H), 3.87 (1H, dt, *J* = 10.2, 7.2 Hz, 5-H_A), 3.79 (OMe), 3.75 (1H, d, *J* = 11.5 Hz, 6-H), 3.62 (1H, ddd, *J* = 10.2, 7.2, 5.7 Hz, 5-H_B), 2.92-3.00 (1H, m, 3-H), 2.07 (1H, dq, *J* = 13.8, 7.2 Hz, 4-H_A), 1.61-1.69 (1H, m, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.4 (C Ar), 148.1 (C Ar), 143.1 (C Ar), 142.9 (C Ar), 134.2 (C Ar), 133.1 (CH Ar), 131.7 (CH Ar), 131.41 (CH Ar), 131.37 (C-8), 129.1 (C Ar), 128.9 (2 x CH Ar), 128.8 (2 x CH Ar), 128.3 (2 x CH Ar), 128.0 (2 x CH Ar), 127.7 (2 x CH Ar), 126.9 (CH Ar), 126.8 (CH Ar), 125.9 (C-7), 123.8 (CH Ar), 113.8 (2 x CH Ar), 66.3 (C-2), 55.4 (OMe), 54.5 (C-6), 50.5 (C-3), 48.0 (C-5), 28.9 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H, between 3-H and 7-H, between 3-H and 8-H. **HRMS** (ESI): calculated for $C_{32}H_{30}N_2O_5SNa$ $[M+Na]^+$ requires *m/z* 577.1773, found *m/z* 577.1761. **IR** (film) ν_{max}: 2980, 2888, 2360, 1381, 1251, 1158 cm^{-1}.

Data for ***cis*-237at** (from the mixture)**: R_f** 0.40 (30% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.93-7.97 (1H, m, Ar), 7.43-7.49 (2H, m, Ar), 7.08-7.39 (11H, m, Ar), 7.02 (2H, d, *J* = 8.7 Hz, Ar), 6.82 (2H, d, *J* = 8.7 Hz, Ar), 5.84 (1H, d, *J* = 15.7 Hz, 8-H), 5.71 (1H, dd, *J* = 15.7, 7.8 Hz, 7-H), 4.65 (1H, t, *J* = 7.4 Hz, 2-H), 3.83 (OMe), 3.74-3.79 (1H, m, 5-H_A), 3.62-3.64 (1H, m, 6-H), 3.48 (1H, td, *J* = 10.2, 7.2 Hz, 5-H_A), 3.17-3.27 (1H, m, 3-H), 1.75-1.89 (1H, m, 4-H_2). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.4 (C Ar), 148.2 (C Ar), 143.5 (C Ar), 142.4 (C Ar), 133.29 (C Ar), 133.25 (C-8), 131.7 (CH Ar), 131.3 (CH Ar), 129.0 (2 x CH Ar), 128.9 (2 x CH Ar), 128.8 (2 x CH Ar), 128.1 (2 x CH Ar), 127.8 (2 x CH Ar), 127.7 (C Ar and 2 x CH Ar), 126.7 (CH Ar), 123.8 (CH Ar), 121.8 (C-7), 114.0 (2 x CH Ar), 64.1 (C-2), 55.4 (OMe), 53.0 (C-6), 48.5 (C-3), 47.5 (C-5), 29.3 (C-4).

5.9.36 (±)-(2*R*,3*R*)-2-[(1'*E*)-4-Methoxystyryl]-1-[(2-nitrophenyl)sulfonyl]-3-[(1''*R*)-3-phenylcyclopent-2-en-1-yl]pyrrolidine (*trans*-237au)

(±)-(2*R*,3*S*)-2-[(1'*E*)-4-methoxystyryl]-1-[(2-nitrophenyl)sulfonyl]-3-[(1''*R*)-3-phenylcyclopent-2-en-1-yl]pyrrolidine (*cis*-237au)



Amine ***E,E*-233q** (12.5 mg, 0.0322 mmol), alcohol ***E*-182w** (5.2 mg, 0.032 mmol) and $Ti(O^iPr)_4$ (2.8 mg, 0.010 mmol) were subjected to the general procedure E except conducting the reaction at 0 °C (FCC: gradient elution: 15% → 25% EtOAc - pentane) to yield ***trans*-237au** as a colorless oil (crude H NMR showed a dr of 9:1) (15.1 mg, 86%).

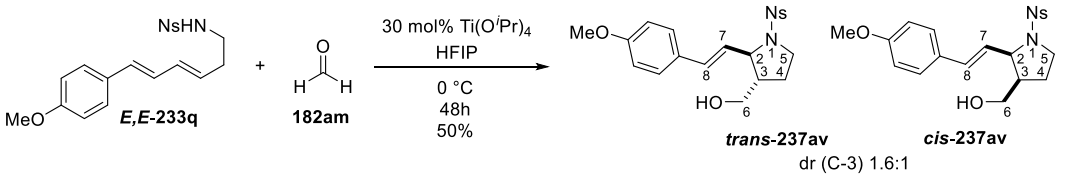
Data for ***trans*-237au: R_f** 0.45 (35% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.91 (1H, dd, *J* = 8.0, 1.4 Hz, Ar), 7.55 (1H, dd, *J* = 7.9, 1.3 Hz, Ar), 7.45-7.50 (1H, m, Ar), 7.37-7.41 (2H, m, Ar), 7.28-7.33 (3H, m, Ar), 7.20-7.25 (1H, m, Ar), 7.04 (2H, d, *J* = 8.7 Hz, Ar), 6.78 (2H, d, *J* = 8.7 Hz, Ar), 6.40 (1H, d, *J* = 15.7 Hz, 12-H), 6.07 (1H, q, *J* = 2.0 Hz, 7-H), 5.61 (1H, dd, *J* = 15.7, 8.7 Hz, 11-H), 4.26 (1H, t, *J* = 8.7 Hz, 2-H), 3.95 (1H, ddd, *J* = 10.8, 6.3, 3.1 Hz, 5-H_A), 3.80 (OMe), 3.53 (td, *J* = 9.9, 6.3 Hz, 5-H_B), 2.93-3.00 (1H, m, 6-H), 2.61-2.75 (2H, m, 9-H_2), 2.18-2.23 (1H, m, 10-H_A), 2.10-2.17 (1H, m, 3-H), 2.02-2.09 (1H, m, 4-H_A), 1.73-1.82 (1H, m, 4-H_B), 1.66-1.73 (1H, m, 10-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.6 (C Ar), 148.0 (C Ar), 144.2 (C Ar), 136.2 (C Ar), 135.0 (C Ar), 133.2 (C-12), 132.9 (CH Ar), 131.6 (CH Ar), 131.4 (CH Ar), 128.9 (C-8), 128.5 (2 x CH Ar), 127.8 (2 x CH Ar), 127.5 (CH Ar), 126.5 (C-7), 126.2 (C-11), 125.8 (2 x CH Ar), 123.8 (CH Ar), 113.9 (2 x

CH Ar), 67.0 (C-2), 55.4 (OMe), 51.9 (C-3), 48.9 (C-5), 47.4 (C-6), 32.9 (C-9), 29.0 (C-10), 28.4 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H, between 2-H and 7-H. **HRMS** (ESI): calculated for $C_{30}H_{30}N_2O_5SNa$ $[M+Na]^+$ requires *m/z* 533.1773, found *m/z* 533.1765. **IR** (film) ν_{max}: 2980, 2889, 2360, 1461, 1381, 1251 cm^{-1}.

Data for ***cis*-237au:** NMR spectra was too weak to characterize.

5.9.37 (±)-{(2*R*,3*S*)-2-[(1'*E*)-4-Methoxystyryl]-1-[(2-nitrophenyl)sulfonyl]pyrrolidin-3-yl}methanol (*trans*-237av)

(±)-{(2*R*,3*R*)-2-[(1'*E*)-4-methoxystyryl]-1-[(2-nitrophenyl)sulfonyl]pyrrolidin-3-yl}methanol (*cis*-237av)



Amine ***E,E*-233q** (12.0 mg, 0.0309 mmol), paraformaldehyde **182am** (18.8 mg, 0.618 mmol) and $Ti(O^iPr)_4$ (2.7 mg, 0.0093 mmol) were subjected to the general procedure **H** except using 20 equivalents of paraformaldehyde **182am** and conducting the reaction at 0 °C for 48 hours (FCC: gradient elution: 15% → 30% EtOAc - pentane) to yield a separable 1.6:1 mixture of ***trans*-237av** and ***cis*-237av** as colorless oil (6.3 mg, 50%).

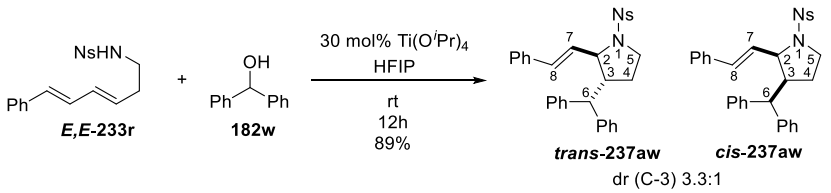
Data for ***trans*-237av:** R_f 0.35 (40% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$)** **δ** 7.93 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.57 (1H, dd, *J* = 7.9, 1.4 Hz, Ar), 7.48-7.53 (1H, m, Ar), 7.35-7.40 (1H, m, Ar), 7.08 (2H, d, *J* = 8.7 Hz, Ar), 6.78 (2H, d, *J* = 8.7 Hz, Ar), 6.41 (1H, d,

J = 15.7 Hz, 8-H), 5.67 (1H, dd, *J* = 15.7, 8.3 Hz, 7-H), 4.31 (1H, dd, *J* = 8.3, 6.5 Hz, 2-H), 3.88 (1H, ddd, *J* = 10.3, 8.0, 4.4 Hz, 5-H_A), 3.80 (OMe), 3.62-3.68 (1H, m, 6-H_A), 3.54-3.61 (2H, m, 6-H_B and 5-H_B), 2.13-2.30 (1H, m, 3-H), 2.06-2.15 (1H, m, 4-H_A), 1.82 (1H, dq, *J* = 12.4, 8.1 Hz, 4-H_B), 1.51 (1H, br s, OH). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.6 (C Ar), 148.0 (C Ar), 134.5 (C Ar), 133.2 (CH Ar), 132.9 (C-8), 131.6 (CH Ar), 131.5 (CH Ar), 128.8 (C Ar), 127.8 (2 x CH Ar), 125.6 (C-7), 123.9 (CH Ar), 114.0 (2 x CH Ar), 64.9 (C-2), 62.9 (C-6), 55.4 (OMe), 48.9 (C-3), 48.6 (C-5), 27.4 (C-4). **HRMS** (ESI): calculated for $C_{20}H_{22}N_2O_6SNa$ $[M+Na]^+$ requires *m/z* 441.1096, found *m/z* 441.1092. **IR** (film) ν_{max}: 3658, 2980, 2889, 2360, 1380, 1251 cm^{-1}.

Data for ***cis*-237av: R_f** 0.30 (40% EtOAc - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.96 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.48-7.54 (2H, m, Ar), 7.41-7.46 (1H, m, Ar), 7.12 (2H, d, *J* = 8.7 Hz, Ar), 6.79 (2H, d, *J* = 8.7 Hz, Ar), 6.42 (1H, d, *J* = 15.7 Hz, 8-H), 5.76 (1H, dd, *J* = 15.7, 8.5 Hz, 7-H), 4.70 (1H, t, *J* = 8.1 Hz, 2-H), 3.80 (OMe), 3.76 (1H, ddd, *J* = 9.8, 8.4, 2.3 Hz, 5-H_A), 3.60-3.66 (2H, m, 6-H_2), 3.57 (1H, td, *J* = 9.8, 7.1 Hz, 5-H_B), 2.52-2.61 (1H, m, 3-H), 2.08 (1H, dtd, *J* = 13.2, 6.7, 2.3 Hz, 4-H_A), 1.77-1.90 (1H, m, 4-H_B), 1.39 (1H, br s, OH). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.7 (C Ar), 148.2 (C Ar), 133.7 (C Ar), 133.3 (C-8), 133.2 (CH Ar), 131.6 (CH Ar), 131.4 (CH Ar), 128.8 (C Ar), 127.9 (2 x CH Ar), 123.9 (CH Ar), 122.4 (C-7), 114.0 (2 x CH Ar). **HRMS** (ESI): calculated for $C_{20}H_{22}N_2O_6SNa$ $[M+Na]^+$ requires *m/z* 441.1096, found *m/z* 441.1092. **IR** (film) ν_{max}: 3658, 2980, 2889, 2360, 1380, 1251 cm^{-1}.

5.9.38 (±)-(2*R*,3*R*)-3-Benzhydryl-1-[(2-nitrophenyl)sulfonyl]-2-[(1'*E*)-styryl]pyrrolidine (*trans*-237aw)

(±)-(2*R*,3*S*)-3-benzhydryl-1-[(2-nitrophenyl)sulfonyl]-2-[(1'*E*)-styryl]pyrrolidine (*cis*-237aw)



Amine ***E,E*-233r** (10.0 mg, 0.0279 mmol), alcohol **182aw** (5.2 mg, 0.28 mmol) and $Ti(O^iPr)_4$ (2.4 mg, 0.0084 mmol) were subjected to the general procedure **H** except conducting the reaction at room temperature (FCC: gradient elution: 10% → 20% EtOAc - pentane) to yield a partially separable 3.3:1 mixture of ***trans*-237aw** and ***cis*-237aw** as a colorless oil (13.0 mg, 89%).

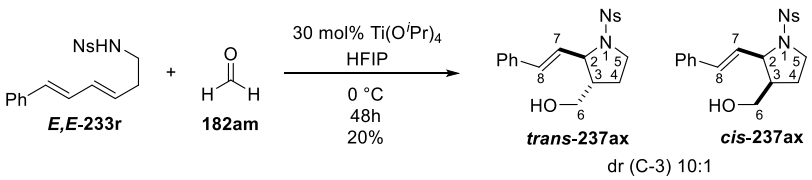
Data for ***trans*-237aw: R_f** 0.50 (30% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.84 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.55 (1H, dd, *J* = 8.0, 1.4 Hz, Ar), 7.47-7.52 (1H, m, Ar), 7.31-7.36 (1H, m, Ar), 7.14-7.29 (12H, m, Ar), 7.07-7.12 (1H, m, Ar), 6.97-7.02 (2H, m, Ar), 5.98 (1H, d, *J* = 15.7 Hz, 8-H), 5.73 (1H, dd, *J* = 15.8, 7.7 Hz, 7-H), 4.30 (1H, dd, *J* = 7.7, 3.6 Hz, 2-H), 3.89 (1H, dt, *J* = 10.3, 7.2 Hz, 5-H_A), 3.76 (1H, d, *J* = 11.5 Hz, 6-H), 3.63 (1H, ddd, *J* = 10.3, 7.5, 5.7 Hz, 5-H_B), 2.98 (1H, dddd, *J* = 11.5, 6.6, 5.1, 3.6 Hz, 3-H), 2.03-2.12 (1H, m, 4-H_A), 1.67 (1H, ddt, *J* = 12.9, 7.2, 5.7 Hz, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 148.1 (C Ar), 143.0 (C Ar), 142.9 (C Ar), 136.2 (C Ar), 134.1 (C Ar), 133.2 (CH Ar), 131.8 (C-8), 131.6 (CH Ar), 131.5 (CH Ar), 128.9 (2 x CH Ar), 128.8 (2 x CH Ar), 128.4 (2 x CH Ar), 128.3 (2 x CH Ar), 128.2 (C-7), 128.0 (2 x CH Ar), 127.8 (CH Ar), 126.93 (CH Ar), 126.85

(CH Ar), 126.5 (2 x CH Ar), 123.8 (CH Ar), 66.1 (C-2), 54.5 (C-6), 50.5 (C-3), 48.0 (C-5), 28.9 (C-4). **HRMS** (ESI): calculated for $C_{31}H_{29}N_2O_4S$ $[M+H]^+$ requires *m/z* 525.1848, found *m/z* 525.1841. **IR** (film) ν_{max}: 2980, 2888, 1738, 1543, 1375, 1162 cm^{-1}.

Data for ***cis*-237aw** (from the mixture)**: R_f** 0.45 (30% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.94 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.52-7.56 (1H, m, Ar), 7.42-7.47 (1H, m, Ar), 7.08-7.36 (14H, m, Ar), 7.04-7.07 (2H, m, Ar), 5.90 (1H, d, *J* = 15.9 Hz, 8-H), 5.83 (1H, dd, *J* = 15.8, 7.2 Hz, 7-H), 4.65 (1H, t, *J* = 7.0 Hz, 2-H), 3.72-3.76 (1H, m, 5-H_A), 3.63 (1H, d, *J* = 12.0 Hz, 6-H), 3.46 (1H, td, *J* = 10.2, 7.1 Hz, 5-H_B), 3.16-3.26 (1H, m, 3-H), 1.73-1.89 (2H, m, 4-H_2). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 148.2 (C Ar), 143.5 (C Ar), 143.0 (C Ar), 142.4 (C Ar), 136.3 (C Ar), 134.1 (C-8), 133.8 (CH Ar), 133.4 (CH Ar), 131.7 (CH Ar), 131.4 (CH Ar), 128.9 (2 x CH Ar), 128.6 (2 x CH Ar), 128.0 (2 x CH Ar), 127.9 (2 x CH Ar), 127.6 (2 x CH Ar), 126.9 (CH Ar), 126.8 (2 x CH Ar), 126.6 (2 x CH Ar), 124.1 (C-7), 123.9 (CH Ar), 64.0 (C-2), 53.0 (C-6), 48.5 (C-3), 47.6 (C-5), 29.3 (C-4).

5.9.39 (±)-{(2*R*,3*S*)-1-[(2-Nitrophenyl)sulfonyl]-2-[(1'*E*)-styryl]pyrrolidin-3-yl}methanol (*trans*-237ax)

(±)-{(2*R*,3*R*)-1-[(2-Nitrophenyl)sulfonyl]-2-[(1'*E*)-styryl]pyrrolidin-3-yl}methanol (*cis*-237ax)



Amine ***E,E*-233r** (9.4 mg, 0.026 mmol), paraformaldehyde **182am** (15.9 mg, 0.525

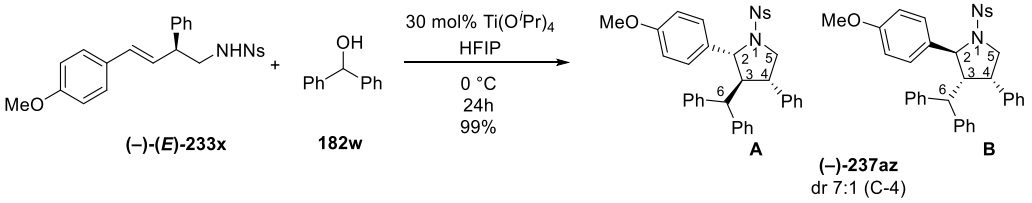
mmol) and $Ti(O^iPr)_4$ (2.3 mg, 0.0079 mmol) were subjected to the general procedure **H** except using 20 equivalents of paraformaldehyde **182am** and conducting the reaction at 0 °C for 48 hours (FCC: gradient elution: 10% → 20% EtOAc - pentane) to yield an inseparable 10:1 mixture of ***trans*-237ax** and ***cis*-237ax** as a colorless oil (3.0 mg, 20%).

Data for ***trans*-237ax** (from the mixture)**: R_f** 0.50 (30% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.94 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.57 (1H, dd, *J* = 7.9, 1.3 Hz, Ar), 7.49-7.53 (1H, m, Ar), 7.36-7.40 (1H, m, Ar), 7.17-7.27 (3H, m, Ar), 7.12-7.17 (2H, m, Ar), 6.47 (1H, d, *J* = 15.8 Hz, 8-H), 5.85 (1H, dd, *J* = 15.7, 8.1 Hz, 7-H), 4.36 (1H, dd, *J* = 8.1, 6.2 Hz, 2-H), 3.88 (1H, ddd, *J* = 10.4, 8.0, 4.6 Hz, 5-H_A), 3.55-3.68 (3H, m, 5-H_B and 6-H_2), 2.28 (1H, dp, *J* = 7.8, 6.2 Hz, 3-H), 2.06-2.16 (1H, m, 4-H_A), 1.83 (1H, dq, *J* = 12.5, 7.8 Hz, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 148.1 (C Ar), 136.0 (C Ar), 134.3 (C Ar), 133.24 (C-8), 133.16 (CH Ar), 131.58 (CH Ar), 131.49 (CH Ar), 128.6 (2 x CH Ar), 128.12 (C-7), 128.0 (CH Ar), 126.6 (2 x CH Ar), 123.9 (CH Ar), 64.6 (C-2), 62.8 (C-6), 48.8 (C-3), 48.6 (C-5), 27.3 (C-4). **HRMS** (ESI): calculated for $C_{19}H_{20}N_2O_5SNa$ $[M+Na]^+$ requires *m/z* 411.0991, found *m/z* 411.0985. **IR** (film) ν_{max}: 3658, 2980, 2888, 1738, 1542, 1378 cm^{-1}.

Data for ***cis*-237ax** (from the mixture)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.96-8.00 (1H, m, Ar), 7.49-7.53 (1H, m, Ar), 7.42-7.46 (1H, m, Ar), 7.17-7.27 (6H, m, Ar), 6.48 (1H, d, *J* = 15.9 Hz, 8-H), 5.93 (1H, dd, *J* = 15.8, 8.3 Hz, 7-H), 4.73 (1H, t, *J* = 8.0 Hz, 2-H), 3.84-3.90 (1H, m, 5-H_A), 3.74-3.81 (1H, m, 5-H_B and 6-H_A), 3.55-3.68 (1H, m, 6-H_B), 2.54-2.63 (1H, m, 3-H), 2.06-2.16 (1H, m, 4-H_A), 1.77-1.88 (1H, m, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 148.1 (C Ar), 136.0 (C Ar), 134.3 (C Ar), 133.6 (CH Ar), 133.4 (C-8), 131.56 (CH Ar), 131.4 (CH Ar), 128.7 (2 x CH Ar), 128.2 (C-7), 128.0 (CH Ar), 126.7 (2 x CH Ar), 124.8 (CH Ar),

63.8 (C-2), 62.1 (C-6), 48.8 (C-3), 46.5 (C-5), 26.9 (C-4).

5.9.40 (±)-(2*R*,3*R*,4*S*)-3-Benzhydryl-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-4-phenylpyrrolidine and (±)-(2*S*,3*S*,4*S*)-3-benzhydryl-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-4-phenylpyrrolidine [(–)-237az]



Amine **(–)-(*E*)-233x** (9.5 mg, 0.022 mmol) and alcohol **182w** (4.0 mg, 0.022 mmol) and $Ti(O^iPr)_4$ (1.9 mg, 0.0065 mmol) were subjected to the general procedure **H** except conducting the reaction at 0 °C for 24 hours (FCC: gradient elution: 15% → 25% EtOAc - pentane) to yield an inseparable 7:1 mixture of diastereomers **(–)-237az** as a colorless oil (12.9 mg, 99%, 99% ee).

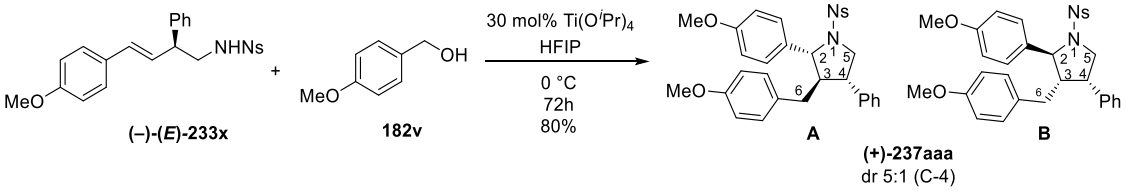
Data for **diastereomer A** of **(–)-237az** (from the mixture): $\mathbf{R_f}$ 0.40 (30% EtOAc - pentane). $[\alpha]_D^{25}$ = –0.159 (*c* = 10.0, $CHCl_3$). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.51 (1H, dd, *J* = 7.9, 1.4 Hz, Ar), 7.43-7.48 (1H, m, Ar), 7.00-7.24 (8H, m, Ar), 6.86-7.00 (6H, m, Ar),6.72-6.85 (3H, m, Ar), 6.62 (2H, d, *J* = 8.6 Hz, Ar), 6.45 (2H, d, *J* = 8.6 Hz, Ar), 4.85 (1H, d, *J* = 5.9 Hz, 2-H), 4.35 (1H, dd, *J* = 10.8, 8.7 Hz, 5-H_A), 4.01 (1H, d, *J* = 10.4 Hz, 6-H), 3.86-3.93 (1H, m, 5-H_B), 3.70 (OMe), 3.43-3.51 (1H, m, 3-H), 3.26 (1H, q, *J* = 8.7 Hz, 4-H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.7 (C Ar), 147.6 (C Ar), 142.5 (C Ar), 141.6 (C Ar), 140.6 (C Ar), 134.0 (C Ar), 133.8 (C Ar), 132.6 (CH Ar), 131.13 (CH Ar), 131.07 (CH Ar), 128.7 (2

x CH Ar), 128.6 (2 x CH Ar), 128.53 (2 x CH Ar), 128.49 (2 x CH Ar), 128.4 (2 x CH Ar), 128.2 (2 x CH Ar), 128.0 (2 x CH Ar), 126.8 (CH Ar), 126.5 (CH Ar), 126.4 (CH Ar), 123.6 (CH Ar), 113.6 (2 x CH Ar), 68.7 (C-2), 61.0 (C-3), 58.8 (C-6), 57.9 (C-5), 55.4 (OMe), 51.0 (C-4). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 4-H, between 2-H and 6-H, between 4-H and 6-H. **HRMS** (ESI): calculated for $C_{36}H_{33}N_2O_5S$ $[M+H]^+$ requires *m/z* 605.2110, found *m/z* 605.2100. **IR** (film) ν_{max}: 2980, 2889, 2360, 1542, 1372, 1162 cm^{-1}.

