Kinetic Resolution in Rhodium-catalyzed [5+2] Cycloisomerization

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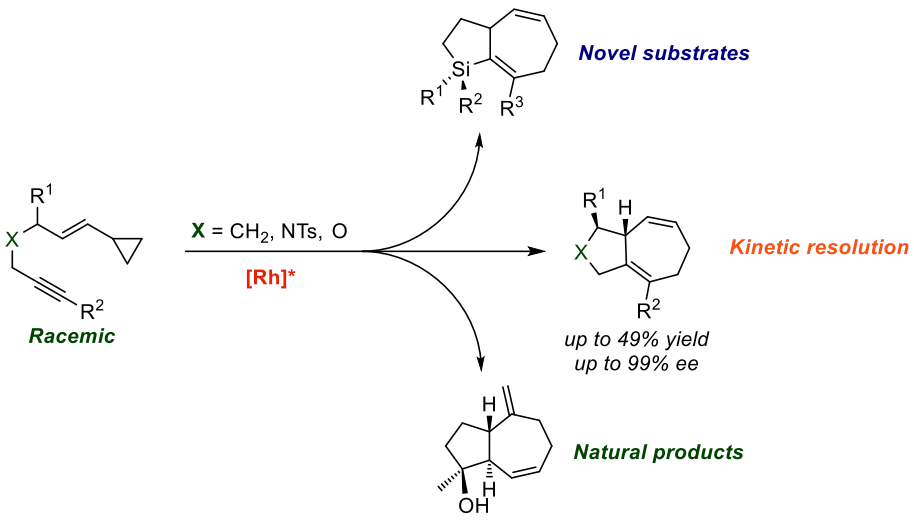


Kinetic Resolution in Rhodium-catalyzed [5+2] Cycloisomerization

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Hilary Term 2020 **Brasenose College**

This thesis demonstrates the ability of a rhodium(I)-phosphoramidite catalyst to effect the first examples of kinetic resolution in [5+2] cycloisomerization (Scheme i). This methodology was applied to a range of diversely substituted enyne substrates, including a novel chiral silane tether. Depending on the substrate, either a classical resolution, or a diastereodivergent resolution was achieved, both with exceptional selectivity.



Scheme i. Kinetic resolution in rhodium-catalyzed [5+2] cycloisomerization.

Furthermore, this methodology was applied to the asymmetric synthesis of the natural product (+)-dictamnol, a trinorguaiane sesquiterpene isolated from the roots of *Dictamnus dascarpus TURCZ*, with diastereodivergent resolution of an allene vinylcyclopropane as the key step.

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Christopher Quinn, for the best mental support and the long walks along Putney Bridge.

Abbreviations

Ar^F	3,5-bis(trifluoromethyl)benzene	naphth	naphthalene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl	NOESY	nuclear Overhauser effect spectroscopy
CBS	Corey–Bakshi–Shibata catalyst	PKR	parallel kinetic resolution
COD	cyclooctadiene	PMB	*p*-Methoxybenzyl
d	doublet	ppm	parts per million
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	Py	pyridine
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone	R_f	retention factor
DIAD	diisopropyl azodicarboxylate	rt	room temperature
DIPT	diisopropyltryptamine	s	singlet
DKR	dynamic kinetic resolution	t	triplet
DMAP	4-dimethylaminopyridine	TBHP	*tert*-butyl hydroperoxide
DMAP	4-dimethylaminopyridine	TCE	trichloroethane
DPPA	diphenylphosphoryl azide	TCM	tetrachloromethane
dr	diastereomeric ratio	q	quartet
eq.	equivalent(s)	TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
ee	enantiomeric excess	R_f	retention factor
ESI	electrospray ionisation	rt	room temperature
EtOAc	ethyl acetate	s	singlet
Fmoc	fluorenylmethyloxycarbonyl	t	triplet
^1H	proton	TBS	*tert*-butyldimethylsilyl
IPA	isopropyl alcohol	THF	tetrahydrofuran
IR	infrared	TLC	thin layer chromatography
J	coupling constant	TMS	tetramethylsilyl
KR	kinetic resolution	Ts	*p*-toluenesulfonyl
LiHMDS	lithium bis(trimethylsilyl)amide	Ms	mesylate

"Strength does not come from winning. Your struggles develop your strengths. When you go through hardships and decide not to surrender, that is strength."

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1. Introduction

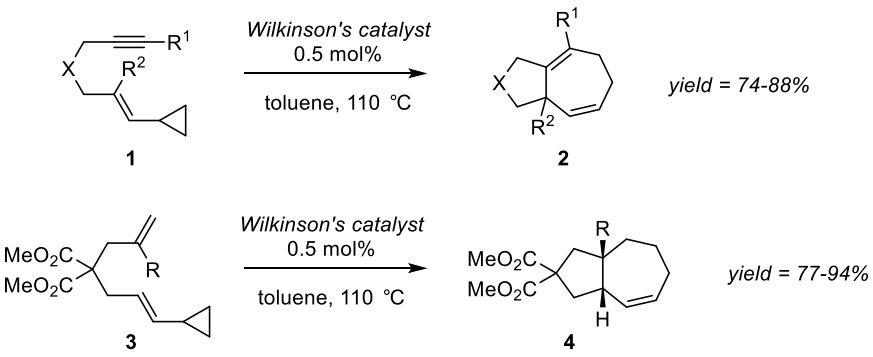
Cycloisomerization is a tool of prime importance in synthetic chemistry. In addition to high atom efficiency, excellent regio- and stereo-chemical control, it is also a powerful tool to construct bicyclic scaffolds, which are the core structures of many bioactive compounds.[1] Significant advances have been made in transition metal-catalyzed higher order cycloisomerization over the last decade.[2] One of the most attractive variants of this methodology is the [5+2] cycloisomerization, first described by Wender *et al.* and extensively studied by Trost *et al.*, where excellent diastereo- and enantio- control can be achieved using transition metal catalysts.[3–5]

1.1 Vinylcyclopropane [5+2] Cycloisomerization

In 1959, Sarel and Breuer described the ability of vinylcyclopropanes (VCPs) to undergo 1,5-conjugate addition reactions to give 7-membered rings when properly activated.[6] Such transformation represents one of the major subclasses of the cycloisomerization field, and has been reported to afford excellent enantio- and diastereo-selectivity under substrate control.[7,8] In particular, transition metal catalyzed [5+2] cycloisomerization has been extensively studied, notably rhodium and ruthenium catalysts.

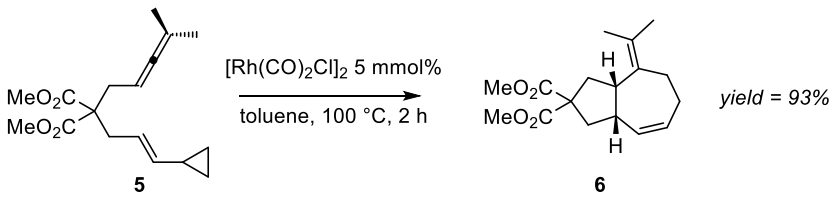
1.1.1 Metal-catalyzed [5+2] Cycloisomerization

The first example of a metal-catalyzed cycloisomerization was reported by Wender *et al.* in 1995 using the Wilkinson's catalyst ($[RhCl(PPh_3)_3]$).[3] These reactions were highly efficient, and substituents on either alkene or alkyne had little effect on the efficiency of cycloisomerization. Other tethered π-systems were also employed such as allenes and dienes (Scheme 1).



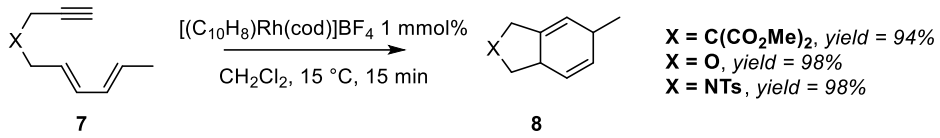
Scheme 1. First example of metal-catalyzed intramolecular [5+2] cycloisomerization.

Since then, several rhodium catalyst systems have been demonstrated to successfully promoted such transformation. Wender *et al.* found modification of the catalytic system was necessary for specific substrates, therefore $[Rh(CO)_2Cl]_2$ was used to enhance the reactivity and promote transformations that could otherwise not be achieved with the Wilkinson's catalyst (Scheme 2).[9] Successful transformation of allene **5** to its corresponding [5+2] cycloisomer **6** was performed using $[Rh(CO)_2Cl]_2$. No reaction was observed when the Wilkinson's catalyst was employed.



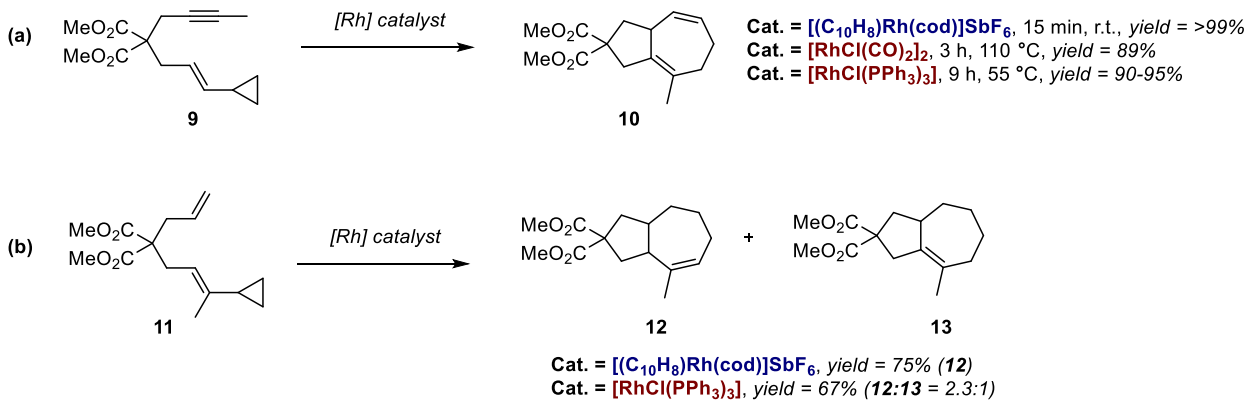
Scheme 2. [5+2] Cycloisomerization with allene **5** using $[Rh(CO_2)Cl]_2$.

A further modification of the catalyst system includes the readily prepared air-stable cationic rhodium(I) complex $[(C_{10}H_8)Rh(COD)]^+SbF_6$. This catalyst was first reported in 1999 by Chung *et al.* where it was found to be an effective promoter of intramolecular [4+2] cycloadditions with 1,3-dienes with nonactivated acetylenes (Scheme 3).[10]



Scheme 3. Original application of $[(C_{10}H_8)Rh(cod)]^+$ in [4+2] cycloadditions.

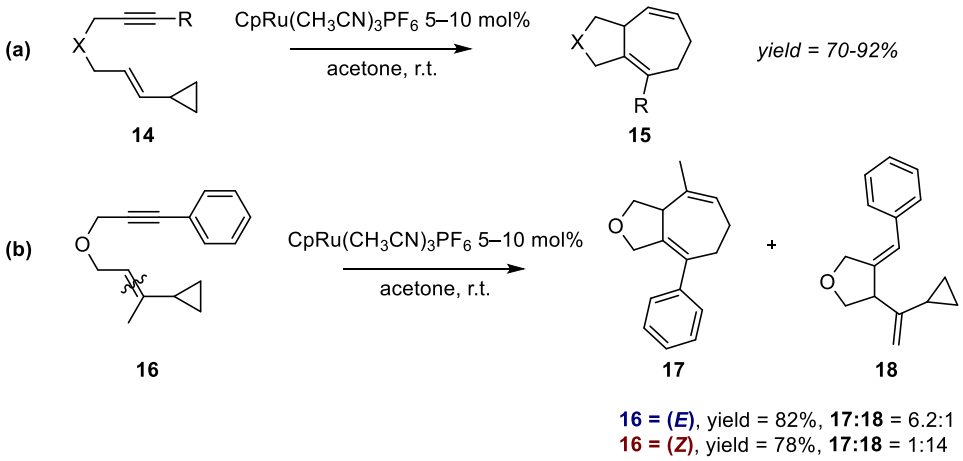
This catalyst was shown to be exceptionally effective in [5+2] cycloisomerizations resulting in significantly shortened reaction times (from hours to 15 minutes, Scheme 4, Equation a) and greater regioselectivity (Scheme 4, Equation b).[11,12]



Scheme 4. Advantages of $[(C_{10}H_8)Rh(COD)]^+$ in [5+2] cycloisomerization reactions.

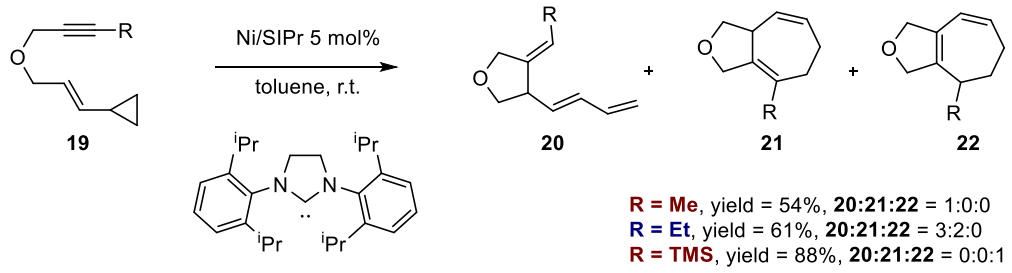
Despite high efficiency, there are downsides associated with rhodium catalysts, including sensitivity ($[(C_{10}H_8)Rh(COD)]^+$ is extremely air sensitive and requires operation in a glovebox) and rarity (rhodium can cost as much as 14 times compared to ruthenium). In order to overcome such shortcomings, other transition metals have also been comprehensively studied.[13] Trost *et al.*

has investigated the use of a cationic Ruthenium(II) catalyst in the intramolecular [5+2] cycloisomerizations (Scheme 5, Equation a).[14] Under mild conditions, vinylcyclopropyl alkyne precursor **14** was converted into cycloisomer **15** in high yield. Regioselectivity was also explored. With trisubstituted alkene substrate **16**, *β*–hydride elimination was observed to produce side product **18**, which was favoured when substrate was bearing an (*Z*)-alkene (Scheme 5, Equation b).



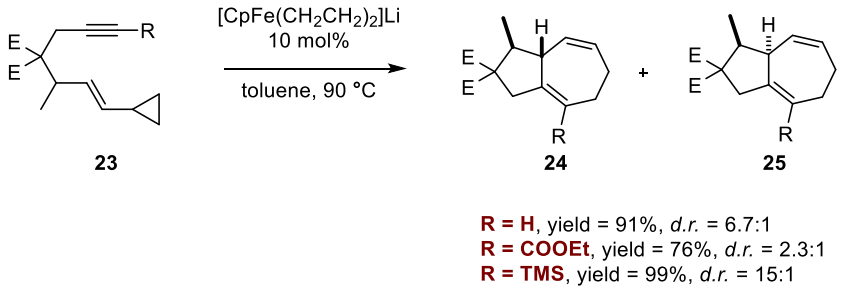
Scheme 5. Intramolecular [5+2] cycloisomerization with ruthenium catalyst.

Alternative attempts to promote such transformation using more readily available, environmentally and economically friendly metals were also explored. Louie *et al.* reported that [5+2] cycloisomerization could be promoted by a nickel/N-heterocyclic carbene (NHC) complexes prepared *in situ.*[15,16] The bicyclic motif **19** was obtained when a bulky alkyne substituent (Et) was used, whilst sterically less hindered substituents resulted in a mixture of 1,3-diene product **20**, seven-membered ring bicycles **21** and **22** (Scheme 6). Although regioselectivity could be controlled *via* modification of alkyne substituent, substrate scope was relatively narrow, and yield was reported at moderate level.



Scheme 6. Nickel-catalyzed intramolecular [5+2] cycloisomerization.

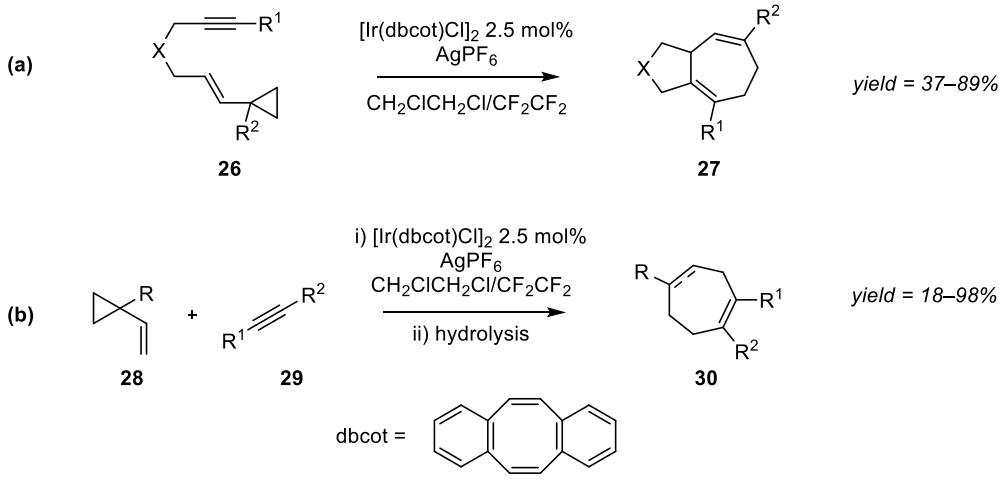
On the other hand, iron-catalyzed [5+2] cycloisomerization developed by Fürstner *et al.* using low-valent anionic complex $[CpFe(CH_2CH_2)_2]Li$ provided a possible alternative (Scheme 7).[7,17,18] Despite economical attractiveness, little advantage was offered by this methodology. Reaction conditions were harsher with elevated temperature required, only limited substrate scope was exploited, both diastereoselectivity and yield was synthetically useful, but inferior to other systems.



Scheme 7. Iron-catalyzed [5+2] cycloisomerization.

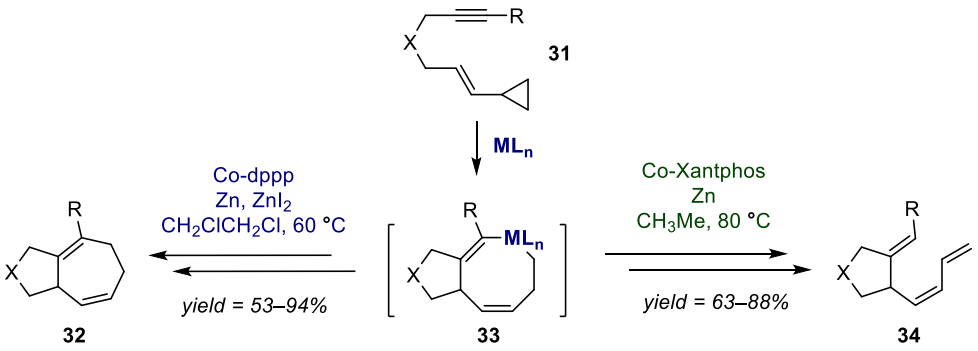
In 2014, Strand *et al.* reported the first example of iridium-catalyzed [5+2] cycloisomerization.[19] Not only reasonable to high yielding was achieved in most cases (Scheme 8, Equation a), theoretical analysis using density functional theory (DFT) model also revealed that under favourable conditions, iridium catalyst $[Ir(COD)]^+$ ($\delta E = 16.03$ kcalmol^{-1}) was as much as 50 times faster than rhodium catalyst $[Rh(COD)]^+$ ($\delta E = 28.22$ kcalmol^{-1}) in same equivalence.[20] Intermolecular reaction was also achieved using same system between 4-octyne **29** and

commercially available vinylcyclopropane **28** (Scheme 8, Equation b). Adduct product **30** was obtained at ambient temperature within 2 minutes at near quantitative yield. It is worth noting that upon this point, such intermolecular transformations were exclusively done with rhodium catalysts developed by Wender *et al.*[3,21]



Scheme 8. Iridium-catalyzed [5+2] cycloisomerization.

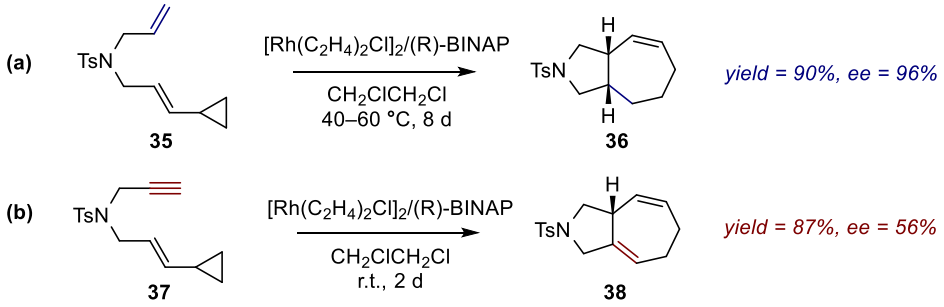
More recently, Wu *et al.* found a highly efficient system using cobalt-diphosphine catalysts.[22] By switching solvents, either [5+2] cycloisomerization product **32** or homo-ene product **34** was formed exclusively with reasonable yield (Scheme 9). DFT was performed to gain insight into the origin of this divergence of reaction pathways.[23–25] Vinylcyclopropane **30** was cleaved by cobalt catalyst to give intermediate **33**, which then underwent reductive elimination to offer [5+2] product **32**, when a non-coordinating solvent such as 1,2-dichloromethane was used. When coordinating solvent such as acetonitrile was used, homo-ene product **34**, as a result of β-hydride elimination, is primarily formed. This method not only revealed the promising potential of a new group of catalysts for [5+2] cycloisomerizations, but also enabled versatile transformations of vinylcyclopropanes under steric control.



Scheme 9. Cobalt-catalyzed switchable [5+2] cycloisomerization.

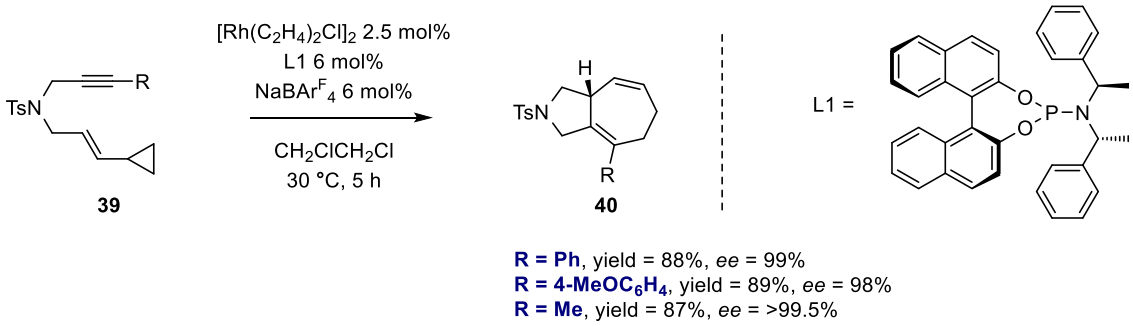
1.1.2 Double Stereodifferentiation in [5+2] Cycloisomerization

Transition metal-catalyzed asymmetric cycloisomerization offers a powerful tool to construct enantioenriched, bicyclic organic molecules, which play a critical role in pharmaceuticals and agrochemicals.[13,26–31] This topic for [5+2] cycloisomerizations remained unexplored until recently when Wender *et al.* demonstrated the first example of an enantioselective [5+2] cycloisomerization using rhodium(I)-diphosphine complex.[32,33] High level of enantioselectivity was achieved when BINAP was used as ligand to give the desired product **36** as a single enantiomer and diastereomer (Scheme 10, Equation a). However, suboptimal results were obtained when an enyne precursor **37** was present instead of dienes (Scheme 10, Equation b).



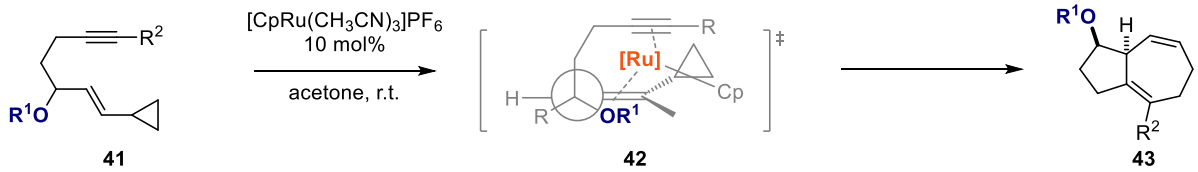
Scheme 10. Enantioselective [5+2] cycloisomerization using BINAP as ligand.

Later, Hayashi *et al.* tackled the problem by developing a novel rhodium(I)-phosphoramidite complex, which showcased its power to transform alkyne–vinylcyclopropanes **39** into desired bicyclic products **40** in an effective manner (Scheme 11).[34] Most reactions were carried out at ambient temperature and completed in hours, delivering excellent yield and high level of enantioselectivity.



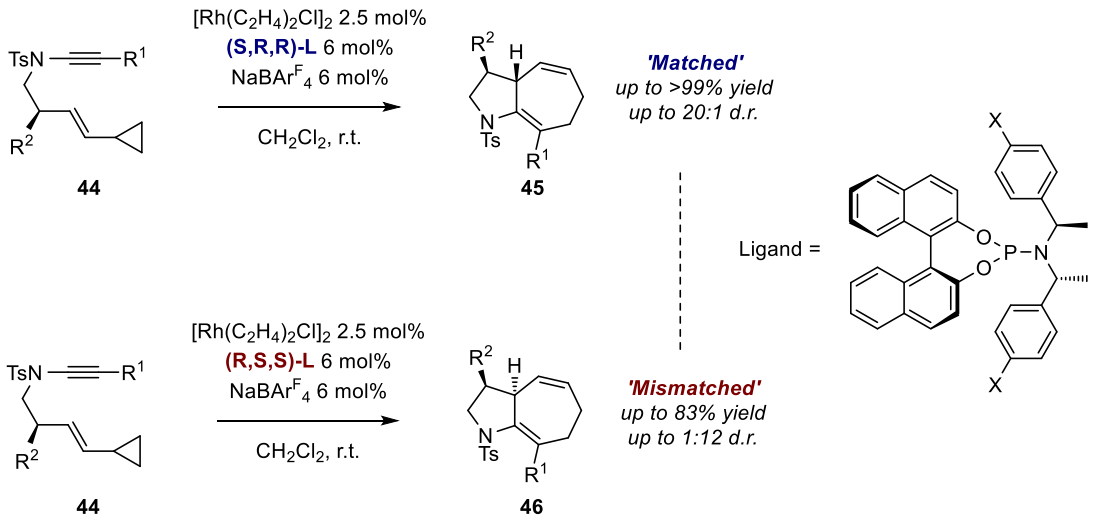
Scheme 11. Enantioselective [5+2] cycloisomerization using phosphoramidite ligand.

On the other hand, diastereoselectivity in [5+2] cycloisomerizations was also examined in the presence of an allylic substituent. Trost *et al.* extensively investigated cyclizations operating under substrate stereocontrol using a wide range of substituted vinylcyclopropanes (Scheme 12).[14] Diastereomer **43** was predominantly formed with exceptional diastereoselectivity (in most cases >20:1), which was rationalized by the 'inside-alkoxy effect', where the presence of an allylic oxygen in **41** provides strong diastereoselectivity towards the formation of *anti*-product **43**.[35,36]



Scheme 12. Diastereoselectivity in ruthenium-catalyzed [5+2] cycloisomerizations.

Given the success in both relative and absolute stereocontrol in such transformation, Anderson *et al.* took a step further to rationally design a double stereodifferentiated ynamide [5+2] cycloisomerization, where a single catalyst system offered both powerful enantio- and diastereo-control at the same time (Scheme 13).[37] Reactions were typically complete within minutes to hours with no elevation of temperature required. By switching to the opposite enantiomer of same ligand ('matched *vs.* mismatched' pairs), different diastereomers **45** and **46** were obtained correspondingly.



Scheme 13. Double Stereodifferentiation in [5+2] cycloisomerization.

In contrast to the ruthenium-catalyzed system presented by Trost *et al.*, examination of inherent substrate control showed that the *syn*-diastereomer was predominantly formed, indicating a different mechanistic pathway might be involved. Two possible mechanisms have been proposed, namely metallacyclopentene pathway (Figure 1, Pathway a) and vinylcyclopropane pathway (Figure 1, Pathway b) by Wender and Trost *et al.*[3,5,9] Both pathways initiated with metal coordination followed by oxidative coupling but diverged with metallacyclopentene intermediate which can be formed by either coordinating with alkene and alkyne units (to give five-membered

ring **49**), or alkene and cyclopropane units (to give six-membered ring **53**). Concomitant migratory insertions give eight-membered metallacycle **50**, which then undergoes reductive to give the cycloisomerized product **51**.

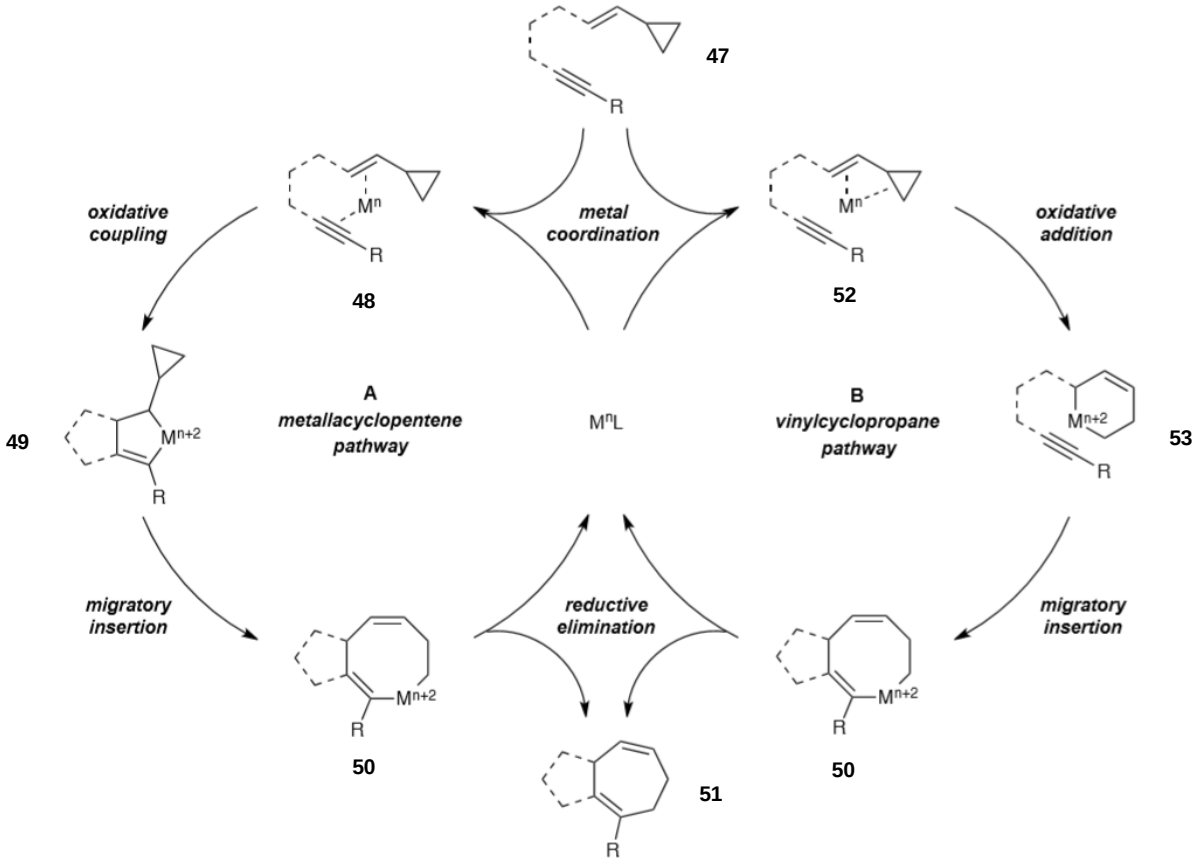


Figure 1. Proposed mechanistic pathways for [5+2] cycloisomerization.[37]

In addition to experimental evidence, computational studies have also suggested that both pathways were indeed possible and might be switchable depending on the electronic properties of substrate used. Wender and Houk conducted mechanistic studies based on $[Rh(CO)_2Cl]_2$-catalyzed intermolecular [5+2] cycloisomerizations between vinylcyclopropanes and alkynes, which indicated that vinylcyclopropane pathway B was energetically preferred (an activation free energy that is 7.8 $kcalmol^{-1}$ lower than pathway A).[38] However, DFT calculations from Anderson *et al.*

based on intramolecular reactions of ynamides suggested the opposite: metallacyclopentene pathway was preferred by 4–12 kcal mol^{-1}. The difference between outcomes was rationalized by Rh(III) intermediate induced by the electron rich ynamide, which provided further stability.[37]

1.1.3 Application of [5+2] Cycloisomerization

The fused five-seven membered ring motif can be found in a variety of natural products, from marine metabolites to plant extracts (Figure 2).[7,39–48] Despite multiple synthetic routes being developed to access this group of compounds, transition metal-catalyzed vinylcyclopropane [5+2] cycloisomerizations have only been applied on a limited number of occasions in this context. To date, most examples reported deploy the rhodium catalyst system developed by catalyzed by rhodium system developed by Wender *et al.*, and rely exclusively on substrate stereocontrol using achiral catalyst systems, with pre-existing stereocenters dictating the reaction outcome.