Data for **diastereomer B of (–)-237az** (from the mixture)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.43-7.48 (1H, m, Ar), 7.32-7.37 (1H, m, Ar), 7.00-7.24 (8H, m, Ar), 6.86-7.00 (6H, m, Ar),6.72-6.85 (3H, m, Ar), 6.54 (2H, d, *J* = 8.6 Hz, Ar), 6.18 (2H, d, *J* = 8.6 Hz, Ar), 4.84 (1H, d, *J* = 12.7 Hz, 2-H), 4.37-4.40 (1H, m, 5-H_A), 4.17-4.22 (1H, m, 5-H_B), 3.74-3.79 (1H, m, 3-H), 3.62 (OMe),3.43-3.51 (2H, m, 4-H and 6-H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.3 (C Ar), 146.6 (C Ar), 142.8 (C Ar), 142.0 (C Ar), 140.2 (C Ar), 134.0 (C Ar), 133.8 (C Ar), 132.0 (CH Ar), 131.13 (CH Ar), 130.8 (CH Ar), 129.0 (2 x CH Ar), 128.6 (2 x CH Ar), 128.53 (4 x CH Ar), 128.3 (2 x CH Ar), 128.1 (2 x CH Ar), 127.9 (2 x CH Ar), 127.2 (CH Ar), 126.6 (CH Ar), 126.35 (CH Ar), 123.4 (CH Ar), 113.2 (2 x CH Ar), 67.4 (C-2), 57.2 (C-3), 56.4 (C-5), 55.4 (OMe), 53.5 (C-6), 46.3 (C-4).

Racemic **(±)-237az** (99%, 7:1 dr) was made with the same procedure with racemic alcohol **(±)-(*E*)-233x**.

5.9.41 (±)-(2*R*,3*R*,4*S*)-3-(4-Methoxybenzyl)-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-4-phenylpyrrolidine and (±)-(2*S*,3*S*,4*S*)-3-(4-methoxybenzyl)-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-4-phenylpyrrolidine [(+)-237aaa]



Amine **(–)-(*E*)-233x** (38.6 mg, 0.0881 mmol) and alcohol **182v** (12.2 mg, 0.0881 mmol) and $Ti(O^iPr)_4$ (7.5 mg, 0.026 mmol) were subjected to the general procedure E except conducting the reaction at 0 °C for 72 hours (FCC: gradient elution: 10% → 30% EtOAc - pentane) to yield an inseparable 5:1 mixture of diastereomers **(–)-237aaa** as a colorless oil (39.4 mg, 80%, 99% ee).

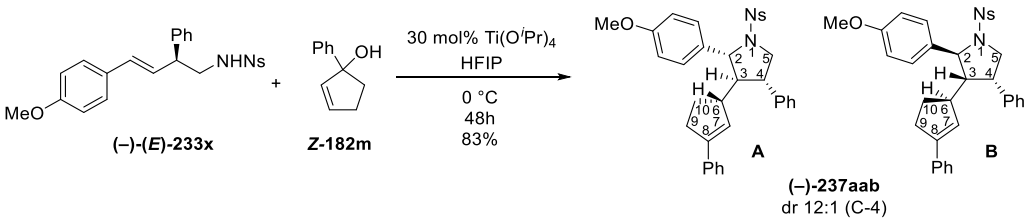
Data for **diastereomer A** of **(+)-237aaa** (from the mixture)**: R_f** 0.40 (30% EtOAc - pentane). $[\alpha]_D^{25}$ = –3.15 (*c* = 10.0, $CHCl_3$). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.49 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.40-7.45 (1H, m, Ar), 7.30-7.36 (2H, m, Ar), 7.24-7.30 (3H, m, Ar), 7.08-7.15 (2H, m, Ar), 7.06 (2H, d, *J* = 8.7 Hz, Ar), 6.78 (2H, d, *J* = 8.7 Hz, Ar), 6.64 (2H, d, *J* = 8.7 Hz, Ar), 6.56 (2H, d, *J* = 8.6 Hz, Ar), 4.62 (1h, d, *J* = 9.6 Hz, 2-H), 4.32 (1H, dd, *J* = 10.7, 7.8 Hz, 5-H_A), 3.74 (3H, s, OMe), 3.73 (3H, s, OMe), 3.67-3.71 (1H, m, 5-H_B), 3.12 (1H, td, *J* = 11.4, 7.8 Hz, 4-H), 2.79 (1H, ddt, *J* = 11.4, 9.6, 5.5 Hz, 3-H), 2.59 (1H, d, *J* = 5.5 Hz, 6-H_2). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.24 (C Ar), 158.2 (C Ar), 147.3 (C Ar), 138.2 (C Ar), 134.5 (C Ar), 132.4 (CH Ar), 131.6 (C Ar), 130.91 (2 x CH Ar), 130.75 (2 x CH Ar), 129.51 (2 x CH Ar), 129.47 (C Ar), 128.99 (2 x CH Ar), 128.15 (2 x CH Ar), 127.5 (CH Ar),

123.6 (CH Ar), 113.69 (2 x CH Ar), 113.67 (2 x CH Ar), 67.2 (C-2), 57.02 (C-5), 56.3 (C-3), 55.5 (OMe), 55.39 (OMe), 48.5 (C-4), 33.8 (C-6). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 4-H, between 2-H and 6-H_2, between 4-H and 6-H_2. **HRMS** (ESI): calculated for $C_{31}H_{30}N_2O_6SNa$ $[M+Na]^+$ requires *m/z* 581.1722, found *m/z* 581.1715. **IR** (film) ν_{max}: 2921, 1711, 1611, 1542, 1511, 1464 cm^{-1}.

Data for **diastereomer B** of **(+)-237aaa** (from the mixture)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.45-7.49 (1H, m, Ar), 7.40-7.45 (1H, m, Ar), 7.30-7.36 (2H, m, Ar), 7.24-7.30 (3H, m, Ar), 7.17-7.21 (2H, m, Ar), 6.95 (2H, d, *J* = 8.7 Hz, Ar), 6.89 (2H, d, *J* = 8.7 Hz, Ar), 6.69-6.73 (2H, m, Ar), 6.52 (2H, d, *J* = 8.7 Hz, Ar), 4.54 (1H, d, *J* = 9.8 Hz, 2-H), 4.27 (1H, dd, *J* = 10.6, 7.8 Hz, 5-H_A), 3.82 (3H, s, OMe), 3.79 (3H, s, OMe), 3.66-3.70 (1H, m, 5-H_B), 3.04 (1H, td, *J* = 11.4, 7.8 Hz, 4-H), 2.68-2.74 (1H, m, 3-H), 2.44-2.49 (2H, m, 6-H_2). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.21 (C Ar), 158.0 (C Ar), 155.9 (C Ar), 143.6 (C Ar), 133.0 (C Ar), 132.3 (CH Ar), 131.7 (C Ar), 130.85 (2 x CH Ar), 130.3 (2 x CH Ar), 130.0 (C Ar), 129.6 (2 x CH Ar), 128.96 (2 x CH Ar), 128.18 (2 x CH Ar), 127.4 (CH Ar), 123.5 (CH Ar), 114.0 (2 x CH Ar), 113.6 (2 x CH Ar), 67.1 (C-2), 56.96 (C-5), 56.0 (C-3), 55.6 (OMe), 55.4 (OMe), 47.8 (C-4), 33.0 (C-6).

Racemic **(±)-237aaa** (99%, 7:1 dr) was made with the same procedure with racemic alcohol **(±)-(*E*)-233x**.

5.9.42 (±)-(2*R*,3*R*,4*S*)-2-(4-Methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-4-phenyl-3-[(1'*S*)-3-phenylcyclopent-2-en-1-yl]pyrrolidine and (±)-(2*S*,3*S*,4*S*)-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-4-phenyl-3-[(1'*R*)-3-phenylcyclopent-2-en-1-yl]pyrrolidine [(–)-237aab]



Amine **(–)-(*E*)-233y** (8.7 mg, 0.020 mmol) and alcohol ***Z*-182m** (3.2 mg, 0.020 mmol) and $Ti(O^iPr)_4$ (1.9 mg, 0.0065 mmol) were subjected to the general procedure E except conducting the reaction at 0 °C for 48 hours (FCC: gradient elution: 15% → 25% EtOAc - pentane) to yield an inseparable 12:1 mixture of diastereomers **(–)-237aab** as a colorless oil (9.6 mg, 83%, 99% ee).

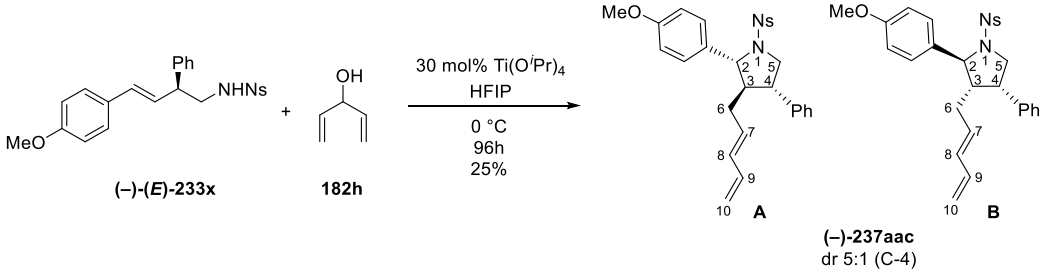
Data for **diastereomer A** of **(–)-237aab** (from the mixture)**: R_f** 0.50 (35% EtOAc - pentane). $[\alpha]_D^{25}$ = –3.12 (*c* = 10.0, $CHCl_3$). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.48-7.52 (1H, m, Ar), 7.39-7.46 (2H, m, Ar), 7.06-7.39 (13H, m, Ar), 6.56 (2H, d, *J* = 8.7 Hz, Ar), 5.55 (1H, q, *J* = 2.3 Hz, 7-H), 4.80 (1H, d, *J* = 9.1 Hz, 2-H), 4.39 (1H, dd, *J* = 10.7, 7.6 Hz, 5-H_A), 3.82-3.90 (1H, m, 5-H_B), 3.73 (OMe), 3.26 (1H, td, *J* = 11.4, 7.5 Hz, 4-H), 2.97-3.04 (1H, m, 6-H), 2.81 (1H, ddd, *J* = 11.4, 9.1, 4.4 Hz, 3-H), 2.46-2.62 (2H, m, 10-H_2), 2.02 (1H, dtd, *J* = 13.3, 9.0, 4.4 Hz, 9-H_A), 1.54-1.66 (1H, m, 9-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.2 (C Ar), 147.4 (C Ar), 142.6 (C Ar), 139.0 (C Ar), 136.2 (C Ar), 134.5 (C Ar), 133.1 (C-8), 132.4 (CH Ar), 131.0 (CH Ar), 130.9 (CH Ar), 129.7 (2 x CH Ar), 129.0 (2 x CH Ar), 128.3 (2 x CH Ar), 128.1 (2 x CH Ar), 127.7 (CH Ar), 127.6 (C-7), 127.3 (CH Ar), 125.8 (2 x CH Ar), 123.6

(CH Ar), 113.7 (2 x CH Ar), 66.7 (C-2), 60.2 (C-3), 57.1 (C-5), 55.5 (OMe), 48.3 (C-4), 45.9 (C-3), 32.7 (C-10), 26.0 (C-9). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 4-H, between 2-H and 6-H, between 4-H and 7-H, between 4-H and 9-H_A, between 4-H and 6-H, between 4-H and 7-H, between 4-H and 9-H_B. **HRMS** (ESI): calculated for $C_{34}H_{32}N_2O_5SNa$ $[M+Na]^+$ requires *m/z* 603.1930, found *m/z* 603.1917. **IR** (film) ν_{max}: 2980, 2889, 1738, 1542, 1372, 1250 cm^{-1}.

Data for **diastereomer B of (–)-237aab** (from the mixture)**:** both ^1H and ^{13}C NMR spectra were too weak to determine the signals.

Racemic **(±)-237aab** (99%, 7:1 dr) was made with the same procedure with racemic alcohol **(±)-(*E*)-233x**.

5.9.43 (±)-(2*R*,3*R*,4*S*)-2-(4-Methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-3-[(1'*E*)-penta-2,4-dien-1-yl]-4-phenylpyrrolidine and (±)-(2*S*,3*S*,4*S*)-2-(4-methoxyphenyl)-1-[(2-nitrophenyl)sulfonyl]-3-[(1'*E*)-penta-2,4-dien-1-yl]-4-phenylpyrrolidine [(–)-237aac]



Amine **(–)-(*E*)-233x** (34.2 mg, 0.0781 mmol) and alcohol **182h** (37.8 mg, 0.390 mmol) and $Ti(O^iPr)_4$ (6.7 mg, 0.023 mmol) were subjected to the general procedure **H** except using 5 equivalents of alcohol **182h** and conducting the reaction at 0 °C for 96

hours (FCC: gradient elution: 12% → 20% EtOAc - pentane) to yield an inseparable 5:1 mixture of diastereomers **(–)-237aac** as a colorless oil (9.9 mg, 25%, 99% ee).

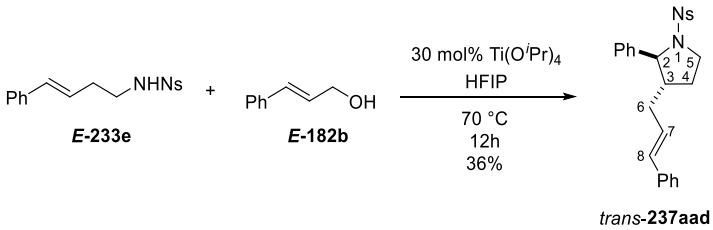
Data for **diastereomer A** of **(–)-237aac** (from the mixture)**: R_f** 0.50 (35% EtOAc - pentane). $[\alpha]_D^{25}$ = –1.23 (*c* = 10.0, $CHCl_3$). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.49-7.57 (1H, m, Ar), 7.43-7.49 (1H, m, Ar), 7.30-7.38 (2H, m, Ar), 7.20-7.29 (3H, m, Ar), 7.05-7.18 (4H, m, Ar), 6.60 (2H, d, *J* = 8.7 Hz, Ar), 6.08 (1H, dt, *J* = 16.8, 10.4 Hz, 9-H), 5.90 (1H, dd, *J* = 15.1, 10.4 Hz, 8-H), 5.34 (dt, *J* = 15.1, 7.4 Hz, 7-H), 5.04 (1H, dd, *J* = 16.8, 1.7 Hz, 10-H_A), 4.95 (1H, dd, *J* = 10.4, 1.7 Hz, 10-H_B), 4.65 (1H, d, *J* = 9.8 Hz, 2-H), 4.39 (1H, dd, *J* = 11.0, 7.8 Hz, 5-H_A), 3.81 (1H, t, *J* = 11.0 Hz, 5-H_B), 3.74 (3H, s, OMe), 3.17 (1H, td, *J* = 11.5, 7.8 Hz, 4-H), 2.45-2.55 (1H, m, 3-H), 2.07-2.12 (2H, m, 6-H_2). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.4 (C Ar), 147.4 (C Ar), 138.2 (C Ar), 136.8 (C-9), 134.5 (C Ar), 134.1 (C-8), 132.5 (CH Ar), 131.6 (C Ar), 131.04 (CH Ar), 130.96 (CH Ar), 130.0 (C-7), 129.5 (2 x CH Ar), 129.0 (2 x CH Ar), 128.1 (2 x CH Ar), 127.6 (CH Ar), 123.6 (CH Ar), 116.0 (C-10), 113.76 (2 x CH Ar), 68.2 (C-2), 56.7 (C-5), 56.0 (C-3), 55.5 (OMe), 48.7 (C-4), 31.7 (C-6). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 4-H, between 2-H and 6-H_2, between 2-H and 7-H, between 4-H and 6-H_2. **HRMS** (ESI): calculated for $C_{28}H_{28}N_2O_5SNa$ $[M+Na]^+$ requires *m/z* 527.1617, found *m/z* 527.1607. **IR** (film) ν_{max}: 2921, 1611, 1541, 1513, 1368, 1249 cm^{-1}.

Data for **diastereomer B** of **(–)-237aac** (from the mixture)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.49-7.57 (2H, m, Ar), 7.30-7.38 (2H, m, Ar), 7.30-7.38 (2H, m, Ar), 7.20-7.29 (3H, m, Ar), 7.05-7.18 (4H, m, Ar), 6.61 (2H, d, *J* = 8.7 Hz, Ar), 6.20 (1H, dt, *J* = 17.0, 10.3 Hz, 9-H), 5.78 (1H, dd, *J* = 15.2, 10.3 Hz, 8-H), 5.42 (1H, dt, *J* = 15.3, 6.9 Hz, 7-H), 4.91-5.07 (2H, m, 10-H_2), 4.72 (1H, d, *J* = 7.0 Hz, 2-H), 4.21-4.30 (2H, m, 5-H_2), 3.73 (3H, s,

OMe), 3.63 (1H, q, *J* = 6.1 Hz, 4-H), 2.45-2.55 (1H, m, 3-H), 1.72-1.78 (2H, m, 6-H_2). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.4 (C Ar), 147.4 (C Ar),139.0 (C Ar), 136.9 (C-9), 133.4 (C-8), 132.8 (C Ar), 131.90 (C Ar), 131.85 (C-7), 131.3 (CH Ar), 131.1 (CH Ar), 131.0 (CH Ar), 128.82 (2 x CH Ar), 128.80 (2 x CH Ar), 128.2 (2 x CH Ar), 127.2 (CH Ar), 123.7 (CH Ar), 115.9 (C-10), 113.78 (2 x CH Ar), 67.1 (C-2), 55.4 (OMe), 54.11 (C-5), 54.06 (C-3), 44.6 (C-4), 30.6 (C-6). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H_2.

Racemic **(±)-237aac** (99%, 7:1 dr) was made with the same procedure with racemic alcohol **(±)-(*E*)-233x**.

5.9.44 (±)-(2*S*,3*S*)-3-Cinnamyl-1-[(2-nitrophenyl)sulfonyl]-2-phenylpyrrolidine (*trans*-237aad)

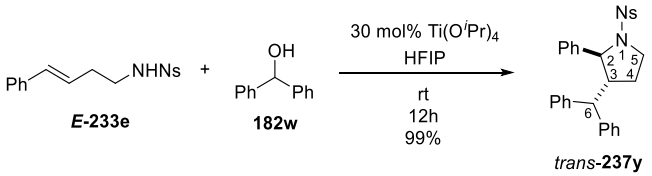


Amine ***E*-233e** (20.0 mg, 0.0602 mmol) and alcohol ***E*-182b** (8.1 mg, 0.0602 mmol) and $Ti(O^iPr)_4$ (5.1 mg, 0.018 mmol) were subjected to the general procedure **H** (FCC: gradient elution: 15% → 25% EtOAc - pentane) to yield a mixture of pyrrolidines ***trans*-237aad** and alcohol ***E*-182b** as a colorless oil (9.7 mg, 36%).

Data for **237aad** (from the mixture)**: R_f** 0.40 (35% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.51 (1H, dd, *J* = 8.0, 1.4 Hz, Ar), 7.42-7.47 (1H, m, Ar), 7.17-7.33 (8H, m, Ar), 7.05-7.17 (4H, m, Ar), 6.36 (1H, d, *J* = 16.0 Hz, 8-H), 6.04 (1H, dt, *J* = 15.7, 7.0 Hz, 7-H), 4.58 (1H, d, *J* = 7.0 Hz, 2-H), 4.10 (1H, ddd, *J* = 10.4, 7.8, 3.6 Hz, 5-H_A), 3.83 (1H,

ddd, *J* = 10.4, 9.1, 6.3 Hz, 5-H_B), 2.28-2.42 (2H, m, 3-H and 6-H_A), 2.17-2.26 (2H, m, 6-H_B and 4-H_A), 1.77 (1H, dtd, *J* = 12.4, 9.1, 7.8 Hz, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 147.5 (C Ar), 140.4 (C Ar), 137.3 (C Ar), 133.9 (C Ar), 132.7 (CH Ar), 132.4 (C-8), 131.02 (CH Ar), 130.95 (CH Ar), 128.7 (2 x CH Ar), 128.4 (2 x CH Ar), 127.7 (CH Ar), 127.6 (2 x CH Ar), 127.4 (C-7), 127.3 (CH Ar), 126.2 (2 x CH Ar), 123.6 (CH Ar), 69.1 (C-2), 50.6 (C-3), 49.7 (C-5), 35.4 (C-6), 30.6 (C-4). **IR** (film) ν_{max}: 2980, 1614, 1542, 1515, 1368, 1249 cm^{-1}.

5.9.45 (±)-(2*S*,3*R*)-3-Benzhydryl-1-[(2-nitrophenyl)sulfonyl]-2-phenylpyrrolidine (*trans*-237y)



E-233e 182w *trans*-237y

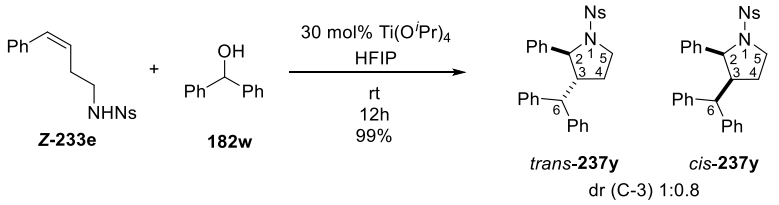
Amine ***E*-233e** (41.2 mg, 0.128 mmol) and alcohol **182w** (23.6 mg, 0.128 mmol) and Ti(O^{i}Pr)$_4$ (10.9 mg, 0.0384 mmol) were subjected to the general procedure **H** except conducting the reaction at room temperature (FCC: gradient elution: 8% → 15% EtOAc - pentane) to yield pyrrolidines ***trans*-237y** as a colorless oil (63.7 mg, 99%).

Data for ***trans*-237y: R_f** 0.50 (30% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.51 (1H, dd, *J* = 8.0, 1.7 Hz, Ar), 7.45-7.49 (1H, m, Ar), 7.34 (1H, dd, *J* = 8.0, 1.3 Hz, Ar), 7.22-7.26 (4H, m, Ar), 7.08-7.21 (7H, m, Ar), 6.97-7.03 (3H, m, Ar), 6.80-6.84 (2H, m, Ar), 4.71 (1H, d, *J* = 3.2 Hz, 2-H), 3.99 (1H, dt, *J* = 10.0, 7.6 Hz, 5-H_A), 3.91 (1H, ddd, *J* = 10.0, 7.8, 4.5 Hz, 5-H_B), 3.80 (1H, d, *J* = 11.7 Hz, 6-H), 3.04-3.13 (1H, m, 3-H), 2.09-2.18 (1H, m, 4-H_A), 1.73 (1H, ddt, *J* = 13.1, 7.1, 4.5 Hz, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 147.7 (C Ar),

142.92 (C Ar), 142.86 (C Ar), 141.6 (C Ar), 133.3 (C Ar), 133.0 (CH Ar), 131.14 (CH Ar), 131.07 (CH Ar), 128.9 (2 x CH Ar), 128.8 (2 x CH Ar), 128.3 (2 x CH Ar), 128.2 (2 x CH Ar), 127.9 (2 x CH Ar), 127.1 (CH Ar), 126.83 (CH Ar), 126.79 (CH Ar), 126.4 (2 x CH Ar), 123.6 (CH Ar), 67.3 (C-2), 54.8 (C-6), 53.6 (C-3), 48.6 (C-5), 28.0 (C-4). **HRMS** (ESI): calculated for $C_{29}H_{27}N_2O_4S$ $[M+H]^+$ requires *m/z* 499.1692, found *m/z* 499.1684. **IR** (film) ν_{max}: 2980, 2889, 2360, 1710, 1542, 1439 cm^{-1}.

5.9.46 (±)-(2*S*,3*R*)-3-Benzhydryl-1-[(2-nitrophenyl)sulfonyl]-2-phenylpyrrolidine (*trans*-237y)

(±)-(2*S*,3*S*)-3-benzhydryl-1-[(2-nitrophenyl)sulfonyl]-2-phenylpyrrolidine (*cis*-237y)



Amine ***Z*-233e** (18.0 mg, 0.0559 mmol) and alcohol **182w** (10.3 mg, 0.0559 mmol) and $Ti(O^iPr)_4$ (4.8 mg, 0.017 mmol) were subjected to the general procedure **H** except conducting the reaction at room temperature (FCC: gradient elution: 8% → 15% EtOAc - pentane) to yield an inseparable 1:0.8 mixture of ***trans*-237y** and ***cis*-237y** as a colorless oil (23.9 mg, 86%).

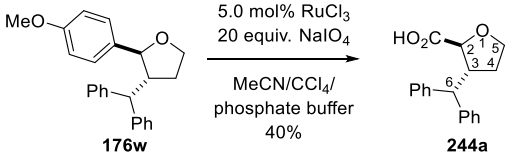
Data for ***cis*-237y** (from the mixture)**:** R_f 0.50 (30% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.42-7.48 (1H, m, Ar), 7.39 (2H, dd, *J* = 7.9, 1.7 Hz, Ar), 6.96-7.29 (12H, m, Ar), 6.93 (2H, t, *J* = 7.7 Hz, 1H), 6.56 (2H, dd, *J* = 7.9, 1.4 Hz, Ar), 5.16 (1H, d, *J* =

7.7 Hz, 2-H), 3.96-4.02 (1H, m, 5-H_A), 3.58 (1H, ddd, *J* = 11.2, 9.7, 6.7 Hz, 5-H_B), 3.39-3.49 (1H, m, 3-H), 3.04 (1H, d, *J* = 11.9 Hz, 6-H), 1.95-2.07 (1H, m, 4-H_A), 1.65-1.72 (1H, m, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 147.6 (C Ar), 143.7 (C Ar), 142.2 (C Ar), 137.7 (C Ar), 133.1 (C Ar), 131.24 (CH Ar), 131.15 (CH Ar), 130.9 (CH Ar), 128.8 (2 x CH Ar), 128.7 (2 x CH Ar), 128.4 (2 x CH Ar), 128.2 (2 x CH Ar), 127.73 (2 x CH Ar), 127.68 (2 x CH Ar), 127.6 (CH Ar), 126.8 (CH Ar), 126.7 (CH Ar), 123.4 (CH Ar), 65.3 (C-2), 52.6 (C-6), 48.6 (C-3), 48.2 (C-5), 29.1 (C-4). **HRMS** (ESI): calculated for $C_{29}H_{27}N_2O_4S$ $[M+H]^+$ requires *m/z* 499.1692, found *m/z* 499.1684. **IR** (film) ν_{max}: 2980, 2889, 2360, 1710, 1542, 1439 cm^{-1}.

Data for ***trans*-237y** matched those previously reported.

5.10 Synthesis of Carboxylic Acid Derivatives *via* Ru-catalyzed Oxidation of Aromatic Rings

5.10.1 (±)-(2S,3R)-3-benzhydryltetrahydrofuran-2-carboxylic acid (244a)

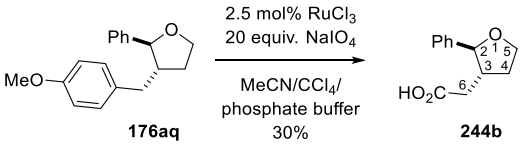


Tetrahydrofurans **176w** (49.0 mg, 0.142 mmol), $RuCl_3$ (1.5 mg, 0.0071 mmol), $NaIO_4$ (0.588 g, 2.84 mmol) and CCl_4:MeCN: Na_2HPO_4 buffer (3.5 mL) were subjected to the general procedure **I** (FCC: 5% DCM - MeOH) to yield **244a** (16.0 mg, 40%) as a colorless oil.

Data for **244a**: **R_f** 0.20 (10% DCM - MeOH). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.38 (2H, d, *J* = 7.6 Hz, Ar), 7.24-7.33 (6H, m, Ar), 7.16-7.21 (2H, m, Ar), 4.28 (1H, d, *J* = 2.4 Hz, 2-H),

4.03-4.14 (2H, m, 5-H_2), 3.87 (1H, d, *J* = 11.9 Hz, 6-H), 3.51 (1H, ddt, *J* = 12.0, 7.7, 2.5 Hz, 3-H), 1.96-2.06 (1H, m, 4-H_A), 1.69-1.76 (1H, m, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 175.5 (C=O), 143.2 (C Ar), 142.9 (C Ar), 129.0 (2 x C-H Ar), 128.9 (2 x C-H Ar), 128.4 (2 x C-H Ar), 128.2 (2 x C-H Ar), 127.0 (C-H Ar), 126.9 (C-H Ar), 80.6 (C-2), 68.8 (C-5), 54.4 (C-6), 47.5 (C-3), 29.5 (C-4). **NOESY-2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H. **HRMS** (ESI): calculated for $C_{18}H_{18}O_3Na$ $[M+Na]^+$ requires *m/z* 305.11482, found *m/z* 305.11484. **IR** (film) ν_{max}: 3658, 2980, 2888, 1461, 1461, 1252 cm^{-1}.

5.10.2 (±)-2-[(2S,3R)-2-Phenyltetrahydrofuran-3-yl]acetic acid (244b)

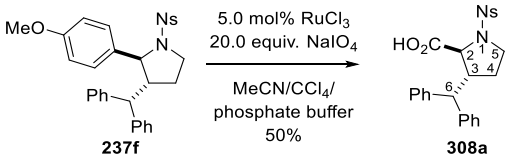


Tetrahydrofurans **176aq** (80.0 mg, 0.299 mmol), $RuCl_3$ (1.6 mg, 0.0075 mmol), $NaIO_4$ (1.270 g, 5.937 mmol) and CCl_4:MeCN: Na_2HPO_4 buffer (3.5 mL) were subjected to the general procedure **I** except using 2.5mol% of $RuCl_3$ (FCC: 5% DCM - MeOH) to yield **244b** (18.8 mg, 30%) as a colorless oil.

Data for **244b**: **R_f** 0.20 (5% DCM - MeOH). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.31-7.35 (4H, m, Ar), 7.25-7.30 (1H, m, Ar), 4.45 (1H, d, *J* = 7.3 Hz, 2-H), 4.16 (1H, dt, *J* = 8.4, 7.3 Hz, 5-H_A), 4.04 (1H ,td, *J* = 8.4, 5.1 Hz, 5-H_B), 2.56 (1H, dd, *J* = 15.0, 4.5 Hz, 6-H_A), 2.42-2.51 (1H, m, 3-H), 2.31-2.41 (2H, m, 4-H_A and 6-H_B), 1.79 (1H, dq, *J* = 12.3, 7.8 Hz, 4-H_B). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 177.7 (C=O), 141.3 (C Ar), 128.6 (2 x C-H Ar), 128.0 (C-H Ar), 126.4 (2 x C-H Ar), 85.7 (C-2), 68.0 (C-5), 44.2 (C-3), 36.2 (C-6), 32.3 (C-4). **HRMS** (ESI): calculated for $C_{12}H_{13}O_3$ $[M-H]^+$ requires *m/z* 205.08702, found *m/z*

205.08693. **IR** (film) ν_{max}: 3658, 2980, 2888, 1461, 1461, 1252 cm^{-1}.

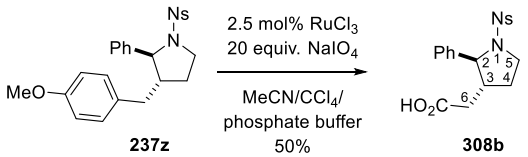
5.10.3 (±)-(2*S*,3*R*)-3-Benzhydryl-1-[(2-nitrophenyl)sulfonyl]pyrrolidine-2-carboxylic acid (308a)



Pyrrolidines **237f** (24.3 mg, 0.0460 mmol), $RuCl_3$ (0.48 mg, 0.0023 mmol), $NaIO_4$ (192.0 mg, 0.9205 mmol) and CCl_4:MeCN: Na_2HPO_4 buffer (3.5 mL) were subjected to the general procedure **I** (FCC: 5% DCM - MeOH) to yield **308a** (10.7 mg, 50%) as a colorless oil.

Data for **308a**: $\mathbf{R_f}$ 0.20 (5% DCM - MeOH). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.96 (1H, dd, *J* = 8.1, 1.4 Hz, Ar), 7.70-7.74 (1H, m, Ar), 7.59-7.67 (2H, m, Ar), 7.11-7.28 (10H, m, Ar), 4.29 (1H, d, *J* = 1.7 Hz, 6-H), 3.81 (1H, td, *J* = 9.4, 7.3 Hz, 5-H_A), 3.71 (1H, td, *J* = 9.4, 3.1 Hz, 5-H_B), 3.64 (1H, d, *J* = 12.1 Hz, 6-H), 3.13-3.20 (1H, m, 3-H), 2.06-2.16 (1H, m, 4-H_A), 1.70-1.77 (1H, m, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 175.6 (C=O), 148.2 (C Ar), 142.3 (C Ar), 142.1 (C Ar), 134.0 (C-H Ar), 132.5 (C Ar), 132.0 (C-H Ar), 131.2 (C-H Ar), 129.1 (2 x C-H Ar), 129.0 (2 x C-H Ar), 128.04 (2 x C-H Ar), 128.00 (2 x C-H Ar), 127.2 (C-H Ar), 127.1 (C-H Ar), 124.3 (C-H Ar), 64.1 (C-2), 53.5 (C-6), 48.1 (C-3), 47.3 (C-5). **HRMS** (ESI): calculated for $C_{24}H_{22}N_2O_6SNa$ $[M+Na]^+$ requires *m/z* 489.1096, found *m/z* 489.1089. **IR** (film) ν_{max}: 3027, 1707, 1543, 1452, 1370, 1200 cm^{-1}.

5.10.4 (±)-2-[(2*S*,3*R*)-1-[(2-Nitrophenyl)sulfonyl]-2-phenylpyrrolidin-3-yl)acetic acid (308b)



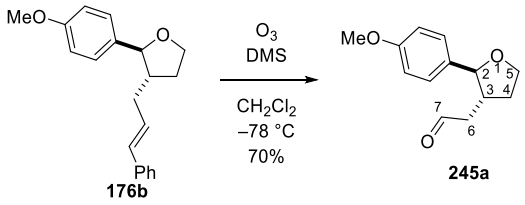
237z **308b**

Pyrrolidines **237z** (34.8 mg, 0.0787 mmol), $RuCl_3$ (0.81 mg, 0.0039 mmol), $NaIO_4$ (337.0 mg, 1.575 mmol) and CCl_4:MeCN: Na_2HPO_4 buffer (3.5 mL) were subjected to the general procedure **I** (FCC: 5% DCM - MeOH) to yield **308b** (15.3 mg, 50%) as a colorless oil.

Data for **308b**: $\mathbf{R_f}$ 0.20 (5% DCM - MeOH). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.53 (1H, dd, *J* = 7.9, 1.3 Hz, Ar), 7.45-7.50 (1H, m, Ar), 7.23-7.27 (1H, m, Ar), 7.17-7.21 (1H, m, Ar), 7.06-7.16 (5H, m, Ar), 4.57 (1H, d, *J* = 7.5 Hz, 2-H), 4.06 (1H, ddd, *J* = 11.2, 7.9, 3.7 Hz, 5-H_A), 3.85 (1H, ddd, *J* = 11.2, 8.9, 6.5 Hz, 5-H_B), 2.54-2.61 (1H, m, 3-H), 2.46 (1H, dd, *J* = 16.4, 5.5 Hz, 6-H_A), 2.28-2.38 (2H, m, 4-H_A and 6-H_B), 1.74 (1H, dq, *J* = 12.4, 8.9 Hz, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 176.6 (C=O), 147.5 (C Ar), 139.3 (C Ar), 133.7 (C Ar), 132.9 (C-H Ar), 131.1 (C-H Ar), 131.0 (C-H Ar), 128.5 (2 x C-H Ar), 128.0 (C-H Ar), 127.5 (2 x C-H Ar), 123.8 (C-H Ar), 68.8 (C-2), 49.4 (C-5), 46.3 (C-3), 35.8 (C-6), 30.5 (C-4). **HRMS** (ESI): calculated for $C_{18}H_{18}N_2O_6SNa$ $[M+Na]^+$ requires *m/z* 413.0783, found *m/z* 413.0769. **IR** (film) ν_{max}: 3029, 1708, 1542, 1438, 1370, 1214 cm^{-1}.

5.11 Synthesis of Aldehyde or Alcohol Derivatives *via* Ozonolysis

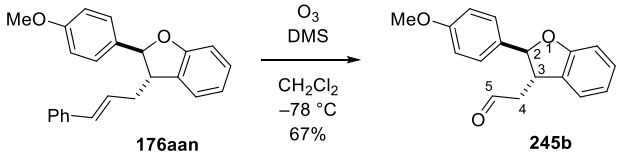
5.11.1 (±)-2-[(2*S*,3*S*)-2-(4-Methoxyphenyl)-2,3-dihydrobenzofuran-3-yl]acetaldehyde (245a)



THFs **176b** (15.0 mg, 0.0510 mmol) was subjected to the general procedure **J** (FCC: gradient elution: 6% → 8% Et_2O - pentane) to afford aldehyde **245a** as a colorless oil (7.9 mg, 70%).

Data for **245a**: **R_f** 0.30 (40% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.69 (1H, s, 7-H), 7.26 (2H, d, *J* = 8.7 Hz, Ar), 6.88 (2H, d, *J* = 8.7 Hz, Ar), 4.34 (1H, d, *J* = 7.4 Hz, 2-H), 4.14 (1H, dt, *J* = 8.4, 7.4 Hz, 5-H_A), 4.01 (1H, td, *J* = 8.4, 4.7 Hz, 5-H_B), 2.55-2.66 (1H, m, 6-H_A), 2.42-2.51 (2H, m, 3-H and 6-H_B), 2.33-2.42 (1H, m, 4-H_A), 1.63-1.75 (1H, m, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 201.0 (C-7), 159.5 (C Ar), 132.9 (C Ar), 127.8 (2 x C-H Ar), 114.1 (2 x C-H Ar), 85.8 (C-2), 67.8 (C-5), 55.4 (OMe), 46.1 (C-6), 42.2 (C-3), 32.5 (C-4). **HRMS** (ESI): calculated for $C_{13}H_{17}O_3$ $[M+H]^+$ requires *m/z* 221.1178, found *m/z* 221.1173. **IR** (film) ν_{max}: 2980, 2887, 2360, 2341, 1720, 1514 cm^{-1}.

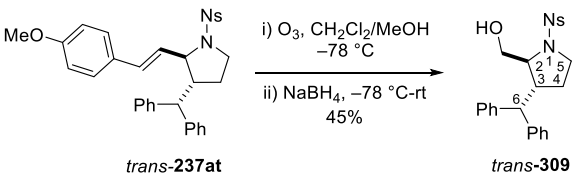
5.11.2 (±)-2-[(2*S*,3*S*)-2-(4-Methoxyphenyl)-2,3-dihydrobenzofuran-3-yl]acetaldehyde (245b)



THFs **176aan** (10.0 mg, 0.0292 mmol) was subjected to the general procedure **J** (FCC: gradient elution: 6% → 8% Et_2O - pentane) to afford aldehyde **245b** as a colorless oil (5.3 mg, 67%).

Data for **245b**: $\mathbf{R_f}$ 0.30 (40% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 9.84 (1H, s, 5-H), 7.34 (2H, d, *J* = 8.6 Hz, Ar), 7.20 (1H, t, *J* = 7.7 Hz, Ar), 7.13 (1H, d, *J* = 8.6 Hz, Ar), 6.86-6.92 (4H, m, Ar), 5.25 (1H, d, *J* = 6.7 Hz, 2-H), 3.93 (1H, q, *J* = 6.7 Hz, 3-H), 3.80 (3H, s, OMe), 2.85-2.99 (2H, m, 4-H_2). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 200.4 (C-5), 159.9 (C Ar), 159.4 (C Ar), 132.5 (C Ar), 129.1 (C-H Ar), 129.0 (C Ar), 127.7 (2 x C-H Ar), 124.6 (C-H Ar), 121.2 (C-H Ar), 114.2 (2 x C-H Ar), 109.9 (C-H Ar), 89.6 (C-2), 55.5 (OMe), 49.0 (C-3), 44.9 (C-4). **HRMS** (ESI): calculated for $C_{17}H_{17}O_3$ $[M+H]^+$ requires *m/z* 269.11722, found *m/z* 269.11731. **IR** (film) ν_{max}: 3649, 2980, 2360, 1382, 1251, 1152 cm^{-1}.

5.11.3 (±)-2-{(2*S*,3*R*)-3-Benzhydryl-1-[(2-nitrophenyl)sulfonyl]pyrrolidin-2-yl}methanol (*trans*-309)



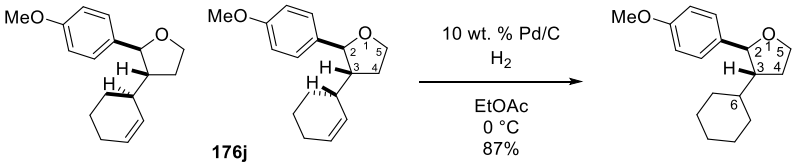
Pyrrolidines *trans*-**237at** (26.4 mg, 0.0475 mmol) was subjected to the general

procedure **J** except conducting the reaction in a 2:1 mixture of CH_2Cl_2 and MeOH, and quenching the reaction with 2 equivalents of $NaBH_4$ (FCC: gradient elution: 10% → 20% acetone - pentane) to afford *trans*-**309** as a colorless oil (9.6 mg, 45%).

Data for *trans*-**309**: **R_f** 0.30 (35% acetone - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.98 (1H, dd, *J* = 8.2, 1.4 Hz, Ar), 7.73-7.79 (1H, m, Ar), 7.62-7.68 (2H, m, Ar), 7.10-7.25 (8H, m, Ar), 7.00-7.05 (2H, m, Ar), 3.72-3.77 (1H, m, 5-H_A), 6.67-3.72 (1H, m, 2-H), 3.56 (1H, ddd, *J* = 11.5, 6.5, 4.6 Hz, 7-H_A), 3.44-3.51 (2H, m, 5-H_B and 6-H), 3.36-3.44 (1H, m, 7-H_B), 2.10 (1H, t, *J* = 6.5 Hz, OH), 1.98-2.07 (1H, m, 4-H_A), 1.49-1.57 (1H, m, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 143.0 (C Ar), 142.8 (C Ar), 134.0 (C-H Ar), 131.9 (C Ar), 131.8 (C-H Ar), 131.5 (C-H Ar), 129.0 (2 x C-H Ar), 128.9 (2 x C-H Ar), 128.1 (C Ar), 128.0 (2 x C-H Ar), 127.9 (2 x C-H Ar), 126.9 (C-H Ar), 126.8 (C-H Ar), 124.2 (C-H Ar), 65.5 (C-2), 65.1 (C-7), 54.6 (C-6), 48.4 (C-5), 45.7 (C-3), 29.0 (C-4). **HRMS** (ESI): calculated for $C_{24}H_{24}N_2O_5S$ $[M+H]^+$ requires *m/z* 475.1304, found *m/z* 475.1295. **IR** (film) ν_{max}: 3026, 2934, 1705, 1543, 1371, 1335 cm^{-1}.

5.12 Hydrogenation of THFs

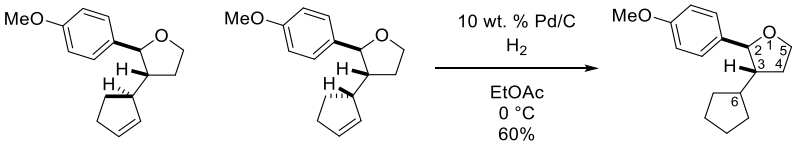
5.12.1 (±)-(2*S*,3*R*)-3-Cyclohexyl-2-(4-methoxyphenyl)tetrahydrofuran (246a)



THFs **176j** (31.0 mg, 0.120 mmol), Pd/C (3.1 mg) and EtOAc (2 mL) were subjected to the general procedure **K** (FCC: gradient elution: 7% → 15% Et_2O - pentane) to yield **246a** as a colorless oil (27.2 mg, 87%).

Data for **246a**: **R_f** 0.40 (40% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.26 (2H, d, *J* = 8.6 Hz, Ar), 6.87 (2H, d, *J* = 8.7 Hz, Ar), 4.54 (1H, d, *J* = 7.7 Hz, 2-H), 4.02 (1H, q, *J* = 8.3 Hz, 5-H_A), 3.91 (1H, td, *J* = 8.1, 4.6 Hz, 5-H_B), 3.80 (3H, s, OMe), 2.10 (1H, dddd, *J* = 11.4, 8.0, 6.8, 4.6 Hz, 4-H_A), 1.96-2.05 (1H, m, 3-H), 1.80-1.87 (1H, m, 4-H_B), 1.70-1.80 (2H, m, 2 x CH cyclohexyl), 1.53-1.65 (2H, m, 2 x CH cyclohexyl), 1.29-1.39 (1H, m, 6-H), 1.06-1.28 (4H, m, 2 x CH_2 cyclohexyl), 0.96-1.05 (1H, m, CH cyclohexyl), 0.79-0.91(1H, m, CH cyclohexyl). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.0 (C Ar), 135.5 (C Ar), 128.2 (2 x CH Ar), 113.8 (2 x CH Ar), 84.1 (C-2), 68.0 (C-5), 55.4 (OMe), 52.9 (C-3), 39.9 (C-6), 32.7 (CH_2 cyclohexyl), 30.5 (CH_2 cyclohexyl), 30.3 (C-4), 26.6 (CH_2 cyclohexyl), 26.53 (CH_2 cyclohexyl), 26.49 (CH_2 cyclohexyl). **HRMS** (ESI): calculated for $C_{17}H_{24}O_2Na$ $[M+Na]^+$ requires *m/z* 283.16685, found *m/z* 283.16675. **IR** (film) ν_{max} : 2980, 1764, 1612, 1514, 1247, 1161 cm^{-1}.

5.12.2 (±)-(2*S*,3*R*)-3-Cyclopentyl-2-(4-methoxyphenyl)tetrahydrofuran (246b)



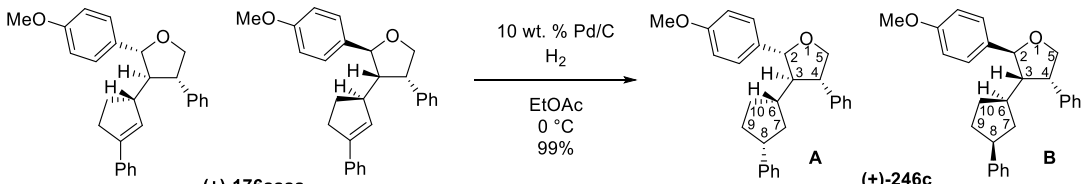
176k
dr (C-6) 3.5:1

246b

THFs **176k** (30.0 mg, 0.122 mmol), Pd/C (3.0 mg) and EtOAc (2 mL) were subjected to the general procedure **K** (FCC: gradient elution: 7% → 15% Et_2O - pentane) to yield **246b** as a colorless oil (18.1 mg, 60%).

Data for **246b**: $\mathbf{R_f}$ 0.40 (40% Et_2O - pentane). **^{1}H NMR (400 MHz, $CDCl_3$) δ** 7.26 (2H, d, *J* = 8.7 Hz, Ar), 6.86 (2H, d, *J* = 8.7 Hz, Ar), 4.46 (1H, d, *J* = 7.4 Hz, 2-H), 4.06 (1H, q, *J* = 8.3 Hz, 5-H_A), 3.94 (1H, td, *J* = 8.2, 5.1 Hz, 5-H_B), 3.80 (3H, s, OMe), 2.11-2.20 (1H, m, 4-H_A), 2.06 (1H, quint, *J* = 7.7 Hz, 3-H), 1.75-1.84 (3H, m, 4-H_B, 6-H and CH cyclopentyl), 1.42-1.66 (5H, m, CH cyclopentyl and 2 x CH_2 cyclopentyl), 1.16-1.28 (1H, m, CH cyclopentyl), 0.85-0.96 (1H, m, CH cyclopentyl). **^{13}C NMR (100 MHz, $CDCl_3$) δ** 159.1 (C Ar), 135.2 (C Ar), 128.2 (2 x CH Ar), 113.8 (2 x CH Ar), 85.9 (C-2), 67.9 (C-5), 55.4 (OMe), 52.8 (C-3), 42.7 (C-6), 31.8 (CH_2 cyclopentyl), 31.6 (C-4), 31.0 (CH_2 cyclopentyl), 25.5 (CH_2 cyclopentyl), 25.0 (CH_2 cyclopentyl). **HRMS** (ESI): calculated for $C_{16}H_{22}O_2Na$ $[M+Na]^+$ requires *m/z* 269.15120, found *m/z* 269.15128. **IR** (film) ν_{max} : 2980, 1764, 1514, 1246, 1169, 1032 cm^{-1}.

5.12.3 (+)-(2*R*,3*R*,4*S*)-2-(4-Methoxyphenyl)-4-phenyl-3-[(1'*S*,3'*R*)-3-phenylcyclopentyl] tetrahydrofuran and (+)-(2*S*,3*S*,4*S*)-2-(4-methoxyphenyl)-4-phenyl-3-[(1'R,3'S)-3-phenylcyclopentyl]tetrahydrofuran [(+)-246c]



(+)-176aaaa
dr (C3-C4) 7:1

(+)-246c
dr (C-4) 7:1

THFs **(+)-176aaaa** (36.3 mg, 0.0917 mmol), Pd/C (3.6 mg) and EtOAc (2 mL) were subjected to the general procedure (FCC: gradient elution: 6% → 8% Et_2O - pentane) to yield an inseparable 7:1 mixture of diastereomers **(+)-246c** as a colorless oil (38.9 mg, 99%).