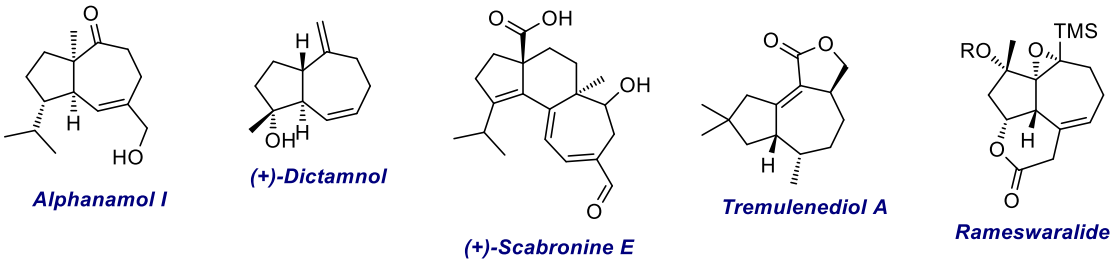
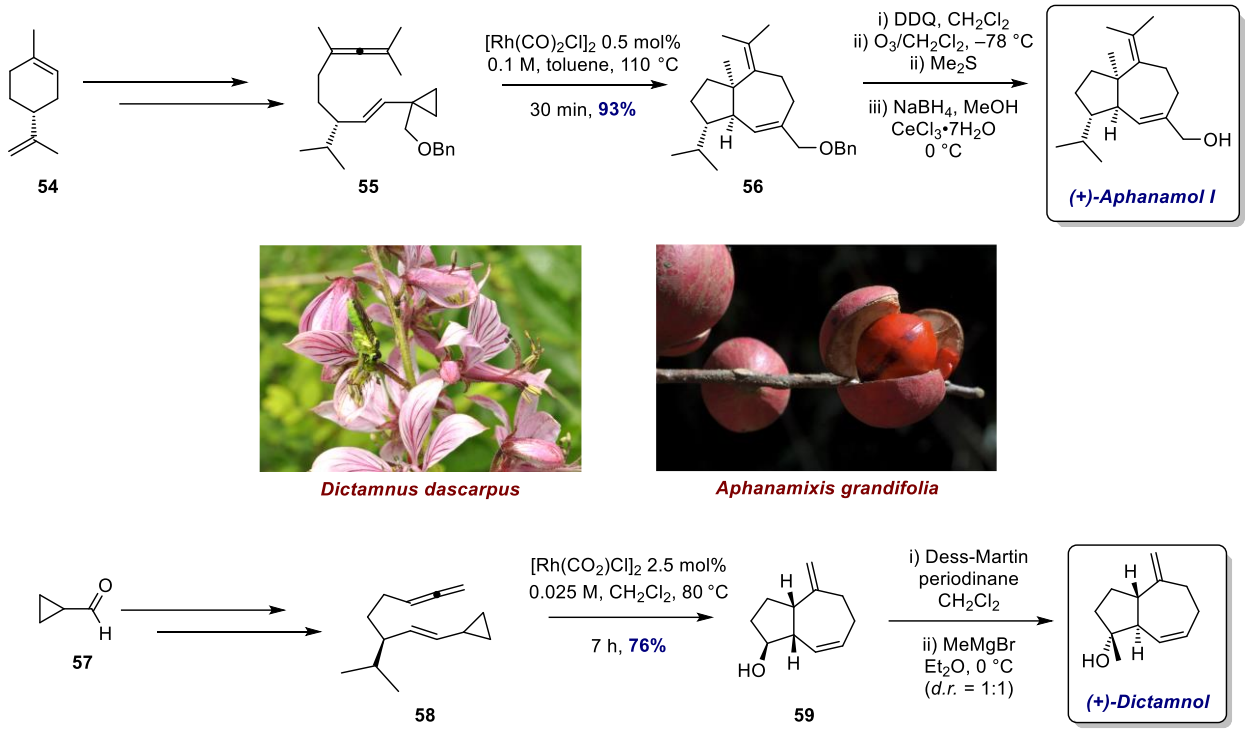


Figure 2. Examples of natural products containing five-seven membered ring motif.

For example, in 1999 and 2000, Wender *et al.* applied the chemistry towards the synthesis of (+)-dictamnol, a trinorguaiane sesquiterpene isolated from the roots of *Dictamnus dascarpus TURCZ* in 1993, and (+)-aphanamol I, a hydroazulenetype sesquiterpene extracted from the fruit peel of *Aphanamixis grandifolia* as a minor toxic principle in 1984, using the same catalyst (Scheme 14).[49,50] Both routes relied on a diastereoselective [5+2] cycloisomerization as the key step and

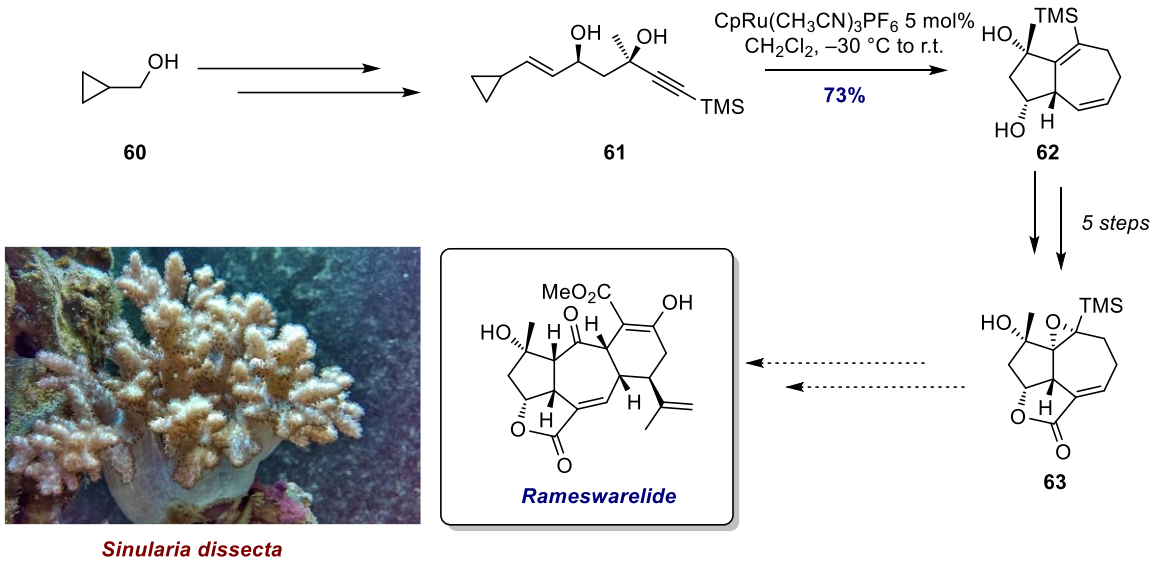
were obtained at high yields in the construction of core bicyclic structure **56** and **59**, which could then be turned into the desired natural products in a few steps.[42,51]



Scheme 14. Synthesis of aphanamol and dictamnol by Wender *et al.*[42,51]

More recently, Trost *et al.* also demonstrated the application of ruthenium-catalyzed [5+2] in constructing the tricyclic core structure of rameswaralide, a novel diterpene isolated from the soft coral *Sinularia dissecta* near the Mandapam coast of India, in 1998.[52,53] Rameswaralide and its derivatives have potential anti-inflammatory effects and can be used to treat common inflammatory disorders such as arthritis and psoriasis. The [5+2] precursor **61** was obtained from commercially available material **60** in 4 steps with 41% overall yield. It then underwent the key cycloisomerization in the presence of $CpRu(CH_3CN)PF_6$, affording the desired product **62** in 73% yield, from there on was converted into tricyclic compound **63** bearing an *α,β*-unsaturated five-

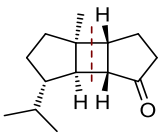
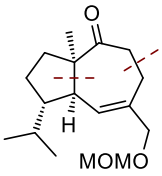
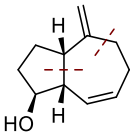
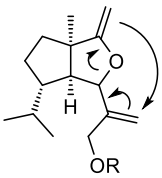
membered lactone in another 5 steps (Scheme 15). Synthetic strategies towards the enantioselective synthesis of rameswaralide is yet to be explored.[53]



Scheme 15. Synthesis of tricyclic core structure of rameswaralide by Trost *et al.*[53]

Unfortunately, transition-metal catalyzed [5+2] cycloisomerization in natural product synthesis has been limited to rhodium and ruthenium catalysts, which is not always superior comparing to other synthetic methods. For example, there have been 5 published methods of enantioselective synthesis of (+)-aphanamol I, including a [2+2] photocycloaddition approach by Hansson *et al.* and [4+3] cycloaddition approach by Harmata *et al.*[32,46,48,54,55] With a 13 longest linear step count (16 total steps) and a 11.3% overall yield, [5+2] cycloisomerization method can hardly be called 'elegant' comparing to other methods published nearly a decade earlier (Table 1).

Table 1. Comparison of different methods in total synthesis of (+)-aphanamol I.

Author	Key transformation	Key structure	Selectivity	Longest linear step count	Overall yield
Hansson, 1992[56]	[2+2] Photocycloaddition		Enantioselective	4	N/A
Harmata, 1997[54]	[4+3] Cycloaddition		Enantioselective	5	4.6%
Wender, 2000[57]	Rh-catalyzed [5+2] cycloisomerization		Enantioselective	13	11.3%
Ferrara, 2016[55]	Ring-expanding Claisen rearrangement		Enantioselective and racemic	11 (enantioselective) 13 (racemic)	12.5%

There are two major limitation when it comes to application of the [5+2] cycloisomerization methodology. Firstly, the synthesis of the 5+2 precursors can be rather lengthy and secondly the effectiveness of the catalyst itself. [5+2] Cycloisomerization could with no doubt become a powerful tool for natural product synthesis if the above problems were resolved.

1.1.4 Summary

Although a variety of transition metal catalysts have been explored in context of the [5+2] cycloisomerization, most examples are limited to rhodium or ruthenium catalysts based on Wender and Trost's work. Both relative, by inherent substrate preference, and absolute stereocontrol, by using phosphoramidite ligand developed by Hayashi *et al.*, has shown to be exceptional, offering the opportunity for double stereodifferentiation in such transformation, where a single catalyst system was shown to be able to offer both enantio- and diastereo- control at the same time (Anderson *et al.*).

Preliminary results from cheaper and more readily available metals such as cobalt and iron still are promising, but no application in natural product synthesis using these catalysts has been made to date. In parallel to developing alternative metal catalysts, substrate scope expansion, ligand optimization, as well as natural product synthesis utilizing the methodology can all become creative future aspects of studies in this field.

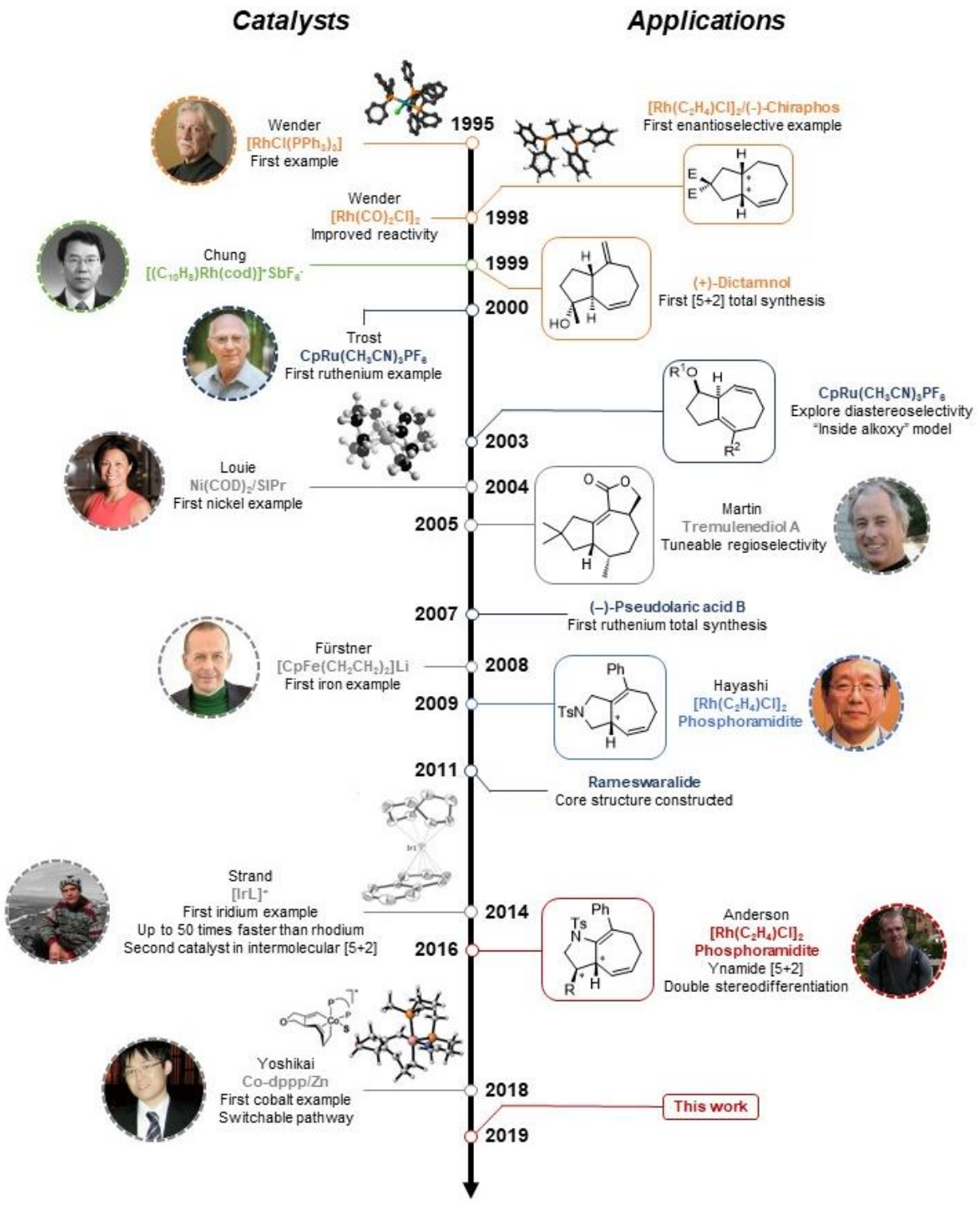


Figure 3. An overview of the history of metal-catalyzed [5+2] cycloisomerization.

1.2 Kinetic Resolution

The importance of enantioriched molecules has driven the development in new methods for enantioselective synthesis in organic chemistry. For example, in 1987, only 57% marketed drugs were chiral, whilst 2% were made as single enantiomers; by 2006, 80% drugs approved by the FDA were chiral, with 75% being single enantiomers.[58]

There are three major methods of preparing enantioriched compounds (Figure 4): the first is *chiral pool synthesis*, where enantiopure, readily available natural products are used to obtain more complex structures.[59,60] The second method is *asymmetric synthesis*, which includes the use of chiral reagents, chiral catalysts, asymmetric induction, and biocatalysis.[61–65] Last but not least, *resolution*, which is a process for the separation of racemic compounds into their enantiomers.[66–75] In particular, kinetic resolution has played a critical role in synthetic chemistry in the past three decades.[76,77]

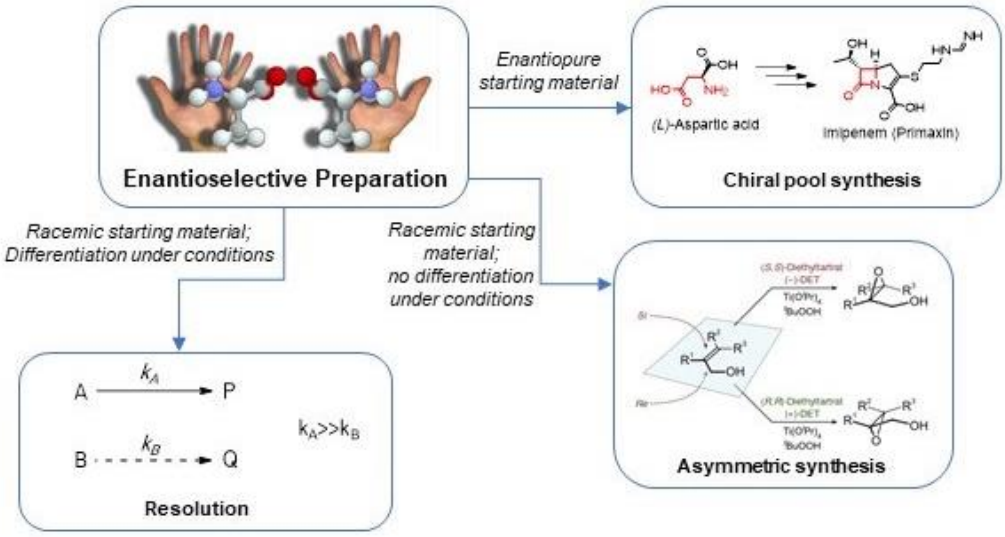


Figure 4. A summary of different methods to prepare enantioriched compounds.

1.2.1 History and Background

In order to achieve resolution, three broad categories of methods are employed: *classic resolution*, the use of a stoichiometric amount of achiral resolving agent to generate a pair of separable diastereomers;[78,79] *chiral column chromatography*, the use of a single enantiomer of a chiral compound in the stationary phase;[80,81] and *kinetic resolution*, the use of a chiral catalyst or reagent to achieve different rates of reaction of the two enantiomers in a racemic starting materials (Figure 5). The concept of kinetic resolution will be discussed in details in the following chapter.[82–85]

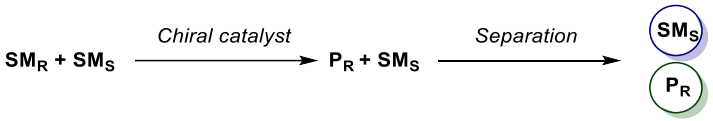
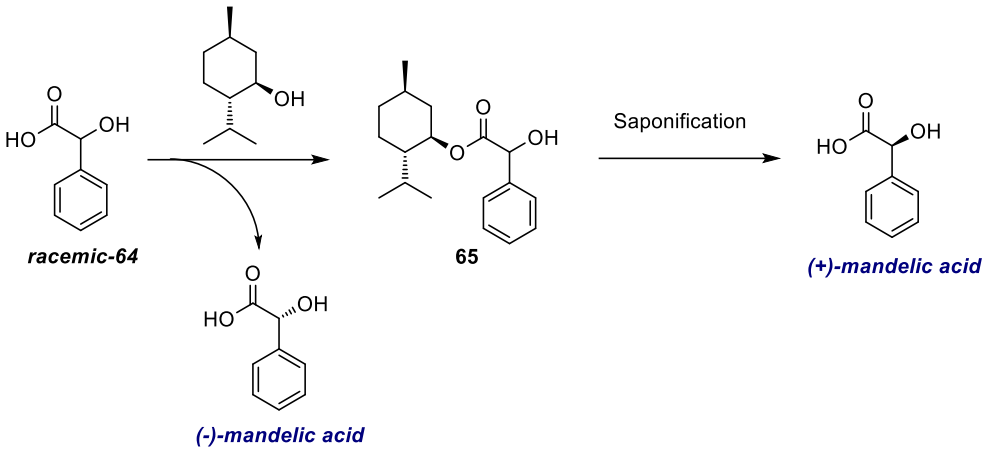


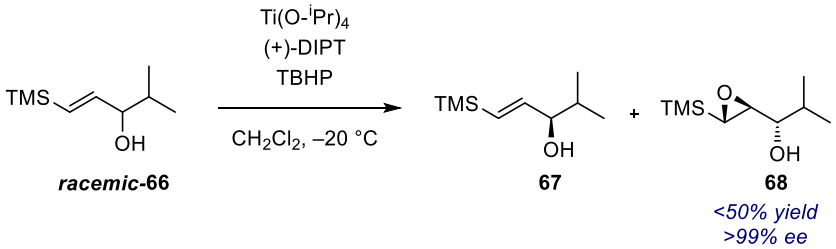
Figure 5. An overview of kinetic resolution.

It is a story that has been told many times, but it is always worth repeating. In 1858, French microbiologist and chemist Louis Pasteur performed fermentation of aqueous racemic ammonium tartrate with a mold from *Penicillium glaucum*, and observed that only the levorotatory isomer was retained.[86] In chemistry terms, *(R,R)*-tartrate was metabolized during the reaction, while *(S,S)*-tartrate remained unreacted under the fermentation conditions. By 1890, several other enzymatic resolutions during fermentation process were reported by Fischer, who based his monumental studies in defining relative and absolute configuration of monosaccharides on these observations.[87] Kinetic resolution was not exploited for synthetic chemistry until 1899, when Marckwald and McKenzie reported when mixing (–)-menthol and racemic mandelic acid **64** in excess, the rate of esterification of (+)-mandelic acid was significantly faster than (–)-mandelic acid. After saponification, optically pure (+)-mandelic acid was isolated, whilst the remaining starting material was enriched in (–)-mandelic acid (Scheme 16).[88]



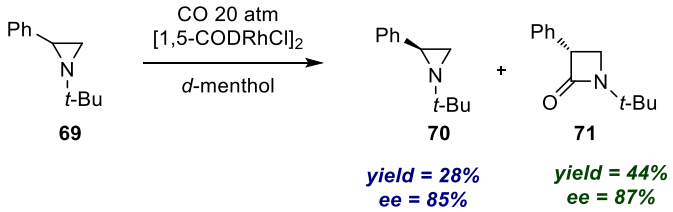
Scheme 16. First example of kinetic resolution in synthetic chemistry.[88]

Kinetic resolution has since become a powerful tool in asymmetric synthesis, and a number of reactions utilizing this method have been reported, including but not limited to: acylation reactions (Fu *et al.*),[89–94] epoxidations and dihydroxylations (Sharpless *et al.*),[65,94–100] epoxide openings (Jacobsen *et al.*),[101,102] oxidations and hydrogenation (Noyori *et al.*),[103,104] and ring closing metathesis (Schrock *et al.*).[105] The Sharpless epoxidation developed in 1980 (Scheme 17) is one of the classic examples, which shared the Nobel Prize in 2001.[95] Racemic secondary alcohols such as **66** are converted into epoxide **68** in its enantiopure form, while leaving (*R*)-**66** unreacted.[106] Excellent enantio-enrichment was obtained in most cases (>95%), which demonstrated the versatility and usefulness of this methodology.



Scheme 17. Sharpless epoxidation and its application in synthesis of methymycin.[106]

Kinetic resolution as a tool for synthetic chemistry remains somehow controversial when it comes to practicality. Except for a few rare cases, kinetic resolution has a maximum theoretical yield of 50%. This results in poor atom economy and is considered suboptimal in industry settings.[76,107] Therefore, the misconception of 'kinetic resolution can never be practical' has led to organic chemists' effort to avoid such approaches due to its inherent inefficiency and potential practical difficulty. However, under careful evaluation, kinetic resolution can become a powerful strategy and has its unique advantages over other enantioselective preparation methods. Compared to classic resolution or chiral chromatography, catalytic kinetic resolution requires neither stoichiometric amounts of chiral resolving agent, nor large volumes of solvents as eluents. Furthermore, the racemates of the starting materials are often considerably cheaper than their enantioriched form. With efficient kinetic resolution, both product and recovered starting material in their enantioriched form are recoverable and valuable, making kinetic resolution not only extremely practical, but also highly desirable in such cases.[76] For example, Alper *et al.* reported an example of carbonylation of aziridines *via* regioselective C-N insertion (Scheme 18).[108] Not only was an extremely simple yet efficient catalyst used, but also access to chiral aziridine **71** was achieved, which was previously prepared by a multistep reaction sequence from an epoxide and was thus challenging to synthesize asymmetrically.[109–111]



Scheme 18. Alper's kinetic resolution *via* regioselective carbonylation.

1.2.2 Definition and Theories

The foundation of kinetic resolution comes from the difference in Gibbs free energy ($\Delta\Delta G^{\ddagger}$, Figure 6). Although enantiomers of both starting materials and products are of the exact same energy, there is a difference in transition state energy, $\Delta G^{\ddagger}$ ($\Delta G^{\ddagger}_S$ - $\Delta G^{\ddagger}_R$) which leads to different rate of reaction *via* the two pathways.

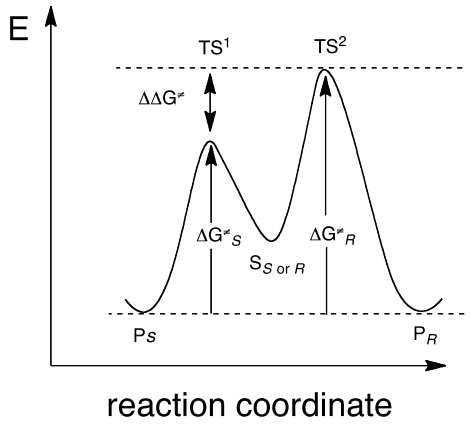


Figure 6. Reaction coordinate for kinetic resolution.

Selectivity factor. By definition, a greater $\Delta\Delta G^{\ddagger}$ will lead to a more optimized resolution and the efficiency of a kinetic resolution is commonly defined by selectivity factor (S), which is referred to the relative rate of reaction for each enantiomer and can be also written in terms of the free energy difference between the high- and low-energy transitions states.[76,82,112] The selectivity factor is denoted as (for $k_R > k_S$):

$$S = k_R/k_S = e^{\Delta\Delta G^{\ddagger}/RT}$$

Kagan *et al.* then combined the equation and definition of enantiomeric excess (*ee*) to demonstrate that selectivity factor could also be expressed by conversion of reaction (C) and *ee* of the

corresponding compounds ($ee_S = S_S - S_R$, $ee_P = P_R - P_S$), which enabled the calculation of selectivity factor from practical measurements:[82]

$$S = k_R/k_S = \ln[(1 - C)(1 - ee_s)]/\ln[(1 - C)/(1 + ee_s)]$$

$$S = k_R/k_S = \ln[(1 - C(1 + ee_P)]/\ln[(1 - C(1 - ee_P)]$$

In 1975, Horeau *et al.* showed that by reversing the equation, the necessary extent of conversion can be calculated if both selectivity factor (S) and desired *ee* was known, where ee_0 is the *ee* of starting material, S_R and S_S are the desired enantiomer composition, and S_R^0 and S_S^0 are the enantiomer composition before resolution ($t = t_0$):[113]

$$(1 - C)^{s - 1} = (1 - ee)/(1 + ee)[(1 + ee_0)/(1 + ee)]^s = S_R/S_R^0(S_S^0/S_S)^s$$

By rearranging the above equation, the lowest conversion necessary to achieve desired *ee* was expressed as following:

$$C = 1 - [(S_R/S_R^0)(S_S^0/S_S)^s]^{1/(s - 1)}$$

For example, with a resolution of S = 5.0, in order to resolve a sample of 80% *ee* (90:10 *e.r.*) to 98% *ee* (99:1 *e.r.*), a minimal 50.1% conversion will be necessary:[112]

$$C = 1 - [(0.01/0.10)(0.90/0.99)^5]^{1/4} = 1 - 0.499 = 0.501$$

To better visualize the relationship between unreacted substrate (S_S) and conversion (C), Sharpless *et al.* constructed the diagram below (Figure 7) for three different values of selectivity factors (S).[84,96] As illustrated, the more efficient a resolution is, the closer to 50% conversion is needed to achieve an enantiopure starting material. There is also always a tradeoff between enantiopurity and isolated yield, and a maximal theoretical yield of 50% for the desired product.

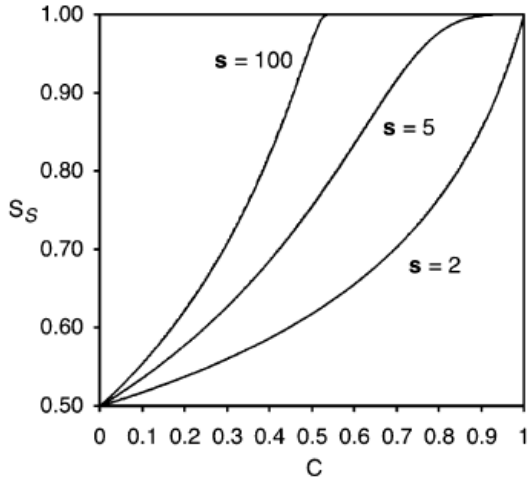


Figure 7. Relationship between conversion (S) and enantiopurity of starting material (S_S).[84]

Although the selectivity factor is useful for assessing the basic properties of a kinetic resolution, evaluating and comparing effectiveness of catalysts, there is no practical way of accurately measuring it. In order to obtain the above simplified equation, a few assumptions have to be made, including but not limited to: [114–117]

1. The reaction is always first order with respect to substrates;
2. Both enantiomers of starting material proceed in the same order;
3. The catalyst is monomeric through the whole reaction;
4. Only one catalyst molecule is present in the transition state of the stereoselective step;

In reality, the true rate laws for kinetic resolutions are rarely investigated due to practical difficulty, thus leading to frequent misreports of selectivity factors in the literature.[76] To avoid this problem, a few approaches have been exploited. The most obvious and seemly easiest practice is to present those parameters as they are (conversion, isolated yield, *ee* etc.) and not use selectivity factor (S) at all.[76] Other effort has also been put into optimizing the equation.[114,115]

Nonlinear effects. To understand the limitation of the concept of selectivity factor (s) and attempt optimization, nonlinear effects must be discussed. In 1976, Wynberg and Feringa reported an antipodal interaction effect, where the same reaction performed differently in the presence of a mixture of enantiomers.[118] Later, several more example have been reported with notable 'Wynberg principles', or nonlinear effects of asymmetric catalysts.[119,120] Due to the non-bonding interaction between reacting substrate and enantiomerically impure compounds present, the relationship between *ee* of obtained product and *ee* of ligand is not always perfectly linear (Figure 8).[112,121,122]

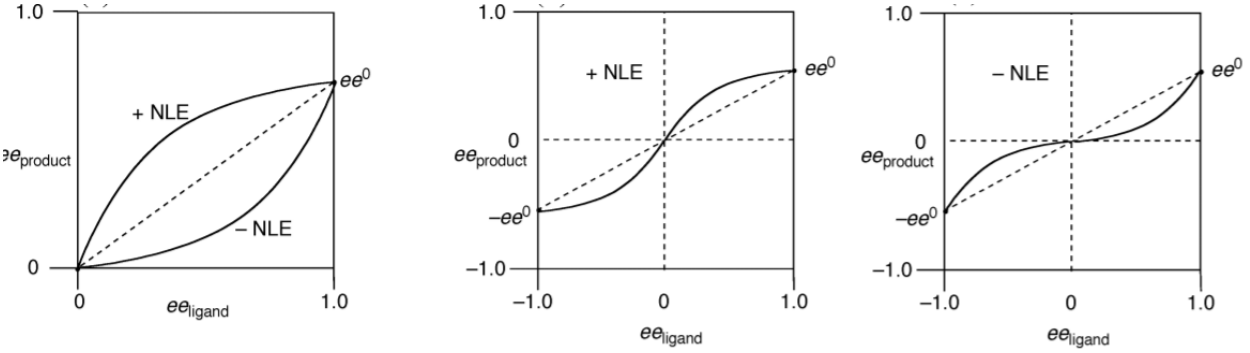


Figure 8. An illustration of different types of nonlinear effect in asymmetric catalysis.[112]

Therefore, the relative rate of formation of both enantiomers of product can be expressed mathematically (*vide infra*) if the concentration of each enantiomer of substrate and asymmetric catalyst is known:[84,115,123]

$$d[R]/d[S] = (k_1[Cat_R] + k_2[Cat_S])/(k_1[Cat_S] + k_2[Cat_R]) = k_R/k_S$$

However, the relationship between $[Cat_R]/[Cat_S]$ and $d[R]/d[S]$ cannot be treated as universally linear and is often pointless when it comes to situations like racemization of product, reactions starting with some excess of an enantiomeric product present, or when k_R/k_S is not constant.[115] A better representation of the relationship can be obtained by manipulating the above equation:

$$([R]/[S] - 1)/([R]/[S] + 1) = (k_R/k_S - 1)/(k_R/k_S + 1)$$

$$= \{(k_1 - k_2)([Cat_R] - [Cat_S])\}/\{(k_1 + k_2)([Cat_R] + [Cat_S])\}$$

The term $(k_R/k_S - 1)/(k_R/k_S + 1)$ was defined as *differential kinetic enantiomeric enhancement* (DKEE) by Singleton *et al.*[115] DKEE provides an unique advantage over selectivity factor (s) as it not only demonstrates the effectiveness of a resolution, but also generalizes the level of nonlinearity when present.

For the sake of simplicity, in this thesis, only major reaction parameters will be reported, and selectivity factors are calculated solely for the purposes of comparison between efficiency of the same catalyst system when processing different substrates. Similarly, concepts involving nonlinearity like DKEE will not be discussed because such effects do not seem to occur in our transformations, as demonstrated by linear effect studies in the following chapter.

1.2.3 Dynamic Kinetic Resolution (DKR) and Other Subtypes

As mentioned, a major drawback of kinetic resolution is the 50% theoretical yield threshold. A few number of techniques have been developed to overcome this limitation.[76] The most well-known modification is dynamic kinetic resolution (DKR), which is based on the same principle as kinetic resolution with rapid, reversible racemization prior to the selective reaction of one enantiomer with the chiral catalyst, which enhance the maximum theoretical yield to 100% (Figure 9).[85,124–127]

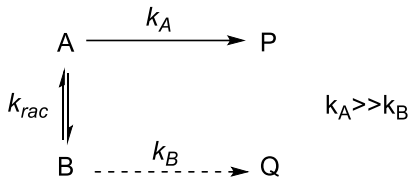
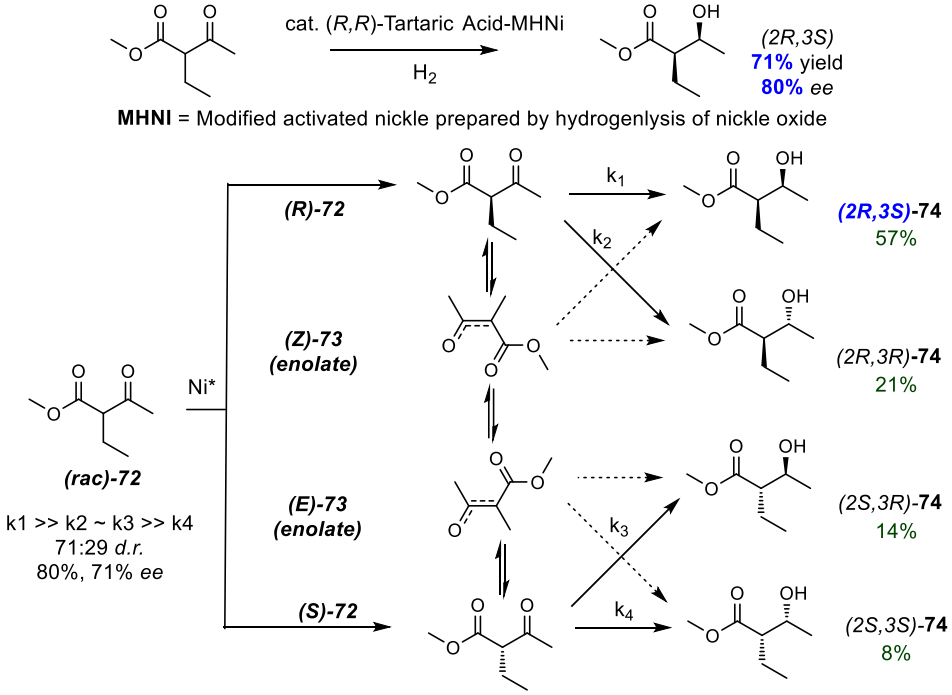


Figure 9. An overview of dynamic kinetic resolution.

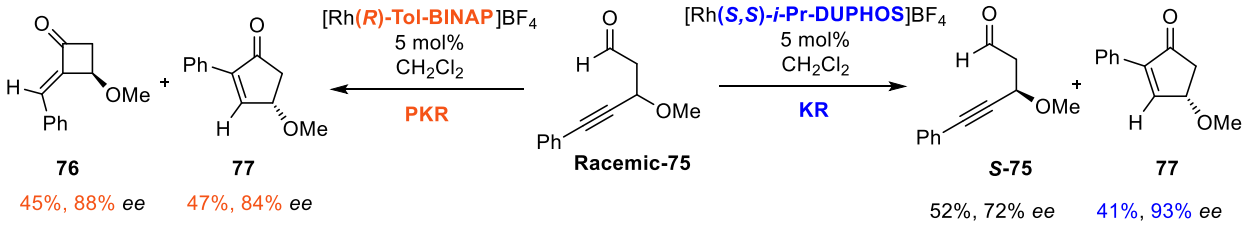
One of the first examples was asymmetric hydrogenation reported by Tai *et al.* in 1979 (Scheme 19).[128] Racemic starting material **72** was rapidly epimerized *via Z/E*-enolates **73**, giving (2*R*, 3*S*) product **74** at the fastest rate. By measuring the ratio of each diastereomer or enantiomer formed (*RS*, *RR*, *SR*, *SS*-**74**) and the overall *d.r.*, the relative rate (k_{rel}) for both hydrogenation (k_{fast}/k_{slow}) and conversion (k_{inv}/k_{fast}) could be calculated accordingly. This transformation was later optimized and modified by Noyori *et al.* by using the more readily available ruthenium-BINAP complex instead of preparing activated nickel. [129]



Scheme 19. Asymmetric hydrogenation using DKR.

The selectivity was also massively improved (up to 99:1 *d.r.*, 93% *ee*), and the stereochemistry of both chiral centers could be fine-tuned by switching handedness of the BINAP motif (governing absolute configuration at C-3) and structure of substrate (governing the absolute configuration at C-2).[129–132]

Another approach to achieve a 100% theoretical yield is to use parallel kinetic resolution (PKR): instead of leaving one enantiomer of starting material unreacted, it is converted to a different product with improved *ee*.[133,134] The concept was formally introduced by Vedejs and Chen in 1997 and a few examples have been reported since, most of which involve transition metal or enzymatic catalysis.[135–139] Fu *et al.* reported a 'tunable' resolution, which provided an excellent comparison between parallel kinetic resolution (PKR, Scheme 20, left hand side) and regular kinetic resolution (KR, Scheme 20, right hand side).[140] Racemic alkynal **75** was converted into enantioriched cyclopentenone **77** by rhodium(I)-DUPHOS whilst (*R*)-**75** stayed unreacted *via* kinetic resolution. However, when a Tol-BINAP ligand was used, (*R*)-**75** was converted into cyclobutanone **76** whilst (*S*)-**75** was converted into cyclopropenone **77** in parallel.



Scheme 20. Example comparing PKR and regular KR.

In the case of PKR, selectivity factor (S) does not play an important role because it does not necessarily have an impact on the reaction outcome.[135] A mathematical treatment was initially developed by Guetté and Horeau as follows, where x and y denote each product formed:[141]

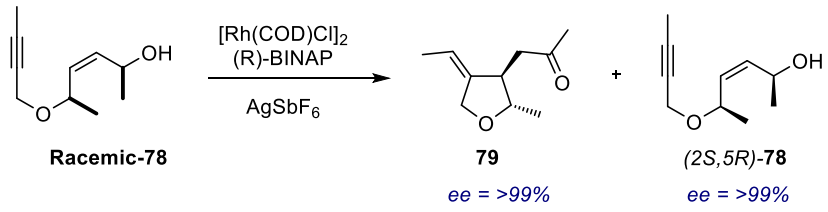
$$ee_x \cdot [x] = ee_y \cdot [y]$$

The equation could only be applied when complete conversion was achieved – as such, it is not difficult to imagine, it is not commonly presented in literature and not practical unless further modification is applied.[142]

Recently, chemists have exploited other subtypes including dynamic kinetic asymmetric transformations (DyKATs), dynamic substrate directed resolution (DSDRs), enantioconvergent process (ECP), desymmetrizations and cyclic de-racemization (CycD).[143–152] Each subtype has its unique feature and limitations, but will not be covered in great detail in this thesis.

1.2.4 Kinetic Resolution in Cycloisomerization

Studies on cycloisomerization reactions with kinetic resolution have been extremely limited. To date, only a handful of examples have been reported, with one example using rhodium as catalyst by Zhang *et al.* (Scheme 21).[153–155] When enantiopure BINAP was used as ligand, reaction was finished within 2 minutes at 15 °C, offering (2*S*, 3*R*)-**79** in 49% isolated yield and >99% *ee*. Remaining starting material (2*S*, 5*R*)-**78** was also recovered in >99% ee.



Scheme 21. Rhodium-catalyzed kinetic resolution of enynes.

1.2.5 Summary

In summary, kinetic resolution is a useful synthetic tool, but many aspects of this topic are still unexplored. It certainly is a powerful strategy when carefully evaluated and even advantageous comparing to traditional asymmetric synthesis in some cases. Mathematical models and application of this method in cycloisomerization reactions, however, have barely been exploited.

1.3 Thesis Summary

This thesis begins with a description of the synthesis towards substituted enyne substrates for [5+2] cycloisomerization, which allows the modification of various substituents into different positions, as well as introducing heteroatoms into the substrate backbone. Next, the kinetic resolution studies of the [5+2] cycloisomerization of a racemic ynamide bearing a substituent at β-position in relation to the heteroatom are described, followed by optimization and exploration of substrate scope, including a chiral silane.

Having established the methodology, a formal synthesis of (+)-dictamnol is described in Chapter 3. Attempts to design new substrates for potential dynamic kinetic resolution (DKR) were also carried out and assessed in Chapter 4.

Finally, in Chapter 5, ongoing research is discussed applying reaction conditions to unsubstituted ynamides bearing aryl groups with the potential to achieve atroposelectivity in [5+2] cycloisomerization.

2. Kinetic Resolution in [5+2] Cycloisomerization

Despite being studied for over a century, it was not until 2003 that kinetic resolution in transition metal catalyzed [5+2] cycloisomerization reactions was reported.[135,153] Whilst in theory, a variety of asymmetric transformations have the potential to be modified to introduce the concept of kinetic resolution, in reality little success has been shown in this area. We thus took the challenge to develop a catalyst system to achieve both highly selective [5+2] cycloisomerization and efficient kinetic resolution.

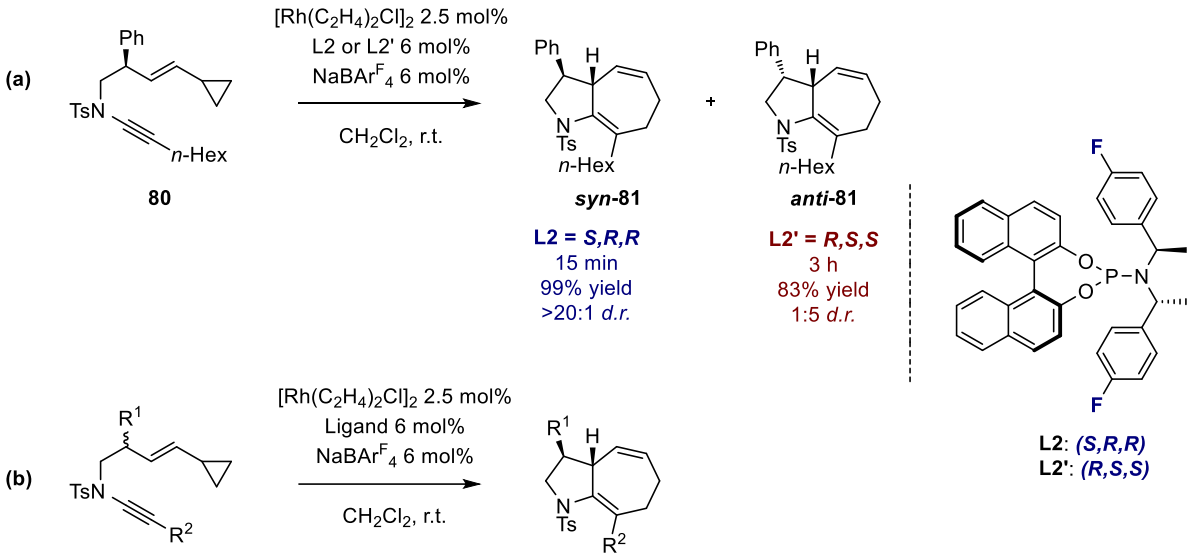
2.1 Previous Work

Recently, our group has described the first example of double stereodifferentiation in ynamide [5+2] cycloisomerization (Scheme 22, Equation a).[37] It was found that rate of reaction and enantioselectivity of this transformation were dramatically influenced by the electronic properties of the phosphoramidite ligand. By substituting the para position of the phenyl ring of the ligand with an electron-withdrawing fluorine atom, great enhancement in both rate and selectivity was observed.

Preliminary results showed not only excellent inherent substrate stereocontrol, but also a significant difference in rate between matched and mismatched reactions with this catalyst-substrate setting. When L2 (*S,R,R*) was used, reaction with enantioriched substrate **80** was complete in 15 minutes at room temperature, giving quantitative yield and >20:1 *d.r.* with *syn*-**81** as the predominant diastereomer. On the other hand, use of the enantiomer L2' (*R,S,S*) required 3

hours to finish the reaction to give *anti*-**81** predominantly. Isolated yield (83%) and *d.r.* (1:5) from this 'mismatched' reaction were both lower.

On the basis of these results, we envisioned the possibility of the first example of [5+2] cycloisomerization kinetic resolution (Scheme 22, Equation b).

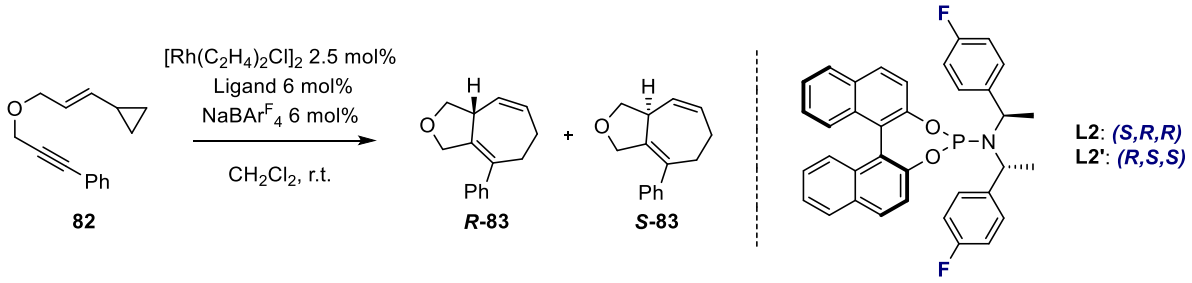


Scheme 22. a) Previous work and b) proposal for the thesis.[37]

2.2 Linear effect studies

In order to examine whether a nonlinear effect existed in our catalyst system, a model [5+2] cycloisomerization reaction using unsubstituted ether **82** was carried out using ligands with different level of enantiopurity. Ligand *ee* was manipulated by mixing enantiopure (*R*,*S*,*S*) and (*S*,*R*,*R*) phosphoramidite L2/L2' in different portions and tested by HPLC as a solution in dichloromethane (Table 2).

Table 2. Results of linear effect studies.



Entry	Ligand Mass		ee_{ligand}[a]	$ee_{product}$[a]
	L2 (S,R,R)	L2' (R,S,S)		
1	~5.0 mg	-	100.0±0.0%	100.0±0.0%
2	~0.5 mg	~4.5 mg	76.1±0.3%	76.9±0.2%
3	~1.0 mg	~4.0 mg	57.0±0.2%	55.6±0.3%
4	~1.5 mg	~3.5 mg	39.4±0.0%	38.7±0.3%
5	~2.5 mg	~2.5 mg	-0.7±0.1%	-0.5±0.0%
6	-	~5.0 mg	-100.0±0.0%	-100±0.0%

[a] *ee* values are based on average of 3 measurements; data were shown in the format of mean±standard deviation.

Upon completion, the [5+2] product **83** was concentrated and subjected to HPLC analysis as a crude mixture. We were delighted to find a linear relationship between *ee* of ligand and product (Figure 10): $ee_{prod} = 0.9985 ee_{ligand}$, $R^2 = 0.9999$.

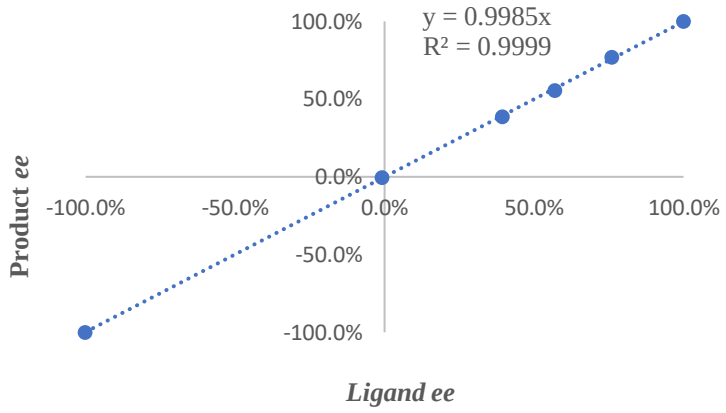
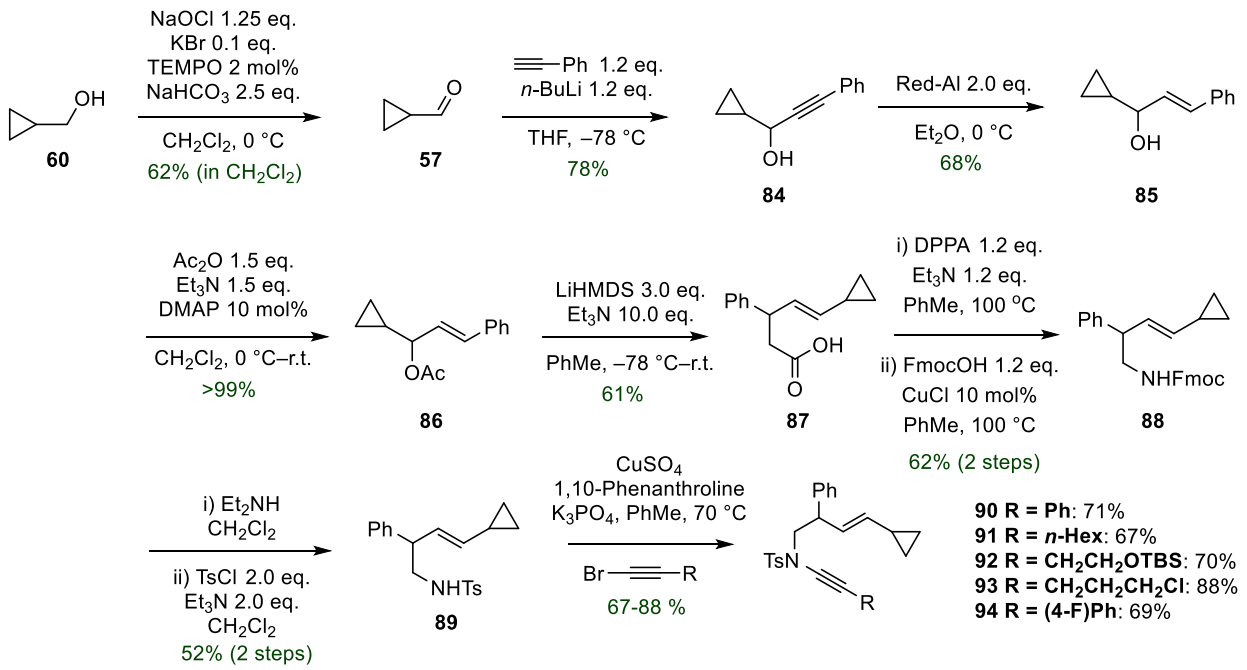


Figure 10. Relationship between ligand *ee* and product *ee*.

2.3 Kinetic Resolution of Ynamide Substrates

2.3.1 Ynamide Substrate Synthesis

Studies began with enynamide **90–94**, which were prepared in 8 steps following the method developed by the Anderson group (Scheme 23).[37,156] Aldehyde **57** as a solution in dichloromethane was freshly prepared by oxidation of readily available primary alcohol **60**. It was immediately subjected to addition of lithium phenyl acetylide to form propargylic alcohol **84** with good yield. Following Rel-Al reduction to alcohol **85** and acetylation, allylic ester **86** was ready to undergo Ireland Claisen rearrangement to give carboxylic acid **87** in moderate yield. A strategy involving subsequent Curtius rearrangement/protecting group switch was employed to give sulfonamide **89** as a substrate for ynamide formation. Finally, copper-catalyzed cross coupling between **89** and a bromoalkyne precursor generated the desired products **90–94**.[157]



Scheme 23. Synthesis of racemic ynamides.

Six allylic substituted ynamides **90–94** bearing different alkynyl groups were prepared in moderate to high yield (67–88%, Figure 11) from this copper-catalyzed cross coupling, although 2-5 equivalents of the corresponding bromoalkyne was necessary to achieve completion of reaction.

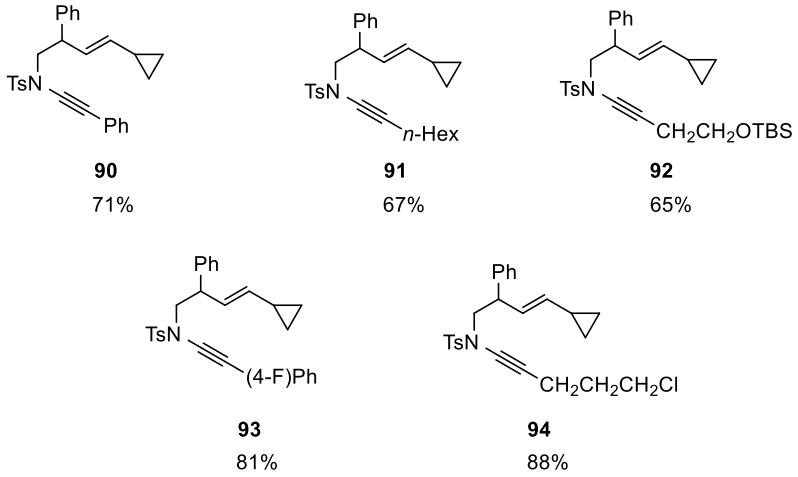
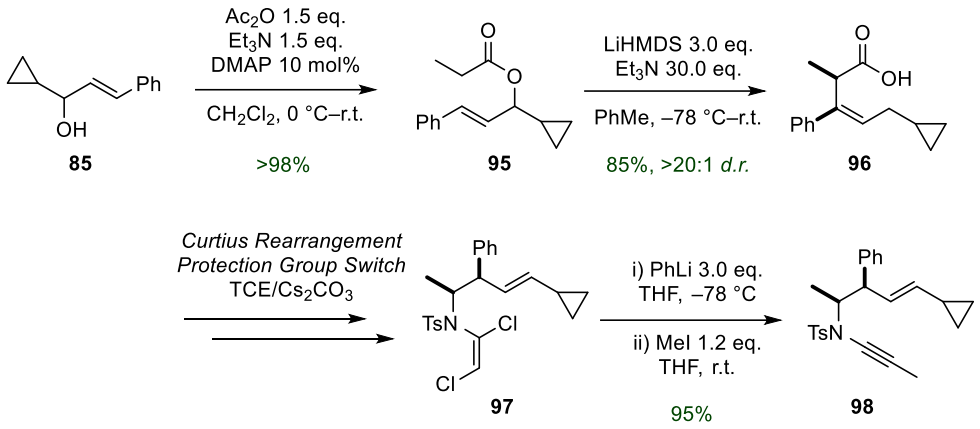


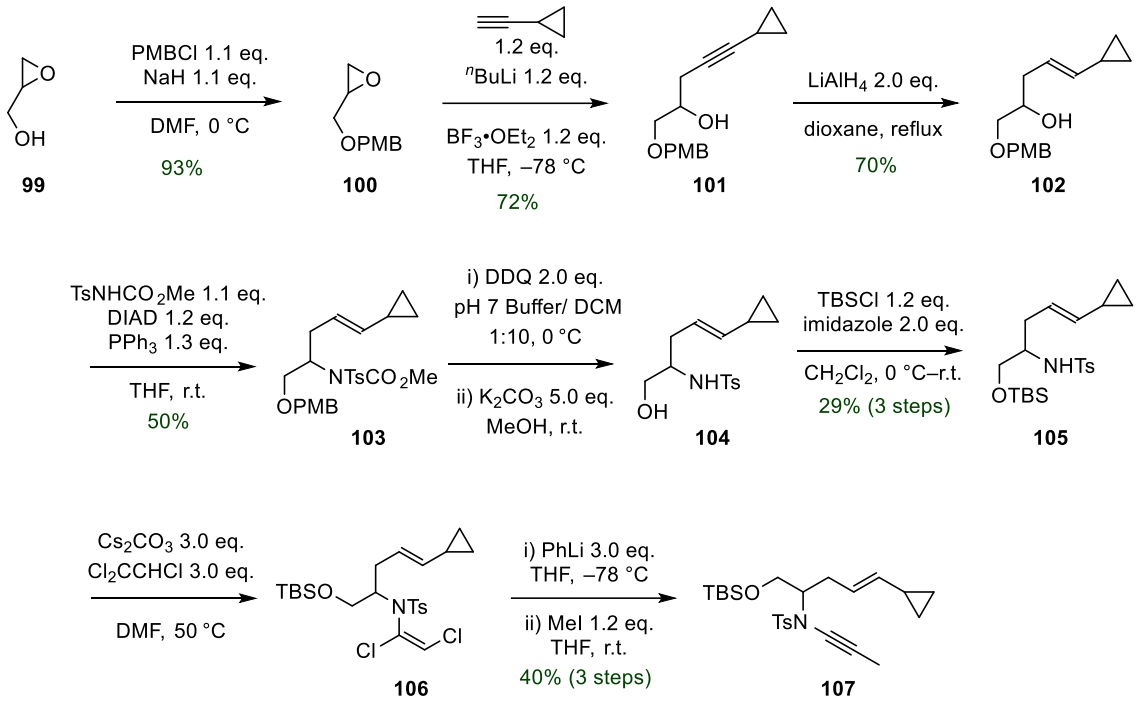
Figure 11. Ynamides prepared from copper-catalyzed cross coupling.

In addition to allylic substituted ynamides, substrates with homo-allylic substituents, and two substituents, were also prepared. A similar approach was used to synthesize doubly substituted ynamide *syn*-**98** starting from esterification of allylic alcohol **85** prepared above (Scheme 24). During the Ireland-Claisen rearrangement reaction, it was necessary to increase the load of triethylamine from 10 equivalents to 30 equivalents in order to achieve high level of diastereoselectivity (9:1 *d.r.* using 10 equivalents *vs.* >20:1 *d.r.* using 30 equivalents). The increased concentration of triethyl amine favours the formation of the (*E*)-enolate intermediate, which leads to the *syn*-diastereomer as drawn.[158] Upon successful protecting group switch, a two-step ynamide synthesis route was exploited *via* dichloroenamide, giving the desired product **98** in excellent yield (95%).[156]



Scheme 24. Preparation of substrate *syn*-**98**.

Homoallylic ynamide substrate *syn*-**107** was prepared *via* an alternative strategy developed by Anderson *et al.* (Scheme 25).[37,156] Glycidol **99** was chosen as starting material because of its ready commercial availability and low cost. After protection as its 4-methoxybenzyl ether (PMB), epoxide opening with cyclopropylacetylide, and reduction by $LiAlH_4$, secondary alcohol **102** was obtained in satisfactory yield. This then underwent Mitsunobu reaction to give methyl carbamate-protected sulfonamide **103**. A similar protecting group switch strategy followed by ynamide synthesis *via* dichloroenamide **106** was applied to obtain the homoallylic substrate **107**.



Scheme 25. Preparation of homo-allylic substrate *syn*-**107**.

Finally, two ynamides bearing a chlorine atom (Figure 12) were synthesized using a similar method, by heating sulfonamides **89** and **105** with cesium carbonate and trichloroethylene to form the corresponding dichloroenamides, which were then treated with lithium bis(trimethylsilyl)amide (LiHMDS) rather than phenyl lithium to avoid terminal alkyne formation. Unfortunately, both **108** and **109** underwent rapid decomposition during purification, resulting in either low yield (8%) or complete decomposition.

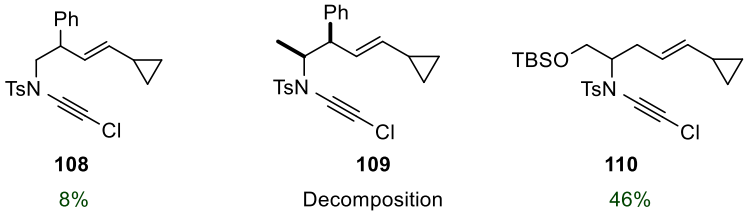
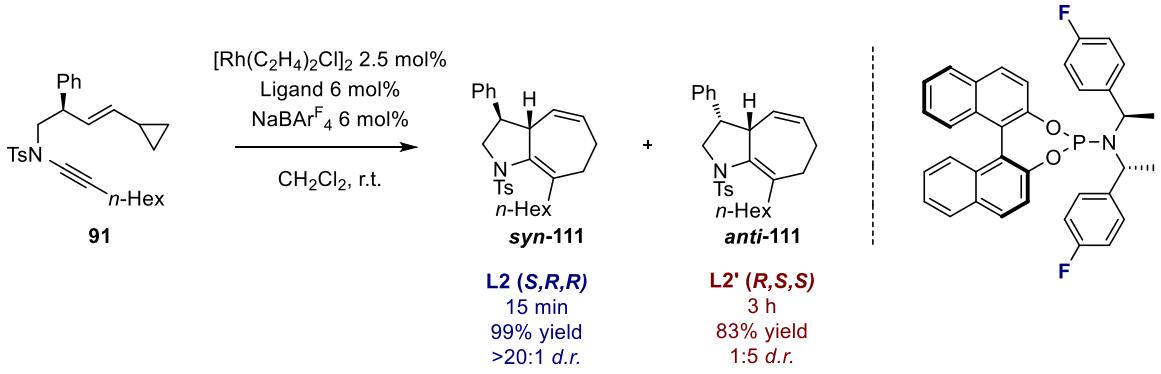


Figure 12. Ynamides prepared from two-step synthesis.

2.3.2 Ynamide Substrate Survey

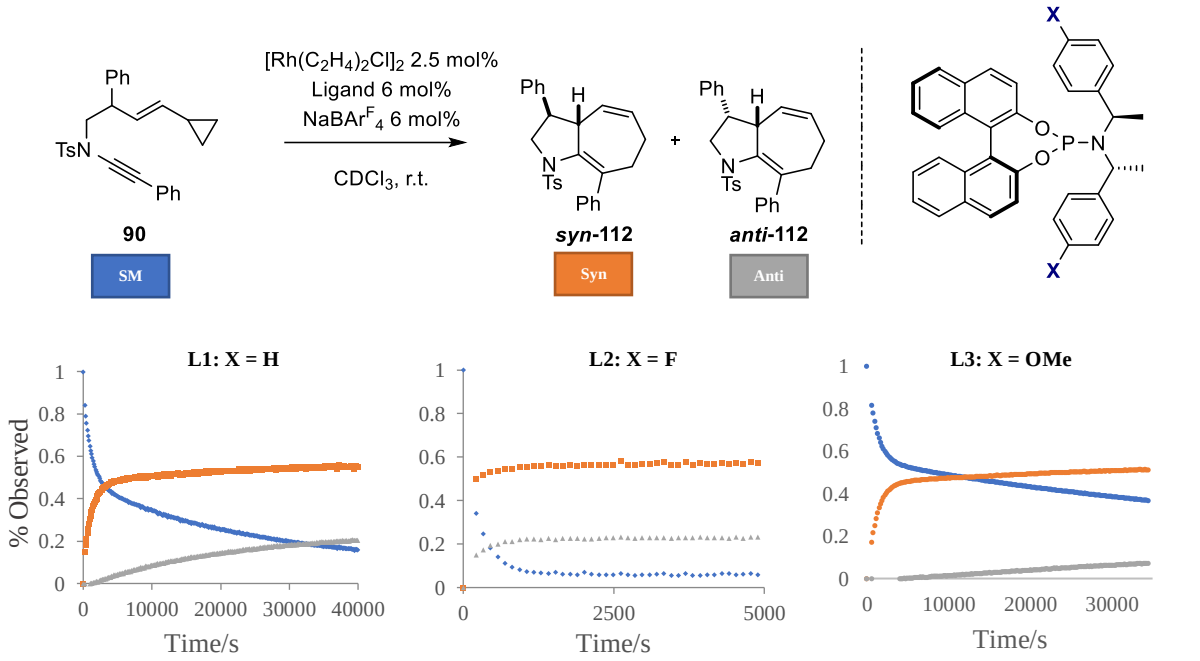
With a range of substrates in hand, our investigations started with *β*-substituted ynamide **91**, which had already demonstrated strong inherent stereocontrol and a large rate difference between matched and mismatched reactions in previous work (Scheme 26).[37]



Scheme 26. Ynamide **91** demonstrating a difference in reaction rate between two enantiomers of the phosphoramidite ligand.