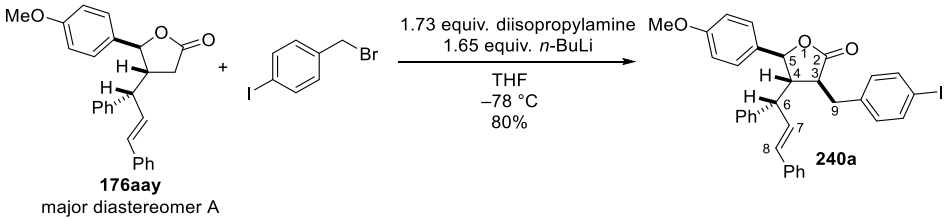
Data for **diastereomer A** of **(+)-246c** (from the mixture): **R_f** 0.50 (25% Et_2O - pentane). $[\alpha]_D^{25}$ = +52.8 (*c* = 4.2, $CHCl_3$). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.40 (2H, d, *J* = 8.7 Hz, Ar), 7.19-7.38 (7H, m, Ar), 7.08-7.17 (3H, m, Ar), 6.92 (2H, d, *J* = 8.7 Hz, Ar), 4.64 (1H, d, *J* = 8.4 Hz, 2-H), 4.23 (1H, dd, *J* = 8.9, 8.0 Hz, 5-H_A), 4.08 (1H, dd, *J* = 8.9, 6.3 Hz, 5-H_B), 3.83 (3H, s, OMe), 3.34 (1H, td, *J* = 7.9, 6.3 Hz, 4-H), 2.96 (1H, dtd, *J* = 11.5, 9.0, 6.3 Hz, 8-H), 2.46 (1H, q, *J* = 8.0 Hz, 3-H), 2.15-2.26 (1H, m, 6-H), 2.10 (1H, dt, *J* = 12.3, 6.2 Hz, 7-H_A), 1.91-2.04 (1H, m, 9-H_A), 1.70 (1H, dddd, *J* = 14.2, 9.3, 8.1, 6.1 Hz, 10-H_A), 1.46-1.55 (1H, m, 9-H_B), 1.24 (1H, q, *J* = 11.9 Hz, 7-H_B), 1.13-1.21 (1H, m, 10-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.44 (C Ar), 146.0 (C Ar), 144.4 (C Ar), 134.2 (C Ar), 128.87 (2 x CH Ar), 128.85 (2 x CH Ar), 128.38 (2 x CH Ar), 127.7 (2 x CH Ar), 127.10 (2 x CH Ar), 126.6 (CH Ar), 126.0 (CH Ar), 114.0 (2 x CH Ar), 87.1 (C-2), 75.9 (C-5), 60.7 (C-3), 55.4

(OMe), 51.8 (C-4), 45.4 (C-8), 43.5 (C-8), 43.5 (C-6), 40.4 (C-7), 33.55 (C-9), 30.2 (C-10). **NOESY-2D (500 MHz, $CDCl_3$)**: between 2-H and 4-H, between 2-H and 6-H**,** between 2-H and 7-H_A, between 6-H and 8-H. **HRMS** (ESI): calculated for $C_{28}H_{30}O_2Na$ $[M+Na]^+$ requires *m/z* 421.21380, found *m/z* 421.21384. **IR** (film) ν_{max} : 2980, 2888, 1513, 1461, 1382, 1249 cm^{-1}.

Data for **diastereomer B** of **(+)-246c** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.40 (2H, d, *J* = 8.7 Hz, Ar), 7.19-7.38 (7H, m, Ar), 7.08-7.17 (3H, m, Ar), 6.92 (2H, d, *J* = 8.7 Hz, Ar), 4.86 (2H, d, *J* = 9.2 Hz, 2-H), 4.49 (1H, dd, *J* = 8.5, 5.8 Hz, 5-H_A), 4.13 (1H, dd, *J* = 8.6, 2.2 Hz, 5-H_B), 3.83 (3H, s, OMe), 3.53-3.60 (1H, m, 4-H), 2.70-2.80 (1H, m, 8-H), 2.55 (1H, td, *J* = 9.6, 6.9 Hz, 3-H), 2.06-2.16 (1H, m, 7-H_A), 1.91-2.04 (1H, m, 9-H_A), 1.75-1.81 (1H, m, 10-H_A), 1.62-1.66 (1H, m, 6-H), 1.40-1.46 (1H, m, 9-H_B), 1.20-1.29 (1H, m, 7-H_B), 1.11-1.19 (1H, m, 10-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.36 (C Ar), 146.5 (C Ar), 142.0 (C Ar), 135.7 (C Ar), 129.0 (2 x CH Ar), 128.5 (2 x CH Ar), 128.42 (2 x CH Ar), 127.8 (2 x CH Ar), 127.06 (2 x CH Ar), 126.7 (CH Ar), 125.89 (CH Ar), 113.9 (2 x CH Ar), 84.8 (C-2), 75.0 (C-5), 58.4 (C-3), 55.4 (OMe), 50.4 (C-4), 44.8 (C-8), 42.0 (C-7), 40.1 (C-6), 33.63 (C-10), 30.7 (C-9). **NOESY-2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H, between 6-H and 8-H**.**

5.13 Acylation and Alkylation of Lactones

5.13.1 (±)-(3*S*,4*S*,5*S*)-4-[(2'*E*)-1,3-diphenylallyl]-3-(4-iodobenzyl)-5-(4-methoxyphenyl) dihydrofuran-2(3*H*)-one (240a)

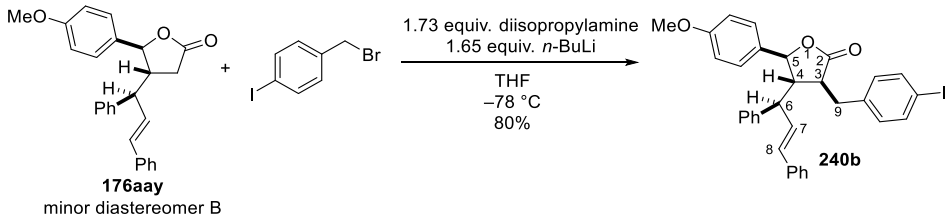


Lactones **176aay-major diastereomer A** (100.0 mg, 0.2603 mmol), benzyl bromide (77.3 mg, 0.260 mmol), diisopropylamine (45.5 mg, 0.450 mmol) and *n*-BuLi (2.5M, 0.17 mL) were subjected to the general procedure except using 1.73 eq. of diisopropylamine, 1.63 eq. of *n*-BuLi (FCC: gradient elution: 15% → 25% Et_2O - pentane) to yield **240a** as a white foam (124.8 mg, 80%).

Data for **240a**: $\mathbf{R_f}$ 0.45 (50% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.59 (2H, d, *J* = 8.2 Hz, Ar), 7.10-7.35 (10H, m, Ar), 6.72 (2H, d, *J* = 8.7 Hz, Ar), 6.67 (2H, d, *J* = 8.2 Hz, Ar), 6.59 (2H, d, *J* = 8.7 Hz, Ar), 6.50 (1H, d, *J* = 15.6 Hz, 8-H), 6.08 (1H, dd, *J* = 15.9, 9.6 Hz, 7-H), 5.21 (1H, d, *J* = 6.0 Hz, 5-H), 3.79 (3H, s, OMe), 3.47 (1H, t, *J* = 10.0 Hz, 6-H), 2.78-2.87 (2H, m, 3-H and 9-H_A), 2.60-2.67 (1H, m, 4-H), 2.06 (1H, dd, *J* = 13.0, 4.7 Hz, 9-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 177.8 (C=O), 159.5 (C Ar), 141.1 (C Ar), 137.8 (2 x C-H Ar), 137.1 (C Ar), 136.4 (C Ar), 132.3 (C-8), 132.0 (2 x C-H Ar), 131.8 (C Ar), 130.2 (C-7), 129.2 (2 x C-H Ar), 128.6 (2 x C-H Ar), 128.0 (2 x C-H Ar),127.79 (2 x C-H Ar), 127.78 (C-H Ar), 127.4 (C-H Ar), 126.4 (2 x C-H Ar), 114.0 (2 x C-H Ar), 92.3 (CAr), 83.6 (C-5), 55.34 (OMe), 55.31 (C-6), 51.0 (C-4), 47.3 (C-3), 35.0 (C-9). **NOESY-2D (500 MHz,**

$CDCl_3$): between 5-H and 3-H, between 5-H and 6-H, between 5-H and 7-H, between 3-H and 6-H. **HRMS** (ESI): calculated for $C_{33}H_{29}IO_3Na$ $[M+Na]^+$ requires *m/z* 623.10536, found *m/z* 623.10535. **IR** (film) ν_{max}: 2980, 2360, 1764, 1461, 1382, 1251 cm^{-1}.

5.13.2 (±)-(3*S*,4*S*,5*S*)-4-[(2'*E*)-1,3-diphenylallyl]-3-(4-iodobenzyl)-5-(4-methoxyphenyl) dihydrofuran-2(3*H*)-one (240b)

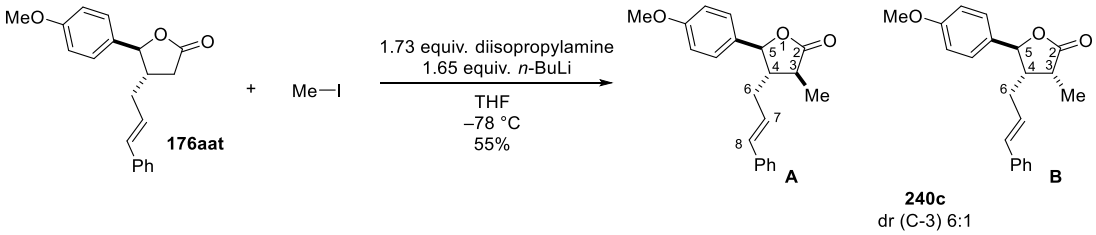


Lactones **176aay-minor diastereomer B** (100.0 mg, 0.2603 mmol), benzyl bromide (77.3 mg, 0.260 mmol), diisopropylamine (45.5 mg, 0.450 mmol) and *n*-BuLi (2.5M, 0.17 mL) were subjected to the general procedure except using 1.73 eq. of diisopropylamine, 1.63 eq. of *n*-BuLi (FCC: gradient elution: 15% → 25% Et_2O - pentane) to yield **240b** as a white solid (124.8 mg, 80%).

Data for **240b**: **R_f** 0.40 (50% Et_2O - pentane). **M.p.**: 78°C (10% EtOAc - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.52 (2H, d, *J* = 8.2 Hz, Ar), 7.16-7.36 (8H, m, Ar), 7.06-7.10 (2H, m, Ar), 6.72 (2H, d, *J* = 8.2 Hz, Ar), 6.70 (2H, d, *J* = 8.7 Hz, Ar), 6.50 (2H, d, *J* = 8.6 Hz, Ar), 6.43 (1H, d, *J* = 15.6 Hz, 8-H), 5.84 (1H, dd, *J* = 15.6, 9.7 Hz, 7-H), 5.08 (1H, d, *J* = 4.9 Hz, 5-H), 3.78 (3H, s, OMe), 3.43 (1H, t, *J* = 9.7 Hz, 6-H), 2.98 (1H, dt, *J* = 7.8, 5.3 Hz, 3-H), 2.90 (1H, dd, *J* = 13.6, 5.0 Hz, 9-H_A), 2.81 (1H, dd, *J* = 13.6, 7.9 Hz, 9-H_B), 2.59-2.66 (1H, m, 4-H). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 178.2 (C=O), 159.4 (C Ar), 141.1 (C Ar), 138.0 (2 x C-H Ar), 137.4 (C Ar), 136.4 (C Ar), 132.7 (C-8), 132.1 (C Ar), 131.9 (2 x C-H Ar), 129.3

(C-7), 129.2 (2 x C-H Ar), 128.8 (2 x C-H Ar), 128.2 (2 x C-H Ar), 128.0 (C-H Ar), 127.5 (C-H Ar), 126.7 (2 x C-H Ar), 126.5 (2 x C-H Ar), 114.0 (2 x C-H Ar), 92.4 (C Ar), 82.8 (C-5), 55.4 (OMe), 53.8 (C-6), 51.3 (C-4), 46.6 (C-3), 36.3 (C-9). **NOESY-2D (500 MHz, $CDCl_3$)**: between 5-H and 3-H, between 5-H and 6-H, between 5-H and 7-H, between 3-H and 6-H. **HRMS** (ESI): calculated for $C_{33}H_{29}IO_3Na$ $[M+Na]^+$ requires *m/z* 623.10536, found *m/z* 623.10535. **IR** (film) ν_{max}: 2980, 2360, 1764, 1461, 1382, 1251 cm^{-1}.

5.13.3 (±)-(3*S*,4*S*,5*S*)-3-Benzyl-4-cinnamyl-5-(4-methoxyphenyl)dihydrofuran-2(3*H*)-one (240c)



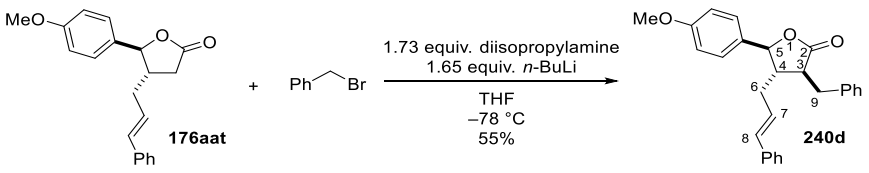
Lactones **176aat** (50.0 mg, 0.162 mmol), iodomethane (34.2 mg, 0.243 mmol), diisopropylamine (28.3 mg, 0.280 mmol) and *n*-BuLi (2.5M, 0.11 mL) were subjected to the general procedure **L** (FCC: gradient elution: 10% → 25% Et_2O - pentane) to yield an inseparable 6:1 mixture of diastereomers **240c** as a colorless oil (35.4 mg, 55%).

Data for **diastereomer A** of **240c** (from the mixture): $\mathbf{R_f}$ 0.50 (50% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.18-7.33 (7H, m, Ar), 6.90 (2H, d, *J* = 8.6 Hz, Ar), 6.47 (1H, d, *J* = 15.8 Hz, 8-H), 6.06 (1H, dt, *J* = 15.8, 6.9 Hz, 7-H), 5.19 (1H, d, *J* = 6.2 Hz, 5-H), 3.81 (OMe), 2.90 (1H, p, *J* = 7.6 Hz, 3-H), 2.55-2.64 (1H, m, 4-H), 2.41-2.50 (1H, m, 6-H_A), 2.21-2.31 (1H, m, 6-H_B), 1.30 (3H, d, *J* = 7.5 Hz, Me). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 179.5 (C=O), 159.9 (C Ar), 137.0 (C Ar), 133.0 (C-8), 130.4 (C Ar), 128.7 (2 x C-H Ar), 127.6

(C-H Ar), 127.3 (2 x C-H Ar), 126.5 (C-7), 126.2 (2 x C-H Ar), 114.3 (2 x C-H Ar), 83.3 (C-5), 55.4755.45 (OMe), 47.4 (C-4), 37.4 (C-3), 30.9 (C-6), 10.5 (Me). **NOESY-2D (500 MHz, $CDCl_3$)**: between 5-H and 3-H, between 5-H and 6-H_2, between 5-H and 7-H, between 5-H and 8-H. **HRMS** (ESI): calculated for $C_{21}H_{22}O_3Na$ $[M+Na]^+$ requires *m/z* 345.1467, found *m/z* 345.1405. **IR** (film) ν_{max}: 2980, 1774, 1524, 1258, 1170, 1040 cm^{-1}.

Data for **diastereomer B** of **240c** (from the mixture): **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.18-7.33 (7H, m, Ar), 7.14 (2H, d, *J* = 8.6 Hz, Ar), 6.23 (1H, d, *J* = 15.8 Hz, 8-H), 5.93 (1H, dt, *J* = 15.8, 6.9 Hz, 7-H), 5.61 (1H, d, *J* = 6.8 Hz, 5-H), 3.82 (OMe), 2.85-2.94 (1H, m, 3-H), 2.55-2.64 (1H, m, 4-H), 2.41-2.50 (1H, m, 6-H_A), 2.21-2.31 (1H, m, 6-H_B), 1.35 (3H, d, *J* = 7.5 Hz, Me). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 179.7 (C=O), 159.8 (C Ar), 137.1 (C Ar), 132.5 (C-8), 130.4 (C Ar), 128.7 (2 x C-H Ar), 127.7 (2 x C-H Ar),127.5 (C-H Ar), 126.7 (C-7), 126.1 (2 x C-H Ar), 114.0 (2 x C-H Ar), 82.0 (C-5), 55.45 (OMe), 47.8 (C-4), 38.9 (C-3), 33.3 (C-6), 15.0 (Me).

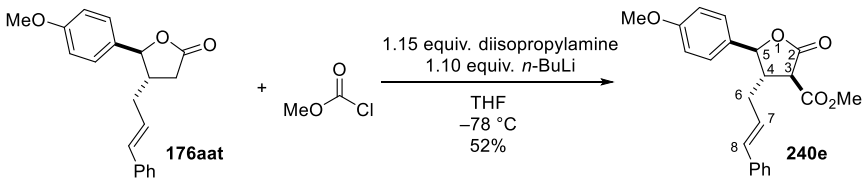
5.13.4 (±)-(3*S*,4*S*,5*S*)-3-Benzyl-4-cinnamyl-5-(4-methoxyphenyl)dihydrofuran-2(3*H*)-one (240d)



Lactones **176aat** (50.0 mg, 0.162 mmol), benzyl bromide (41.5 mg, 0.243 mmol), diisopropylamine (28.3 mg, 0.280 mmol) and *n*-BuLi (2.5M, 0.11 mL) were subjected to the general procedure **L** (FCC: gradient elution: 15% → 25% Et_2O - pentane) to yield **240d** as a colorless oil (35.4 mg, 55%).

Data for **240d**: **R_f** 0.50 (60% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.16-7.34 (10H, m, Ar), 7.03 (2H, d, *J* = 8.7 Hz, Ar), 6.81 (2H, d, *J* = 8.7 Hz, Ar), 6.21 (1H, d, *J* = 15.7 Hz, 8-H), 5.84 (1H, dt, *J* = 15.4, 7.4 Hz, 7-H), 4.95 (1H, d, *J* = 9.0 Hz, 5-H), 3.77 (3H, s, OMe), 3.17 (1H, dd, *J* = 14.0, 5.2 Hz, 9-H_A), 3.07 (1H, dd, *J* = 14.0, 6.6 Hz, 9-H_B), 2.86 (1H, ddd, *J* = 10.5, 6.5, 5.2 Hz, 3-H), 2.34 (1H, ddt, *J* = 10.6, 8.8, 5.9 Hz, 4-H), 2.20-2.27 (2H, m, 6-H_2). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 177.7 (C=O), 160.1 (C Ar), 138.0 (C Ar), 136.7 (C Ar), 133.5 (C-8), 130.2 (C Ar), 129.7 (2 x C-H Ar), 128.9 (2 x C-H Ar), 128.7 (2 x C-H Ar), 128.3 (2 x C-H Ar), 127.7 (C-H Ar), 127.0 (C-H Ar), 126.2 (2 x C-H Ar), 125.3 (C-7), 114.2 (2 x C-H Ar), 83.9 (C-5), 55.5 (OMe), 48.3 (C-4), 47.0 (C-3), 35.3 (C-9), 33.9 (C-6). **NOESY-2D (500 MHz, $CDCl_3$)**: between 5-H and 6-H_2, between 5-H and 7-H, between 5-H and 8-H, between 5-H and 3-H, between 3-H and 6-H_2. **HRMS** (ESI): calculated for $C_{27}H_{26}O_3Na$ $[M+Na]^+$ requires *m/z* 421.17742, found *m/z* 421.17722. **IR** (film) ν_{max}: 2980, 1764, 1514, 1248, 1160, 1030 cm^{-1}.

5.13.5 (±)-Methyl-(3*R*,4*S*,5*S*)-4-cinnamyl-5-(4-methoxyphenyl)-2-oxotetrahydrofuran-3-carboxylate (240e)



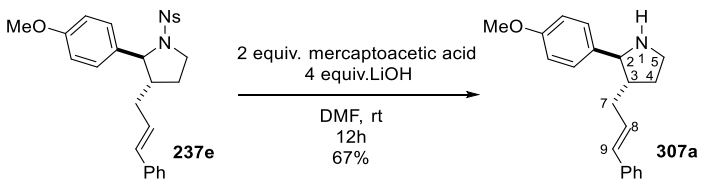
Lactones **176aat** (40.0 mg, 0.130 mmol), methyl chloroformate (18.3 mg, 0.195 mmol), diisopropylamine (15.2 mg, 0.149 mmol) and *n*-BuLi (2.5M, 0.057 mL) were subjected to the general procedure **L** (FCC: gradient elution: 25% → 35% Et_2O - pentane)

to yield **240e** as a colorless oil (24.7 mg, 52%).

Data for **240e**: **R_f** 0.50 (70% Et_2O - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.34 (2H, d, *J* = 8.7 Hz, Ar), 7.19-7.30 (5H, m, Ar), 6.94 (2H, d, *J* = 8.7 Hz, Ar), 6.43 (1H, d, *J* = 15.6 Hz, 8-H), 5.95 (1H, ddd, *J* = 15.8, 8.4, 6.5 Hz, 7-H), 5.03 (1H, d, *J* = 9.8 Hz, 5-H), 3.83 (3H, s, OMe), 3.66 (3H, s, OMe), 3.54 (1H, d, *J* = 11.7 Hz, 3-H), 3.14 (1H, dddd, *J* = 11.7, 9.8, 8.5, 5.0 Hz, 4-H), 2.47-2.56 (1H, m, 6-H_A), 2.29-2.38 (1H, m, 6-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 170.8 (C=O), 168.2 (C=O), 160.5 (C Ar), 136.7 (C Ar), 133.6 (C-8), 128.73 (2 x C-H Ar), 128.69 (2 x C-H Ar), 128.6 (C Ar), 127.8 (C-H Ar), 126.3 (2 x C-H Ar), 125.0 (C-7), 114.4 (2 x C-H Ar), 85.0 (C-5), 55.5 (OMe), 53.3 (C-3), 53.1 (OMe), 48.9 (C-4), 33.8 (C-6). **NOESY-2D (500 MHz, $CDCl_3$)**: between 5-H and 6-H_A, between 5-H and 6-H_B, between 5-H and 7-H, between 5-H and 3-H, between 3-H and 6-H_A, between 3-H and 6-H_B. **HRMS** (ESI): calculated for $C_{22}H_{22}O_5Na$ $[M+Na]^+$ requires *m/z* 389.13594, found *m/z* 389.13577. **IR** (film) ν_{max}: 2980, 1777, 1736, 1515, 1250, 1147 cm^{-1}.

5.14 Removal of Ns Protecting Group

5.14.1 (±)- (2*S*,3*S*)-3-Cinnamyl-2-(4-methoxyphenyl)pyrrolidine (307a)

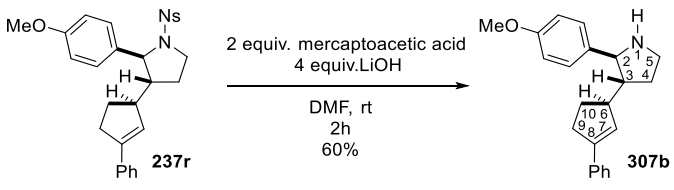


Pyrrolidines **237e** (42.6 mg, 0.0891 mmol), LiOH (8.6 mg, 0.36 mmol), and mercaptoacetic acid (0.0123 mL, 0.178 mmol) were subjected to the general procedure

M (FCC: gradient elution: 0.3% → 0.6% MeOH - CH_2Cl_2) to yield **307a** as a colorless oil (17.8 mg, 67%).

Data for **307a**: **R_f** 0.40 (20% MeOH - CH_2Cl_2). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.23-7.31 (6H, m, Ar), 7.15-7.21 (1H, m, Ar), 6.87 (2H, d, *J* = 8.7 Hz, Ar), 6.36 (1H, dt, *J* = 15.7, 1.4 Hz, 8-H), 6.11 (1H, dt, *J* = 15.8, 7.1 Hz, 7-H), 3.80 (3H, s, OMe), 3.67 (1H, d, *J* = 8.0 Hz, 2-H), 3.22 (1H, ddd, *J* = 10.1, 7.5, 6.1 Hz, 5-H_A), 3.07 (1H, ddd, *J* = 10.1, 8.5, 5.4 Hz, 5-H_B), 2.38 (1H, dddd, *J* = 13.5, 6.6, 4.8, 1.4 Hz, 6-H_A), 2.10-2.21 (2H, m, 4-H_A and 6-H_B), 2.03-2.10 (1H, m, 3-H), 1.64 (1H, dddd, *J* = 11.8, 8.5, 7.5, 6.1 Hz, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 158.9 (C Ar), 137.8 (C Ar), 135.8 (C Ar), 131.0 (C-8), 129.3 (C-7), 128.6 (2 x C-H Ar), 128.5 (2 x C-H Ar), 127.0 (C-H Ar), 126.1 (2 x C-H Ar), 114.0 (2 x C-H Ar), 68.3 (C-2), 55.4 (OMe), 47.7 (C-3), 46.0 (C-5), 36.5 (C-6), 32.0 (C-4). **HRMS** (ESI): calculated for $C_{20}H_{24}ON$ $[M+H]^+$ requires *m/z* 294.1858, found *m/z* 294.1852. **IR** (film) ν_{max}: 2980, 2360, 1764, 1461, 1382, 1251 cm^{-1}.

5.14.2 (±)-(2*S*,3*R*)-2-(4-methoxyphenyl)-3-[(1'*R*)-3-phenylcyclopent-2-en-1-yl]pyrrolidine (307b)

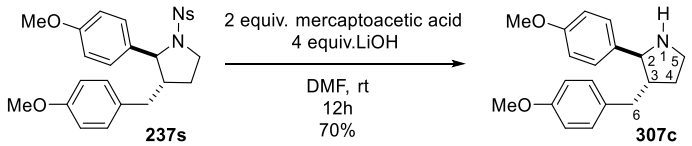


Pyrrolidines **237r** (26.6 mg, 0.0528 mmol), LiOH (8.6 mg, 0.21 mmol), and mercaptoacetic acid (0.0080 mL, 0.11 mmol) were subjected to the general procedure **M** except conducting the reaction for 2 hours (FCC: gradient elution: 1% → 15% MeOH -

CH_2Cl_2) to yield **307b** as a colorless oil (9.9 mg, 60%).

Data for **307b**: $\mathbf{R_f}$ 0.40 (15% MeOH - CH_2Cl_2). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.37-7.40 (2H, m, Ar), 7.37-7.35 (4H, m, Ar), 7.20-7.24 (1H, m, Ar), 6.86 (2H, d, *J* = 8.7 Hz, Ar), 3.89 (1H, d, *J* = 9.0 Hz, 2-H), 3.79 (3H, s, OMe), 3.23 (1H, dt, *J* = 10.5, 7.3 Hz, 5-H_A), 3.03 (1H, ddd, *J* = 10.5, 8.9, 5.2 Hz, 5-H_B), 2.88-2.95 (1H, m, 6-H), 2.55-2.68 (2H, m, 9-H_2), 2.19-2.27 (1H, m, 3-H), 2.13 (1H, dtd, *J* = 12.6, 8.0, 5.2 Hz, 4-H_A), 1.98-2.06 (1H, m, 10-H_A), 1.75 (1H, dtd, *J* = 12.6, 8.9, 6.8 Hz, 4-H_B), 1.48 (1H, ddt, *J* = 13.0, 9.1, 7.1 Hz, 10-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 159.3 (C Ar), 143.9 (C Ar), 136.5 (C Ar), 129.1 (2 x C-H Ar), 128.4 (2 x C-H Ar and C-8), 127.4 (C-H Ar), 127.2 (C-7), 125.8 (2 x C-H Ar), 114.1 (2 x C-H Ar), 67.0 (C-2), 55.4 (OMe), 51.6 (C-3), 48.2 (C-6), 45.5 (C-5), 32.9 (C-9), 29.2 and 29.1 (C-4 and C-10). **NOESY-2D (500 MHz, $CDCl_3$)**: between 2-H and 6-H, between 2-H and 7-H, between 2-H and 10-H_A. **HRMS** (ESI): calculated for $C_{22}H_{26}ON$ $[M+H]^+$ requires *m/z* 320.2014, found *m/z* 320.2007. **IR** (film) ν_{max}: 2980, 2888, 2360, 1738, 1382, 1251 cm^{-1}.

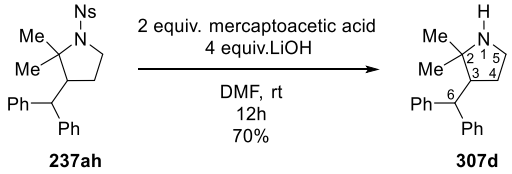
5.14.3 (±)-(2*S*,3*S*)-3-(4-Methoxybenzyl)-2-(4-methoxyphenyl)pyrrolidine (307c)



Pyrrolidines **237s** (33.8 mg, 0.0701 mmol), LiOH (6.7 mg, 0.28 mmol), and mercaptoacetic acid (0.0097 mL, 0.14 mmol) were subjected to the general procedure **M** (FCC: gradient elution: 10% → 15% MeOH - CH_2Cl_2) to yield **307c** as a colorless oil (14.6 mg, 70%).

Data for **307c**: **R_f** 0.30 (15% MeOH - CH_2Cl_2). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.36 (2H, d, *J* = 8.7 Hz, Ar), 6.95 (2H, d, *J* = 8.7 Hz, Ar), 6.87 (2H, d, *J* = 8.7 Hz, Ar), 6.77 (2H, d, *J* = 8.7 Hz, Ar), 3.85 (1H, d, *J* = 9.9 Hz, 2-H), 3.79 (3H, s, OMe), 3.77 (3H, s, OMe), 3.19 (1H, dt, *J* = 11.7, 8.2 Hz, 5-H_A), 3.05 (1H, td, *J* = 11.7, 10.4, 3.9 Hz, 5-H_B), 2.69 (1H, dd, *J* = 13.6, 4.1 Hz, 6-H_A), 2.40-2.49 (1H, m, 3-H), 2.36 (1H, dd, *J* = 13.5, 9.6 Hz, 6-H_B), 1.95-2.04 (1H, m, 4-H_A), 1.59-1.69 (1H, m, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 160.0 (C Ar), 158.3 (C Ar), 131.4 (C Ar), 129.9 (C Ar and 2 x C-H Ar), 129.5 (2 x C-H Ar), 114.4 (2 x C-H Ar), 114.0 (2 x C-H Ar), 67.6 (C-2), 55.43 (OMe), 55.40 (OMe), 47.7 (C-3), 44.2 (C-5), 36.8 (C-6), 30.3 (C-4). **HRMS** (ESI): calculated for $C_{19}H_{24}O_2N$ $[M+H]^+$ requires *m/z* 298.1807, found *m/z* 298.1801. **IR** (film) ν_{max}: 2980,2888, 2360, 1738, 1612, 1512 cm^{-1}.

5.14.4 (±)-(2*S*,3*S*)-3-(4-Methoxybenzyl)-2-(4-methoxyphenyl)pyrrolidine (307d)



237ah **307d**

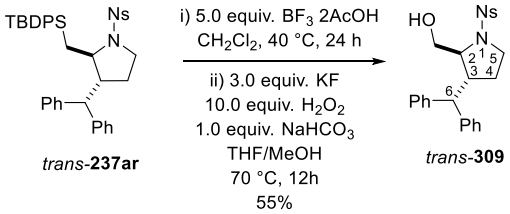
Pyrrolidines **237ah** (41.7 mg, 0.0927 mmol), LiOH (6.7 mg, 0.28 mmol), and mercaptoacetic acid (0.0097 mL, 0.14 mmol) were subjected to the general procedure **M** (FCC: gradient elution: 5% → 10% MeOH - CH_2Cl_2) to yield **307d** as a colorless oil (14.6 mg, 70%).

Data for **307d**: **R_f** 0.40 (15% MeOH - CH_2Cl_2). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.33-7.38 (4H, m, Ar), 7.20-7.26 (4H, m, Ar), 7.09-7.16 (2H, m, Ar), 3.68 (1H, d, *J* = 11.7 Hz, 6-H), 2.87 (1H, dd, *J* = 8.4, 6.4 Hz, 5-H_2), 2.66 (1H, ddd, *J* = 11.7, 10.7, 8.4 Hz, 3-H),

1.85 (1H, ddt, *J* = 13.0, 8.4, 6.4 Hz, 4-H_A), 1.46 (1H, ddt, *J* = 13.2, 10.7, 8.4 Hz, 4-H_B), 1.05 (3H, s, Me), 0.70 (3H, s, Me). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 145.7 (C Ar), 144.3 (C Ar), 128.7 (2 x C-H Ar), 128.6 (2 x C-H Ar), 128.3 (2 x C-H Ar), 127.8 (2 x C-H Ar), 126.5 (C-H Ar), 126.2 (C-H Ar), 60.6 (C-2), 55.1 (C-6), 52.7 (C-3), 42.3 (C-5), 33.2 (C-4), 29.7 (Me), 22.3 (Me). **HRMS** (ESI): calculated for $C_{20}H_{24}ON$ $[M+H]^+$ requires *m/z* 266.1909, found *m/z* 266.1904. **IR** (film) ν_{max}: 2980, 2886, 2360, 1738, 1451, 1380 cm^{-1}.

5.15 Synthesis of Alcohol Derivatives *via* Flemming-Tamao Oxidation

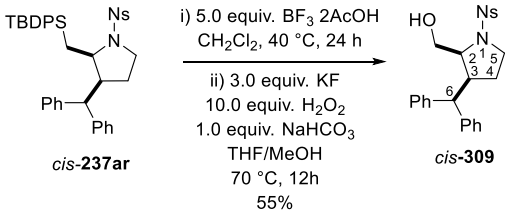
5.15.1 (±)-2-{(2*S*,3*R*)-3-Benzhydryl-1-[(2-nitrophenyl)sulfonyl]pyrrolidin-2-yl}methanol (*trans*-309)



Pyrrolidines *trans*-**237ar** (24.0 mg, 0.0356 mmol), BF3 · 2 HOAc (0.025 mL, 0.18 mmol), $NaHCO_3$ (3.0 mg, 0.036 mmol), KF (6.2 mg, 0.11 mmol) and H_2O_2 (30%, 0.34 mL, 0.36 mmol)was subjected to the general procedure **N** (FCC: gradient elution: 10% → 20% acetone - pentane) to afford *trans*-**309** as a colorless oil (8.8 mg, 55%).

Data for *trans*-**309** matched those previously reported.

5.15.2 (±)-2-{(2*S*,3*S*)-3-Benzhydryl-1-[(2-nitrophenyl)sulfonyl]pyrrolidin-2-yl}methanol (*cis*-309)

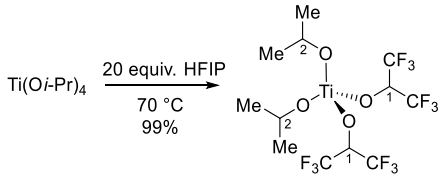


Pyrrolidine *trans*-**237ar** (29.4 mg, 0.0436 mmol), BF3·2 HOAc (0.031 mL, 0.22 mmol), $NaHCO_3$ (3.7 mg, 0.044 mmol), KF (7.6 mg, 0.13 mmol) and H_2O_2 (30%, 0.42 mL, 0.44 mmol)was subjected to the general procedure **N** (FCC: gradient elution: 10% → 20% acetone - pentane) to afford *cis*-**309** as a colorless oil (8.8 mg, 55%).

Data for *cis*-**309**: $\mathbf{R_f}$ 0.40 (35% acetone - pentane). **^{1}H NMR (500 MHz, $CDCl_3$) δ** 8.09 (1H, dd, *J* = 7.8, 1.5 Hz, Ar), 7.68-7.77 (2H, m, Ar), 7.67 (1H, dd, *J* = 7.8, 1.5 Hz, Ar), 7.34-7.38 (2H, m, Ar), 7.28-7.33 (2H, m, Ar), 7.17-7.22 (4H, m, Ar), 7.09-7.16 (2H, m, Ar), 4.08 (1H, dt, *J* = 7.4, 3.6 Hz, 2-H), 3.97 (1H, d, *J* = 11.9 Hz, 6-H), 3.65 (1H, ddd, *J* = 12.2, 5.3, 3.6 Hz, 7-H_A), 3.50-3.59 (2H, m, 7-H_B and 5-H_A), 3.30 (1H, td, *J* = 10.0, 7.3 Hz, 5-H_B), 3.01-3.10 (1H, m, 3-H), 1.98-2.10 (1H, m, 4-H_A), 1.93 (1H, dd, *J* = 7.7, 5.3 Hz, OH), 1.62 (1H, dt, *J* = 13.1, 7.3 Hz, 4-H_B). **^{13}C NMR (125 MHz, $CDCl_3$) δ** 143.9 (C Ar), 142.5 (C Ar), 134.0 (C Ar and C-H Ar), 131.9 (C Ar and C-H Ar), 131.7 (C-H Ar), 129.2 (2 x C-H Ar), 128.8 (2 x C-H Ar), 127.6 (4 x C-H Ar), 127.0 (C-H Ar), 126.7 (C-H Ar), 124.3 (C-H Ar), 63.2 (C-2), 62.4 (C-7), 52.2 (C-6), 47.7 (C-5), 46.5 (C-3), 30.4 (C-4). **HRMS** (ESI): calculated for $C_{24}H_{24}N_2O_5S$ $[M+H]^+$ requires *m/z* 475.1304, found *m/z* 475.1295. **IR** (film) ν_{max}: 3026, 2934, 1705, 1543, 1371, 1335 cm^{-1}.

5.16 Isolation of Titanium Complex

5.16.1 Isolation of stable titanium complex Ti(O*i*-Pr)$_2$(OHFIP)$_2$ (242)

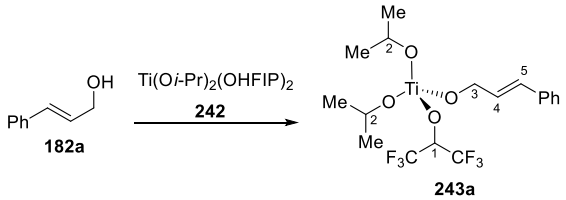


242

To a microwave vial charged with a stirring bar was added Ti(O*i*-Pr)$_4$ (100.0 mg, 0.3521 mmol) and HFIP (0.74 mL, 7.0 mmol), the solution was stirred under Ar at 70°C for 2 hours. Then the solvent was removed under reduced pressure to obtain a white foam.

Data for **242** Ti(O*i*-Pr)$_2$(OHFIP)$_2$: **^{1}H NMR (500 MHz, CDCl$_3$) δ** 4.82 (2H, m, 2 x 1-H), 4.64 (2H, m, 2 x 2-H), 1.29 (12H, d, *J* = 6.1 Hz, 4 x Me). **^{13}C NMR (125 MHz, CDCl$_3$) δ** 121.8 (q, *J* = 284.4 Hz, 4 x CF$_3$), 82.0 (2 x C-2), 78.9 (2 x C-1), 25.7 (4 x Me). **^{19}F NMR (471 MHz, CDCl$_3$) δ** -76.15 (12F, s, 4 x CF$_3$). **^{19}F (471 MHz, CDCl$_3$) - ^{1}H(500 MHz, CDCl$_3$) HOESY**: between CF$_3$ and Me (irradiate **^{19}F** @ -76.15 ppm). **HRMS** (EI): m/z (ESI+) 147.0 [100], 295.0 [81], 499.0 [1.2], 500.0 [0.3], 501.0 [0.8], $C_{12}H_{16}F_{12}O_4Ti$ $[M]^+$ predicted *m/z* 500.0331, found *m/z* 500.0311, Delta = + 3.9 ppm.

5.16.2 Evidence of intermediate complex (243a)



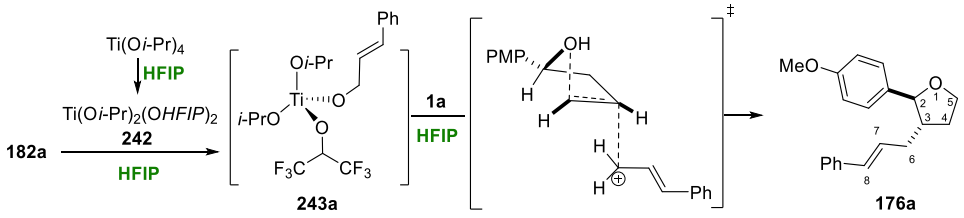
182a **243a**

To a microwave vial charged with a stirring bar was added cinnamyl alcohol

***E*-182a** (23.5 mg, 0.175 mmol), Ti(O*i*-Pr)$_2$(OHFIP)$_2$ **242** (74.6 mg, 0.353 mmol) and $CDCl_3$ (2.0 mL). The solution was stirred under Ar for 10 min. and then the solution was transferred to an NMR tube for NMR experiments (the present of broad peaks in proton NMR made integration difficult).

Data for **243a**: **^{1}H NMR (500 MHz, $CDCl_3$) δ** 7.21-7.40 (5H, m, Ar), 6.60 (1H, d, *J* = 15.9 Hz, 5-H), 6.37 (1H, dt, *J* = 14.9, 5.8 Hz, 4-H), 4.38-4.66 (3H, m, 1-H and 3-H$_2$), 3.95-4.24 (2H, m, 2 x 2-H), 1.22 (12H, d, *J* = 6.2 Hz, 4 x Me). **^{19}F NMR (471 MHz, $CDCl_3$) δ** -75.65 (6F, s, 2 x CF_3). **NOESY- 2D (500 MHz, $CDCl_3$)**: between 3-H$_2$ and Me, between 2-H and Me.

5.16.3 Evidence of formation of product 3a from complex 243a



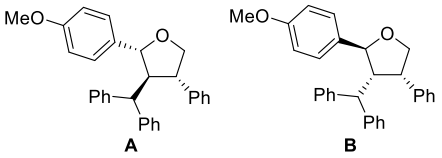
To a microwave vial charged with a stirring bar was added cinnamyl alcohol ***E*-182a** (23.5 mg, 0.175 mmol), Ti(O*i*-Pr)$_2$(OHFIP)$_2$ **242** (74.6 mg, 0.353 mmol) and $CDCl_3$ (2.0 mL). The solution was stirred under Ar for 10 min. and then alcohol **178a** (31.1 mg, 0.175 mmol) and HFIP (1.75 mL) were added. The reaction was heated overnigh at 70°C. Solvent was then removed by evaporator. Purification using silica gel flash chromatography (gradient elution: 12% → 20% Et_2O - pentane) afforded **176a** as a colorless oil (20.6 mg, 40%).

Data for **243a** matched those previously reported.

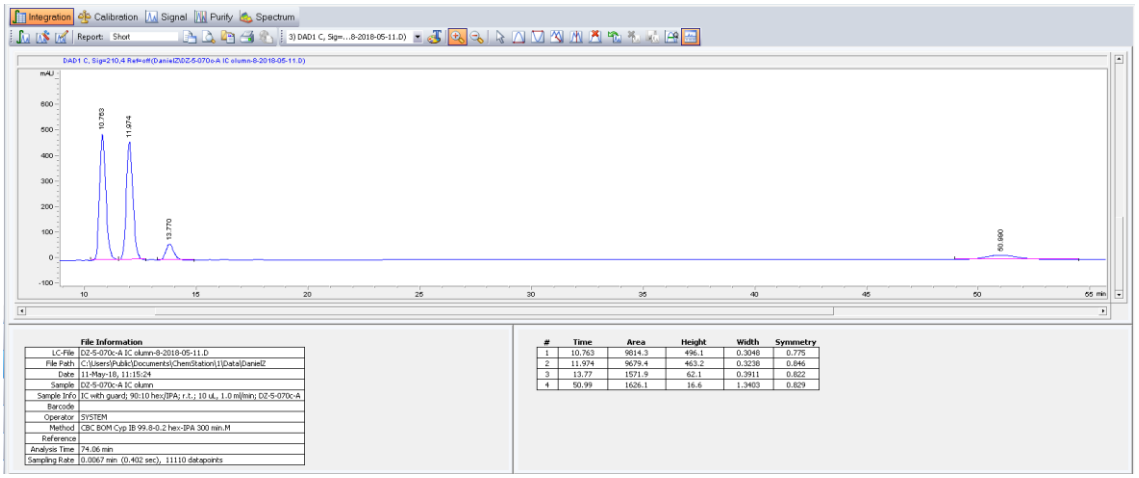
5.17 HPLC Chromatograms

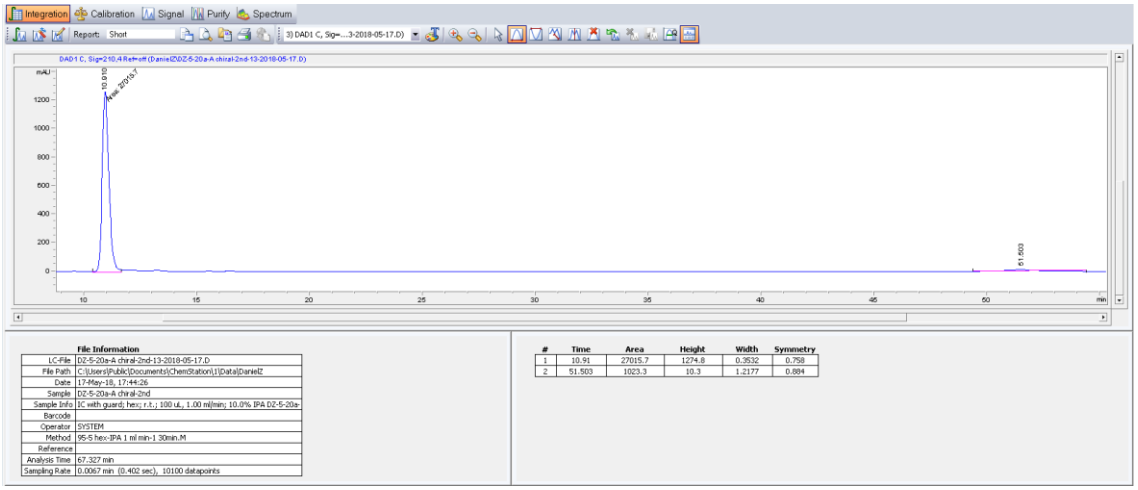
Chiral high performance liquid chromatography (HPLC) was performed on Agilent 1200 series instruments using 4.6 mm * 250 mmL Chiralpak IC columns.

i) HPLC traces of **(±)-176aah** and **(+)-176aah**



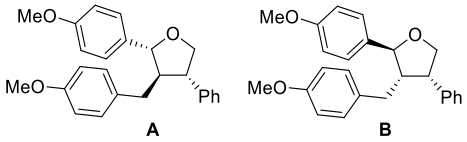
(+)-176aah
dr 8:1 (C-4)



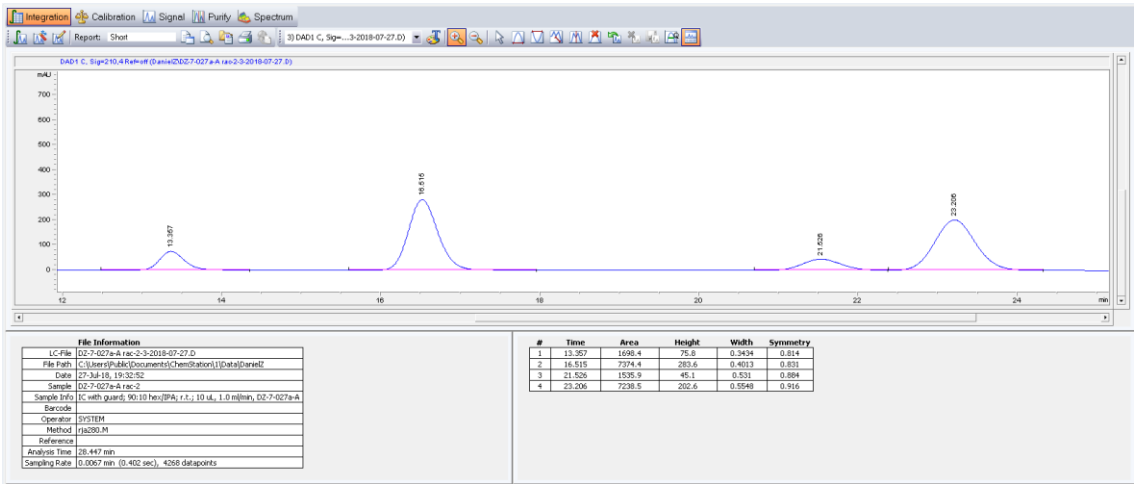


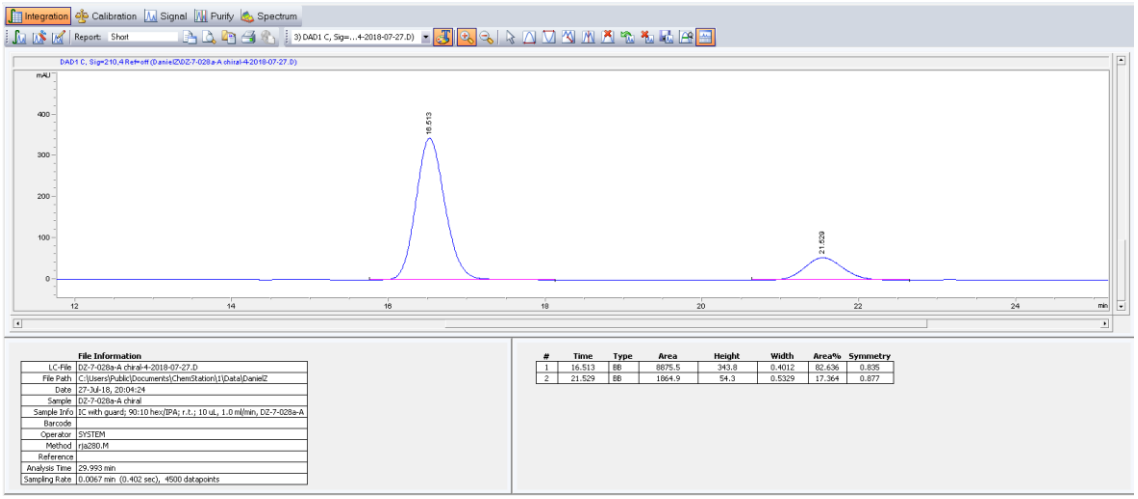
Compound **(+)-176aah** was determined to be > 99% ee by chiral HPLC (Chiralpak IC); 90:10 Hexane–*i*-PrOH at 1.0 mL/min; 210 nm.

ii) HPLC traces of **(±)-176aaz** and **(+)-176aaz**



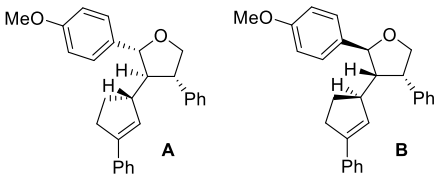
(+)-176aaz
dr 5:1 (C-4)