The Racemic substrates were subjected to an asymmetric rhodium(I)/phosphoramidite system and monitored by time-course ^{1}H NMR spectroscopy to study the relative rates of formation of the two product diastereomers. Phosphoramidite ligands bearing different substituents were also surveyed (Figure 13). Initial results suggested a kinetic resolution was indeed possible: a significant difference between matched (*syn*-**112**) and mismatched (*anti*-**112**) reactions was observed with all three phosphoramidite ligands, and *syn*-**112** was obtained with high *ee* (94-99%). Furthermore, both the rate of reaction and enantioselectivity were considerably influenced by the electronic density of the ligand aryl group. The electron poor *p*-fluorinated ligand **L2** gave the 'matched' product *syn*-**112** in highest *ee* (>99%, *c.f.* 98% for **L1** and 94% for **L3**) and fastest reaction rate (achieved 50% conversion in around 10 minutes, *c.f.* 3 hours for **L3** and 1 hour for **L1**), whereas the electron rich *p*-methoxy substituted ligand **L3** and unsubstituted ligand **L1** displayed slower

reaction and poorer product *ee* at room temperature, which was consistent with our previous results.[37]



Entry	L*	Time/ h	Conversion/%[a]	*d.r.* (*syn:anti*)[a]	*ee* (*syn*-112[b]
1[c]	L1	6	>98	1.1:1	98%
2[c]	L2	5	>98	1.2:1	>99%[d]
3[c]	L3	8	>98	1.6:1	94%

[a] Determined by ^{1}H NMR; [b] Determined by HPLC; [c] Conducted in an NMR tube with $CDCl_3$ as solvent; [d] high *ee* was achieved because reaction yield was low (78%).

Figure 13. Ligand screening of ynamide **90**.

Similar results were observed with other *β*-substituted ynamides **91**–**94** (Figure 14). Most substrates displayed evident rate difference between 'matched' and 'mismatched' reactions according to ^{1}H NMR, and complete conversion was achieved within 3–12 hours. The only exception was ynamide **108** bearing a terminal chloride, which failed to react under the reaction conditions. Subsequent variable temperature (VT) NMR experiments were performed between 35–65 °C in deuterated chloroform, but unfortunately, no reaction was observed with elevated temperature.

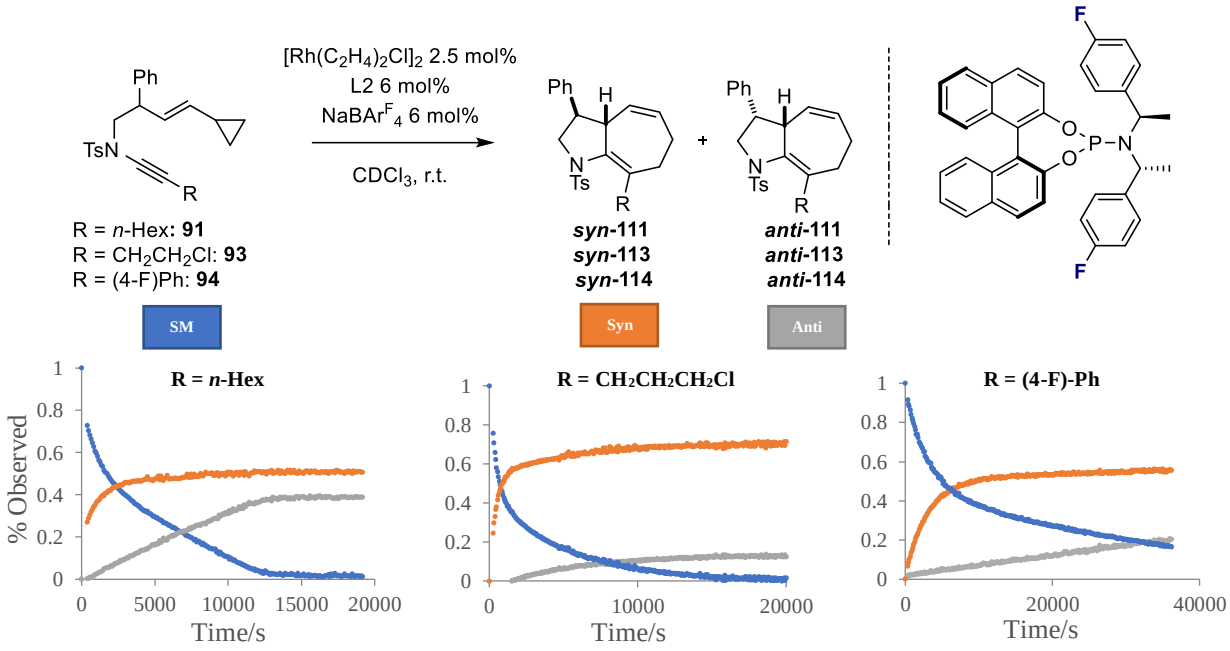


Figure 14. Kinetic profile of ynamides **91**–**94**.

However, although initial results seemed promising, it was highly challenging to reproduce those results on the bench with effective stirring, or using non-deuterated laboratory solvents such as dichloromethane or chloroform, where both 'matched' and 'mismatched' reactions became too rapid such that full conversion was reached within minutes. As these reactions were rather fast at room temperature, we decided to investigate the effect of lowered temperature on the system. To our delight, at 0 °C, the matched reaction still proceeded smoothly with a slightly slower rate, whilst the mismatched reaction was suppressed (Figure 15). After 1 hour, the desired diastereomer *syn*-**112** was isolated in 52% yield, with 20:1 *d.r.* and 90% *ee* on a 10-milligram scale. The slight overrun of the reaction and formation of the 'mismatched product' *anti*-**112** in minor quantity was likely due to the fact that it was practically impossible to maintain a stable low temperature for the crude mixture inside the NMR tube when it was ejected from the machine. Given the sensitive nature of this transformation towards elevated temperature, it would not be surprising that the selectivity of isolated product was less optimal than what was observed in the kinetic profile.

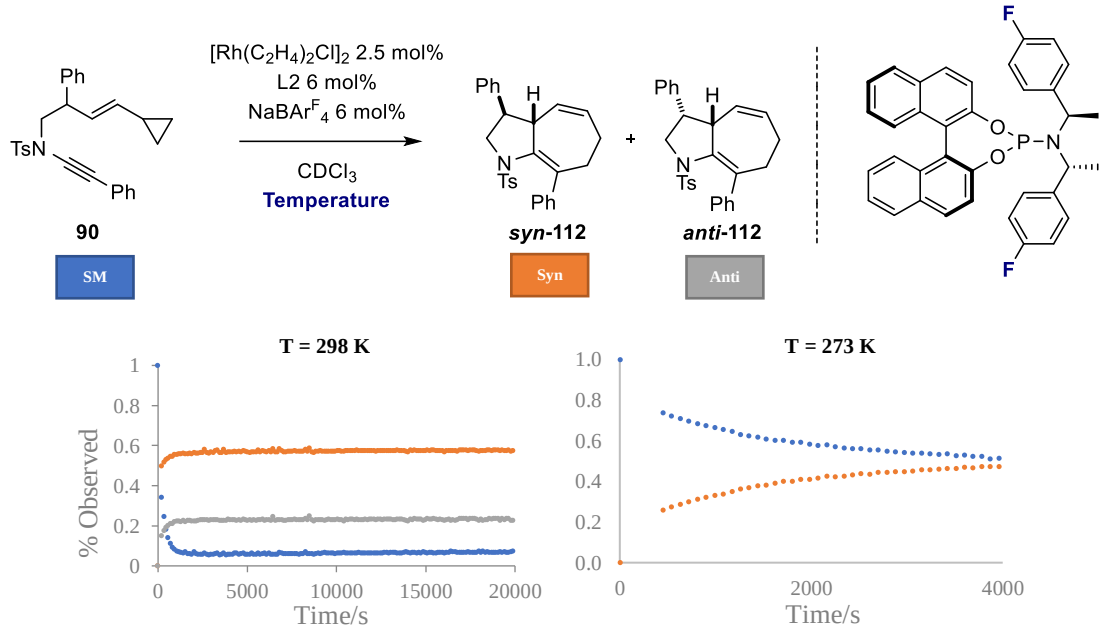


Figure 15. Kinetic profile of ynamide **90** under different temperatures.

Pleasingly, for ligand **L2** (X = F), this result could be translated to the laboratory, albeit lower temperatures (typically –15 °C) and shortened reaction times were generally required to avoid formation of the 'mismatched diastereomer'. A selection of vinylcyclopropane ynamides substituted at the allylic position were submitted to these optimized conditions (Figure 16).

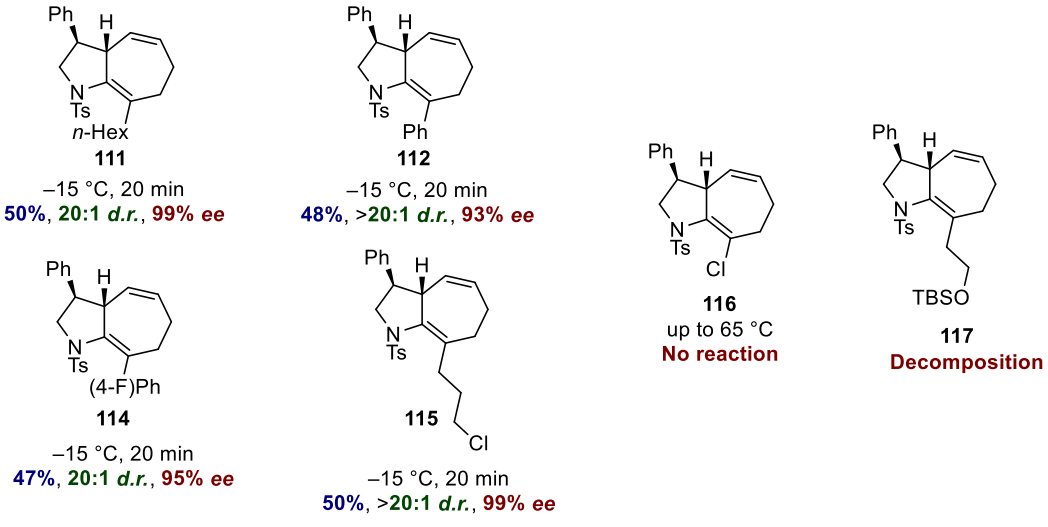
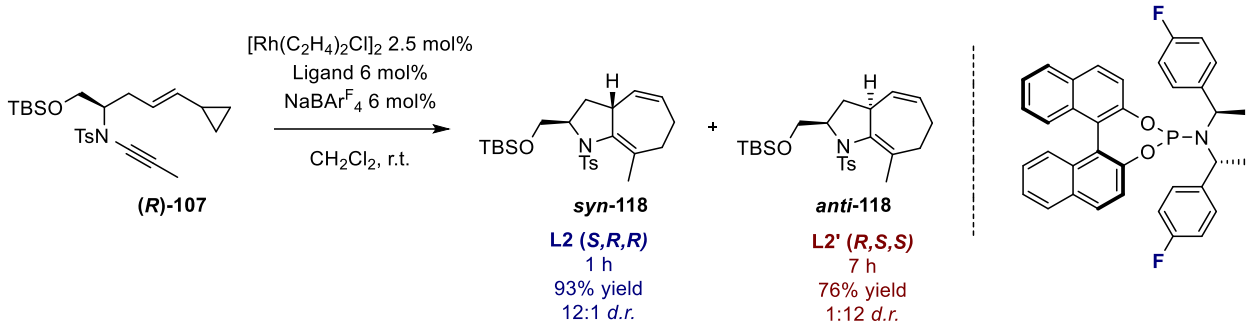


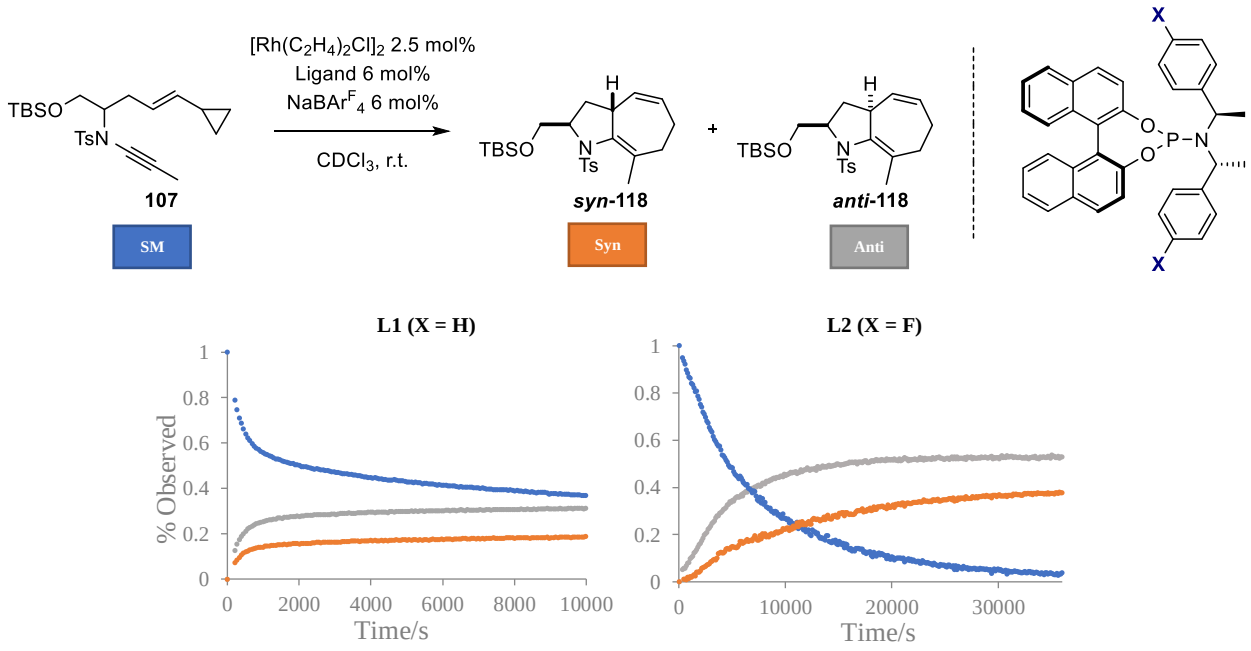
Figure 16. Optimization and substrate scope for allylic-substituted ynamides.

When it came to substrates with homoallylic or double substitution, kinetic profiles were rather intriguing. From the previous results, enantioriched ynamide (*R*)-**107** showed slightly poorer selectivity between the 'matched' and 'mismatched' reactions; where the 'matched' reaction was complete in 1 hour, giving **118** in 93% isolated yield and 12:1 *d.r.* (*syn:anti*) and the 'mismatched' reaction 7 hours, giving 76% isolated yield and 1:12 *d.r.* (*syn:anti*, Scheme 27).[37] Given the less optimal, but still substantial rate difference, it was expected kinetic resolution on ynamide **98** would be more challenging.



Scheme 27. Ynamide (*R*)-**107** demonstrating a difference in reaction rate between two enantiomers of ligand **L2**/**L2'**.[37]

To our surprise, racemic ynamide **107** underwent no reaction with *p*-methoxy substituted ligand **L3** at room temperature, whilst less electron-rich ligands **L1** and **L2** gave the unexpected 'mismatched' product *anti*-**118** as the major diastereomer, with 1:1.4 (**L1**) and 1:1.7 (**L2**) *d.r.* (*syn:anti)* respectively upon full conversion (Figure 17). When the temperature was reduced to –5 °C, both the rate of reaction and selectivity was significantly reduced (only 18% conversion and 1:1 *d.r.* after 3 days), whilst further reduction of temperature suppressed the reaction completely. Conversely, ynamide **110** with the same homoallylic substituent and a terminal chloride atom proved inert under the reaction conditions, resulting in no conversion when heated up to 65 °C. These results indicated that it would not be possible to resolve a homoallylic-substituted substrate.



Entry	Substrate	Temperature/ °C	Time/ h	Conversion/%[a]	*d.r.* (*syn:anti*)[a]
1[b]	**107**	r.t.	12	>98	1:1.4 (**L1**)
			12	>98	1:1.7 (**L2**)
2[b]	**107**	–5	72	18	1:1
3[b]	**107**	–15	1	0	n.d.
4[b]	**110**	Up to 65	1	0	n.d.

[a] Determined by ^{1}H NMR; [b] Conducted in an NMR tube with $CDCl_3$ as solvent;

Figure 17. Kinetic profile of ynamide **107**.

Double substituted ynamide *syn*-**98**, on the other hand, showed promising results during initial investigation. At room temperature, complete conversion was observed in around 2 hours with a distinct difference between the rate of formation of two diastereomers, giving *syn*-**119** as the predominant product as expected in 4:1 *d.r.* (*syn:anti*, Figure 18). However, when subjected to the same reaction conditions at 0 °C, a new compound **120** was observed as the second main product. The formation of **120** presumably resulted from an unusual premature *β*-hydride elimination after oxidative coupling step in the metallacyclopentene pathway, leaving the cyclopropane ring intact.[37,38]

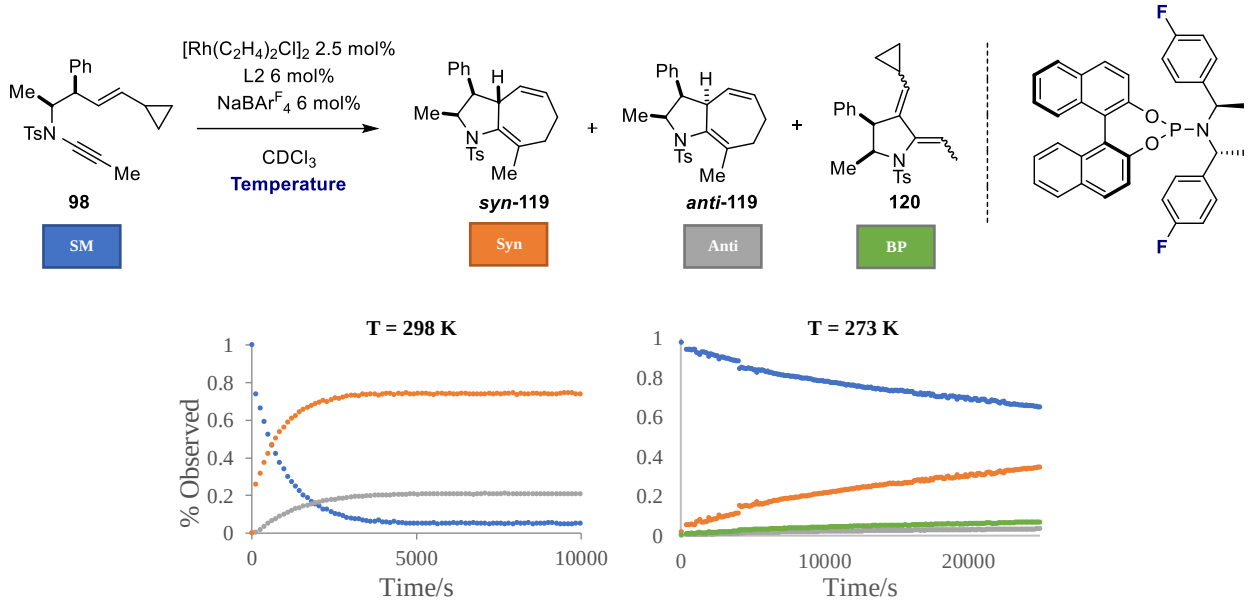
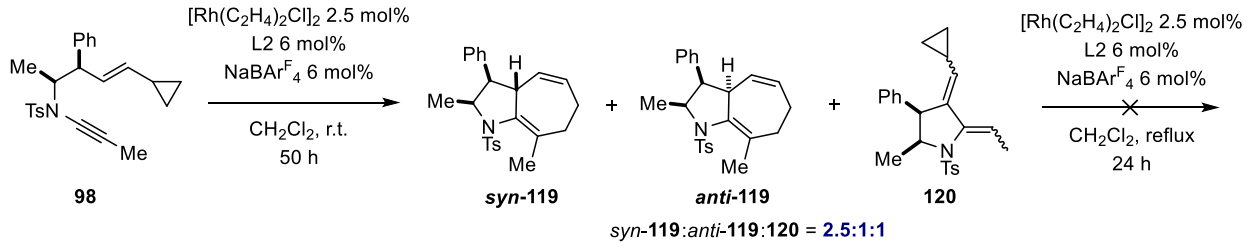


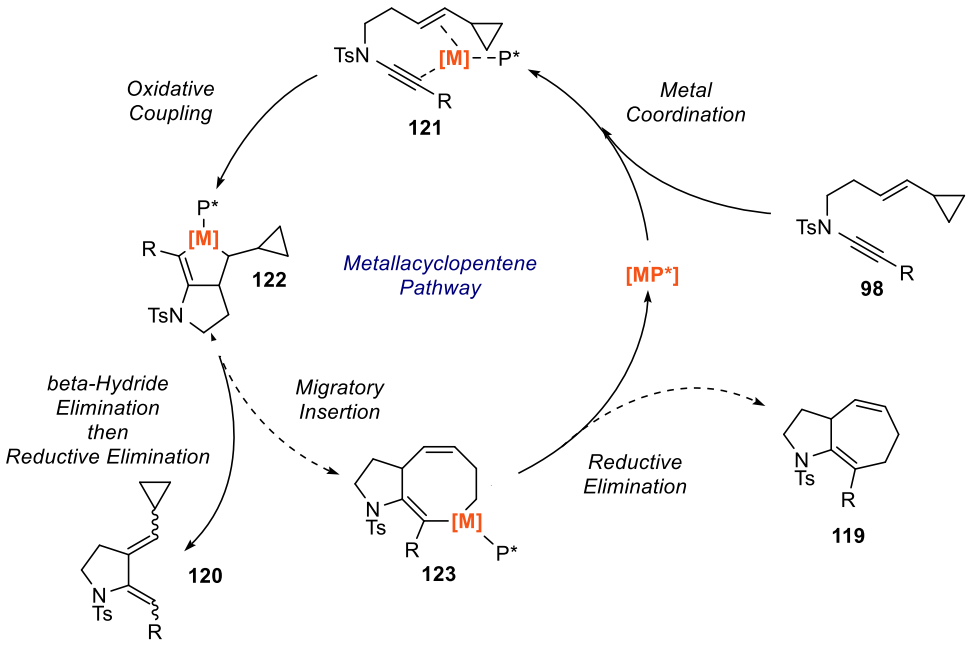
Figure 18. Kinetic profile of ynamide **98**.

In order to rationalize this effect and optimize the reaction outcome, further investigation was conducted. First, racemic ynamide **98** was subjected to the same catalyst system in dichloromethane at room temperature. After 50 hours, full conversion was achieved to give the mixture of *syn*-**119**, *anti*-**119** and byproduct **120** in 2.5:1:1 ratio (Scheme 28). The crude mixture was briefly purified by filtration through silica, then injected into a freshly prepared batch of rhodium(I)/phosphoramidite solution in dichloromethane under reflux.



Scheme 28. Reaction of mixture of *syn*-**119**, *anti*-**119** and byproduct **120**.

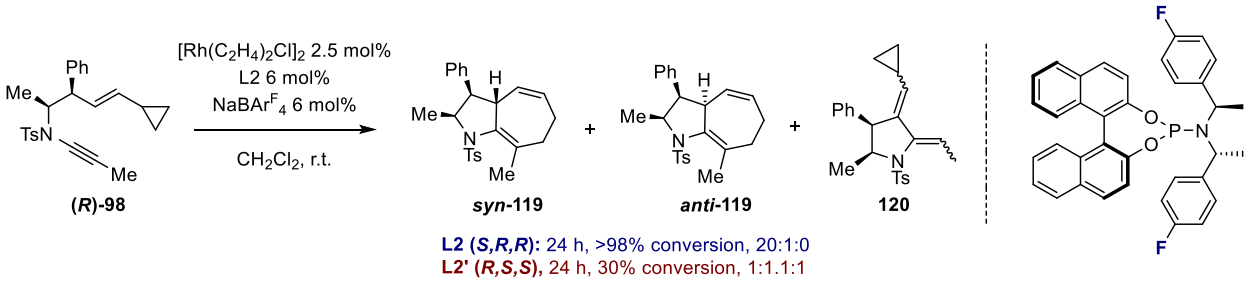
After 24 hours, no further reaction was observed and the ratio of the three compounds remained constant. This indicated that **120** was likely formed from the oxidative coupling complex **122** by *β*-hydride elimination, presumably the migratory insertion was disfavoured due to conformational effects prohibiting suitable bond alignment (Scheme 29).



Scheme 29. Proposed mechanism for formation of byproduct **120**.

We next explored the inherent selectivity for the 'matched' and 'mismatched' reactions individually. Enantiopure ynamide (*R*)-**98** was submitted to the reaction conditions using *p*-fluoro substituted ligand **L2**/**L2'** in both its (*R*,*S*,*S*) and (*S*,*R*,*R*) form. As expected, the 'matched' reaction proceeded smoothly at room temperature, giving *syn*-**119** in quantitative yield and >20:1 *d.r.* after 24 hours with no trace of byproduct. On the other hand, the 'mismatched' reaction not only showed a significantly slower rate (only 30% conversion after 24 hours), but also generated a significant amount of byproduct **120** (*syn*-**119**:*anti*-**119**:**120** = 1:1.1:1.6, Scheme 30). This indicated that in order to prevent the formation of byproduct **120**, the 'mismatched' reaction had to be suppressed.

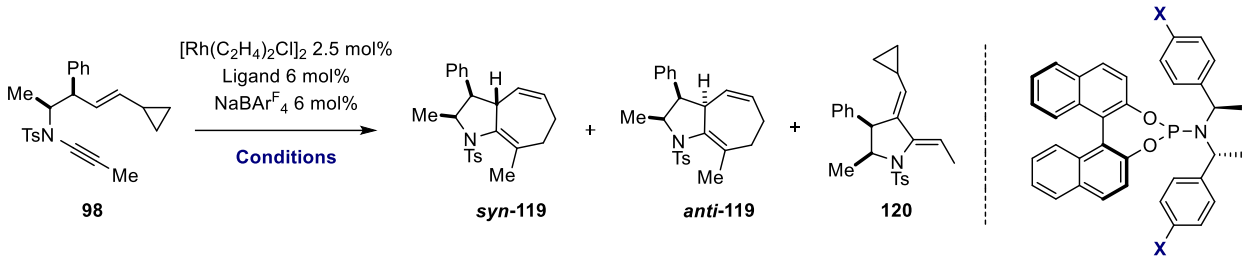
In other words, this transformation could be optimized by maximizing the rate difference between 'matched' and 'mismatched' reactions, which in theory, would enhance kinetic resolution whilst minimizing byproduct formation.



Scheme 30. Inherent substrate selectivity of *(R)*-**98**.

However, a crucial problem occurred when effect of temperature, electronic nature of ligands, and solvent was surveyed. When temperature was suppressed, byproduct **120** surprisingly overpowered *anti*-**119** and became the second dominating product (none at room temperature, 1:1 to *anti*-**119** at –5 °C; Table 3, Entry 1 and 2); when temperature was elevated, diastereoselectivity worsened to compensate for increased chemoselectivity (1:1.9 to *anti*-**119** at room temperature, none at 35 °C; Table 3, Entry 3 and 4). Electron poor **L3** gave better chemo- and diastereo-selectivity compared to the parent 'Feringa' ligand **L1** (*syn*-**119**:*anti*-**119** = 4:1 *vs.* 3:1, Table 3, Entry 1 and 3). Solvent did not have a major impact on selectivity, although dichloromethane again appeared to accelerate the reaction comparing to deuterated chloroform (79% *vs.* 40% at –10 °C; Table 3, Entry 2 and 6).

Table 3. Optimization for *syn*-**98** for [5+2] cycloisomerization.



Entry	Ligand	Solvent	Temperature/°C	Time/h	Conversion/%	Result (*syn*-119:*anti*-119:120)[a]
1[b]	X = F	$CDCl_3$	r.t.	1	>98	80:20:0
2[b]	X = F	$CDCl_3$	–10	12	40	33:2:5
3	X = H	CH_2Cl_2	r.t.	1	47	24:8:15
4	X = H	CH_2Cl_2	35	1	54	39:15:0
5	X = F	CH_2Cl_2	–5	12	76	44:12:20
6	X = F	CH_2Cl_2	–10	12	79	51:9:9
7	X = F	CH_2Cl_2	–20	12	50	33:7:10

[a] Determined by ^1H NMR; [b] Conducted in an NMR tube with $CDCl_3$ as solvent;

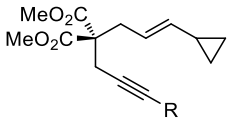
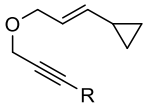
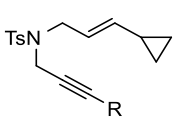
Unfortunately, attempts to isolate the three compounds from the crude product mixture proved unsuccessful, thus making it impossible to determine *ee* values. Considering the rather lengthy synthesis of starting material *syn*-**98** (10 steps) and its sub-optimal potential for kinetic resolution, we decided to move on to other substrates.

2.4 Expansion of Substrate Scope

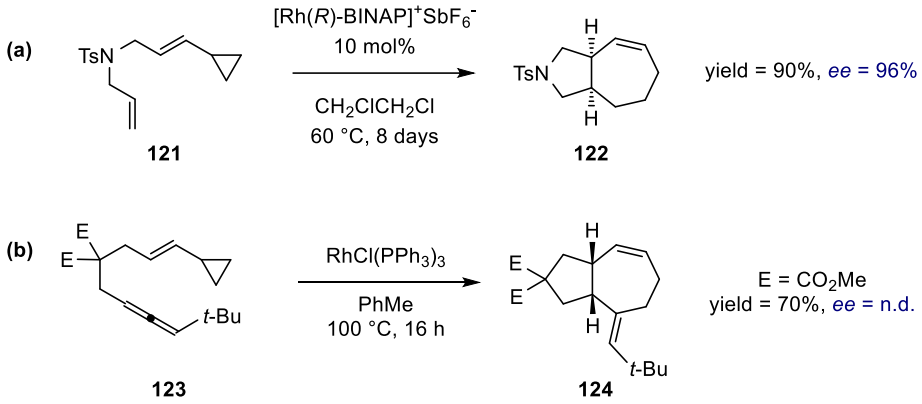
Having established a suitable catalytic system for ynamide vinylcyclopropane kinetic resolution, we next aimed to explore the kinetic resolution of other enynes. This could enable future application of this methodology to the enantioselective synthesis of various natural products or other target molecules.[42,51]

In the literature, there have only been a handful examples of transition metal-catalyzed intramolecular [5+2] cycloisomerizations. It is also perhaps unsurprising that substrate variation was rather limited because there are only two positions readily accessible for modification: the heteroatom on the five membered ring, and the alkynyl substituent (Table 4). Ethers (X = O),[3,33,159,160] sulfonamides (X = NTs),[11,17,19,34,160] and carbon tethers (X = $C(EWG)_2$) are among the most commonly reported due to their relative ease of preparation.[14,161]

Table 4. Examples of substrate variation in transition metal-catalyzed [5+2] cycloisomerization.

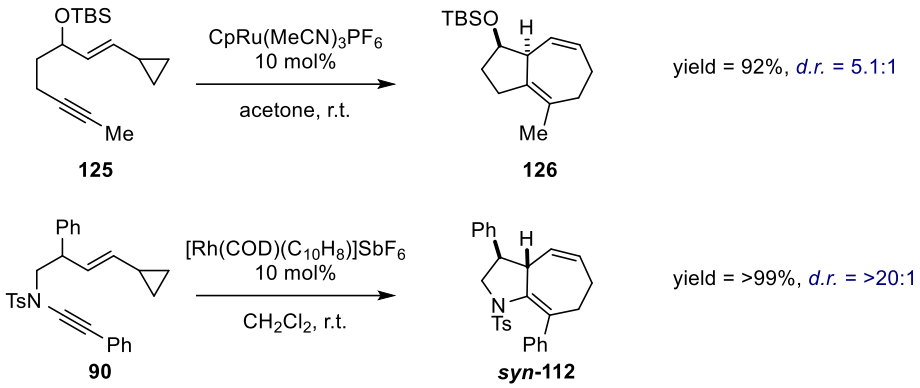
Position of Modification	Example	Substrate	Metal Catalyst	Results
X	X = $CEWG_2$		[Ru(COD)(cot)] $[(arene)Rh(COD)]SbF_6$	50-95% yield[14,152]
	X = O		Rh(BINAP) Ni-NHC	50-99% yield 22-95% *ee* (Rh catalyst)[33]
	X = NTs		Rh(BINAP) $[[Ir(dbcot)Cl]_2$ $[CpFe(CH_2CH_2)_2]Li$	37-89% yield 46-99% *ee* (Rh catalyst)[3,17,19]
R	R = H, Alkane, Arene, SiR_3		Varied	

Other types of substrate modification, although rare, has also been exploited and produced mixed results. In general, harsher reaction conditions were required to promote cycloisomerization on these more challenging substrates, and results were generally poorer due to additional substrate complexity. When the alkyne unit is replaced by a less electronegative, partially substituted alkene, prolonged reaction times and elevated temperatures become necessary. For example, it took 8 days under heating to convert dienyl sulfonamide **121** into its corresponding [5+2] adduct **122** under heated conditions, whereas the corresponding enynyl derivative underwent complete reaction within hours at room temperature (Scheme 31, Equation a).[7,33] Allenes as precursors for [5+2] cycloisomerization are even less commonly reported, which is likely because each substrate required fine-tuning for the reaction conditions, even with minor modification of their molecular structure.[42] A typical example of allene [5+2] cycloisomerization reported by Wender *et al.* is presented below (Scheme 31, Equation b).[42] In the same study, seven different reaction conditions varying in rhodium(I) catalyst, solvent, substrate concentration, and temperature were reported in order to obtain eleven successful examples. Needless to say, it seems extremely challenging to expand substrates bearing an allene motif.