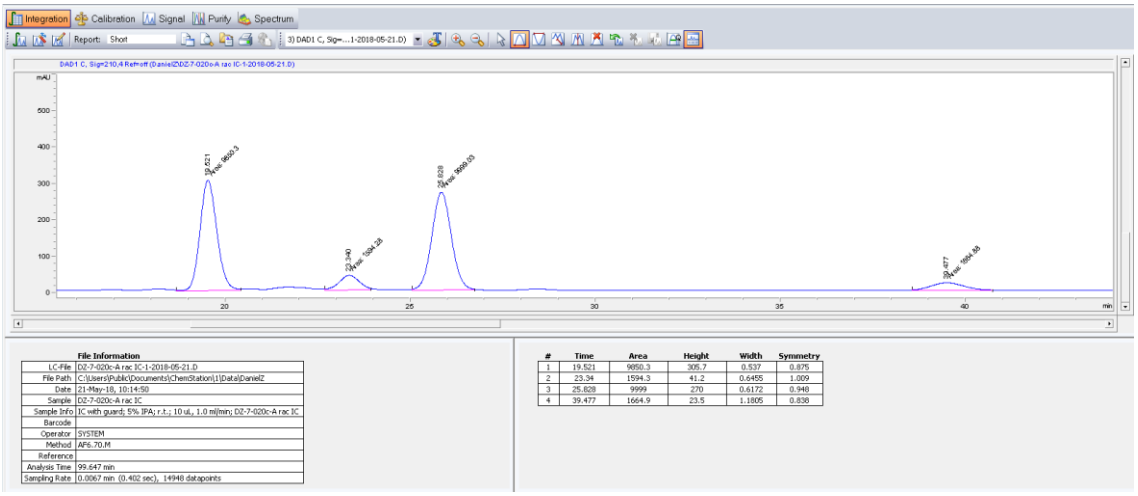


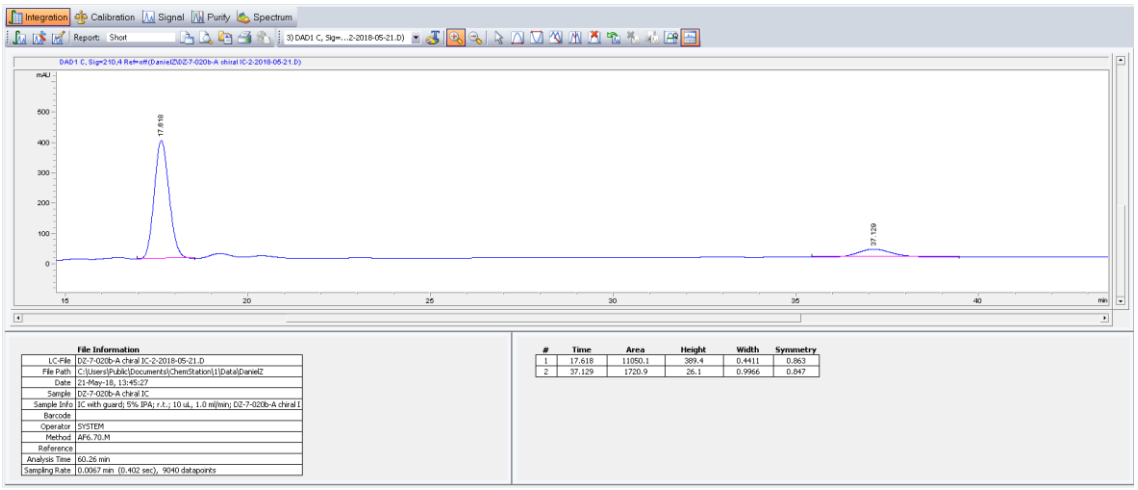
Compound **(+)-176aaz** was determined to be > 99% ee by chiral HPLC (Chiralpak IC); 90:10 Hexane–*i*-PrOH at 1.0 mL/min; 210 nm.

iii) HPLC traces of **(±)-176aaaa** and **(+)-176aaaa**



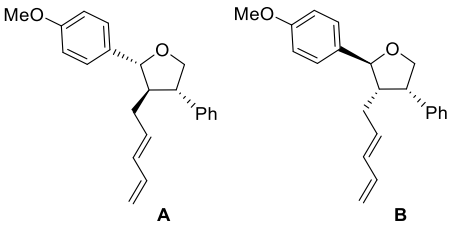
(+)-176aaaa
dr 7:1 (C-4)



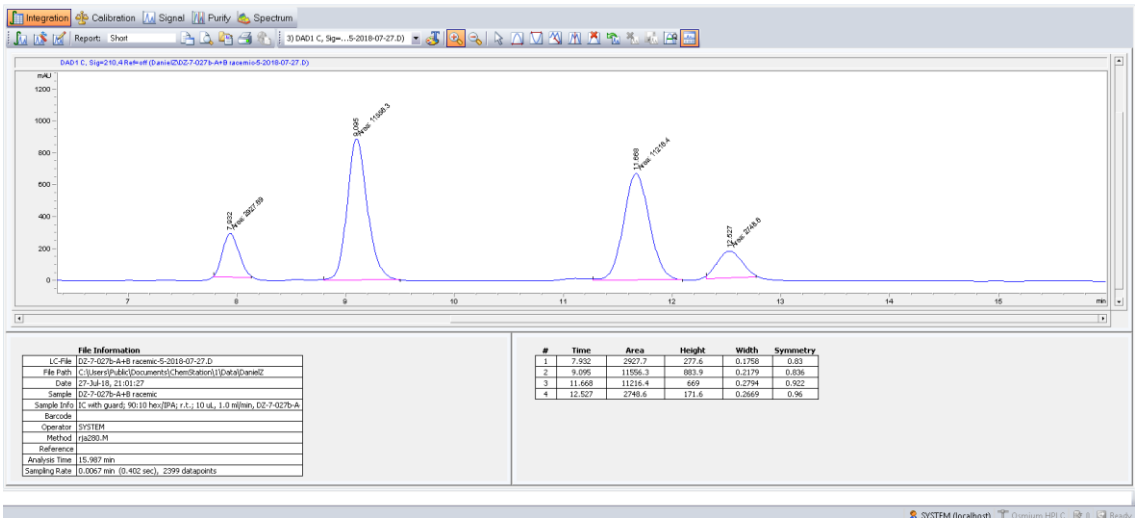


Compound **(+)-176aaaa** was determined to be > 99% ee by chiral HPLC (Chiralpak IC); 90:10 Hexane–*i*-PrOH at 1.0 mL/min; 210 nm.

iv) HPLC traces of **(±)-176aaab** and **(+)-176aaab**

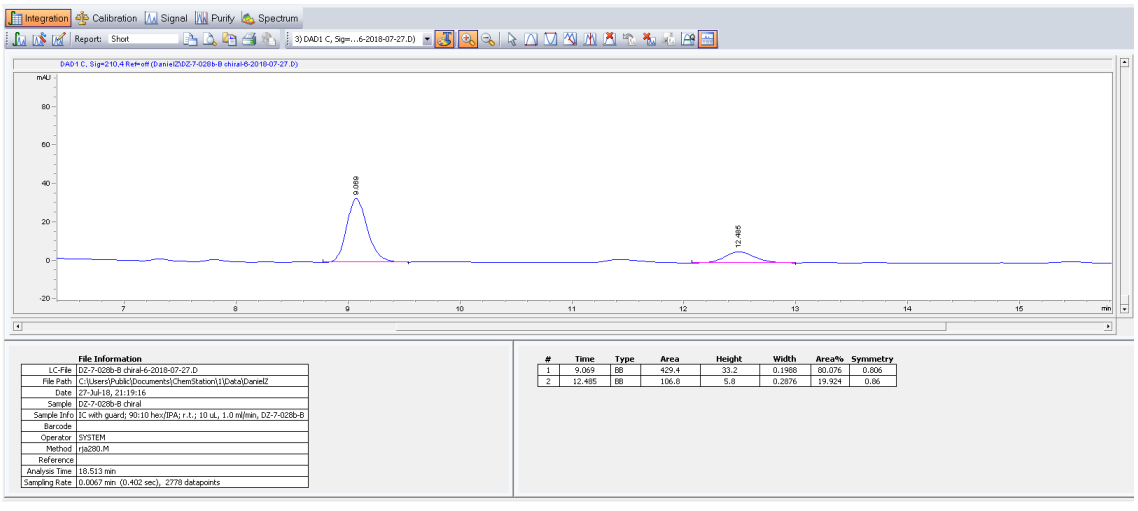


(+)-176aaab
dr 5:1 (C-4)



File Information	
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File Path	C:\Users\Public\Documents\ChemStation\1\Data\DanielZ
Date	27-Jul-18, 21:01:27
Sample	DZ-7-027b-A+B racemic
Sample Info	IC with guard; 90:10 hex/IPA; r.t.; 10 uL, 1.0 ml/min, DZ-7-027b-A
Barcode	
Operator	SYSTEM
Method	rja280.M
Reference	
Analysis Time	15.987 min
Sampling Rate	0.0067 min (0.402 sec), 2399 datapoints

#	Time	Area	Height	Width	Symmetry
1	7.932	2927.7	277.6	0.1758	0.83
2	9.095	11556.3	883.9	0.2179	0.836
3	11.668	11216.4	669	0.2794	0.922
4	12.527	2748.6	171.6	0.2669	0.96

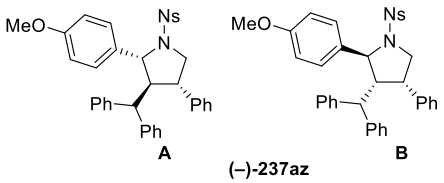


File Information	
LC-File	DZ-7-028b-B chiral-6-2018-07-27.D
File Path	C:\Users\Public\Documents\ChemStation\1\Data\DanielZ
Date	27-Jul-18, 21:19:16
Sample	DZ-7-028b-B chiral
Sample Info	IC with guard; 90:10 hex/IPA; r.t.; 10 uL, 1.0 ml/min, DZ-7-028b-B
Barcode	
Operator	SYSTEM
Method	rja280.M
Reference	
Analysis Time	18.513 min
Sampling Rate	0.0067 min (0.402 sec), 2778 datapoints

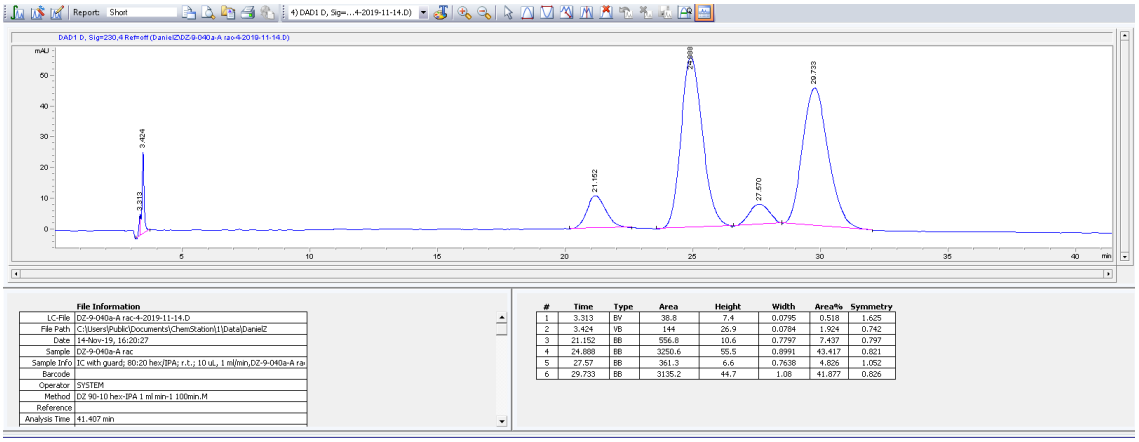
#	Time	Type	Area	Height	Width	Area%	Symmetry
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2	12.485	BB	106.8	5.8	0.2876	19.924	0.86

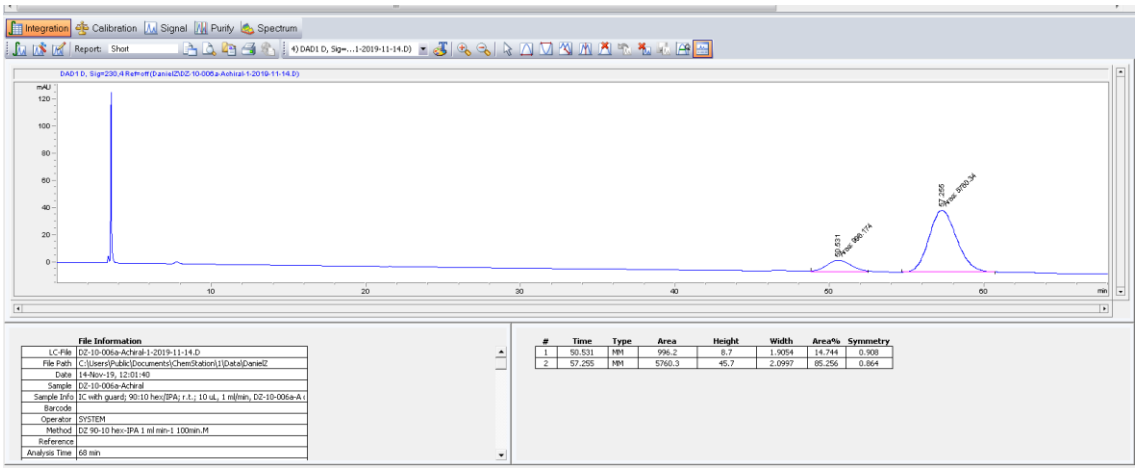
Compound **(+)-176aaab** was determined to be > 99% ee by chiral HPLC (Chiralpak IC); 90:10 Hexane–*i*-PrOH at 1.0 mL/min; 210 nm.

v) HPLC traces of **(±)-237az** and **(–)-237az**



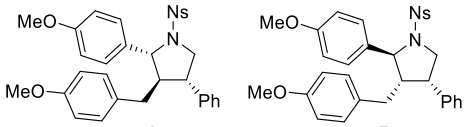
(–)-237az
dr 7:1 (C-4)



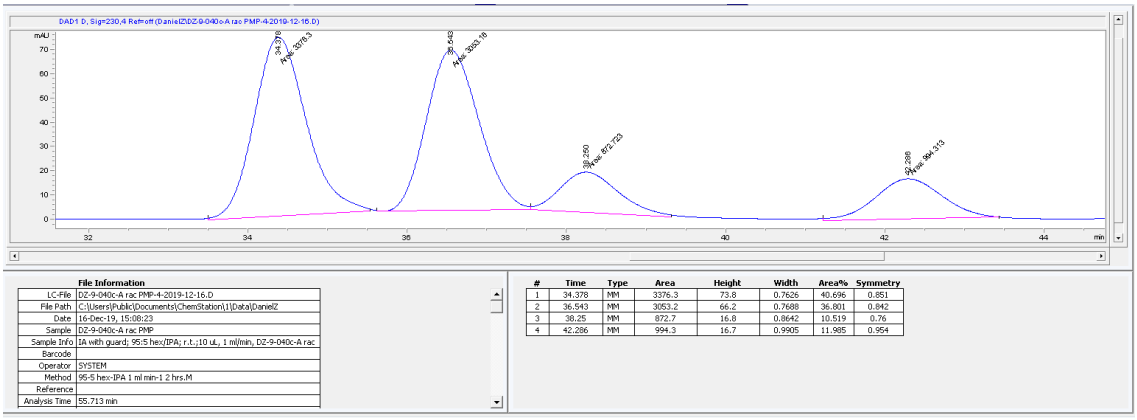


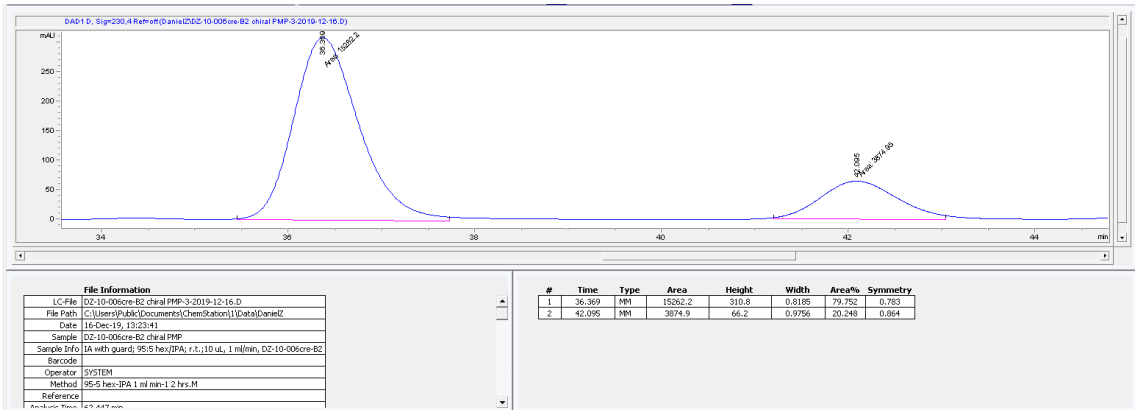
Compound **(–)-237az** was determined to be > 99% ee by chiral HPLC (Chiralpak IC); 90:10 Hexane–*i*-PrOH at 1.0 mL/min; 210 nm.

vi) HPLC traces of **(±)-237aaa** and **(–)-237aaa**



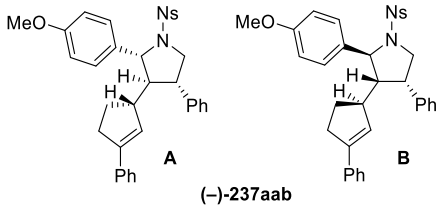
(+)-237aaa
dr 5:1 (C-4)



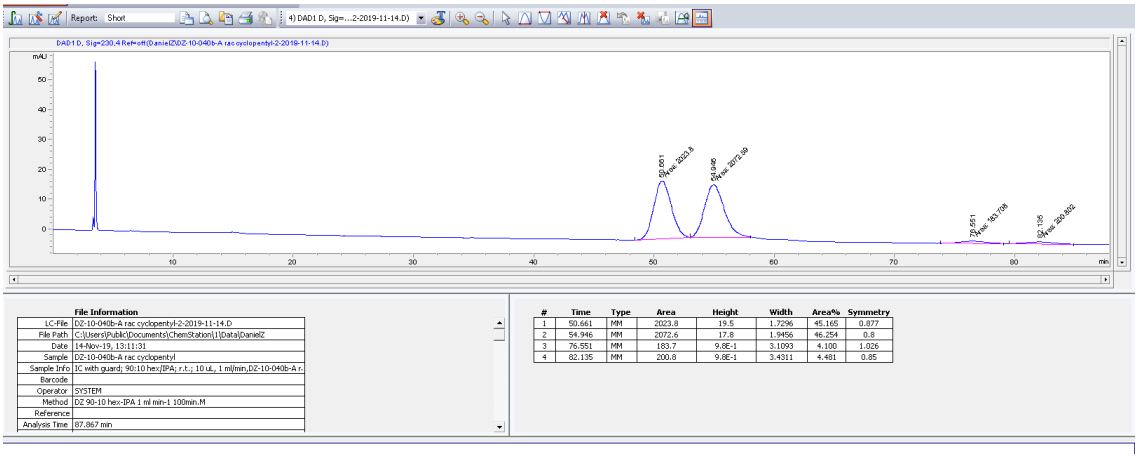


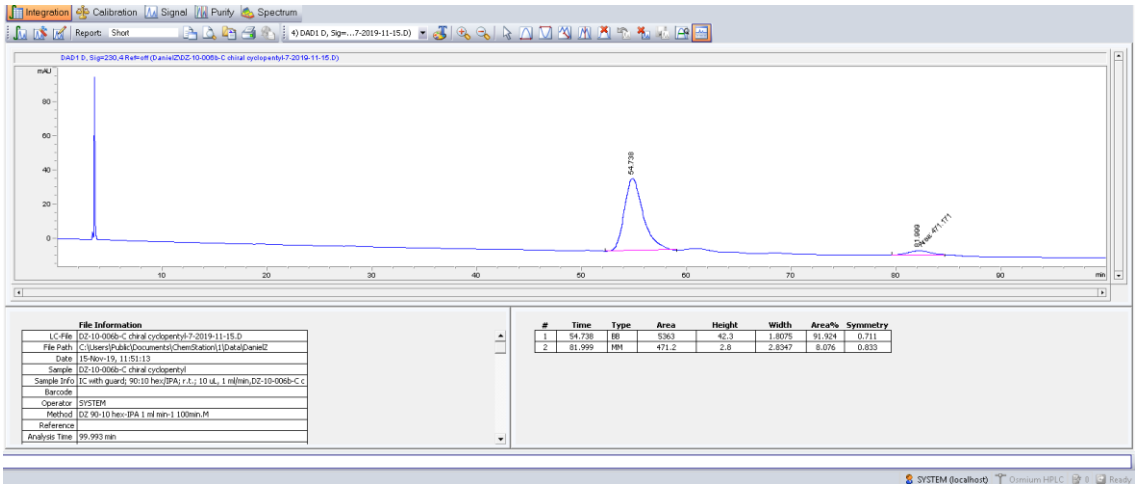
Compound **(–)-237aaa** was determined to be > 99% ee by chiral HPLC (Chiralpak IC); 95:5 Hexane–*i*-PrOH at 1.0 mL/min; 210 nm.

vii) HPLC traces of **(±)-237aab** and **(–)-237aab**



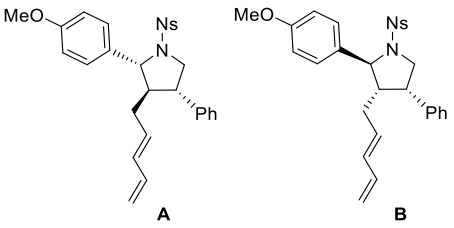
(–)-237aab
dr 12:1 (C-4)



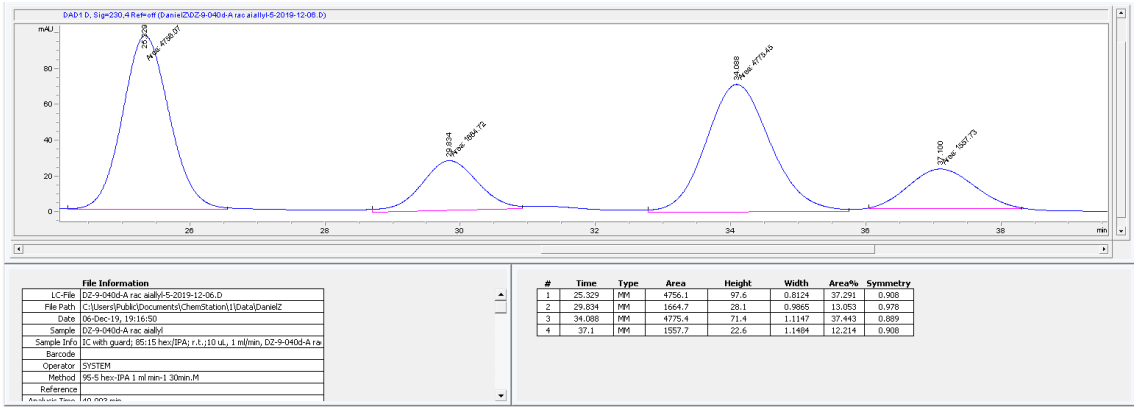


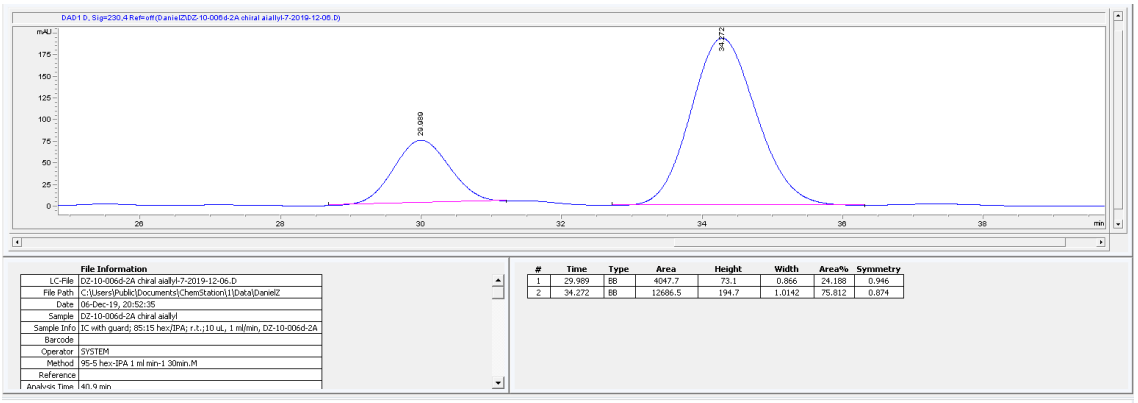
Compound **(–)-237aab** was determined to be > 99% ee by chiral HPLC (Chiralpak IC); 90:10 Hexane–*i*-PrOH at 1.0 mL/min; 210 nm.

viii) HPLC traces of **(±)-237aac** and **(–)-237aac**



(–)-237aac
dr 5:1 (C-4)





Compound **(–)-237aac** was determined to be > 99% ee by chiral HPLC (Chiralpak IC); 95:5 Hexane–*i*-PrOH at 1.0 mL/min; 210 nm.

5.18 Crystallography data

i) Crystallography data for THFs **176aad**

Table 1. Crystal data and structure refinement for 6991.

Identification code	6991	
Empirical formula	C26 H30 O3	
Formula weight	390.52	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 13.8835(2) Å	α= 90°.
	b = 13.7039(3) Å	β= 96.2374(17)°.
	c = 11.1974(2) Å	γ = 90°.
Volume	2117.78(7) Å^3	
Z	4	
Density (calculated)	1.225 Mg/m^3	
Absorption coefficient	0.617 mm^{-1}	
F(000)	840	
Crystal size	0.11 x 0.07 x 0.03 mm^3	
Theta range for data collection	4.547 to 76.359°.	
Index ranges	-16<=h<=17, -17<=k<=15, -13<=l<=13	
Reflections collected	26917	
Independent reflections	4397 [R(int) = 0.028]	
Completeness to theta = 74.832°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.98 and 0.91	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4397 / 0 / 262	
Goodness-of-fit on F^2	0.9961	
Final R indices [I>2sigma(I)]	R1 = 0.0418, wR2 = 0.1079	
R indices (all data)	R1 = 0.0500, wR2 = 0.1167	
Largest diff. peak and hole	0.28 and -0.17 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 6991. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	6463(1)	6595(1)	7430(1)	40
O(2)	5855(1)	7444(1)	7382(1)	46
C(3)	5265(1)	7470(1)	6229(1)	39
C(4)	5689(1)	6691(1)	5453(1)	42
C(5)	6675(1)	6440(1)	6129(1)	39
C(6)	7036(1)	5417(1)	5872(1)	46
C(7)	7056(1)	5187(1)	4559(1)	45
C(8)	7839(1)	4704(1)	4316(1)	44
C(9)	8510(1)	4548(1)	5453(1)	63
C(10)	8090(1)	5197(1)	6384(1)	60
C(11)	7322(1)	6745(1)	8351(1)	41
C(12)	7587(1)	6016(1)	9181(1)	44
C(13)	8401(1)	6102(1)	10014(1)	47
C(14)	8955(1)	6935(1)	10028(1)	46
C(15)	8692(1)	7686(1)	9219(1)	49
C(16)	7885(1)	7586(1)	8384(1)	46
O(17)	9774(1)	7094(1)	10804(1)	62
C(18)	10114(1)	6305(2)	11563(2)	69
C(21)	5336(1)	8498(1)	5743(1)	47
C(22)	4875(1)	9224(1)	6537(1)	52
O(23)	3889(1)	8995(1)	6634(1)	54
C(24)	3803(1)	8060(1)	7173(1)	52
C(25)	4215(1)	7266(1)	6433(1)	48
C(31)	8038(1)	4308(1)	3145(1)	47
C(32)	7346(1)	4328(1)	2150(1)	49
C(33)	7514(1)	3901(1)	1072(1)	58
C(34)	8391(2)	3468(1)	952(2)	71
C(35)	9093(2)	3464(2)	1909(2)	83
C(36)	8918(2)	3869(2)	3004(2)	70

Table 3. Bond lengths [Å] and angles [°] for 6991.

C(1)-O(2)	1.4351(16)	C(15)-H(151)	0.952
C(1)-C(5)	1.5326(17)	C(16)-H(161)	0.953
C(1)-C(11)	1.5036(18)	O(17)-C(18)	1.424(2)
C(1)-H(11)	0.993	C(18)-H(181)	0.987
O(2)-C(3)	1.4522(15)	C(18)-H(182)	1.004
C(3)-C(4)	1.5344(18)	C(18)-H(183)	0.982
C(3)-C(21)	1.5170(19)	C(21)-C(22)	1.520(2)
C(3)-C(25)	1.5249(19)	C(21)-H(212)	0.963
C(4)-C(5)	1.5300(18)	C(21)-H(211)	0.979
C(4)-H(42)	0.959	C(22)-O(23)	1.421(2)
C(4)-H(41)	0.979	C(22)-H(222)	0.992
C(5)-C(6)	1.5268(19)	C(22)-H(221)	1.012
C(5)-H(51)	0.971	O(23)-C(24)	1.427(2)
C(6)-C(7)	1.5062(19)	C(24)-C(25)	1.518(2)
C(6)-C(10)	1.542(2)	C(24)-H(241)	0.995
C(6)-H(61)	0.975	C(24)-H(242)	0.973
C(7)-C(8)	1.327(2)	C(25)-H(252)	0.992
C(7)-H(71)	0.955	C(25)-H(251)	0.966
C(8)-C(9)	1.509(2)	C(31)-C(32)	1.390(2)
C(8)-C(31)	1.4733(19)	C(31)-C(36)	1.386(2)
C(9)-C(10)	1.534(2)	C(32)-C(33)	1.383(2)
C(9)-H(91)	1.005	C(32)-H(321)	0.960
C(9)-H(92)	0.997	C(33)-C(34)	1.375(3)
C(10)-H(102)	0.999	C(33)-H(331)	0.939
C(10)-H(101)	0.962	C(34)-C(35)	1.368(3)
C(11)-C(12)	1.3863(19)	C(34)-H(341)	0.959
C(11)-C(16)	1.391(2)	C(35)-C(36)	1.391(3)
C(12)-C(13)	1.390(2)	C(35)-H(351)	0.958
C(12)-H(121)	0.952	C(36)-H(361)	0.955
C(13)-C(14)	1.376(2)		
C(13)-H(131)	0.937	O(2)-C(1)-C(5)	104.45(10)
C(14)-C(15)	1.393(2)	O(2)-C(1)-C(11)	109.55(11)
C(14)-O(17)	1.3713(17)	C(5)-C(1)-C(11)	116.77(11)
C(15)-C(16)	1.386(2)	O(2)-C(1)-H(11)	109.4

C(5)-C(1)-H(11)	107.2	C(8)-C(9)-H(92)	109.7
C(11)-C(1)-H(11)	109.2	C(10)-C(9)-H(92)	110.4
C(1)-O(2)-C(3)	109.04(10)	H(91)-C(9)-H(92)	108.2
O(2)-C(3)-C(4)	105.79(10)	C(6)-C(10)-C(9)	106.03(13)
O(2)-C(3)-C(21)	106.79(11)	C(6)-C(10)-H(102)	108.8
C(4)-C(3)-C(21)	113.53(11)	C(9)-C(10)-H(102)	108.1
O(2)-C(3)-C(25)	108.55(11)	C(6)-C(10)-H(101)	110.7
C(4)-C(3)-C(25)	112.91(12)	C(9)-C(10)-H(101)	113.8
C(21)-C(3)-C(25)	108.94(11)	H(102)-C(10)-H(101)	109.2
C(3)-C(4)-C(5)	104.72(10)	C(1)-C(11)-C(12)	119.62(13)
C(3)-C(4)-H(42)	112.3	C(1)-C(11)-C(16)	122.21(12)
C(5)-C(4)-H(42)	112.2	C(12)-C(11)-C(16)	118.15(13)
C(3)-C(4)-H(41)	109.0	C(11)-C(12)-C(13)	121.74(14)
C(5)-C(4)-H(41)	110.4	C(11)-C(12)-H(121)	119.3
H(42)-C(4)-H(41)	108.1	C(13)-C(12)-H(121)	119.0
C(1)-C(5)-C(4)	100.66(10)	C(12)-C(13)-C(14)	119.40(13)
C(1)-C(5)-C(6)	114.06(11)	C(12)-C(13)-H(131)	121.7
C(4)-C(5)-C(6)	114.03(11)	C(14)-C(13)-H(131)	118.9
C(1)-C(5)-H(51)	109.4	C(13)-C(14)-C(15)	119.90(13)
C(4)-C(5)-H(51)	110.2	C(13)-C(14)-O(17)	124.27(14)
C(6)-C(5)-H(51)	108.3	C(15)-C(14)-O(17)	115.83(14)
C(5)-C(6)-C(7)	114.66(12)	C(14)-C(15)-C(16)	120.12(14)
C(5)-C(6)-C(10)	115.23(13)	C(14)-C(15)-H(151)	120.1
C(7)-C(6)-C(10)	101.84(12)	C(16)-C(15)-H(151)	119.7
C(5)-C(6)-H(61)	107.0	C(11)-C(16)-C(15)	120.67(13)
C(7)-C(6)-H(61)	108.2	C(11)-C(16)-H(161)	119.5
C(10)-C(6)-H(61)	109.7	C(15)-C(16)-H(161)	119.8
C(6)-C(7)-C(8)	114.01(13)	C(14)-O(17)-C(18)	117.11(14)
C(6)-C(7)-H(71)	121.7	O(17)-C(18)-H(181)	105.0
C(8)-C(7)-H(71)	124.3	O(17)-C(18)-H(182)	111.4
C(7)-C(8)-C(9)	110.02(13)	H(181)-C(18)-H(182)	110.2
C(7)-C(8)-C(31)	127.15(13)	O(17)-C(18)-H(183)	110.2
C(9)-C(8)-C(31)	122.74(13)	H(181)-C(18)-H(183)	111.2
C(8)-C(9)-C(10)	104.21(12)	H(182)-C(18)-H(183)	108.9
C(8)-C(9)-H(91)	112.4	C(3)-C(21)-C(22)	110.50(11)
C(10)-C(9)-H(91)	111.9	C(3)-C(21)-H(212)	108.2

C(22)-C(21)-H(212)	111.9	C(24)-C(25)-H(251)	109.3
C(3)-C(21)-H(211)	108.1	H(252)-C(25)-H(251)	108.4
C(22)-C(21)-H(211)	109.0	C(8)-C(31)-C(32)	121.74(13)
H(212)-C(21)-H(211)	109.1	C(8)-C(31)-C(36)	120.92(14)
C(21)-C(22)-O(23)	111.75(13)	C(32)-C(31)-C(36)	117.31(14)
C(21)-C(22)-H(222)	109.4	C(31)-C(32)-C(33)	121.56(15)
O(23)-C(22)-H(222)	108.3	C(31)-C(32)-H(321)	119.4
C(21)-C(22)-H(221)	108.8	C(33)-C(32)-H(321)	119.1
O(23)-C(22)-H(221)	109.1	C(32)-C(33)-C(34)	120.21(17)
H(222)-C(22)-H(221)	109.5	C(32)-C(33)-H(331)	120.6
C(22)-O(23)-C(24)	110.87(11)	C(34)-C(33)-H(331)	119.2
O(23)-C(24)-C(25)	111.03(12)	C(33)-C(34)-C(35)	119.20(16)
O(23)-C(24)-H(241)	109.6	C(33)-C(34)-H(341)	120.4
C(25)-C(24)-H(241)	109.5	C(35)-C(34)-H(341)	120.3
O(23)-C(24)-H(242)	105.6	C(34)-C(35)-C(36)	120.77(18)
C(25)-C(24)-H(242)	112.8	C(34)-C(35)-H(351)	120.2
H(241)-C(24)-H(242)	108.2	C(36)-C(35)-H(351)	119.0
C(3)-C(25)-C(24)	111.94(12)	C(35)-C(36)-C(31)	120.90(18)
C(3)-C(25)-H(252)	109.2	C(35)-C(36)-H(361)	121.6
C(24)-C(25)-H(252)	109.7	C(31)-C(36)-H(361)	117.4
C(3)-C(25)-H(251)	108.3		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for 6991. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	42(1)	44(1)	36(1)	3(1)	7(1)	2(1)
O(2)	48(1)	55(1)	34(1)	-4(1)	2(1)	14(1)
C(3)	42(1)	42(1)	33(1)	2(1)	4(1)	2(1)
C(4)	46(1)	46(1)	35(1)	-1(1)	3(1)	4(1)
C(5)	42(1)	41(1)	34(1)	1(1)	6(1)	2(1)
C(6)	53(1)	43(1)	42(1)	2(1)	8(1)	6(1)
C(7)	47(1)	44(1)	43(1)	-4(1)	1(1)	4(1)
C(8)	51(1)	41(1)	41(1)	1(1)	4(1)	6(1)
C(9)	69(1)	73(1)	46(1)	-6(1)	-2(1)	30(1)
C(10)	68(1)	68(1)	41(1)	-4(1)	-4(1)	26(1)
C(11)	42(1)	46(1)	34(1)	-2(1)	8(1)	4(1)
C(12)	48(1)	48(1)	37(1)	2(1)	7(1)	-1(1)
C(13)	52(1)	52(1)	37(1)	3(1)	4(1)	6(1)
C(14)	45(1)	55(1)	39(1)	-8(1)	2(1)	6(1)
C(15)	50(1)	46(1)	50(1)	-6(1)	5(1)	-2(1)
C(16)	50(1)	45(1)	42(1)	1(1)	6(1)	5(1)
O(17)	56(1)	69(1)	57(1)	-9(1)	-12(1)	3(1)
C(18)	63(1)	83(1)	56(1)	3(1)	-14(1)	9(1)
C(21)	55(1)	46(1)	41(1)	5(1)	11(1)	-1(1)
C(22)	66(1)	42(1)	50(1)	2(1)	10(1)	1(1)
O(23)	55(1)	54(1)	52(1)	-1(1)	4(1)	14(1)
C(24)	43(1)	59(1)	55(1)	-1(1)	12(1)	2(1)
C(25)	45(1)	49(1)	52(1)	0(1)	7(1)	-2(1)
C(31)	55(1)	44(1)	44(1)	1(1)	9(1)	6(1)
C(32)	55(1)	49(1)	44(1)	4(1)	10(1)	-2(1)
C(33)	77(1)	56(1)	41(1)	3(1)	8(1)	-7(1)
C(34)	105(2)	61(1)	48(1)	-3(1)	24(1)	15(1)
C(35)	95(2)	93(2)	65(1)	-3(1)	22(1)	44(1)
C(36)	72(1)	83(1)	54(1)	-5(1)	6(1)	32(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 6991.

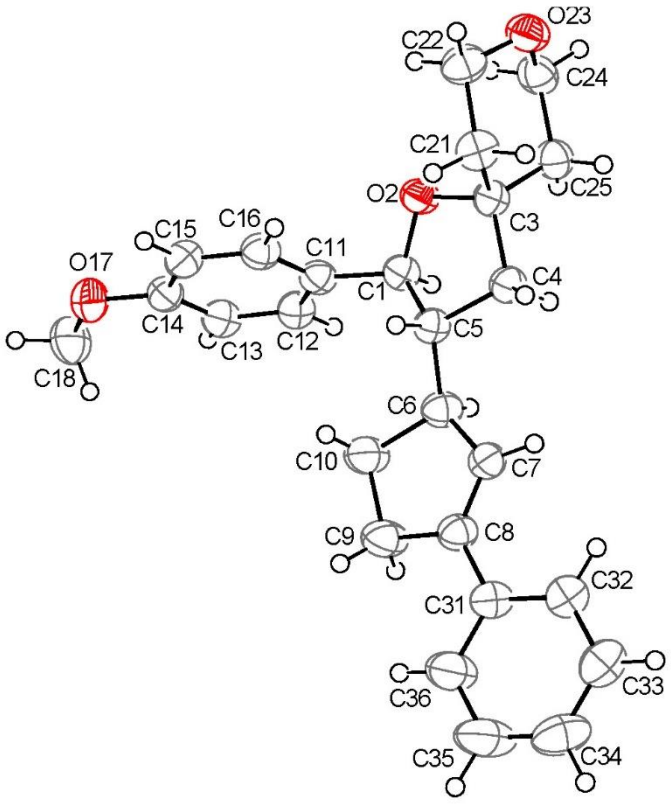
	x	y	z	U(eq)
H(11)	6089	6019	7659	47
H(42)	5743	6916	4652	51
H(41)	5266	6118	5401	49
H(51)	7160	6907	5934	45
H(61)	6600	4956	6202	54
H(71)	6532	5359	3974	54
H(91)	9200	4723	5354	77
H(92)	8493	3849	5698	77
H(102)	8463	5822	6445	71
H(101)	8111	4906	7168	72
H(121)	7204	5440	9179	52
H(131)	8576	5613	10581	57
H(151)	9071	8265	9229	59
H(161)	7715	8096	7821	53
H(181)	10710	6551	12027	102
H(182)	9625	6115	12120	101
H(183)	10251	5735	11077	101
H(212)	6009	8642	5692	55
H(211)	4986	8517	4936	54
H(222)	4905	9887	6189	63
H(221)	5247	9214	7365	60
H(241)	4152	8062	7998	59
H(242)	3115	7974	7240	61
H(252)	4179	6628	6844	58
H(251)	3835	7225	5659	57
H(321)	6733	4637	2213	59
H(331)	7038	3918	409	70
H(341)	8513	3177	204	84
H(351)	9710	3169	1837	100
H(361)	9402	3871	3680	84

Table 6. Hydrogen bonds for 6991 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(12)-H(121)...O(23)#1	0.95	2.60	3.507(2)	160
C(33)-H(331)...O(23)#2	0.94	2.50	3.422(2)	166

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y-1/2,-z+3/2 #2 -x+1,y-1/2,-z+1/2



ii) Crystallography data for lactones **240b**

Table 1. Crystal data and structure refinement for DIA0363.

Identification code	DIA0363	
Empirical formula	C33 H29.00 I1 O3	
Formula weight	600.50	
Temperature	100 K	
Wavelength	0.68890 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 26.1120(3) Å	α= 90°.
	b = 7.19960(10) Å	β= 94.2377(10)°.
	c = 29.2680(3) Å	γ = 90°.
Volume	5487.22(11) Å^3	
Z	8	
Density (calculated)	1.454 Mg/m^3	
Absorption coefficient	1.089 mm^{-1}	
F(000)	2431.986	
Crystal size	0.030 x 0.010 x 0.010 mm^3	
Theta range for data collection	1.501 to 36.072°.	
Index ranges	-42<=h<=43, -10<=k<=11, -49<=l<=49	
Reflections collected	90125	
Independent reflections	24521 [R(int) = 0.116]	
Completeness to theta = 28.855°	98.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.99 and 0.76	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	15998 / 0 / 667	
Goodness-of-fit on F^2	1.0369	
Final R indices [I>2sigma(I)]	R1 = 0.0818, wR2 = 0.0857	
R indices (all data)	R1 = 0.1101, wR2 = 0.0916	
Largest diff. peak and hole	4.05 and -1.87 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for DIA0363. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
I(1)	3506(1)	6847(1)	4272(1)	25
C(2)	3294(1)	7119(3)	4944(1)	22
C(3)	3361(1)	5620(3)	5246(1)	23
C(4)	3247(1)	5835(3)	5698(1)	22
C(5)	3068(1)	7526(3)	5859(1)	22
C(6)	2977(1)	8977(3)	5550(1)	23
C(7)	3088(1)	8788(3)	5093(1)	24
C(8)	2996(1)	7801(3)	6364(1)	22
C(9)	3469(1)	8722(3)	6624(1)	19
C(10)	3553(1)	10669(3)	6444(1)	20
O(11)	3242(1)	11913(2)	6400(1)	23
O(12)	4040(1)	10913(2)	6338(1)	21
C(13)	4365(1)	9295(3)	6462(1)	19
C(14)	3988(1)	7748(3)	6587(1)	18
C(15)	4190(1)	6737(3)	7031(1)	18
C(16)	4718(1)	5919(3)	6974(1)	18
C(17)	5140(1)	6515(3)	7257(1)	22
C(18)	5631(1)	5875(3)	7195(1)	26
C(19)	5708(1)	4612(3)	6848(1)	25
C(20)	5289(1)	3950(3)	6570(1)	23
C(21)	4797(1)	4605(3)	6638(1)	21
C(22)	3827(1)	5288(3)	7186(1)	19
C(23)	3672(1)	5261(3)	7612(1)	21
C(24)	3363(1)	3835(3)	7815(1)	20
C(25)	3363(1)	3738(3)	8294(1)	21
C(26)	3100(1)	2336(3)	8508(1)	24
C(27)	2830(1)	1004(4)	8242(1)	25
C(28)	2815(1)	1105(4)	7766(1)	24
C(29)	3075(1)	2501(3)	7552(1)	21
C(30)	4687(1)	8844(3)	6071(1)	19
C(31)	5221(1)	8738(3)	6138(1)	20

C(32)	5516(1)	8249(3)	5783(1)	20
C(33)	5275(1)	7870(3)	5347(1)	19
O(34)	5598(1)	7369(2)	5020(1)	22
C(35)	5358(1)	6928(3)	4578(1)	23
C(36)	4741(1)	7999(3)	5271(1)	20
C(37)	4455(1)	8475(3)	5636(1)	19
I(51)	1557(1)	1671(1)	4478(1)	33
C(52)	1730(1)	1896(3)	5188(1)	25
C(57)	1944(1)	3507(4)	5375(1)	27
C(56)	2039(1)	3662(3)	5844(1)	25
C(55)	1922(1)	2203(3)	6137(1)	22
C(58)	1985(1)	2465(3)	6652(1)	23
C(59)	1523(1)	3441(3)	6848(1)	19
C(60)	1457(1)	5402(3)	6665(1)	22
O(61)	1778(1)	6608(2)	6662(1)	26
O(62)	970(1)	5717(2)	6495(1)	23
C(63)	634(1)	4118(3)	6561(1)	20
C(64)	1002(1)	2517(3)	6735(1)	19
C(65)	788(1)	1527(3)	7150(1)	19
C(66)	258(1)	713(3)	7017(1)	20
C(67)	-165(1)	1333(3)	7243(1)	25
C(68)	-653(1)	720(3)	7108(1)	26
C(69)	-731(1)	-507(3)	6744(1)	26
C(70)	-312(1)	-1187(3)	6530(1)	26
C(71)	178(1)	-589(3)	6663(1)	22
C(72)	1148(1)	77(3)	7359(1)	20
C(73)	1310(1)	132(3)	7801(1)	21
C(74)	1631(1)	-1229(3)	8065(1)	21
C(79)	1911(1)	-2627(3)	7856(1)	21
C(78)	2189(1)	-3932(3)	8124(1)	24
C(77)	2208(1)	-3819(4)	8598(1)	26
C(76)	1942(1)	-2422(4)	8810(1)	25
C(75)	1655(1)	-1142(3)	8543(1)	22
C(80)	321(1)	3726(3)	6120(1)	20
C(81)	-218(1)	3613(3)	6107(1)	21
C(82)	-507(1)	3173(3)	5708(1)	23

C(83)	-264(1)	2841(3)	5308(1)	20
O(84)	-583(1)	2399(2)	4931(1)	25
C(85)	-340(1)	2018(3)	4517(1)	26
C(86)	271(1)	2958(3)	5311(1)	23
C(87)	554(1)	3384(3)	5719(1)	21
C(54)	1726(1)	560(3)	5942(1)	24
C(53)	1629(1)	392(3)	5471(1)	24

Table 3. Bond lengths [Å] and angles [°] for DIA0363.