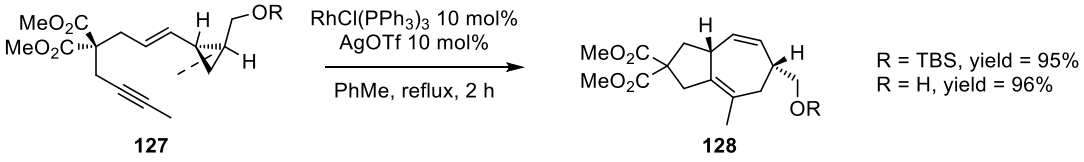
Scheme 31. Rhodium-catalyzed [5+2] cycloisomerization of allenes and dienes.

Another strategy to expand substrate scope was to explore additional substituents. Allylic and vinylcyclopropyl substituents are generally well tolerated: both the Trost group and our group have reported [5+2] cycloisomerization reactions using ruthenium(II) and rhodium(I) catalysts respectively with excellent diastereoselectivity (Scheme 32).[5,37]



Scheme 32. Examples of diastereoselective [5+2] cycloisomerization.

Similarly, substrates with substituents on the cyclopropane ring were investigated for regioselectivity. Wender *et al.* explored the effect of substitution on the cyclopropane ring on the regioselectivity of the ring-opening event using Wilkinson's catalyst (Scheme 33). It was found that regardless of stereochemistry or electronic properties of the ring substituent, cleavage of the less substituted *σ*-bond was always favoured to give the same regioisomer **128** with inverted diastereomeric configuration (*cis*-distributed **127** resulted in *trans*-distributed **128**, and *vice versa*).[162]



Scheme 33. Regioselectivity of [5+2] cycloisomerization.

On the other hand, little success has been demonstrated in more complicated molecules. Highly substituted alkenes **129, 130**,[9,37] *cis*-alkenes **131**,[4] and substrates set up for further ring expansion **132–134** have all failed using both ruthenium and rhodium catalysts (Figure 19).[32,163]

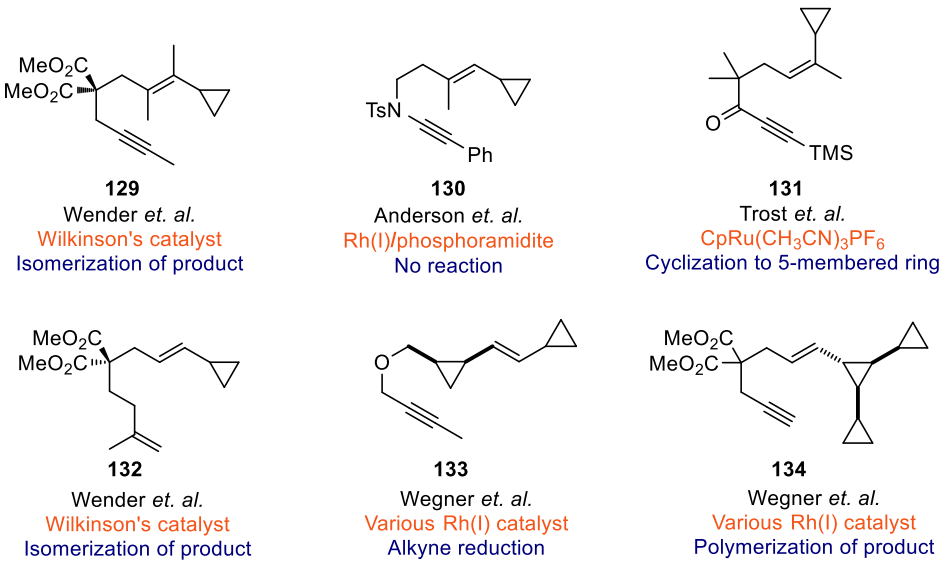


Figure 19. Failed substrates for [5+2] cycloisomerization in the literature.

2.4.1 Enyne Substrate Synthesis

A variety of both 'conventional' and 'unconventional' enyne substrates were identified as potential kinetic resolution substrates. The 'conventional' group included enynes and dienes substituted in the allylic position, whilst the 'unconventional' group consisted of propargylically substituted enynes, silyl tethered enynes, as well as substrates bearing a cyclobutane ring (Figure 20).

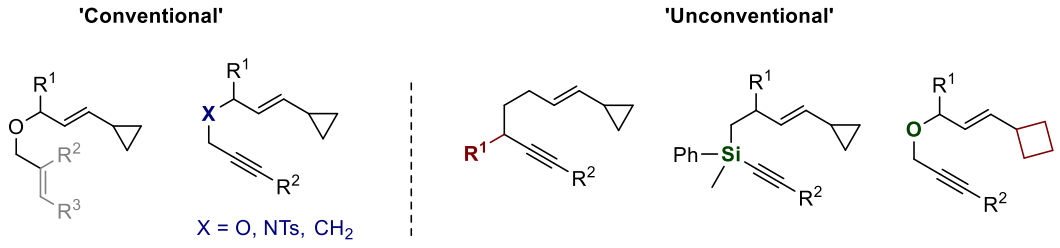
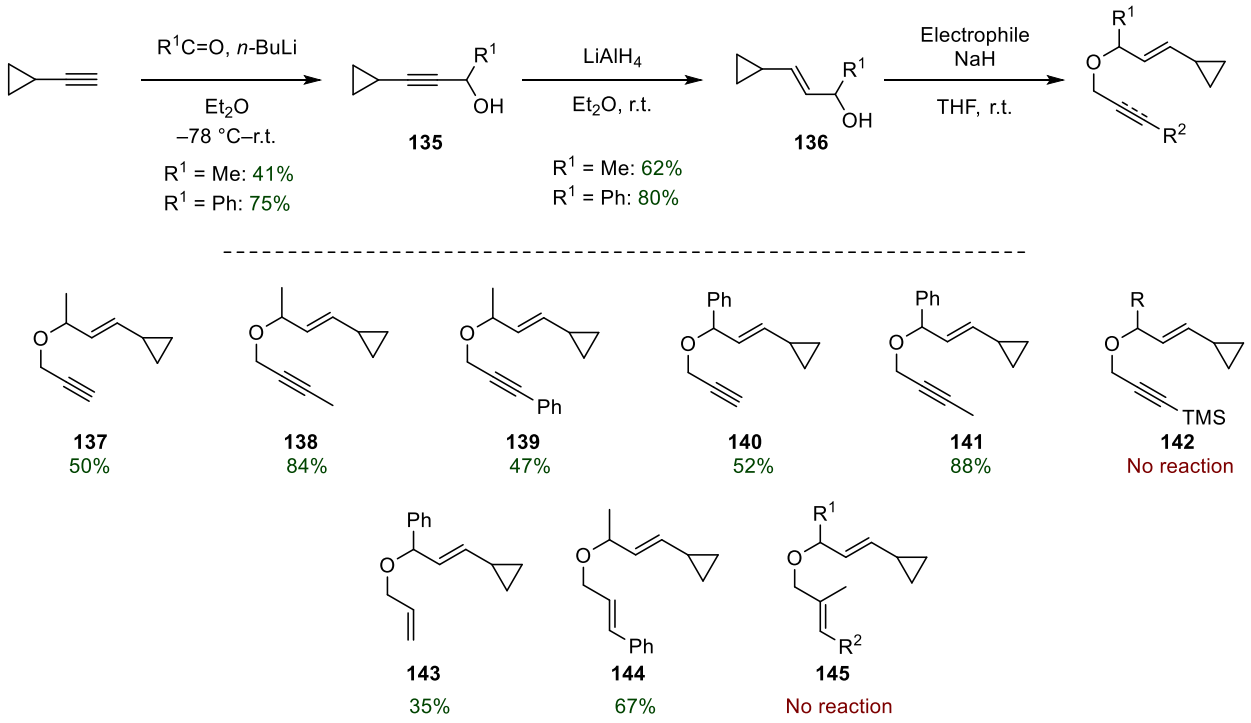


Figure 20. An overview of enyne substrates prepared.

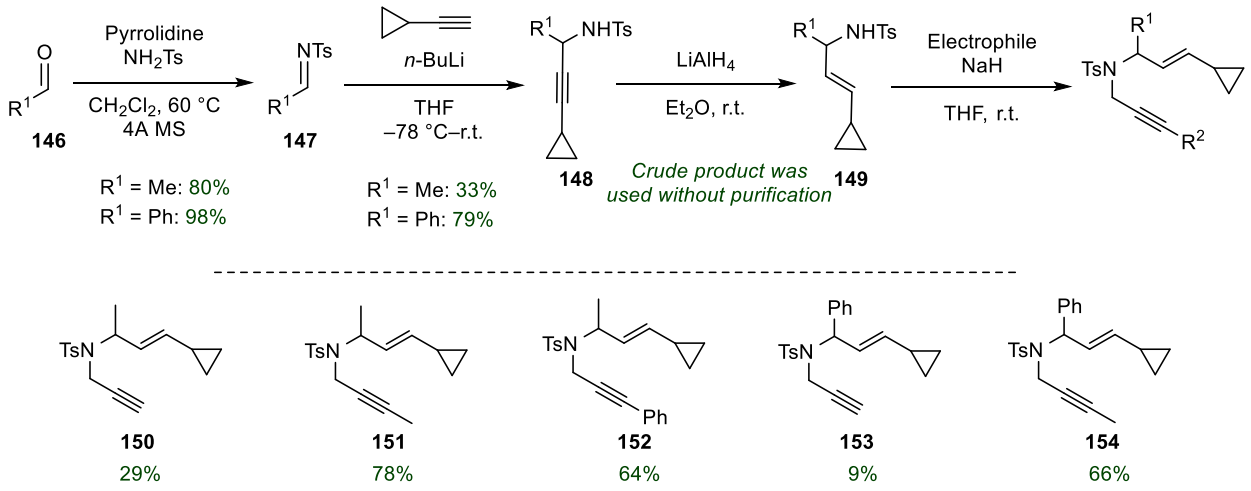
Vinylcyclopropyl ethers **137–145** were prepared according to the method of Trost *et al.* (Scheme 34).[4,152] Synthesis routes were fairly trivial and straight-forward: nucleophilic addition of commercially available ethynyl cyclopropane to various aldehydes (using *n*-butyllithium as base) gave substituted butynol **135** in moderate to high yield. Subsequent alkyne reduction with lithium aluminum hydride and Williamson ether synthesis with sodium hydride as base, gave seven vinylcyclopropyl ethers **137–144** in moderate to high yield (35-88%). Exceptions included substrates bearing a terminal trimethylsilane group (**142**), and tri-substituted dienes (**145**), which failed to react even under modified conditions (more reactive organohalides, stronger base, and elevated temperature).



Scheme 34. Preparation of vinylcyclopropyl ether substrates **137–145**.

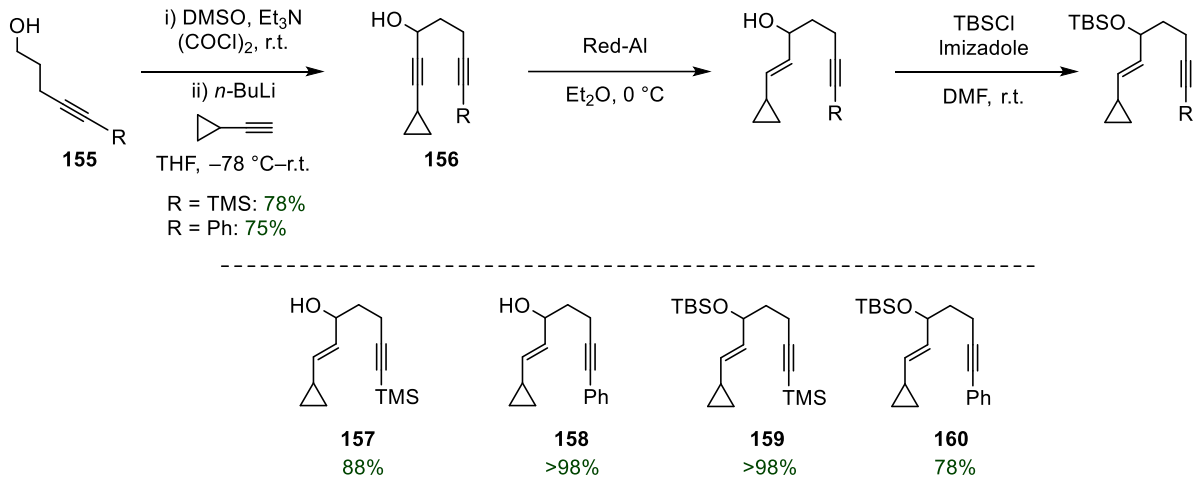
Similar strategies were exploited to obtain vinylcyclopropyl sulfonamides **150–154** (Scheme 35). Aldimine **147** was prepared from readily available aldehyde **146** using pyrrolidine as

aminocatalyst in excellent yield (80–98%).[164] The same procedures as above were performed subsequently to give five sulfonamides **150–154** with allylic substituents. Poor stability was observed in substrates with a terminal alkyne (**150** and **153**), which partially decomposed upon purification to give poor isolated yield (29% and 9% respectively).



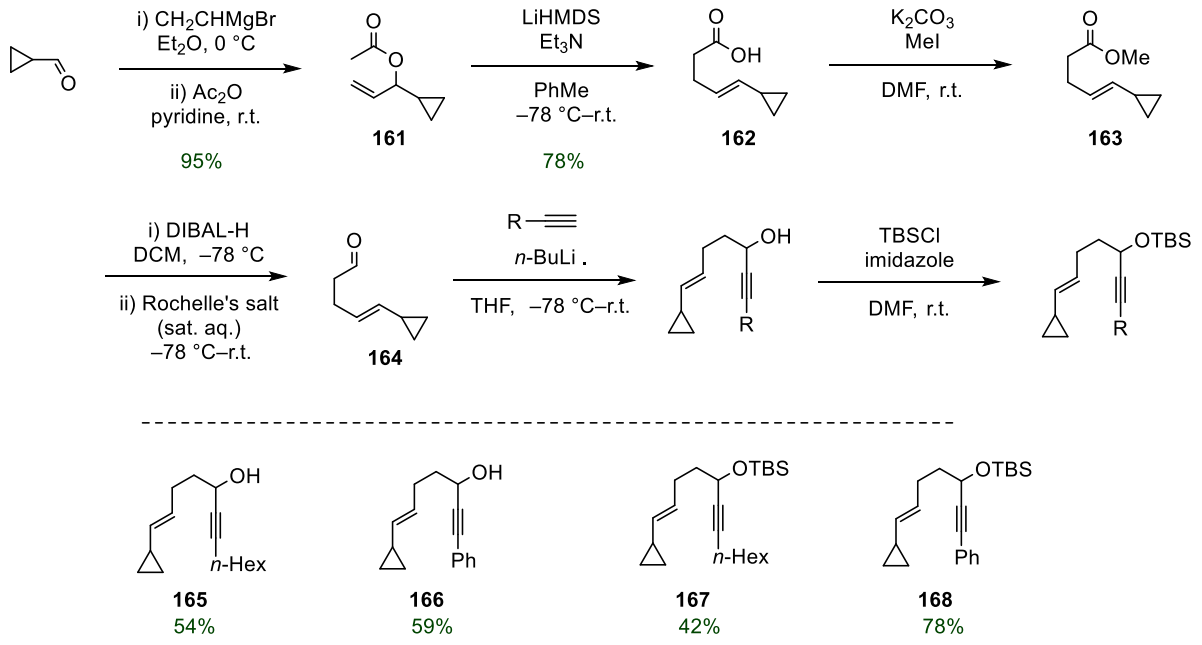
Scheme 35. Preparation of vinylcyclopropyl sulfonamide substrates **150–154**.

Carbon tethered enynes **157–160** were also prepared following Trost's procedure (Scheme 36).[14] Primary alcohol **155** was converted into 1,6-diyne **156** by Swern oxidation followed by nucleophilic addition to ethynyl cyclopropane in high yield. Selective alkyne reduction by Red-Al was then conducted carefully at 0 °C to obtain desired 1-en-6-yne compound **157** and **158**. A total reaction time of 2–14 days were required to reach completion of reaction, and it was necessary to use a cryostat to maintain stable low temperature. Any minor increase in loading of Red-Al (from 1.0 equivalents to 1.2 equivalents) or temperature elevation (0 °C to 5 °C) resulted in rapid over-reduction of the second triple bond, whose reactivity only differs slightly to the desired reduction site. Upon purification, free alcohol **157** and **158** could then be protected to enhance its stability under [5+2] conditions.



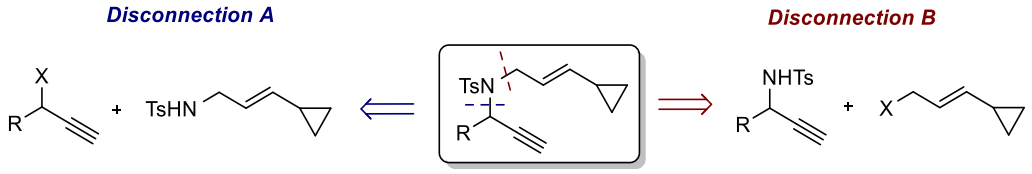
Scheme 36. Preparation of carbon tethered substrates **157–160**.

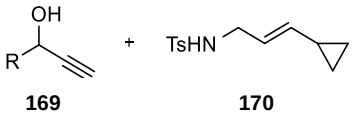
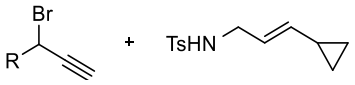
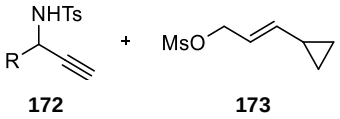
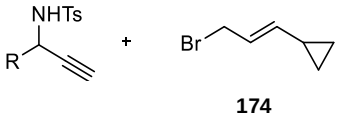
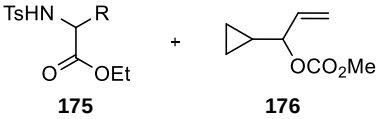
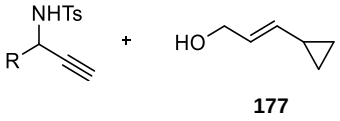
For the 'unconventional' substrates, we started with the simplest, carbon tethered enynes bearing a propargylic substituent. Enoic acid **162** was prepared according to the procedure from Anderson *et al.*,[37] which was then methylated and reduced to its corresponding aldehyde **164**. Addition of acetylenic nucleophiles gave substrates **165–168** in moderate to high yield (Scheme 37).



Scheme 37. Preparation of carbon tethered substrates **165–168**.

It turned out to be rather challenging to access propargylic-substituted sulfonamides. Two disconnection strategies were explored, both of which relied on amine coupling or alkylation reactions as the key step (Scheme 38). Secondary amine **170** from disconnection strategy A could be prepared as reported in literature in two steps, whilst its reaction partner **169** was commercially available. Unfortunately, no reaction was observed under Mitsunobu reaction conditions (X = OH). A more reactive coupling partner **171** (X = Br) was also prepared *in situ* for amine alkylation, which also failed to deliver product.

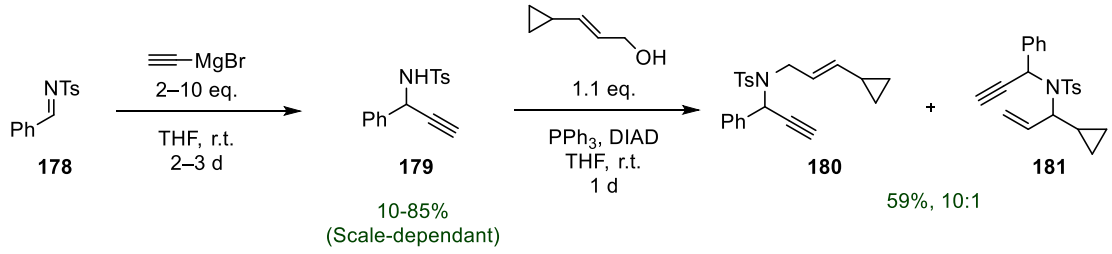


Disconnection Type	Reaction Partners[a]	Conditions	Results
A	 **169** + **170**	Mitsunobu reaction	No reaction
	 **171**	Amine alkylation	Trace product formed; inseparable from large amount of impurities
B	 **172** + **173**	Amine alkylation	Decomposition of starting material
	 **174**	Amine alkylation	Cyclopropane ring opening
	 **175** + **176**	Palladium-catalyzed N-alkylation	Wrong regioisomer
	 **177**	Modified Mitsunobu reaction	Mixture of regioisomers (up to 10:1)

[a] All organohalide compounds were prepared *in situ* from corresponding alcohol.

Scheme 38. Attempts to synthesize sulfonamides.

Disconnection strategy B offered little success. Alkylation partner **173** and **174** could be prepared *in situ* from primary alcohol **177**, both of which were extremely unstable and needed to be handled at –78 °C. Unfortunately, methanesulfonate **173** decomposed within minutes upon mixing with its coupling partner, and bromide **174** underwent cyclopropane ring opening without further reaction. Palladium-catalyzed *N*-alkylation and Mitsunobu reaction provided more promising results, but regioselectivity became a major issue: coupling between **175** and **176** only gave the wrong regioisomer, whereas Mitsunobu reaction between **172** and **177** could be modified to enhance regioselectivity (Scheme 39). It has been reported in the literature that regioselectivity of Mitsunobu reactions could be improved by modifying the oxidizing agent, temperature, or additives such as catalytic palladium(0).[165,166] Unfortunately, in our case, little improvement was made and a 10:1 mixture of desired: undesired regioisomers (**180**:**181**) were obtained after optimization in 59% yield.

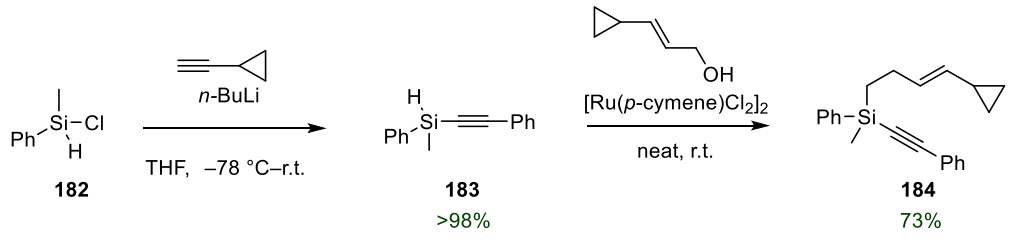


Scheme 39. Regioselectivity of sulfonamide **180**.

Due to the inefficiency of the synthetic route and the great difficulty in isolating pure regioisomers, no further attempt was made in the preparation of propargylic substituted sulfonamide **180**.

On the other hand, the preparation of silyl tethered substrate **184** was relatively effortless (Scheme 40). Nucleophilic addition of ethynyl cyclopropane to commercially available chlorohydrosilane

182 gave ethynylsilane intermediate **183** in quantitative yield. Ruthenium-catalyzed alkynylsilyl ether formation as developed by Lee *et al.* gave the desired substrate **184** in high yield.[167]

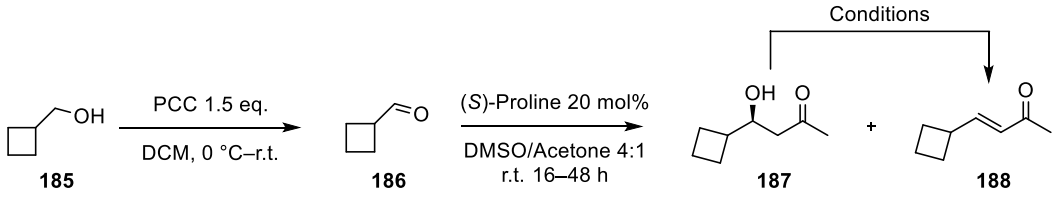


Scheme 40. Preparation of silyl ether substrate **184**.

Last but not least, substrate **191** was synthesized with a vinylcyclobutane substituent. Cyclobutanecarbaldehyde **186** was prepared by oxidation using pyridinium chlorochromate (PCC) in dichloromethane. Spiga *et al.* reported exclusive formation of enone **188** as the only product during proline catalyzed aldol reaction between **186** and acetone, which turned out to be irreproducible in our laboratory.[168] A mixture of aldol product **187** and enone **188** was always obtained, despite variation of proline loading, solvent ratio and dryness. This was possibly due to water content from dichloromethane in previous step, as it was impractical to isolate volatile compound **186** in its solvent-free form.

Attempts to convert aldol product **187** into **188** were also conducted, including re-subjecting the mixture into original conditions for prolonged time (Table 5, Entry 2), dehydration under basic (Table 5, Entry 1, 5), Lewis acid-catalyzed conditions (Table 5, Entry 3), as well as Martin-sulfurane dehydration (Table 5, Entry 4). Unfortunately, no product formation was observed in any of the above conditions, and the presence of acid-sensitive cyclobutane ring limited choice of available conditions. Nevertheless, the desired enone product **188** could be isolated by column chromatography in 20% yield.

Table 5. Attempts to convert aldol product **187** into enone product **188**.



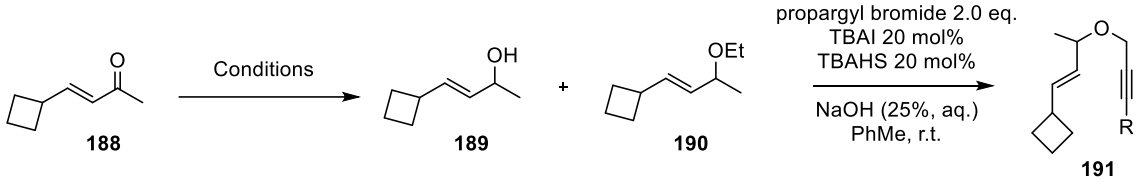
Entry	Condition	Result
1	Ac_2O, DMAP, Et_3N, DBU	Decomposition
2	10 mol% Proline, r.t.–reflux	Decomposition
3	$CeCl_3$, NaI, MeCN, reflux	Decomposition
4	Martin-sulfurane, DCM, r.t.–reflux	No reaction
5	MsCl, Et_3N, DCM, r.t.–reflux	No reaction

With enone **188** in hand, we then aimed to reduce it to secondary alcohol **189**, which could then be coupled with propargylic bromide for etherification. Initial screening of reducing agents offered little success: sodium borohydride resulted in unwanted solvolysis product **190** as 1:1 mixture with the desired product (Table 6, Entry 1); lithium aluminum hydride resulted in polymerization of product (Table 6, Entry 2), whilst diisobutylaluminium hydride (DIBAL-H) decomposed the starting material completely (Table 6, Entry 3). From TLC analysis, it was likely that decomposition took place during quenching instead of the reaction itself; therefore, same reaction was repeated using Fieser work-up, or so called 'the Magic Formula'. Pleasingly, alcohol **189** was isolated as the exclusive product in excellent yield (89%).

Finally, [5+2] precursor **191** was assembled from etherification between **189** and propargylic bromide. To our surprise, Williamson etherification conditions only resulted in rapid

decomposition of starting materials. A variety of bases ranging from tertiary amines to inorganic bases such as *n*-butyllithium, sodium hydride and cesium carbonate all failed to deliver product. Milder conditions using tetrabutylammonium iodide (TBAI) and tetrabutylammonium hydrogensulfate (TBAHS) as phase transfer catalyst (PTC) were tested, which could result in a more controlled reaction.[169,170] Indeed, these conditions yielded the desired enyne **191** in moderate yield (R = H, 59%).

Table 6. Conditions for reduction reaction of **188**.



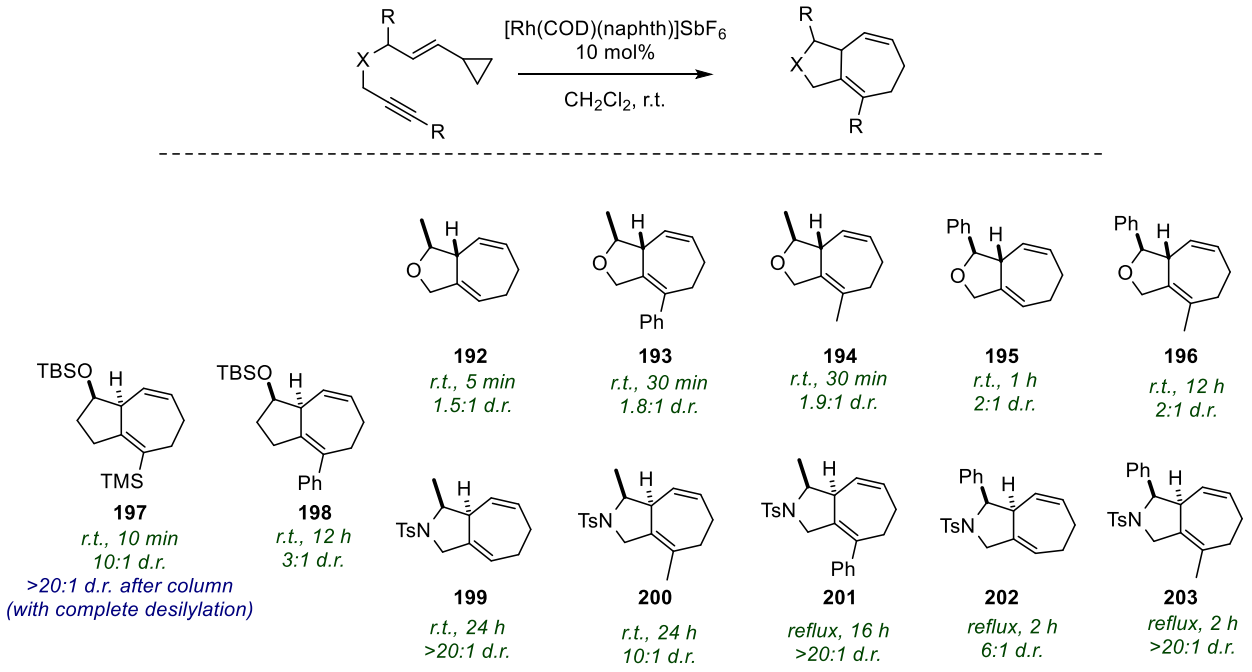
188 **189** **190** **191**

Entry	Condition	Result
1	$NaBH_4$, EtOH	**189:190** = 1:1
2	$LiAlH_4$, Et_2O or THF	Polymerization
3	DIBAL-H, DCM, Rochelle's salt	Decomposition
4	DIBAL-H, DCM, Fieser work-up	**189** only

Unfortunately, the precious ether slowly decomposed into a complex mixture of compounds after being left in a sealed vial over the weekend, thus no further attempts were made to synthesize **191**.

2.4.2 Enyne Substrate Survey

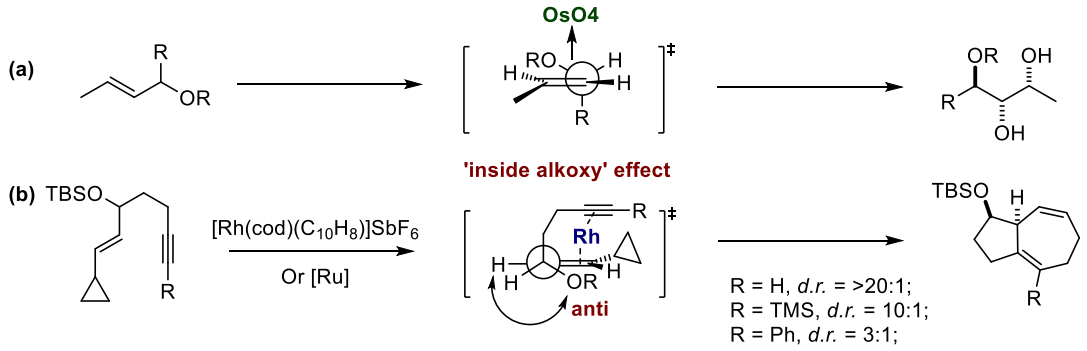
Investigation of alkyne vinylcyclopropane resolution began by testing the inherent substrate stereocontrol using rhodium(I) complex [Rh(COD)(naphth)]SbF_6, which is commonly used as a cheap and air-stable alternative for [5+2] cycloisomerization reactions (Scheme 41).[171] Intriguingly, most substrates showed a strong preference for the formation of *anti*-diastereomer (**197**–**203**), which is in contrast to most ynamides, which form exclusively the *syn*-diastereomer under the same conditions.[37,172] Ethers, on the other hand, yielded the *syn*-diastereomer as the major product, albeit with significantly poorer substrate stereocontrol comparing to other substrates (maximum 2:1 *d.r.*, **192**–**196**).



Scheme 41. Inherent substrate control of alkyne vinylcyclopropanes.

The preference for the *anti*-diastereomer from TBS ether-protected enynes **197** and **198** could be explained by the 'inside-alkoxy' effect, where the presence of an allylic oxygen provides strong diastereoselectivity towards the *anti*-product.[36,173,174] The 'inside-alkoxy' model was firstly

proposed by Houk *et al.* in 1986 to describe the stereocontrol effect during osmium tetroxide mediated dihydroxylation, when staggered transition states forced allylic oxygen to avoid 'outside' position due to repulsive electrostatic interactions with the incoming catalyst and give the *anti*-diastereomer as result (Scheme 42, Equation a).[36] Trost *et al.* observed the same effect and used it to rationalize the high level of substrate stereocontrol in [5+2] cycloisomerizations (Scheme 42, Equation b).[5] From our result, it was clear that such effect (or an allylic oxygen atom) was not a prerequisite for high stereoselectivity, providing further feasibility of substrate scope expansion.



Scheme 42. Rationalization of the 'inside alkoxy' effect.

Not all substrates were tolerated the reaction conditions, including **157** and **158**, with a hydroxyl group present; dienes **143** and **144**; and **165**–**168** bearing a propargylic substituent (Figure 21).

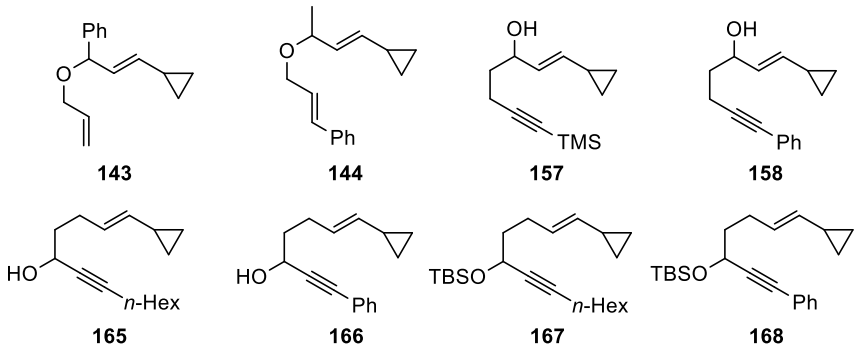
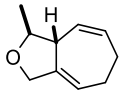
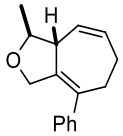
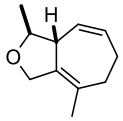
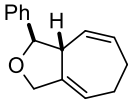
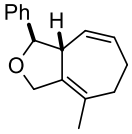
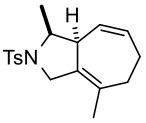
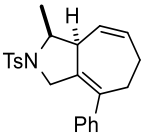


Figure 21. Failed substrate in substrate stereocontrol screening.

With a number of vinylcyclopropanes displaying excellent substrate stereocontrol in hand, we set about examining their potential for kinetic resolution. Five substrates (**193–196**, **200**) displayed noticeable rate difference between formation of the *syn*- and *anti*-diastereomers in kinetic profile experiments as monitored by ^{1}H NMR (Table 7).

Table 7. Optimization of novel enyne substrates.

Substrate	Results using [Rh(COD)(naphth)]SbF$_6$	^{1}H NMR kinetic profile[a]	Bench results[b]
 **192**	r.t., 5 min 1.5:1 *d.r.* (*syn:anti*)	No reaction in $CDCl_3$ up to 65 °C	Poor resolution/unstable product
 **193**	r.t., 30 min 1.8:1 *d.r.* (*syn:anti*)	$CDCl_3$, r.t., 1 h >98% conversion 5:1 *d.r.* (*syn:anti*)	CH_2Cl_2, 0 °C, 30 min 40% conversion >20:1 *d.r.* (*syn:anti*) >99% *ee*
 **194**	r.t., 30 min 1.9:1 *d.r.* (*syn:anti*)	$CDCl_3$, 0 °C, 1 h >98% conversion 3:1 *d.r.* (*syn:anti*)	CH_2Cl_2, –5 °C, 1 h 49% conversion >20:1 *d.r.* (*syn:anti*) >99% *ee*
 **195**	r.t., 1 h 2:1 *d.r.* (*syn:anti*)	No reaction in $CDCl_3$ up to 65 °C	CH_2Cl_2, 45 °C, 2-3 d 29% conversion >20:1 *d.r.* (*syn:anti*) 62% *ee*
 **196**	r.t., 12 h 2:1 *d.r.* (*syn:anti*)	$CDCl_3$, r.t., <1 min >98% conversion 1.5:1 *d.r.* (*syn:anti*)	$CDCl_3$, r.t., 6-12 h 48% conversion >20:1 *d.r.* (*syn:anti*) >99% *ee*
 **200**	r.t., 24 h 10:1 *d.r.* (*anti:syn*)	$CDCl_3$, r.t., 30 min 32% conversion 5:1 *d.r.* (*anti:syn*)	CH_2Cl_2, 0 °C, 4 h 36% conversion 10:1 *d.r.* (*syn:anti*) 62% ee
 **201**	reflux, 16 h >20:1 *d.r.* (*anti:syn*)	$CDCl_3$, r.t., 1 h 34% conversion 1.5:1 *d.r.* (*anti:syn*)	Poor resolution/unstable product

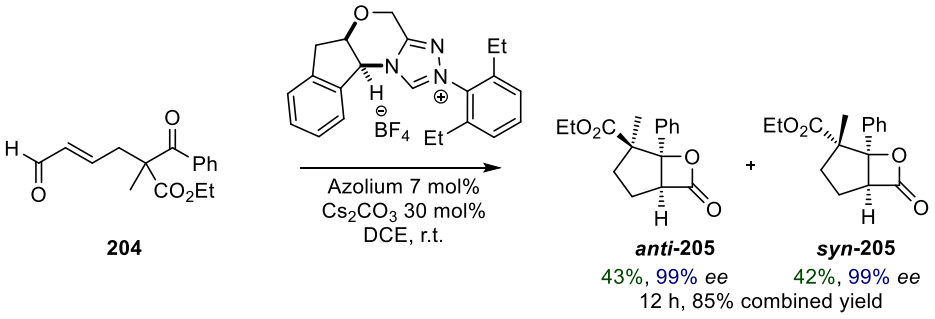
[a] Conversion monitored by ^{1}H VT NMR and calculated with nitromethane as internal standatd; [b] Isolated yield; *ee* determined by HPLC.

Interestingly, our rhodium(I)/phosphoramidite catalyst system demonstrated an extremely high level of stereoselectivity that overpowered the inherent stereo-preference of the substrates. For example, sulfonamides **200** and **201** switched from predominantly forming the *anti*-diastereomer in an achiral setting to predominantly forming *syn*-diastereomer under the influence of our catalyst. Due to the confliction between substrate's (*anti*-diastereomer) and catalyst's (*syn*-diastereomer) stereocontrol, decreased overall selectivity was observed. **200** could reach 10:1 *d.r.* at 36% conversion, and *ee* of the *syn*-diastereomer was only 62% (*c.f.* 95-99% in other substrates that achieved kinetic resolution), whilst **201** failed to undergo resolution in a bench setup.

On the other hand, rapid resolution was achieved with vinylcyclopropane ethers. Similar to reactions with ynamides, a low temperature between –5 to 0 °C was required to avoid over-reaction. The heterocyclic products **193–196** were obtained in under 30 minutes to a few hours, in high conversion (40–49%), and with exceptional selectivity (>20:1 *d.r.*, >99% *ee*) in most cases. Exceptions included terminal alkyne **137** and **140**, which did not react in deuterated chloroform even when heated to 65 °C. Phenyl substituted **140** (product: **195**) only yielded 29% conversion after being heated in dichloromethane for 3 days, with >20:1 *d.r.* and 62% *ee*, whilst methyl substituted **137** (product: **192**) failed to show resolution under optimized conditions. Another exception was enyne **141** (product: **196**), which demonstrated excellent level of resolution in deuterated chloroform (6–12 hours, 48% conversion, >20:1 *d.r.*, >99% *ee*) but could not be reproduced in common laboratory solvents such as dichloromethane, 1,2-dichloroethane, or chloroform.

2.5 Diastereodivergent reactions

One of the major challenges in medicinal and synthetic chemistry is the accessibility to the precise binding sites defined by natural products or known drugs.[175] The stereochemistry of small molecules and building blocks plays a critical role because even slight alternation could influence the physiological and biological activity of the molecule.[176] Although various strategies have been extensively investigated to control absolute and relative stereochemistry, it is not always straightforward to alter both at the same time, due to the inherent preference of forming one diastereomer in many reactions.[177] One of the recent advances is *divergent synthesis*, where efficiency of reaction could be improved by synthesizing a small library of chemical compounds at the same time. This is usually achieved by modifying solvents, additives, substrates, or catalysts.[178,179] For example, Cheong *et al.* reported the formation of *β*-lactones **205** using *N*-heterocyclic carbene catalyst, both in excellent yield and *ee* (Scheme 43).[180]



Scheme 43. Divergent synthesis of *β*-lactones reported by Cheong *et al.*[177]

With our catalyst system, certain substrates exhibited no difference in kinetic profile between reaction of the 'matched' and 'mismatched' reactions. For example, vinylcyclopropane **168**

featuring an allylic silyl ether was observed to give products *syn*-**198** and *anti*-**198** at equivalent rates, despite variation in temperature or electronic property of ligands (Figure 22).

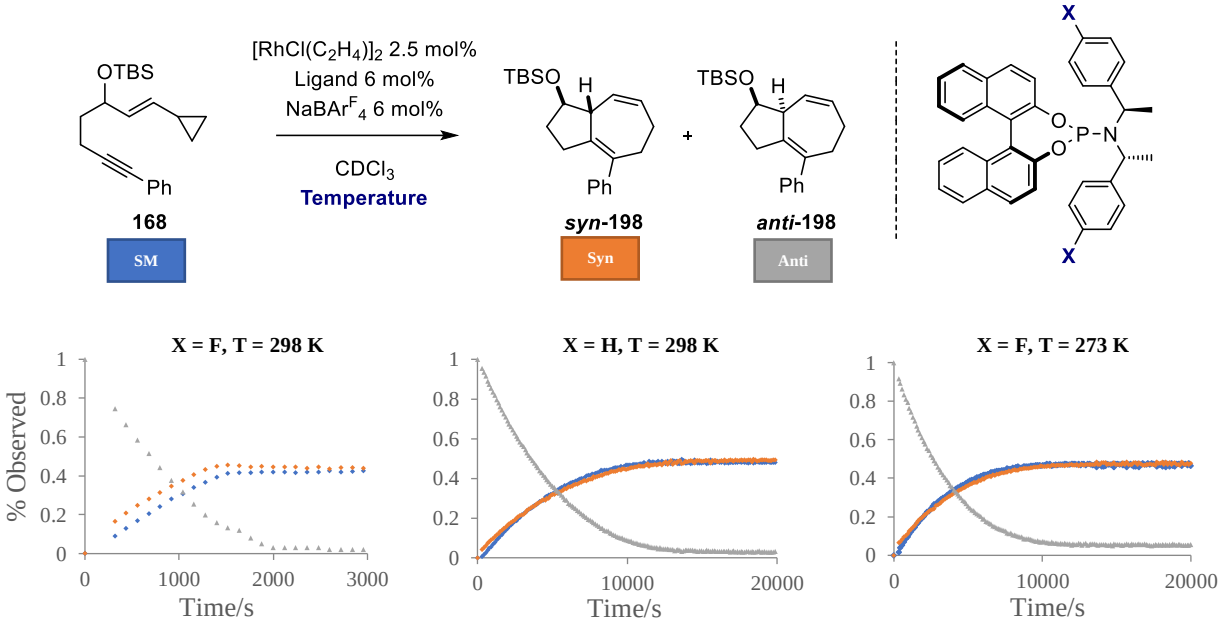
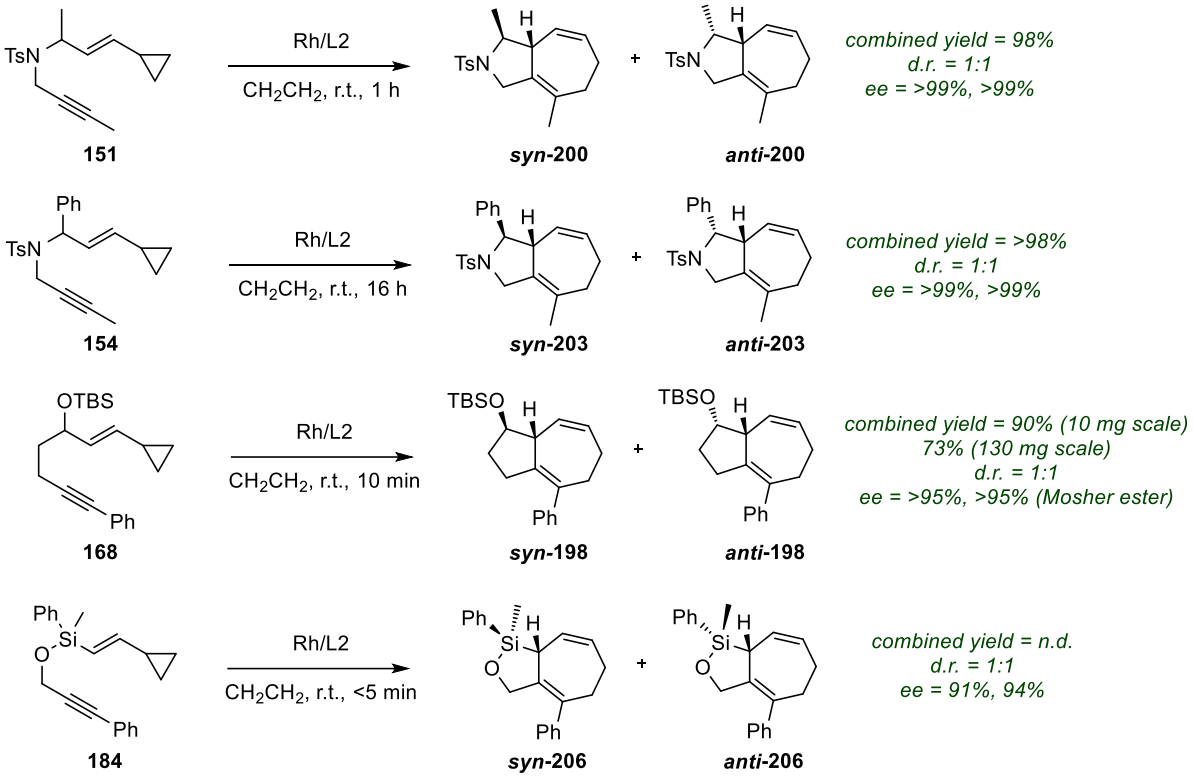


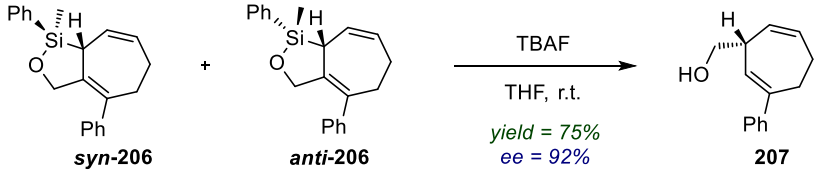
Figure 22. Kinetic profile of vinylcyclopropane **168** under different conditions.

Pleasingly, the two diastereomeric products *syn*-**198** and *anti*-**198** (1:1 *d.r.*) could be isolated separately with high enantiopurity, indicating that a diastereodivergent resolution had instead taken place. This switch in the mode of resolution was not limited to carbon-tethered substrates: sulfonamide **151**, **154** and alkynyl silyl ether **184** also underwent highly selective diastereodivergent resolution, delivering the corresponding diastereomers in excellent *ee* (Scheme 44). Notably, this represents the first example of resolution of a racemic silane *via* cycloisomerization chemistry.



Scheme 44. Diastereodivergent reactions using our catalyst system.

Desilylation of the somewhat unstable product mixture *syn*-**206** and *anti*-**206** (1:1) afforded the enantioenriched 7-membered ring **207** (75% yield over two steps, 92% *ee*, Scheme 45). This two step sequence overall corresponds to a formal asymmetric intermolecular [5+2] cycloisomerization, a challenge that has thus far eluded the field but is here rendered possible *via* a temporary silicon tether.



Scheme 45. Desilylation of mixture *syn*-**206** and *anti*-**206**.

Intrigued to understand more of the basis for this mechanistic dichotomy, we targeted a theoretical approach to understanding the possible reaction pathways. Collaborating with Dr. Alexandra Dürr from the Anderson group, DFT calculations are currently carried out based on the vinylcyclopropane pathway.

2.6 Conclusion

We have developed a highly efficient and selective catalyst system for kinetic resolution in [5+2] cycloisomerizations. This system proved successful not only for ynamides, but also a broad range of other enyne substrates, offering excellent diastereo- and enantio-selectivity.

In the process of optimization, we discovered an intriguing effect of substrate on the mechanism of the reaction. Whilst the vast majority of substrates underwent kinetic resolution, a few diastereodivergent resolutions was also observed, including the first example of resolution of a racemic silane *via* cycloisomerization chemistry.

The ultimate test for any synthetic methodology is arguably its application to complex molecule synthesis. Therefore, we took the challenge further by applying our methodology to natural product total synthesis (Chapter 3).

3. Formal Synthesis of (+)-Dictamnol

The work in the previous chapter had demonstrated the power of the rhodium/phosphoramidite system in achieving kinetic resolution in [5+2] cycloisomerizations, with exceptional efficiency, selectivity, and versatility. In order to further explore this methodology, we aimed to apply it in natural product synthesis.

3.1 Introduction

Soon after the first example of enantioselective transition metal-catalyzed [5+2 cycloisomerization, this chemistry was exploited in total synthesis since 1999.[42] Its application on a number of occasions in this context has proved successful, from small terpenoid molecules such as aphanamol I and (+)-dictamnol,[42,50,57] to complex structures such as (-)-pseudolaric acid B (Figure 23).[41]

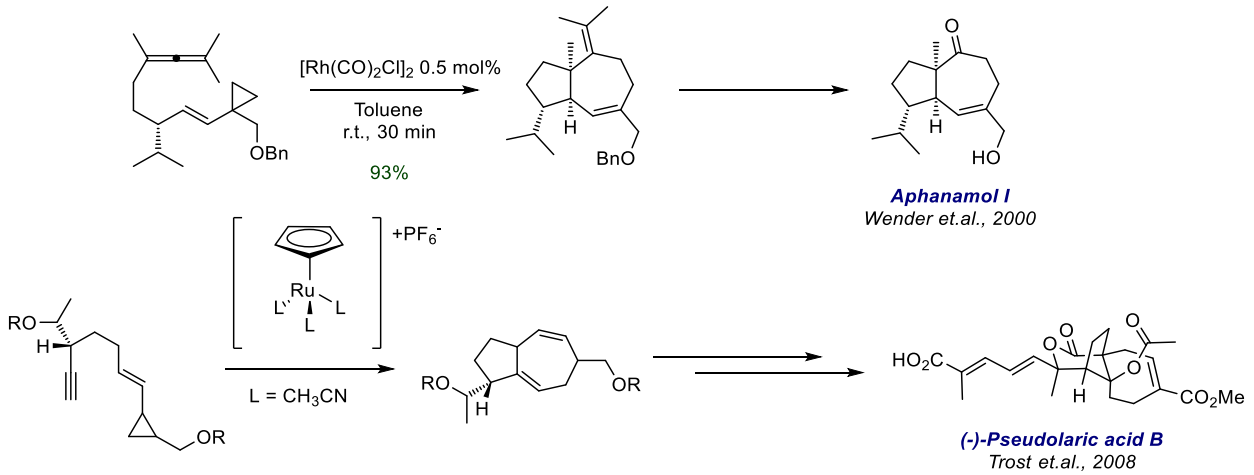
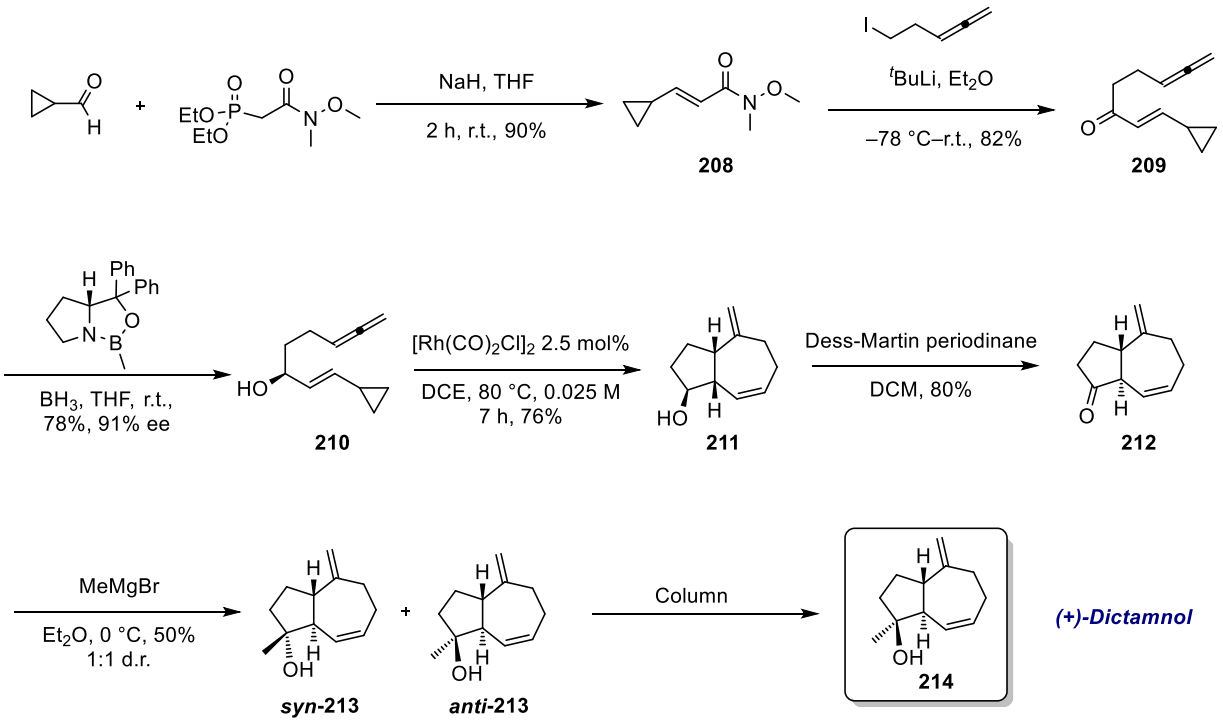


Figure 23. Examples of [5+2] cycloisomerization in natural product synthesis.[41,42]

We selected (+)-dictamnol as a target, a trinorguaiane sesquiterpene isolated from the roots of *Dictamnus dascarpus TURCZ.*[49,181] Dictamnol was identified as one of the major components in Chinese medicine Bai Xian Pi, which has demonstrated *in vitro* anti-cancer.[182,183] It was considered a suitable target structure, as this molecule had already been addressed by the Wender group *via* [5+2] cycloaddition using an enantioenriched precursor **210** (Scheme 46).[42]



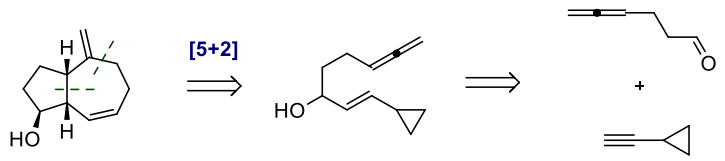
Scheme 46. Wender's asymmetric synthesis of (+)-dictamnol.

Despite being synthetically successful with moderate yield, there were a few drawbacks to this work:

1. Use of *tert*-butyllithium, an extremely pyrophoric compound was necessary when converting Weinreb amide **208** into ketone **209**;
2. Enantioselectivity solely relied on the effectiveness of the following CBS reduction into alcohol **210**;

3. A 1:1 mixture of diastereomers *syn*-**213** and *anti*-**213** were formed during Grignard addition of ketone **212**, which required further separation by running a flash column chromatography manually, after which half of the material was wasted, whilst the desired product (+)-dictamnol was obtained in only 8.7% overall yield in seven steps.

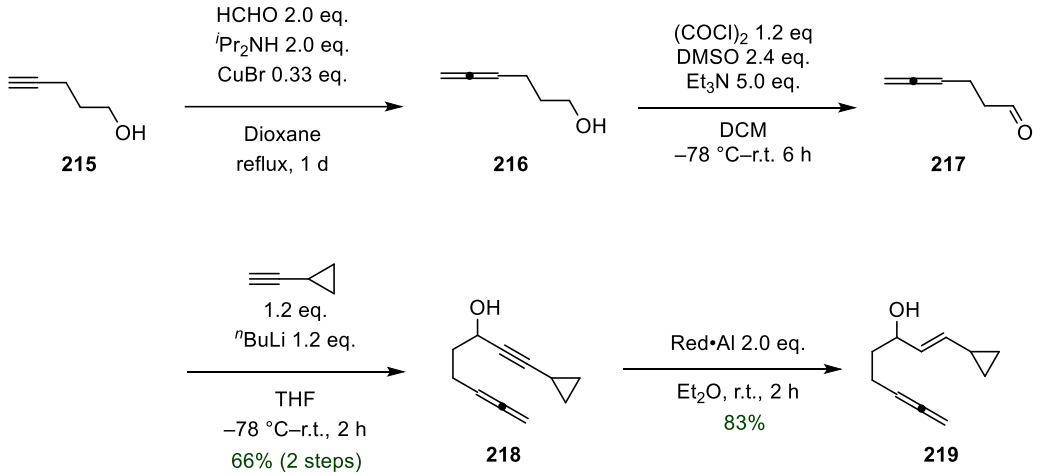
In order to develop an efficient asymmetric synthetic route with mild conditions to (+)-dictamnol, we designed the following strategy, in which dictamnol not only provided an opportunity to test the application of [5+2] kinetic resolution in total synthesis, but also further challenged the catalyst by requiring resolution of an untested substrate – an allene vinylcyclopropane (Scheme 47).



Scheme 47. Our retrosynthesis strategy for (+)-dictamnol.

3.2 Asymmetric Synthesis of (+)-Dictamnol

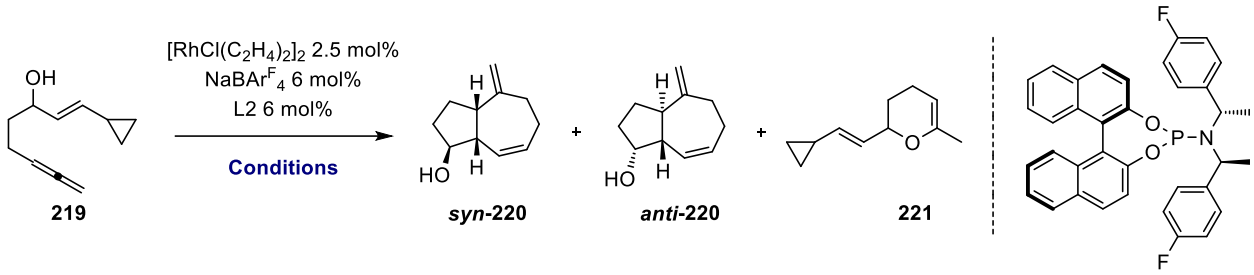
The synthesis began with allenyl aldehyde **217**, which was prepared in two steps from pent-4-yn-1-ol by the Heck alkynylation (copper-Free Sonogashira coupling) developed by Buchwald *et al.*, followed by Swern oxidation in moderate yield (66% over 2 steps).[184,185] Addition of cyclopropyl acetylene to **217**, followed by stereoselective reduction by Red-Al, afforded allylic alcohol **219** as the precursor for kinetic resolution (Scheme 48).



Scheme 48. Preparation of [5+2] precursor **219**.

Exposure of precursor **219** to the rhodium(I)/phosphoramidite catalyst system revealed this allene to be a challenging substrate (Table 8). When Wender's conditions were applied, a mixture of three compounds were obtained: two diastereomers of [5+2] cycloadduct *syn*-**220** and *anti*-**220**, and dihydropyran **221** in 1:1:10 ratio (Table 8, Entry 1), while [Rh(COD)(naphth)]SbF_6 only afforded trace product (Table 8, Entry 2). Luckily, with our catalyst system ($[RhCl(C_2H_4)_2]_2$/phosphoramidite), formation of the byproduct **221** could be suppressed in most cases (Table 8, Entry 2–6).

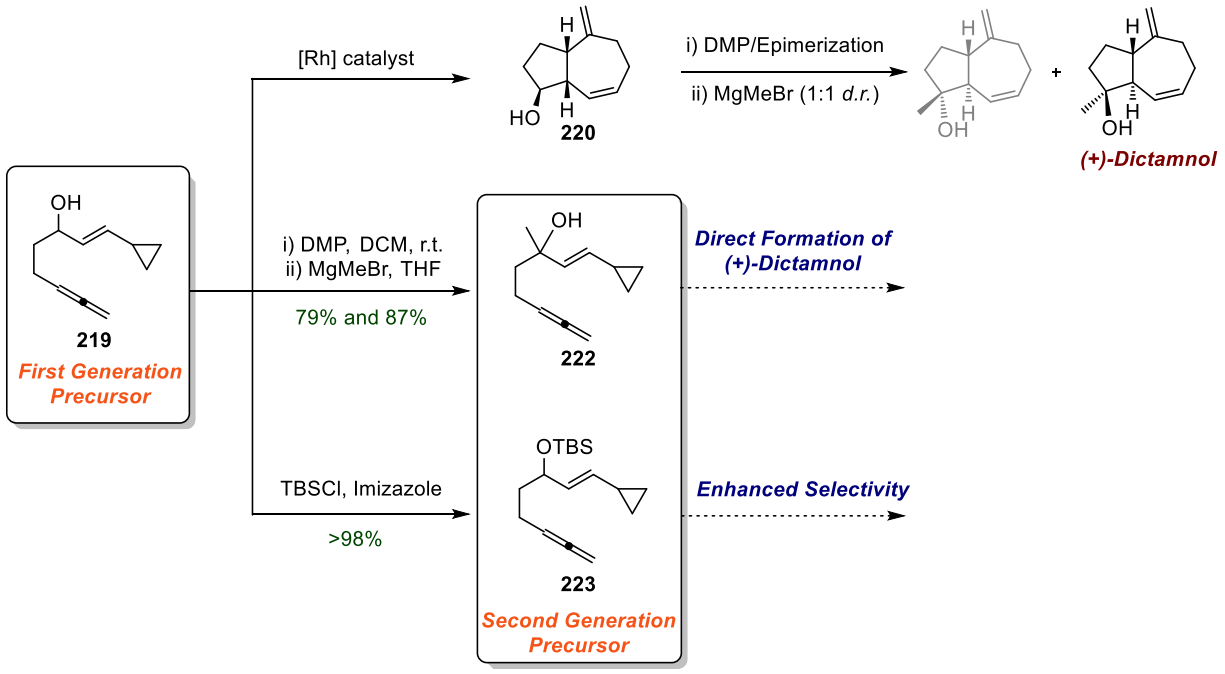
Table 8. Optimization of [5+2] cycloisomerization step.



Entry	Catalyst	Condition	Time	Results[a]
1	$[Rh(CO)_2Cl]_2$ 2.5–5 mol%	DCE or DCM (0.025–0.1 M), 80 ˚C	8–16 h	70%, *syn*-**220**:*anti*-**220**:**221** = 1:1:10
2	$[Rh(COD)(naphth)]SbF_6$ 2.5–5 mol%	DCE (0.025 M), 80 ˚C	16 h	Trace
3		DCM (0.05 M), 80 ˚C	8–16 h	52%, *syn*-**220**:*anti*-**220**:**221** = 1:0.8:trace
4		DCM (0.025–0.01 M), 80 ˚C		40-52% *syn*-**220**:*anti*-**220**:**221** = 1:0.8:trace
5		DCM (0.05 M) w*ith base wash*, 80 ˚C		60% *syn*-**220**:*anti*-**220**:**221** = 1:0.8:trace
6	$[RhCl(C_2H_4)_2]_2$/L2 2.5 mol%	DCE (0.05 M), 80 ˚C	8 h	Trace
7		DCE or DCM (0.05 M), 40 ˚C		No reaction
8		Toluene or TCM (0.05 M), 80 ˚C		Exclusively **221**
9		TCE or Acetonitrile (0.05 M), 80 ˚C		No reaction or decomposition

[a] Product ratio monitored by ^{1}H NMR in the crude mixture, because the two diastereomers *syn*-**220** and *anti*-**220** were only partially separatable; Isolated yield measured by product mass.