I(1)-C(2)	2.089(2)	C(18)-H(181)	0.952
C(2)-C(3)	1.398(3)	C(19)-C(20)	1.399(3)
C(2)-C(7)	1.399(3)	C(19)-H(191)	0.980
C(3)-C(4)	1.387(3)	C(20)-C(21)	1.397(3)
C(3)-H(31)	0.972	C(20)-H(201)	0.984
C(4)-C(5)	1.399(3)	C(21)-H(211)	0.974
C(4)-H(41)	0.976	C(22)-C(23)	1.340(3)
C(5)-C(6)	1.392(3)	C(22)-H(221)	0.978
C(5)-C(8)	1.517(3)	C(23)-C(24)	1.458(3)
C(6)-C(7)	1.395(3)	C(23)-H(231)	0.981
C(6)-H(61)	0.948	C(24)-C(25)	1.405(3)
C(7)-H(71)	0.955	C(24)-C(29)	1.412(3)
C(8)-C(9)	1.552(3)	C(25)-C(26)	1.395(3)
C(8)-H(81)	0.969	C(25)-H(251)	0.939
C(8)-H(82)	0.976	C(26)-C(27)	1.393(4)
C(9)-C(10)	1.520(3)	C(26)-H(261)	0.948
C(9)-C(14)	1.537(3)	C(27)-C(28)	1.393(3)
C(9)-H(91)	1.000	C(27)-H(271)	0.955
C(10)-O(11)	1.210(3)	C(28)-C(29)	1.388(3)
C(10)-O(12)	1.342(3)	C(28)-H(281)	1.003
O(12)-C(13)	1.470(3)	C(29)-H(291)	0.969
C(13)-C(14)	1.547(3)	C(30)-C(31)	1.396(3)
C(13)-C(30)	1.507(3)	C(30)-C(37)	1.393(3)
C(13)-H(131)	0.983	C(31)-C(32)	1.383(3)
C(14)-C(15)	1.547(3)	C(31)-H(311)	0.961
C(14)-H(141)	0.991	C(32)-C(33)	1.406(3)
C(15)-C(16)	1.519(3)	C(32)-H(321)	0.943
C(15)-C(22)	1.503(3)	C(33)-O(34)	1.371(3)
C(15)-H(151)	0.996	C(33)-C(36)	1.399(3)
C(16)-C(17)	1.397(3)	O(34)-C(35)	1.430(3)
C(16)-C(21)	1.390(3)	C(35)-H(351)	0.964
C(17)-C(18)	1.388(4)	C(35)-H(352)	0.947
C(17)-H(171)	0.967	C(35)-H(353)	0.985
C(18)-C(19)	1.388(4)	C(36)-C(37)	1.391(3)

C(36)-H(361)	0.954	C(70)-C(71)	1.378(3)
C(37)-H(371)	0.966	C(70)-H(701)	0.955
I(51)-C(52)	2.098(3)	C(71)-H(711)	0.959
C(52)-C(57)	1.384(4)	C(72)-C(73)	1.333(3)
C(52)-C(53)	1.400(3)	C(72)-H(721)	0.987
C(57)-C(56)	1.380(4)	C(73)-C(74)	1.471(3)
C(57)-H(571)	0.969	C(73)-H(731)	0.968
C(56)-C(55)	1.404(3)	C(74)-C(79)	1.410(3)
C(56)-H(561)	0.938	C(74)-C(75)	1.397(3)
C(55)-C(58)	1.516(3)	C(79)-C(78)	1.393(3)
C(55)-C(54)	1.395(3)	C(79)-H(791)	0.966
C(58)-C(59)	1.543(3)	C(78)-C(77)	1.385(4)
C(58)-H(581)	0.994	C(78)-H(781)	0.945
C(58)-H(582)	0.968	C(77)-C(76)	1.395(4)
C(59)-C(60)	1.516(3)	C(77)-H(771)	0.977
C(59)-C(64)	1.530(3)	C(76)-C(75)	1.391(3)
C(59)-H(591)	0.976	C(76)-H(761)	0.943
C(60)-O(61)	1.207(3)	C(75)-H(751)	0.973
C(60)-O(62)	1.352(3)	C(80)-C(81)	1.408(3)
O(62)-C(63)	1.469(3)	C(80)-C(87)	1.384(3)
C(63)-C(64)	1.561(3)	C(81)-C(82)	1.380(3)
C(63)-C(80)	1.500(3)	C(81)-H(811)	0.983
C(63)-H(631)	0.999	C(82)-C(83)	1.392(3)
C(64)-C(65)	1.549(3)	C(82)-H(821)	0.951
C(64)-H(641)	0.976	C(83)-O(84)	1.370(3)
C(65)-C(66)	1.526(3)	C(83)-C(86)	1.400(4)
C(65)-C(72)	1.504(3)	O(84)-C(85)	1.435(3)
C(65)-H(651)	0.996	C(85)-H(851)	0.969
C(66)-C(67)	1.402(3)	C(85)-H(852)	0.938
C(66)-C(71)	1.402(3)	C(85)-H(853)	0.963
C(67)-C(68)	1.380(3)	C(86)-C(87)	1.391(3)
C(67)-H(671)	0.979	C(86)-H(861)	0.968
C(68)-C(69)	1.386(4)	C(87)-H(871)	0.974
C(68)-H(681)	0.975	C(54)-C(53)	1.387(3)
C(69)-C(70)	1.391(4)	C(54)-H(541)	0.973
C(69)-H(691)	0.976	C(53)-H(531)	0.959

		O(12)-C(13)-C(30)	109.12(18)
I(1)-C(2)-C(3)	119.50(18)	C(14)-C(13)-C(30)	115.13(19)
I(1)-C(2)-C(7)	120.60(18)	O(12)-C(13)-H(131)	108.9
C(3)-C(2)-C(7)	119.9(2)	C(14)-C(13)-H(131)	110.8
C(2)-C(3)-C(4)	119.5(2)	C(30)-C(13)-H(131)	107.4
C(2)-C(3)-H(31)	119.1	C(9)-C(14)-C(13)	105.50(17)
C(4)-C(3)-H(31)	121.5	C(9)-C(14)-C(15)	113.69(19)
C(3)-C(4)-C(5)	121.3(2)	C(13)-C(14)-C(15)	110.74(18)
C(3)-C(4)-H(41)	120.9	C(9)-C(14)-H(141)	108.6
C(5)-C(4)-H(41)	117.7	C(13)-C(14)-H(141)	108.7
C(4)-C(5)-C(6)	118.6(2)	C(15)-C(14)-H(141)	109.5
C(4)-C(5)-C(8)	120.7(2)	C(14)-C(15)-C(16)	110.19(18)
C(6)-C(5)-C(8)	120.6(2)	C(14)-C(15)-C(22)	113.33(18)
C(5)-C(6)-C(7)	120.9(2)	C(16)-C(15)-C(22)	111.22(18)
C(5)-C(6)-H(61)	119.9	C(14)-C(15)-H(151)	109.0
C(7)-C(6)-H(61)	119.3	C(16)-C(15)-H(151)	106.0
C(2)-C(7)-C(6)	119.7(2)	C(22)-C(15)-H(151)	106.8
C(2)-C(7)-H(71)	118.9	C(15)-C(16)-C(17)	119.8(2)
C(6)-C(7)-H(71)	121.4	C(15)-C(16)-C(21)	121.6(2)
C(5)-C(8)-C(9)	112.44(19)	C(17)-C(16)-C(21)	118.6(2)
C(5)-C(8)-H(81)	108.4	C(16)-C(17)-C(18)	121.0(2)
C(9)-C(8)-H(81)	109.4	C(16)-C(17)-H(171)	120.5
C(5)-C(8)-H(82)	111.0	C(18)-C(17)-H(171)	118.4
C(9)-C(8)-H(82)	107.6	C(17)-C(18)-C(19)	119.9(2)
H(81)-C(8)-H(82)	107.9	C(17)-C(18)-H(181)	120.6
C(8)-C(9)-C(10)	110.72(18)	C(19)-C(18)-H(181)	119.5
C(8)-C(9)-C(14)	116.42(19)	C(18)-C(19)-C(20)	119.9(2)
C(10)-C(9)-C(14)	104.20(18)	C(18)-C(19)-H(191)	120.4
C(8)-C(9)-H(91)	109.1	C(20)-C(19)-H(191)	119.7
C(10)-C(9)-H(91)	110.4	C(19)-C(20)-C(21)	119.4(2)
C(14)-C(9)-H(91)	105.8	C(19)-C(20)-H(201)	121.2
C(9)-C(10)-O(11)	127.4(2)	C(21)-C(20)-H(201)	119.4
C(9)-C(10)-O(12)	111.37(19)	C(20)-C(21)-C(16)	121.0(2)
O(11)-C(10)-O(12)	121.2(2)	C(20)-C(21)-H(211)	120.3
C(10)-O(12)-C(13)	112.22(17)	C(16)-C(21)-H(211)	118.6
O(12)-C(13)-C(14)	105.32(17)	C(15)-C(22)-C(23)	122.1(2)

C(15)-C(22)-H(221)	119.1	O(34)-C(35)-H(351)	107.6
C(23)-C(22)-H(221)	118.9	O(34)-C(35)-H(352)	108.6
C(22)-C(23)-C(24)	127.1(2)	H(351)-C(35)-H(352)	108.8
C(22)-C(23)-H(231)	116.5	O(34)-C(35)-H(353)	108.5
C(24)-C(23)-H(231)	116.4	H(351)-C(35)-H(353)	113.9
C(23)-C(24)-C(25)	118.8(2)	H(352)-C(35)-H(353)	109.2
C(23)-C(24)-C(29)	123.1(2)	C(33)-C(36)-C(37)	118.6(2)
C(25)-C(24)-C(29)	118.0(2)	C(33)-C(36)-H(361)	119.8
C(24)-C(25)-C(26)	121.5(2)	C(37)-C(36)-H(361)	121.6
C(24)-C(25)-H(251)	118.7	C(30)-C(37)-C(36)	121.8(2)
C(26)-C(25)-H(251)	119.8	C(30)-C(37)-H(371)	120.1
C(25)-C(26)-C(27)	119.4(2)	C(36)-C(37)-H(371)	118.1
C(25)-C(26)-H(261)	120.5	I(51)-C(52)-C(57)	120.57(18)
C(27)-C(26)-H(261)	120.1	I(51)-C(52)-C(53)	119.34(18)
C(26)-C(27)-C(28)	120.0(2)	C(57)-C(52)-C(53)	120.1(2)
C(26)-C(27)-H(271)	119.6	C(52)-C(57)-C(56)	120.0(2)
C(28)-C(27)-H(271)	120.4	C(52)-C(57)-H(571)	118.1
C(27)-C(28)-C(29)	120.7(2)	C(56)-C(57)-H(571)	122.0
C(27)-C(28)-H(281)	120.0	C(57)-C(56)-C(55)	121.0(2)
C(29)-C(28)-H(281)	119.3	C(57)-C(56)-H(561)	119.6
C(24)-C(29)-C(28)	120.4(2)	C(55)-C(56)-H(561)	119.4
C(24)-C(29)-H(291)	119.3	C(56)-C(55)-C(58)	120.1(2)
C(28)-C(29)-H(291)	120.4	C(56)-C(55)-C(54)	118.4(2)
C(13)-C(30)-C(31)	120.9(2)	C(58)-C(55)-C(54)	121.5(2)
C(13)-C(30)-C(37)	120.4(2)	C(55)-C(58)-C(59)	113.31(19)
C(31)-C(30)-C(37)	118.8(2)	C(55)-C(58)-H(581)	108.8
C(30)-C(31)-C(32)	120.8(2)	C(59)-C(58)-H(581)	107.9
C(30)-C(31)-H(311)	119.7	C(55)-C(58)-H(582)	109.3
C(32)-C(31)-H(311)	119.3	C(59)-C(58)-H(582)	109.7
C(31)-C(32)-C(33)	119.7(2)	H(581)-C(58)-H(582)	107.5
C(31)-C(32)-H(321)	120.0	C(58)-C(59)-C(60)	111.4(2)
C(33)-C(32)-H(321)	120.3	C(58)-C(59)-C(64)	115.46(19)
C(32)-C(33)-O(34)	115.4(2)	C(60)-C(59)-C(64)	104.60(18)
C(32)-C(33)-C(36)	120.4(2)	C(58)-C(59)-H(591)	108.1
O(34)-C(33)-C(36)	124.3(2)	C(60)-C(59)-H(591)	107.8
C(33)-O(34)-C(35)	116.04(18)	C(64)-C(59)-H(591)	109.4

C(59)-C(60)-O(61)	127.7(2)	C(71)-C(70)-H(701)	119.1
C(59)-C(60)-O(62)	111.45(19)	C(66)-C(71)-C(70)	120.3(2)
O(61)-C(60)-O(62)	120.9(2)	C(66)-C(71)-H(711)	119.7
C(60)-O(62)-C(63)	112.09(17)	C(70)-C(71)-H(711)	119.9
O(62)-C(63)-C(64)	105.20(17)	C(65)-C(72)-C(73)	121.1(2)
O(62)-C(63)-C(80)	109.09(18)	C(65)-C(72)-H(721)	119.6
C(64)-C(63)-C(80)	115.12(19)	C(73)-C(72)-H(721)	119.3
O(62)-C(63)-H(631)	107.9	C(72)-C(73)-C(74)	128.2(2)
C(64)-C(63)-H(631)	111.0	C(72)-C(73)-H(731)	117.9
C(80)-C(63)-H(631)	108.3	C(74)-C(73)-H(731)	113.9
C(59)-C(64)-C(63)	105.47(17)	C(73)-C(74)-C(79)	122.8(2)
C(59)-C(64)-C(65)	113.39(18)	C(73)-C(74)-C(75)	118.5(2)
C(63)-C(64)-C(65)	110.33(19)	C(79)-C(74)-C(75)	118.7(2)
C(59)-C(64)-H(641)	109.7	C(74)-C(79)-C(78)	120.1(2)
C(63)-C(64)-H(641)	110.1	C(74)-C(79)-H(791)	122.0
C(65)-C(64)-H(641)	107.8	C(78)-C(79)-H(791)	117.9
C(64)-C(65)-C(66)	110.40(18)	C(79)-C(78)-C(77)	120.3(2)
C(64)-C(65)-C(72)	112.78(19)	C(79)-C(78)-H(781)	119.7
C(66)-C(65)-C(72)	111.33(18)	C(77)-C(78)-H(781)	120.0
C(64)-C(65)-H(651)	105.9	C(78)-C(77)-C(76)	120.3(2)
C(66)-C(65)-H(651)	108.7	C(78)-C(77)-H(771)	120.5
C(72)-C(65)-H(651)	107.5	C(76)-C(77)-H(771)	119.2
C(65)-C(66)-C(67)	119.2(2)	C(77)-C(76)-C(75)	119.5(2)
C(65)-C(66)-C(71)	122.0(2)	C(77)-C(76)-H(761)	122.5
C(67)-C(66)-C(71)	118.8(2)	C(75)-C(76)-H(761)	117.9
C(66)-C(67)-C(68)	120.5(2)	C(74)-C(75)-C(76)	121.0(2)
C(66)-C(67)-H(671)	119.6	C(74)-C(75)-H(751)	118.8
C(68)-C(67)-H(671)	119.9	C(76)-C(75)-H(751)	120.2
C(67)-C(68)-C(69)	120.3(2)	C(63)-C(80)-C(81)	120.9(2)
C(67)-C(68)-H(681)	119.4	C(63)-C(80)-C(87)	121.2(2)
C(69)-C(68)-H(681)	120.3	C(81)-C(80)-C(87)	117.9(2)
C(68)-C(69)-C(70)	119.7(2)	C(80)-C(81)-C(82)	121.3(2)
C(68)-C(69)-H(691)	121.9	C(80)-C(81)-H(811)	119.5
C(70)-C(69)-H(691)	118.4	C(82)-C(81)-H(811)	119.2
C(69)-C(70)-C(71)	120.4(2)	C(81)-C(82)-C(83)	119.8(2)
C(69)-C(70)-H(701)	120.5	C(81)-C(82)-H(821)	121.3

C(83)-C(82)-H(821)	118.9	C(83)-C(86)-H(861)	119.7
C(82)-C(83)-O(84)	115.5(2)	C(87)-C(86)-H(861)	121.3
C(82)-C(83)-C(86)	120.1(2)	C(86)-C(87)-C(80)	121.9(2)
O(84)-C(83)-C(86)	124.4(2)	C(86)-C(87)-H(871)	118.9
C(83)-O(84)-C(85)	116.46(19)	C(80)-C(87)-H(871)	119.1
O(84)-C(85)-H(851)	109.2	C(55)-C(54)-C(53)	120.9(2)
O(84)-C(85)-H(852)	110.3	C(55)-C(54)-H(541)	120.1
H(851)-C(85)-H(852)	109.1	C(53)-C(54)-H(541)	118.9
O(84)-C(85)-H(853)	110.2	C(52)-C(53)-C(54)	119.5(2)
H(851)-C(85)-H(853)	111.1	C(52)-C(53)-H(531)	120.5
H(852)-C(85)-H(853)	106.7	C(54)-C(53)-H(531)	120.0
C(83)-C(86)-C(87)	119.0(2)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for DIA0363. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
I(1)	27(1)	27(1)	20(1)	-2(1)	-3(1)	-2(1)
C(2)	20(1)	31(1)	15(1)	-1(1)	-2(1)	-6(1)
C(3)	20(1)	20(1)	27(1)	-1(1)	-4(1)	0(1)
C(4)	17(1)	21(1)	28(1)	1(1)	-3(1)	-4(1)
C(5)	17(1)	24(1)	24(1)	2(1)	-1(1)	-1(1)
C(6)	20(1)	22(1)	26(1)	0(1)	-1(1)	3(1)
C(7)	23(1)	22(1)	26(1)	3(1)	-3(1)	1(1)
C(8)	19(1)	22(1)	24(1)	3(1)	1(1)	1(1)
C(9)	19(1)	20(1)	19(1)	2(1)	0(1)	1(1)
C(10)	23(1)	18(1)	18(1)	1(1)	-1(1)	-1(1)
O(11)	25(1)	18(1)	26(1)	1(1)	3(1)	2(1)
O(12)	22(1)	15(1)	26(1)	2(1)	1(1)	-1(1)
C(13)	20(1)	16(1)	22(1)	1(1)	0(1)	0(1)
C(14)	17(1)	16(1)	20(1)	2(1)	-1(1)	-2(1)
C(15)	20(1)	15(1)	17(1)	1(1)	-1(1)	-2(1)
C(16)	21(1)	13(1)	20(1)	3(1)	1(1)	-4(1)
C(17)	25(1)	20(1)	19(1)	4(1)	-4(1)	-4(1)
C(18)	25(1)	21(1)	31(1)	7(1)	-7(1)	-5(1)
C(19)	19(1)	24(1)	31(1)	10(1)	0(1)	1(1)
C(20)	26(1)	19(1)	25(1)	2(1)	3(1)	1(1)
C(21)	20(1)	21(1)	21(1)	4(1)	-1(1)	-2(1)
C(22)	19(1)	18(1)	19(1)	2(1)	-3(1)	0(1)
C(23)	20(1)	21(1)	22(1)	1(1)	-2(1)	0(1)
C(24)	14(1)	22(1)	23(1)	3(1)	1(1)	1(1)
C(25)	19(1)	22(1)	21(1)	1(1)	0(1)	1(1)
C(26)	20(1)	31(1)	22(1)	10(1)	0(1)	3(1)
C(27)	18(1)	28(1)	28(1)	8(1)	-4(1)	-3(1)
C(28)	18(1)	30(1)	24(1)	3(1)	-1(1)	-4(1)
C(29)	18(1)	23(1)	22(1)	0(1)	-1(1)	1(1)
C(30)	22(1)	12(1)	22(1)	4(1)	1(1)	-3(1)
C(31)	24(1)	18(1)	18(1)	2(1)	-2(1)	-2(1)

C(32)	18(1)	18(1)	24(1)	3(1)	-1(1)	-1(1)
C(33)	22(1)	12(1)	23(1)	2(1)	1(1)	0(1)
O(34)	22(1)	25(1)	19(1)	0(1)	0(1)	4(1)
C(35)	30(1)	22(1)	19(1)	0(1)	0(1)	1(1)
C(36)	25(1)	17(1)	19(1)	0(1)	0(1)	0(1)
C(37)	20(1)	15(1)	23(1)	2(1)	0(1)	-3(1)
I(51)	45(1)	31(1)	22(1)	-1(1)	0(1)	5(1)
C(52)	26(1)	24(1)	23(1)	1(1)	-1(1)	2(1)
C(57)	28(1)	27(1)	25(1)	4(1)	2(1)	3(1)
C(56)	23(1)	22(1)	29(1)	1(1)	0(1)	-2(1)
C(55)	15(1)	26(1)	25(1)	3(1)	0(1)	5(1)
C(58)	18(1)	25(1)	25(1)	2(1)	-4(1)	-1(1)
C(59)	19(1)	21(1)	17(1)	1(1)	-4(1)	-2(1)
C(60)	23(1)	24(1)	19(1)	-1(1)	-4(1)	-1(1)
O(61)	29(1)	24(1)	26(1)	1(1)	-3(1)	-5(1)
O(62)	23(1)	18(1)	26(1)	1(1)	-4(1)	-1(1)
C(63)	19(1)	18(1)	22(1)	1(1)	-2(1)	-2(1)
C(64)	19(1)	16(1)	21(1)	2(1)	-2(1)	1(1)
C(65)	20(1)	17(1)	18(1)	1(1)	-3(1)	0(1)
C(66)	19(1)	16(1)	23(1)	4(1)	-1(1)	1(1)
C(67)	26(1)	21(1)	27(1)	3(1)	0(1)	2(1)
C(68)	22(1)	22(1)	35(1)	7(1)	3(1)	2(1)
C(69)	20(1)	26(1)	31(1)	10(1)	-4(1)	-1(1)
C(70)	30(1)	21(1)	25(1)	3(1)	-4(1)	-2(1)
C(71)	23(1)	21(1)	22(1)	4(1)	-1(1)	3(1)
C(72)	17(1)	20(1)	24(1)	-1(1)	0(1)	1(1)
C(73)	20(1)	20(1)	24(1)	-1(1)	0(1)	0(1)
C(74)	16(1)	23(1)	23(1)	1(1)	-3(1)	-2(1)
C(79)	17(1)	24(1)	22(1)	-1(1)	-2(1)	-3(1)
C(78)	18(1)	24(1)	30(1)	3(1)	1(1)	2(1)
C(77)	18(1)	29(1)	32(1)	5(1)	0(1)	5(1)
C(76)	24(1)	31(1)	21(1)	4(1)	-1(1)	1(1)
C(75)	18(1)	26(1)	22(1)	1(1)	-1(1)	-5(1)
C(80)	24(1)	14(1)	22(1)	1(1)	-1(1)	2(1)
C(81)	22(1)	20(1)	22(1)	4(1)	-1(1)	1(1)
C(82)	24(1)	20(1)	24(1)	2(1)	-1(1)	-2(1)

C(83)	24(1)	17(1)	19(1)	2(1)	-6(1)	-2(1)
O(84)	26(1)	28(1)	20(1)	0(1)	-4(1)	-4(1)
C(85)	32(1)	24(1)	21(1)	-1(1)	-1(1)	-2(1)
C(86)	30(1)	16(1)	22(1)	1(1)	-1(1)	3(1)
C(87)	22(1)	17(1)	22(1)	3(1)	-2(1)	5(1)
C(54)	22(1)	24(1)	27(1)	1(1)	2(1)	2(1)
C(53)	22(1)	23(1)	28(1)	-1(1)	-1(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for DIA0363.

	x	y	z	U(eq)
H(31)	3487	4447	5133	30
H(41)	3297	4815	5916	28
H(61)	2849	10126	5651	29
H(71)	3035	9786	4880	30
H(81)	2934	6599	6499	29
H(82)	2698	8585	6407	31
H(91)	3415	8762	6959	27
H(131)	4601	9618	6728	25
H(141)	3953	6845	6331	24
H(151)	4238	7663	7283	24
H(171)	5095	7380	7504	28
H(181)	5916	6285	7390	31
H(191)	6056	4191	6794	31
H(201)	5334	3035	6327	31
H(211)	4499	4114	6456	27
H(221)	3694	4348	6967	28
H(231)	3781	6309	7810	26
H(251)	3542	4648	8471	26
H(261)	3102	2291	8832	31
H(271)	2658	23	8388	32
H(281)	2612	167	7574	31
H(291)	3053	2591	7221	27
H(311)	5386	8942	6438	26
H(321)	5877	8206	5831	24
H(351)	5626	6681	4377	36
H(352)	5168	7974	4467	37
H(353)	5122	5877	4611	37
H(361)	4582	7800	4971	27
H(371)	4086	8504	5584	26
H(571)	2018	4508	5169	35

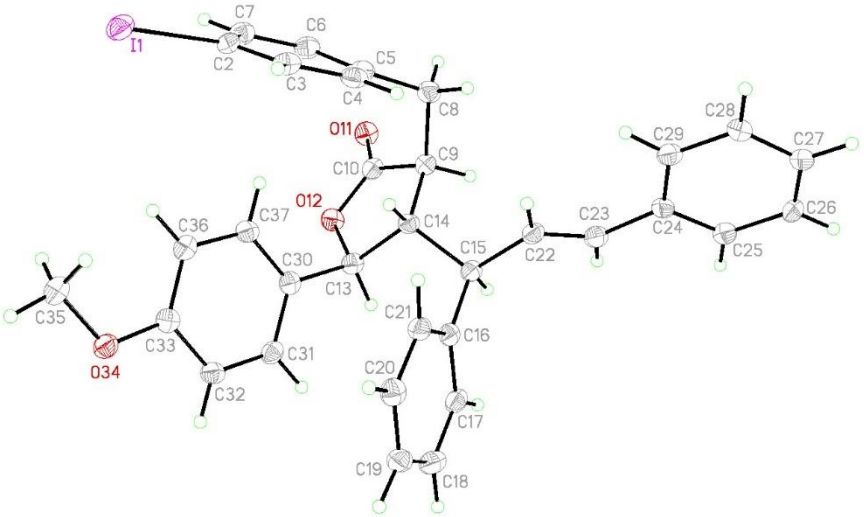
H(561)	2183	4760	5969	33
H(581)	2296	3236	6729	31
H(582)	2041	1270	6798	30
H(591)	1590	3520	7180	25
H(631)	394	4461	6798	26
H(641)	1030	1595	6494	24
H(651)	752	2510	7386	26
H(671)	-113	2226	7494	31
H(681)	-945	1201	7261	36
H(691)	-1075	-882	6626	34
H(701)	-360	-2058	6284	31
H(711)	463	-1029	6506	30
H(721)	1271	-924	7164	28
H(731)	1204	1175	7981	27
H(791)	1917	-2720	7527	26
H(781)	2359	-4907	7982	29
H(771)	2413	-4703	8787	35
H(761)	1945	-2310	9131	31
H(751)	1467	-166	8688	28
H(811)	-393	3862	6387	27
H(821)	-870	3054	5702	29
H(851)	-601	1768	4272	41
H(852)	-144	3041	4436	41
H(853)	-107	987	4562	40
H(861)	438	2724	5032	31
H(871)	928	3382	5725	26
H(541)	1639	-471	6137	30
H(531)	1498	-751	5341	33

Table 6. Hydrogen bonds for DIA0363 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(4)-H(41)...O(11)#1	0.98	2.53	3.492(3)	167
C(29)-H(291)...O(11)#1	0.97	2.54	3.459(3)	159
C(79)-H(791)...O(61)#1	0.97	2.58	3.528(3)	169

Symmetry transformations used to generate equivalent atoms:

#1 x,y-1,z



The second molecule is numbered as above with an offset of fifty.

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