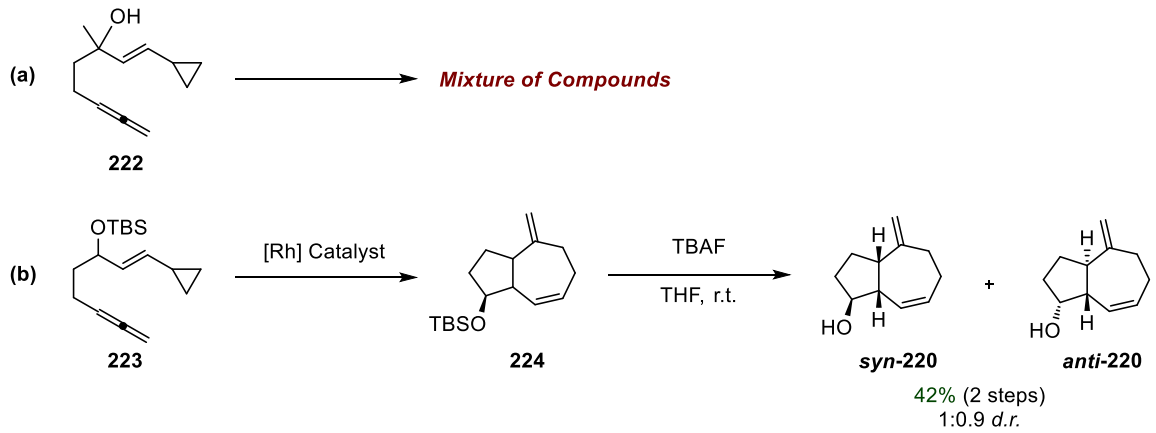
Heating to 80 °C was required to undergo reaction (Table 8, Entry 3–6). In addition, pre washing of the reactions' vials using saturated potassium hydroxide solution improved both yield and cleanness of the reaction (Table 8, Entry 3 and 5), which was consistent with Wender's observation.[42] Unfortunately, little room was available for further optimization: catalyst loading (Table 8, Entry 1), substrate concentration (Table 8, Entry 3 and 4), temperature (Table 8, Entry 6 and 7), as well as solvent variation (Table 8, Entry 8 and 9) all provided sub-optimal results. Nonetheless, a diastereodivergent resolution had been successfully achieved, with the desired diastereomer (assigned by comparison to Wender's work, see also below) obtained as the major product. Two further steps (DMP oxidation and Grignard addition, Scheme 46) were required to install an additional methyl group in the original synthetic route reported,[42] which was not only the lowest yielding step, but also made it practically challenging by requiring separation of diastereomers on column chromatography.



Scheme 49. New substrates designed for optimizing asymmetric synthesis of (+)-dictamnol.

Furthermore, the poor diastereoselectivity observed (1:0.8 *d.r.* under optimized conditions) possibly resulted from the fact that a hydroxyl substituent was simply not bulky enough to direct substrate stereoselectivity control. In order to optimize the route further, attention was turned into two 'second generation' substrates: one with a tertiary carbonyl center by the addition of a pre-installed methyl substituent, **222**; and the TBS-protected precursor, ether **223** (Scheme 49). The preparation of these 'second generation' precursors was fairly straight-forward: **222** was prepared by oxidizing allene **219** into its corresponding ketone, followed by Grignard addition using methylmagnesium bromide, with both steps offering satisfying yields (79% and 87%). **223** was prepared by standard *tert*-butyldimethylsilyl ether protection in quantitative yield (Scheme 49).

When submitted to [5+2] conditions, the pre-methylated precursor **222** produced a mixture of at least six isomeric compounds in approximately equimolar ratio. Due to practical difficulty in separation, as well as poor yield, no further optimization was conducted (Scheme 50, Equation a). In contract, the [5+2] cycloisomerization of **223** turned out to be successful under optimized conditions (Scheme 50, Equation b). However, little change of selectivity was observed after deprotection (1:0.9 *vs.* 1:0.8). with a slight drop of isolated yield (42% *vs.* 60%).

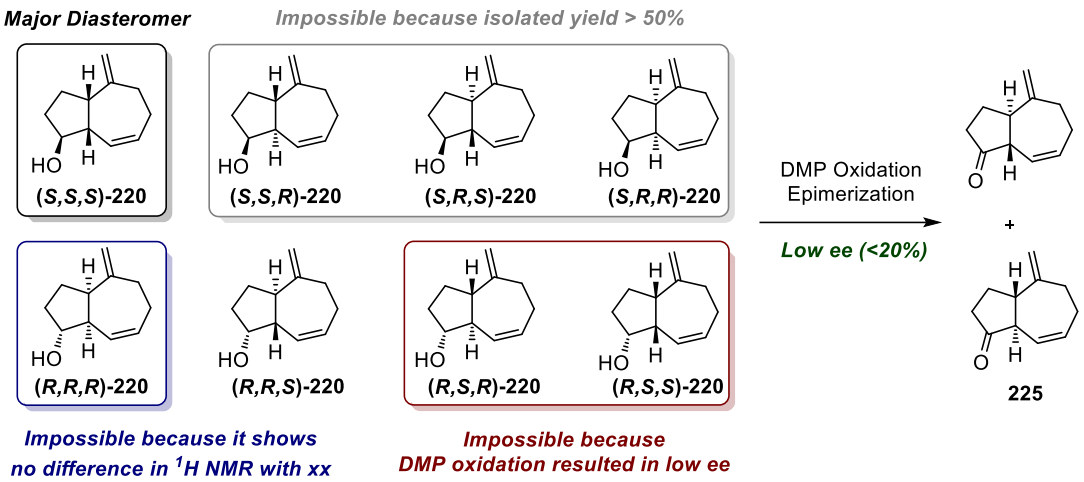


Scheme 50. Reactions of the 'second generation' substrates.

3.3 Assignment of the Stereochemistry

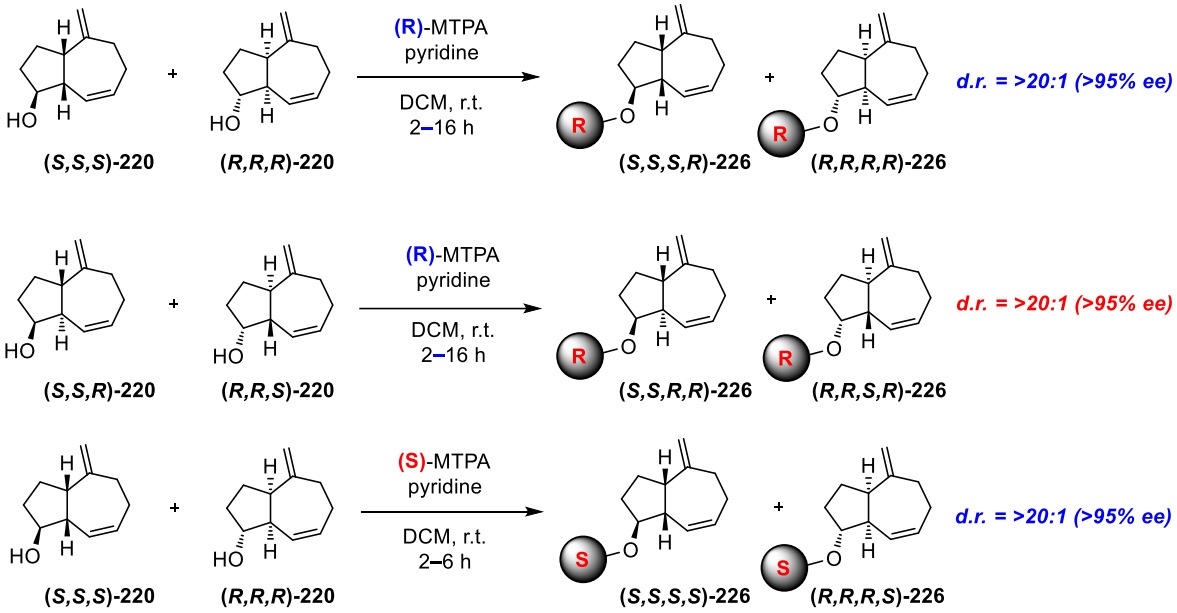
Under optimized conditions, a diastereodivergent resolution (60% yield, 1:0.8 *d.r.*) was observed, with the major product assigned as **220** with protons from all three steric centers sharing same configuration (*R,R,R* or *S,S,S*), by comparison with spectroscopic data from the Wender synthesis.[42]

The identity of the minor stereoisomer at first proved challenging to establish, but by oxidation of the two products to the corresponding ketone **225** (an intermediate in the Wender synthesis; an epimerization at the 5,7-ring bridge occurs during this process),[42] we were able to assign the minor diastereomer as (*R,R,S*)-**220**. Since the isolated yield was greater than 50%, the minor diasteromer must have a different configuration at the hydroxyl center undergoing oxidation (*i.e.*, if the major diasteromer is assigned as *R,R,R*, the minor diasteromer must have *S* at the first stereogenic center, and *vice versa*, indicated in Scheme 51, **grey box**). The minor diasteromer could also not be (*R,R,R*)-**220**, which is the enantiomer of the major diasteromer, and would thus show no difference in the ^{1}H NMR spectra (Scheme 51, **blue box**). Finally, since the two alcohol starting materials for this oxidation gave opposite enantiomers of ketone **225** as judged by a low *ee* of the isolated ketone product (<20%), it is only possible if the seven-membered ring of the minor isomer has the configuration of (*R,R,S*) (Scheme 51, **red box**).



Scheme 51. Identifying the minor diastereomer (*R*,*R*,*S*)-**220**.

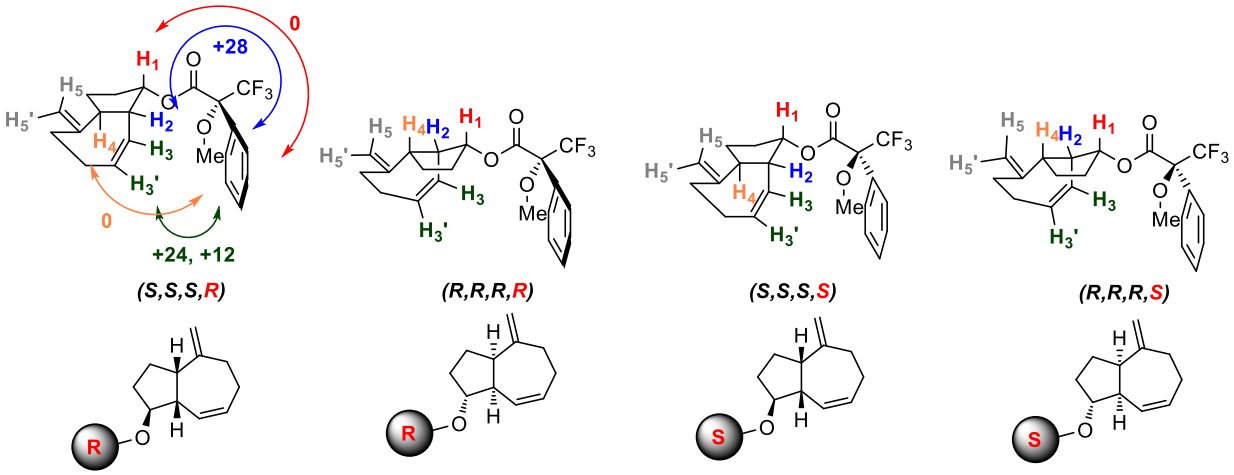
Pleasingly, both (*S*,*S*,*S*)-**220** and (*R*,*R*,*S*)-**220** were isolated in >95% *ee*, as determined by preparation of the corresponding Mosher esters (Scheme 52).



Scheme 52. Preparation of Mosher ester **226**.

Comparison of the ΔδSR values of each proton, it revealed the success of the rhodium phosphoramidite catalyst system in selectively transforming the (*S*)-enantiomer of the starting material into the desired diastereomer (Table 9).

Table 9. Determination of the absolute configuration of major diastereomer (*S,S,S*)-**220**.



Proton	δ *R*-ester (ppm)	δ *S*-ester (ppm)	$\Delta\delta^{SR}$ (= δ*S* - δ*R*)	
			ppm	Hz (400 MHz)
H_1	5.14	5.14	0.00	0
H_2	2.89	2.96	+0.07	+28
H_3	5.19	5.25	+0.06	+24
H_3'	5.55	5.58	+0.03	+12
H_4	2.44	2.44	0.00	0
H_5	4.74	4.74	0.00	0

In addition, 1H–1H 2D NOESY NMR spectra confirmed our interpretation of each compound's relative stereochemistry (Figure 24). When a ~1:1 mixture of (*S*,*S*,*S*)-**220** and (*R*,*R*,*S*)-**220** was submitted to this experiment, a clear interaction between protons **red** and **orange** was observed, whilst the same protons (**blue** and **green**) were spatially more distant in (*S*,*S*,*S*)-**220**.

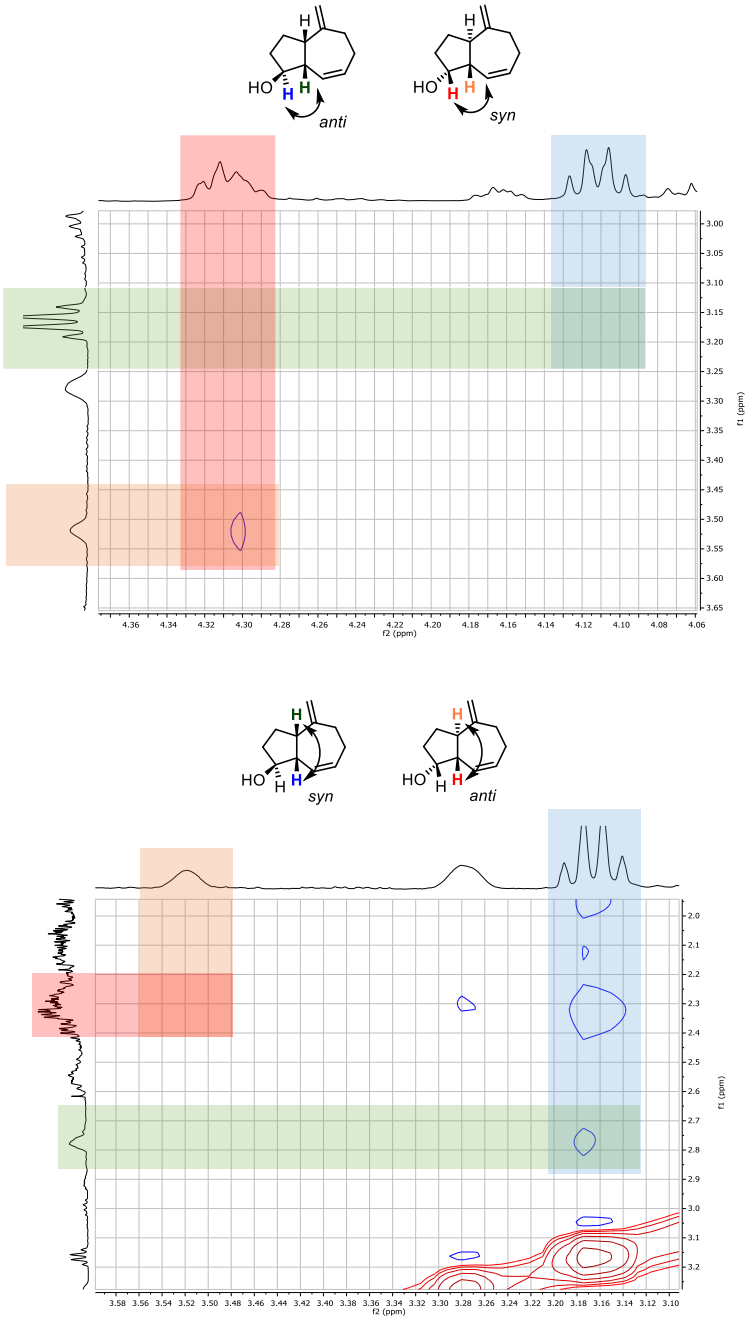


Figure 24. NOESY NMR of two diastereomers (*S*,*S*,*S*)-**220** and (*R*,*R*,*S*)-**220**.

3.4 Conclusion

We have applied our methodology to the diastereodivergent resolution of an allene vinylcyclopropane, in the context of a formal synthesis of the natural product (+)-dictamnol. Given the importance of [5+2] cycloisomerization as a source of 7-membered ring systems, we envisage this resolution offering significant opportunities in the asymmetric synthesis of cycloheptane-containing bioactive molecules.

In the process of optimization, one of the major limitations was the maximum theoretical yield being 50% as of all kinetic resolution reactions. In order to overcome this and make our methodology more applicable, we investigated on the possibility of an unprecedented dynamic kinetic resolution (DKR) in [5+2] cycloisomerizations (Chapter 4).

4. Dynamic Kinetic Resolution in [5+2] Cycloisomerization

Dynamic kinetic resolution (DKR) has been utilized in asymmetric synthesis as a type of kinetic resolution, in which 100% of a racemic compound can be converted into an enantiopure compound, thus achieving a maximum quantitative theoretical yield.[127] As stated in the previous chapters, DKR offers the distinct advantage of greater atom economy, and is therefore desirable in both academic and industrial settings.

4.1 Introduction

DKR relies on a center of substrate that can be easily epimerized, so that both (*R*) and (*S*) starting materials can interconvert *in situ* as reaction proceeds. The interconversion process must be reversible ($k_{rac} >> 0$), rapid (fast k_{rac}), and independent of the catalyst (Figure 25). It is also a classic example of a system under Curtin-Hammett control, where the product composition (product enantiomeric excess in the case of DKR) is solely dependent on the free energies of each transition state (k_R and k_S), instead of composition of starting materials (k_{rac}).[186]

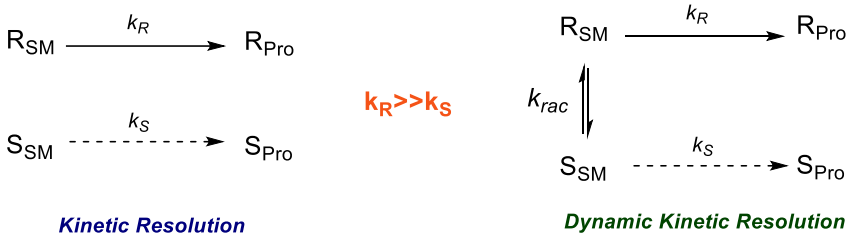


Figure 25. Comparison of reaction kinetics between traditional KR and DKR.

Depending on the driving force for epimerization, DKR is divided into two subgroups: *classical DKR* and *non-classical DKR* (Figure 26).[180] In classical DKR, epimerization is driven by the catalyst whilst in non-classical DKR, an exogenous substance (such as a base) is the mediator of epimerization. Other types of classification have also been proposed: for example, El Gihani *et al.* categorized DKR into spontaneous racemization, base-catalyzed racemization, enzyme-catalyzed racemization, and transition metal-catalyzed racemization.[127]

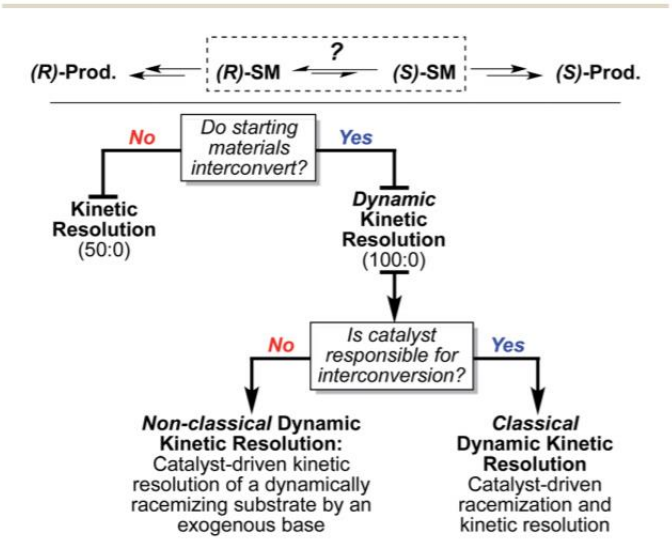
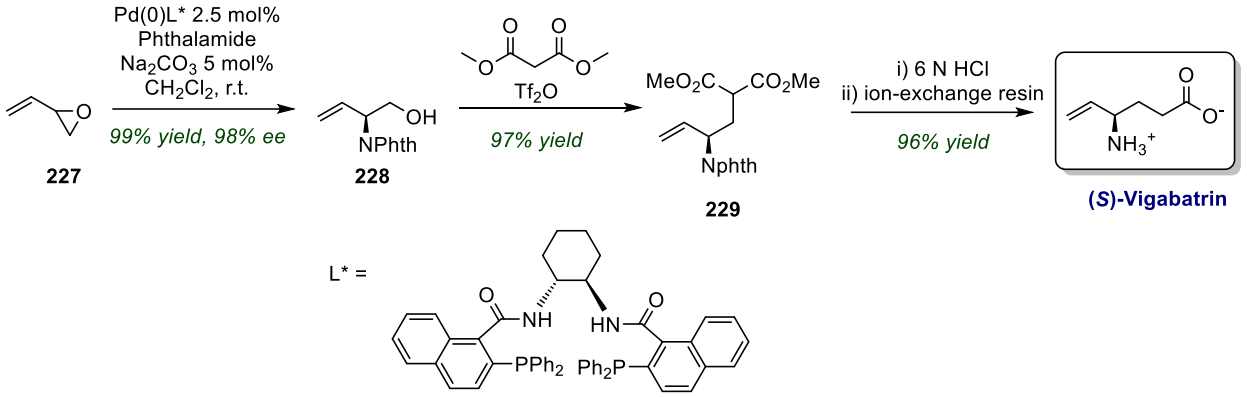


Figure 26. Classification of KR and DKR. Figure taken from Johnston *et al.*[177]

In terms of application, DKR has been utilized as a powerful approach in agricultural and pharmaceutical chemistry in the last few decades.[143,180,187] For example, (*S*)-vigabatrin (brand name Sabril), an anti-epilepsy drug acting by inhibiting the breakdown of γ-aminobutyric acid (GABA) was prepared efficiently by Trost *et al.* using DKR as key step (Scheme 53).[143,188,189] Commercially available butadiene monoepoxide **227** was exposed to phthalimide and palladium catalyst to afford regioisomer **228** *via* attacking at the more substituted allyl terminus, in excellent yield (99%) and *ee* (98%). S_N2 displacement of **228** followed by global deprotection using 6 N hydrochloric acid afforded (*S*)-vigabatrin in 96% yield. This is a remarkable synthetic strategy, not

only because of its extreme efficiency (3 steps, 92% overall yield), but also because it provided facile access to enantiopure vigabatrin, which is only effective in its (*S*) form.



Scheme 53. Preparation of (*S*)-vigabratin by Trost *et al.*

4.2 Substrate Synthesis

In order to achieve successful DKR, both a powerful asymmetric catalyst and a substrate that undergoes facile epimerization are essential. In addition to our well-established catalytic system, we also made the following modifications to the existing substrate model to meet the criteria (Figure 27):

1. The substituent was moved to homoallylic/homopropargilic position, in order to avoid potential isomerization of the double bond into conjugation as side reaction;
2. More electron withdrawing substituents (nitro, methyl ester, and aldehyde) were utilized, to facilitate epimerization of the α-proton under the reaction conditions.

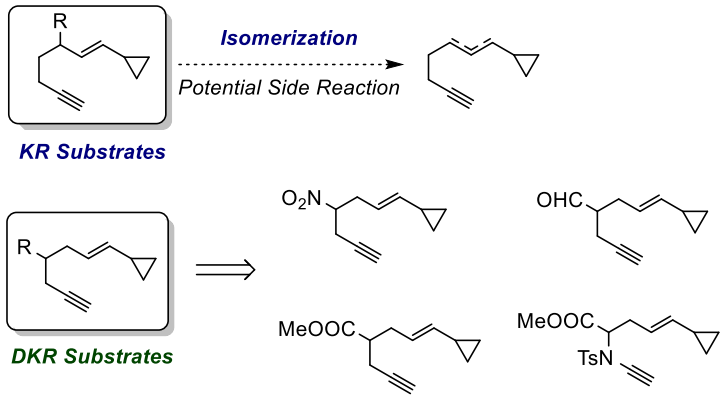
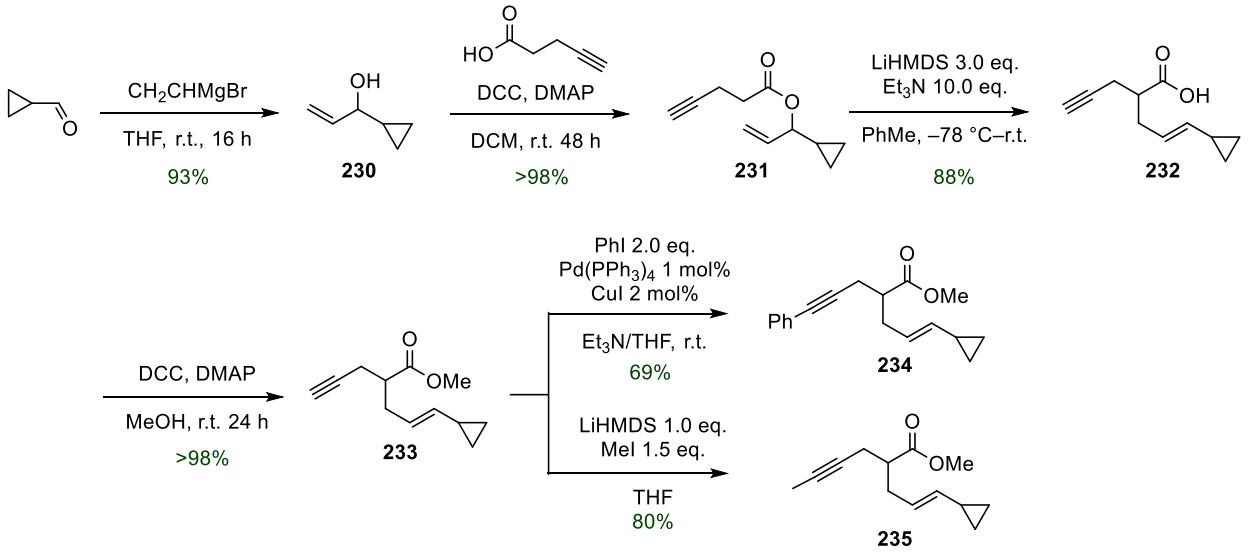


Figure 27. Designed substrates for DKR.

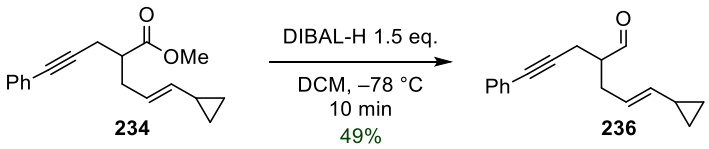
The preparation of methyl ester-substituted enynes **234** and **235** proceeded smoothly and efficiently (Scheme 54). Grignard addition of vinyl magnesium bromide to cyclopropane carbaldehyde gave secondary allylic alcohol **230** in 93% yield. Steglich esterification of **230** then afforded **231** as precursor for Curtius rearrangement in quantitative yield. A second esterification of the Curtius product **232** formed the desired enyne with a terminal alkyne **233** in quantitative

yield, which could be easily modified by cross-coupling reaction (**234**, 69% yield) or deprotonation/electrophilic addition *in situ* (**235**, 80% yield).



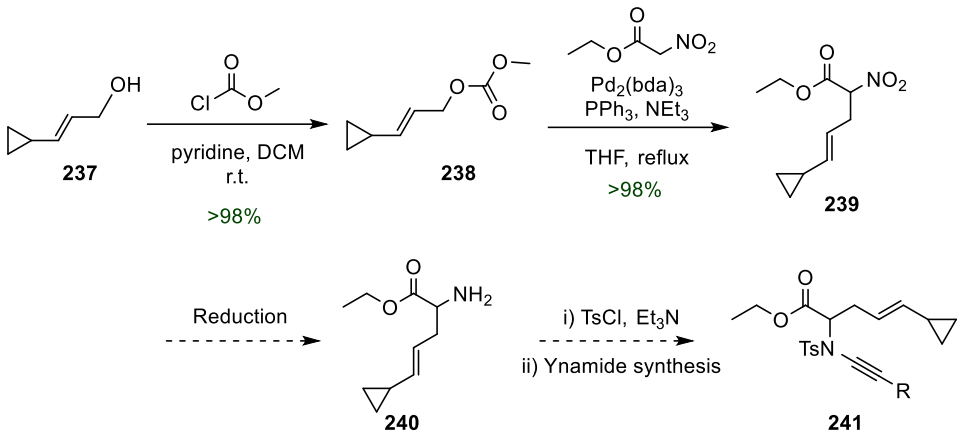
Scheme 54. Preparation of methyl ester substituted substrates **234** and **235**.

234 was converted to aldehyde **236** by DIBAL-H reduction, which also served as a potential substrate for DKR with slightly increased acidity (Scheme 55).



Scheme 55. Preparation of aldehyde **236**.

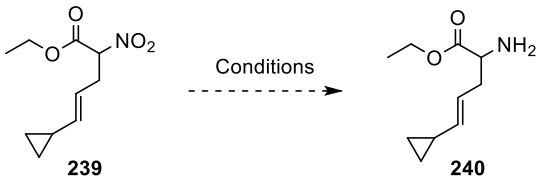
A new retrosynthetic approach to ynamide vinylcyclopropanes **241** was also designed. It relied on the formation of pentanoate **239**, which was converted into desired substrate in two further steps (4 steps in total), nine steps shorter than our previous synthesis for homoallylic substituted ynamides (Scheme 56).



Scheme 56. Proposed synthesis of homoallylic substituted ynamides.

Preparation of **239** was achieved conveniently by acylation of starting material **237**, followed by Tsuji–Trost reaction with readily available ethyl 2-nitroacetate as the nucleophile. Both steps afforded quantitative yield on a large scale (~2 grams). Reduction of **239** provided an unexpected challenge: due to the sensitive nature of the vinylcyclopropane moiety, mild conditions were required, which greatly restricted available options for nitro reduction. Reduction by palladium on carbon under hydrogen, arguably the most common strategy, offered a mixture of inseparable compounds (Table 10, Entry 2). The analogous conditions using palladium hydroxide on carbon preferentially reduced the alkene over the nitro group (Table 10, Entry 1). An alternative reducing agent, samarium(II) iodide, is commonly used in the reduction of nitroarenes into the corresponding anilines, and has also found successful in aliphatic nitro compounds under mild conditions.[190] Unfortunately, with our substrate, no reaction occurred even under elevated temperature (Table 10, Entry 3). Other conditions, including $LiAlH_4$ and $HSiCl_3$-mediated reduction, also failed due to decomposition of the starting material.[191]

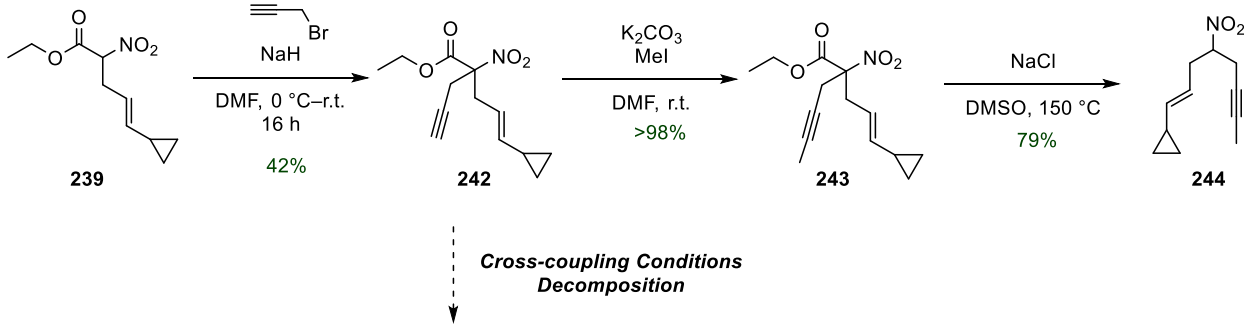
Table 10. Attempted reduction of nitro compound **239**.



Entry	Condition	Result
1	50% $Pd(OH)_2/C$, 1 atm H_2	Over-reduction
2	Pd/C, 1 atm H_2	Mixture of compounds
3	SmI_2, MeOH[a]	No reaction
4	$LiAlH_4$, THF	Decomposition
5	$SiHCl_3$, DIPEA, MeCN	Decomposition

[a] SmI_2 from commercial source as 0.1 M solution in THF.

Despite the discouraging results in preparation for previous substrates, pentenoate **239** still came in handy. Base-mediated enolization and reaction with propargylic bromide, followed by methylation and decarboxylation afforded nitro-substituted enyne **244** in good yield (Scheme 57).



Scheme 57. Preparation of nitro substituted enyne **244**.

4.3 Reaction Optimization

Having the above substrates in hand, we began our investigation into the possibility of DKR. First of all, the ability of undergoing standard kinetic resolution needed to be demonstrated before using additives to promote epimerization. As before, kinetic profiling *via* ^{1}H NMR spectroscopy was conducted for each substrate (Figure 28).

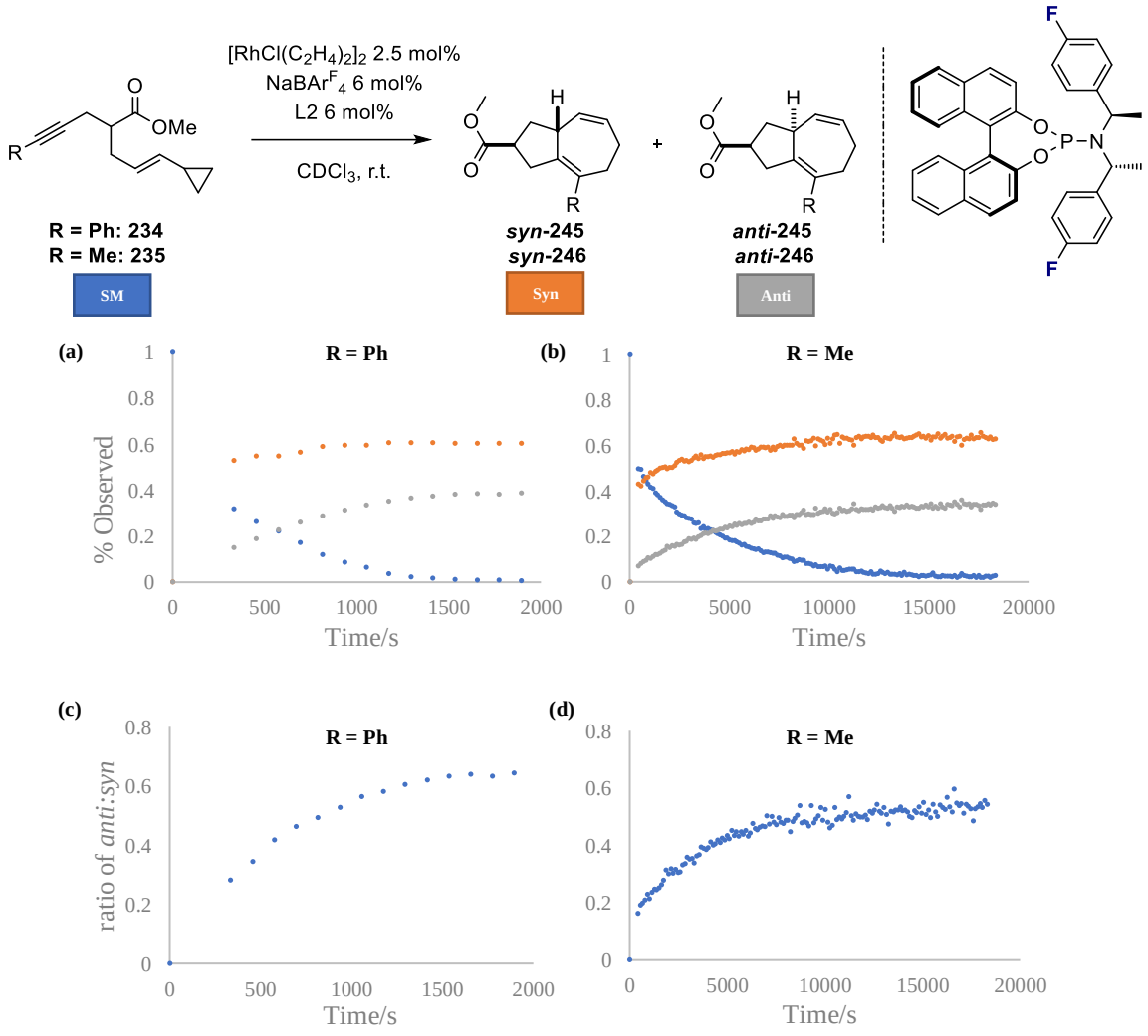


Figure 28. Kinetic profile of methyl ester substituted substrates **234** and **235**.

Pleasingly, both substrates demonstrated a significant rate difference between formation of the 'matched' and 'mismatched' products (Figure 28, a and b). In order to visualize the time-variant shift in product *d.r.*, the ratio of *syn:anti* product was plotted as a function of the reaction time (Figure 28, c and d). It clearly illustrated the potential of kinetic resolution: *syn*-product was formed predominantly in the beginning of the reactions, and *anti*-product slowly built up towards the completion of each reaction.

The next step was to test these reactions on the bench. When dichloromethane was used as the solvent, the temperature-sensitive nature of our catalyst system was highlighted: for example, substrate **235** showed no reaction at room temperature, yet full conversion was observed at 30 °C within 20 minutes (Figure 29, right).

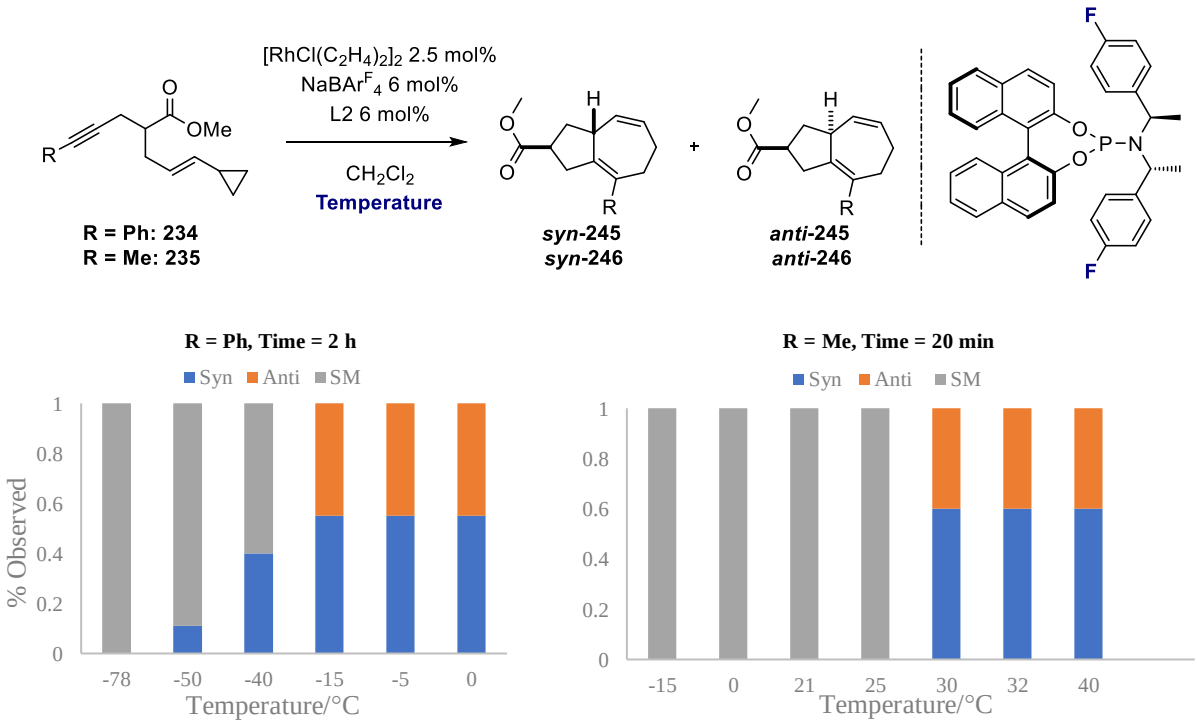


Figure 29. Influence of temperature on formation of both products.

Although the optimal temperature for **235** seemed to be between 25 and 30 °C in dichloromethane, it was not practical to fine-tune and monitor temperature within such a small range with our existing equipment. We then decided to survey the effect of solvents. Pleasingly, chloroform achieved kinetic resolution at 30 °C. Interestingly, phenyl substituted substrate **234** required a much lower temperature of –40 °C (Figure 30).

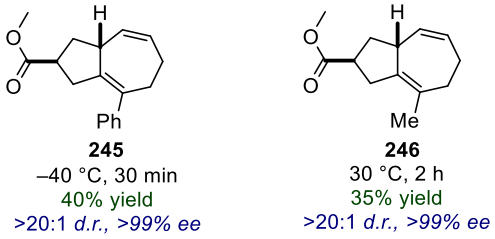
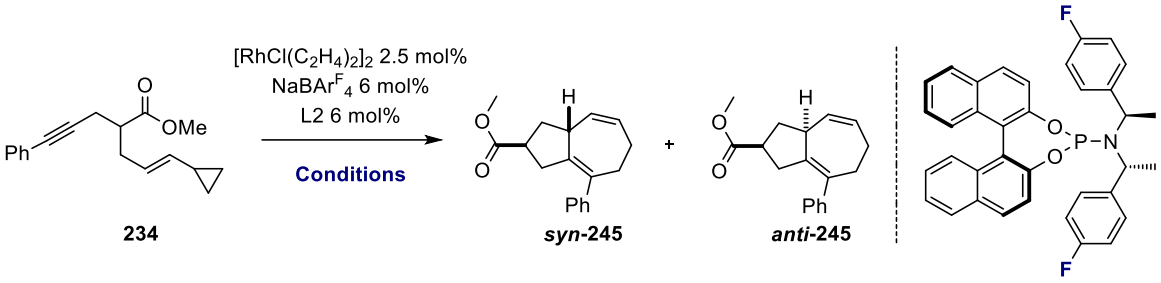


Figure 30. Optimal conditions for **234** and **235** to undergo kinetic resolution.

Having discovered the optimal conditions for kinetic resolution, our next task was to enable epimerization under these conditions. The first variable surveyed was solvent: although dichloromethane has been a fast and efficient solvent for our system, its solubility for most inorganic bases is extremely poor. As such, we would not be able to determine the amount of base present in the system if it cannot be fully dissolved. Four more polar solvents were surveyed: methanol, tetrahydrofuran (THF), acetone, and dimethylformamide (DMF). Without an additive, all four solvents apart from DMF provided sub-optimal results for kinetic resolution (Table 11, Entry 2-4). In DMF, only decomposition of starting material was observed at room temperature (Table 11, Entry 5). Perhaps unsurprisingly, 'non-standard' solvents seem to have slowed down the reaction, whilst providing worsened diastereo- and enantioselectivity. However, this was not entirely bad news: as long as kinetic resolution was still possible, those solvents could still be used as co-solvent if solubility issue did become a problem.

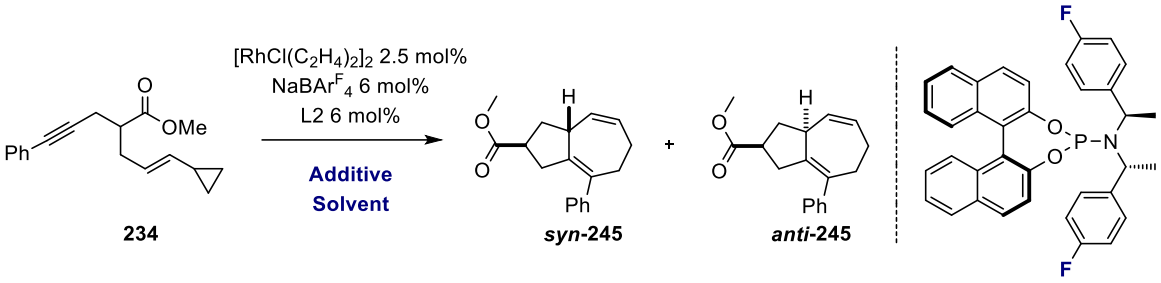
Table 11. The effect of solvent in kinetic resolution without additive.



Entry	Solvent	Condition	Result
1	CH_2CH_2	–40 °C, 30 min	40%, >20:1 *d.r.*, >99% *ee*
2	MeOH	r.t., 3 h	26%, 5:1 *d.r.*, 86% *ee*
3	THF	r.t., 3 h	22%, 20:1 *d.r.*, 90% *ee*
4	Acetone	r.t., 3 h	28%, 8:1 *d.r.*, 80% *ee*
5	DMF	r.t., 3 h	Decomposition

A selection of bases was then investigated in order to promote epimerization. In the literature, inorganic bases have been widely utilized with rhodium catalysts to promote DKR.[192,193] In the present system, the use of *t*-BuOK suppressed the reaction (Table 12, Entry 1–3), whilst proton sponge, guanidine, LiHMDS, DBU, and most inorganic bases afforded either no reaction or only trace product (Table12, Entry 5, 7, 8, 10–12). *n*-Bu_4NOH resulted in complete and rapid reaction at –40 °C, but only hydrolyzed the starting material (Table 12, Entry 6).

Table 12. Survey of additives on substrate **234**.

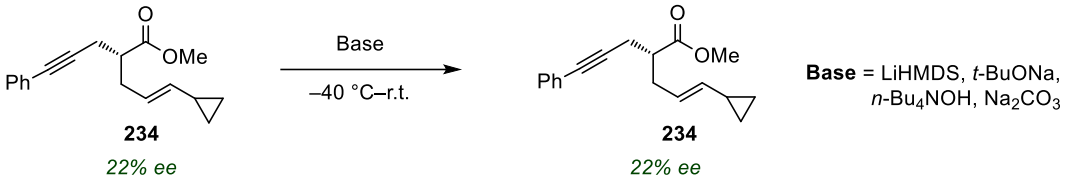


Entry	Solvent[a]	Additive[b]	Condition	Result
1	MeOH	*t*-BuOK	r.t. to reflux, 24 h	No reaction
2	DCM	*t*-BuOK	–40 °C, 30 min	35%, >20:1 *d.r.*, >99% *ee*
3	THF	*t*-BuOK	r.t. to reflux, 24 h	No reaction
4	DCM	*t*-BuONa	r.t., 30 min	60%, 8:1 *d.r.*
5	DCM	Proton Sponge	r.t. to reflux, 12 h	Trace
6	MeOH/DCM	*n*-Bu_4NOH	–40 °C, 30 min	>98%, hydrolysis only
7	MeOH/DCM	K_3PO_4	r.t., 30 min	25%, 8:1 *d.r.*
8	MeOH/DCM	Cs_2CO_3 or K_2CO_3	r.t., 30 min	No reaction
9	MeOH/DCM	Na_2CO_3	r.t., 30 min	54%, 7:1 *d.r.*
10[c]	MeOH/DCM	Guanidine	2 h + 30 min	Trace
11	THF/DCM	*n*-Bu_4NF	r.t., 30 min	No reaction
12	Multiple Solvents	NaF, KF, *n*-Bu_4NX, DBU, LiHMDS		No reaction

[a] A ratio of 1:30 was used in mixed solvents to enhance solubility. [b] Quantitative amount of additive was used. [c] Extracted with Na_2CO_3 or *t*-BuONa.

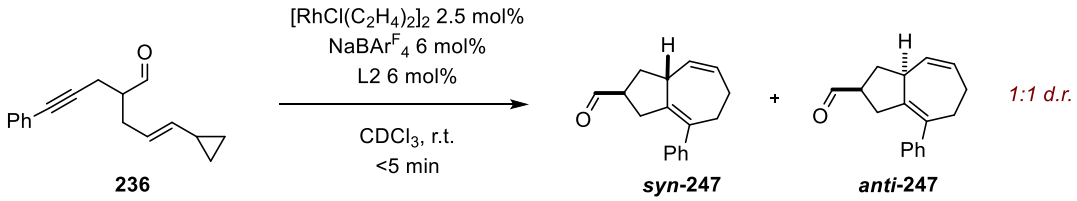
Only two conditions gave promising results, by driving the reaction past 50% conversion, whilst maintaining high *d.r.* (Table 12, Entry 4 and 9). In order to examine if this was the result of

epimerization/DKR, or simply a kinetic resolution proceeding too far, we measured the *ee* of the remaining starting material for each entry. Unfortunately, in both cases, *ee* = >99% was obtained, which indicated there was likely no epimerization. A non-racemic sample of **234** from isolating previous reaction mixture was also subjected to each of the basic additives without the presence of rhodium catalyst. Unfortunately, it turned out none of the additives were capable of promoting epimerization as no change in *ee* was observed (Scheme 58). This indicated a more reactive substrate might be necessary.



Scheme 58. Examination of epimerization with reactive additives.

To our disappointment, the more acidic substrate **236** gave less encouraging result. When [5+2] cycloisomerization was conducted in deuterated chloroform for kinetic studies, the reaction was complete within 5 minutes (before the first scan was taken), with 1:1 *d.r.* (Scheme 59). Furthermore, the resulting compounds were particularly unstable, and we failed to isolate them. Due to the practical difficulty and its overly sensitive nature, no further investigation was carried out.



Scheme 59. Kinetic profiling reaction of substrate **236**.

Finally, substrate **244** with a nitro substituent also demonstrated extremely promising initial results. Among all the substrates, **244** perhaps had the most 'convincing' kinetic profile: not only a clear rate difference was observed (Figure 31, left), but also no *anti*-**248** was formed until ~2000 seconds (Figure 31, right).

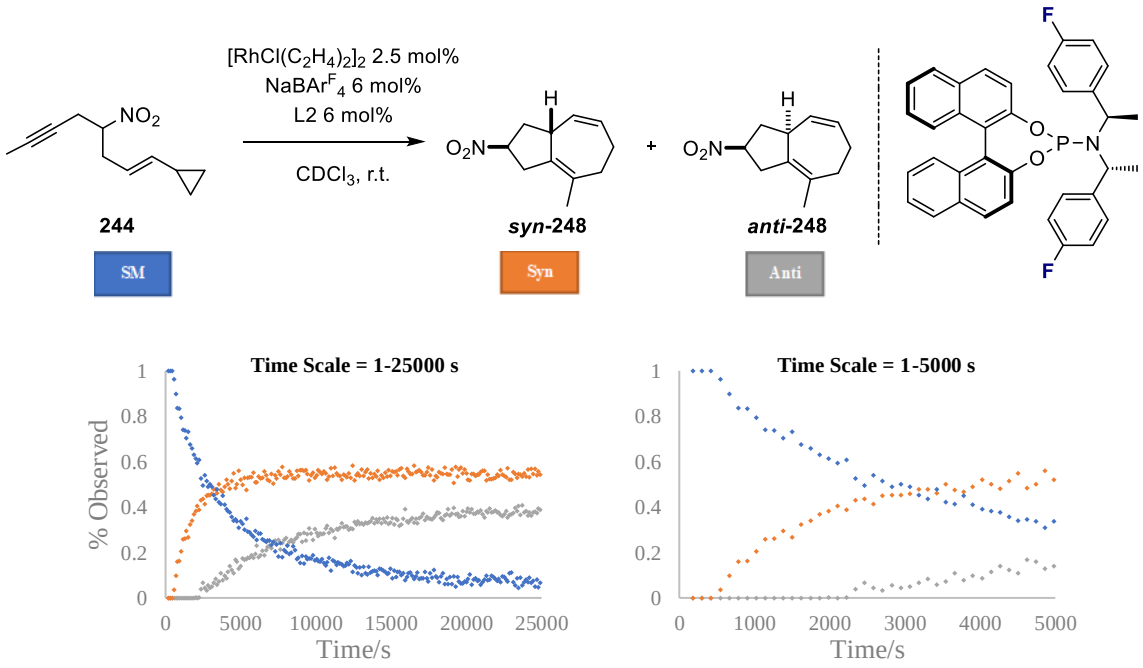


Figure 31. Kinetic profile of substrate **244**.

Unfortunately, the reaction was completely inhibited on addition of a base (*t*-BuONa, Na_2CO_3, K_2CO_3). Due to the limit of time, further investigation was not possible.

4.4 Conclusion

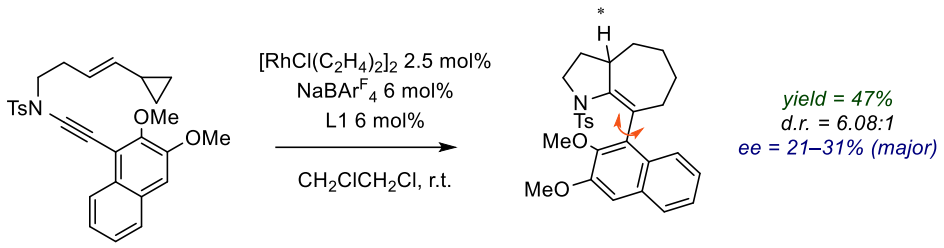
During the course of this DKR research, we discovered three more substrates that successfully underwent kinetic resolution during [5+2] cycloisomerization. Further survey of their potential in DKR reactions turned out challenging. However, this need not mean that a dead end has been reached in research of DKR in [5+2] cycloisomerizations. Exploring substrates that can undergo different modes of epimerization, further evaluation of solvent, and novel additives could all be the key to achieve a successful DKR.

5. Conclusion and Future Work

In the course of this work, the first examples of kinetic resolution in rhodium-catalyzed [5+2] cycloisomerization were developed. These processes were found to occur with high substrate diastereo- and enantioselectivity, and we expanded the substrate scope from ynamides to generic enynes bearing a variety of different functional groups, including the resolution of a silane-tethered substrate which, through desilylation, delivers the product of a formal intermolecular asymmetric [5+2] cyclization. We next applied our methodology to asymmetric synthesis of dictamnol by resolving an allene vinylcyclopropane. Finally, we explored the potential of DKR in the context of [5+2] cycloisomerization. Although no breakthrough has been made, early results indicated that DKR may indeed possible with careful evaluation of substrate design and additive/solvent system. Our results in this area were also applied in more complicated ynamides, which was published in *Angewandte Chemie International Edition*.[156]

5.1 Atroposelective Resolution in [5+2] Cycloisomerization

Atropoisomers represent a unique category of stereoisomers: axis of chirality (*c.f.* point of chirality for enantiomers), which are usually formed from hindered bond rotation, where energy differences due to steric strain create a barrier. Together with Zhong Hui Lim, a Part II student in the Anderson group, we investigated the potential of atroposelective [5+2] reactions using our catalyst system. Preliminary results suggested that atroposelectivity is indeed possible: a clear preference of phenyl substituent being syn-periplanar to the bridging proton was shown in all cases (Scheme 60).



Scheme 60. Initial results for atroposelective reactions, from Zhong Hui Lim.

This research is ongoing; a number of ynamides have been assessed due to the increased bulkiness of the tosyl group. According to Zhong's finding, an interesting inverse relationship between *d.r.* and *ee* was observed, which was hypothesized from the domino effect where substrate-rhodium binding was hindering effective ligand rhodium binding.

During the course of research, a number of exciting results were discovered in relation to kinetic resolution of substituted enynes, and the critical role of temperature in switching mode of reaction. In the meantime, a deeper insight into the mechanistical questions will undoubtfully enrich our understanding of such transformation.

6. Experimental

6.1 General Comments

Characterization: ^{1}H and ^{13}C NMR spectra of all compounds were recorded on Bruker DPX200, AVB400 and AVF400 spectrometers in deuterated solvents. The ^{1}H spectra were measured at 400 MHz. The ^{13}C spectra were measured at 101 MHz unless elsewhere stated. Nitromethane (NO_2Me) was the NMR internal standard. The chemical shifts (relative to Me_4Si, $\delta = 0$) are quoted in ppm (parts per million). The spectra were referenced to deuterated solvents in which they were measured, and the multiplicities were characterized as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), multiplet (m). HPLC experiments were performed on an Agilent 1260 Infinity HPLC. Low resolution mass spectra were recorded on a Waters LCT Premier EX mass spectrometer, using electrospray ionization (ESI). High resolution mass spectra were recorded by the Departmental Mass Spectrometry Service, University of Oxford, using electrospray ionization (ESI). The parent ion $[M]^+$, $[M+H]^+$ or $[M+Na]^+$ is quoted in daltons. Infrared (IR) absorption spectra were obtained on a Bruker Tensor 27 FT-IR spectrometer; the sample was prepared as a thin film on a diamond/ZnSe PIKE Miracle ATR module. Wavelengths of maximum absorbance (ν_{max}) are quoted in cm^{-1}. Only selected, characteristic IR data are provided for each compound.

Experimental techniques: Unless otherwise stated, all reactions were carried out in oven-dried glassware under an atmosphere of argon. Chromatography refers to normal phase column chromatography and was performed on silica gel (Merck Kieselgel 60 F254 230-400 mesh). Thin-

layer chromatography was performed on Merck Kieselgel 60 F254 plates with visualization by ultraviolet light (254 nm) and/or heating the plate after staining with vanillin. Compounds were visualized at 254 nm under UV, or by staining with potassium permanganate, iodine or cerium(IV) sulfate stain.

Solvents: Ether, dichloromethane, tetrahydrofuran and toluene were dried over activated alumina before use. All other commercially available reagents and solvents, where appropriate, were dried and purified before use using standard procedures. Petroleum ether refers to the fraction of light petroleum ether boiling at 40-60 °C.

Materials: Unless otherwise stated, all reactions were carried out in flame-dried glassware under an atmosphere of nitrogen. Achiral catalyst $[(C_{10}H_8)Rh(COD)]SbF_6$ and ligands L1-L3 were given as gifts by Dr. Robert Straker.

6.2 General Experimental Procedures

General Procedure A: Ireland-Claisen rearrangement

To a solution of lithium hexamethyldisilazide (1 M in toluene, 3.0 equiv.) and triethylamine (10 eq.) in toluene (10 mL/mmol of ester) at –78 °C was added dropwise a solution of ester (1.0 eq.) in toluene (1 mL/mmol of ester), and the reaction mixture stirred for 30 min before being allowed to reach room temperature and stirred for a further 5 h. Sodium hydroxide (10 mL/mmol of ester, 1 M) was added and the solution stirred for 30 min. The aqueous layer was separated, washed with diethyl ether (2 x 10 mL/mmol of ester) and acidified with citric acid (1 M) to pH ~ 4. The aqueous layer was extracted with diethyl ether (3 x 10 mL/mmol of ester) and the combined organic extracts washed with brine (10 mL/mmol of ester), dried over magnesium sulfate and concentrated under reduced pressure.

General Procedure B: Copper(II)-catalyzed ynamide synthesis

Sulfonamide (1.0 equiv.), K_3PO_4 (2.0 equiv.), $CuSO_4 \bullet 5H_2O$ (0.4 eq.) and 1,10-phenanthroline (0.8 eq.) was placed in an oven-dried 7 mL vial equipped with a stirrer bar, which was evacuated and backfilled with nitrogen three times. A solution of bromoalkyne (2.0 eq.) in anhydrous toluene (3.0 mL/mmol of sulfonamide) was added, then the vial was sealed, and the reaction mixture was stirred at 70 °C for the stated time. After cooling to room temperature, the mixture was filtered through Celite (diethyl ether eluent). The filtrate was concentrated under reduced pressure, then purified by flash column chromatography (5% ethyl acetate in petroleum ether) to yield the ynamide.

General Procedure C1: [5+2] Cycloisomerization (NMR Time-course Experiment)

A 5 mm NMR tube was dried in oven overnight and cooled under argon. Substrate (1.0 equiv.) was added, the tube was sealed with a Precision Seal® rubber septa cap, and then evacuated and backfilled with argon (three times). Freeze-pump-thaw degassed CDCl3 (0.4 mL) and nitromethane (internal standard, 1.0 eq.) was added. Meanwhile, a solution of chlorobis(ethylene)rhodium(I) dimer (2.5 mol%), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (6 mol%) and ligand (6 mol%) in degassed $CDCl_3$ (0.3 mL) was stirred for 20 min at room temperature. The catalyst stock solution and substrate solution were cooled to 0 °C in an ice bath (for low temperature experiments) for 10 min. The catalyst solution was then injected into the NMR tube containing substrate (1.0 eq.). Upon finish, the reaction was quenched by directly filtering through a silica gel plug (dichloromethane eluent), then the filtrate was and purified by flash column chromatography (eluent: 5% ethyl acetate in petroleum ether) to yield the [5+2] product.

Time-course experiment spectra were collected at 60 s intervals (DS = 0, NS = 2, d1 = 11 s; 34 s of delay time was added before the initiation of the next acquisition to allow for automated spectrometer processes. The spectra were automatically phased, baseline corrected, and integrated (cross-checked against the internal standard peak when an internal standard is used) using the TOPSPIN multi_integ3 command. The integration values were plotted using Microsoft Excel as a percentage of the total starting material originally present (proportional to concentration).

General Procedure C2: [5+2] Cycloisomerization (under laboratory conditions)

The catalyst stock solution and substrate solution were prepared from the same procedure as *general procedure C1* using degassed dichloromethane (0.4 mL). The catalyst solution was then injected into a 14 mL sealed vial containing substrate (1.0 eq.) at given temperature. Upon finish, the reaction was quenched by directly filtering through a silica gel plug (dichloromethane eluent), then the filtrate was and purified by flash column chromatography (eluent: 5% ethyl acetate in petroleum ether) to yield the [5+2] product.

General Procedure D: Caesium carbonate promoted synthesis of 1,2-dichloroenamides

To a stirred suspension of amide (1.0 eq.), powdered caesium carbonate (1.5 eq.) and dimethylformamide (0.75 mL/mmol of amide substrate) at 50 °C was added trichloroethylene (1.1 eq.) dropwise over 10 minutes. The resulting mixture was stirred at 50 ºC until reaction completion. Upon cooling to room temperature, the mixture was partitioned between ethyl acetate and water. The organic layer was separated and further washed with water. The organic layer was dried over sodium sulfate, filtered and concentrated. Purification by flash column chromatography gave the dichloroenamide.

General Procedure E: Synthesis of ynamides using phenyllithium/electrophilic quench

To a solution of 1,2-dichloroenamide (1.0 eq.) in tetrahydrofuran (10 mL/mmol of enamide) at –78 °C was added dropwise phenyllithium solution (2.0 M in dibutyl ether, 2.2 eq.) over 10 minutes. The reaction mixture was stirred at –78 °C for 1 h, after which time the electrophile (1.2 eq.) was

added. The solution was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was quenched with water and the aqueous layer extracted with diethyl ether (x 2). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated.

General Procedure F: Alkyne reduction by Red-Al or lithium aluminum hydride

To a solution of sodium bis(2-methoxyethoxy)aluminum hydride or lithium aluminum hydride (1.5 eq.) in toluene (1.0 mL/mmol) at 0 °C was added dropwise a solution of alkyne (1.0 eq.) in diethyl ether over 5 min. The resulting mixture was slowly warmed to room temperature, and allowed to stir for the stated time. The reaction was quenched by slow addition of HCl (1 N, aq.) at 0 °C, then stirred for 15 min. The mixture was warmed to room temperature, extracted with diethyl ether, washed with HCl (1 N, aq.), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The product was purified by flash column chromatography.

General procedure G: S_N2 reaction of allylic alcohols and sulfonamides

To a solution of allylic alcohol or sulfonamide (1.0 eq.) in tetrahydrofuran (5.0 mL/mmol of substrate) was added sodium hydride (1.5 eq.) at 0 °C. The resultant suspension was gradually warmed to room temperature and stirred for 30 min. Propargylic bromide (2.0 eq.) was added and the mixture was stirred overnight before quenched with ammonium chloride (sat., aq.). The aqueous layer was extracted with diethyl ether, dried over magnesium sulfate and concentrated. Crude product was purified by flash column chromatography to yield the desired product.

General procedure H: Nucleophilic addition to aldehydes or imines

A solution of nucleophile (1.2 eq.) in dry tetrahydrofuran was cooled to −78 °C in a dry-ice–acetone bath. *n*-Butyllithium (1.1 eq.) was added dropwise over a period of 10 min. The resulting mixture was stirred at −78 °C for 0.5 h, then added aldehyde or imine (1.0 eq.) slowly. Reaction mixture was slowly warmed to room temperature, and allowed to stir for 2 h. Reaction was quenched with ammonium chloride (sat. aq.). The organic layer was extracted with ethyl acetate, washed with ammonium chloride (sat. aq.), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Crude product was purified by flash column chromatography to yield the desired product.

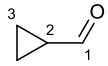
General procedure I: Protection of alcohol with silyl groups

To a solution of corresponding alcohol (1.0 eq.) in dimethylformamide (1.0 mL/mmol of substrate) was added silyl chloride (1.5 eq.) and imidazole (1.5 eq.). Reaction was stirred at room temperature for 2 h, before participated between diethyl ether and water. The aqueous layer was extracted with diethyl ether, washed with water/brine (1:1) three times, dried over magnesium sulfate and concentrated. Crude product was purified by flash column chromatography to yield the desired product.

6.3 Characterization of Selected Compounds

6.3.1 Synthesis of ynamide substrates

Cyclopropanecarboxaldehyde, 57

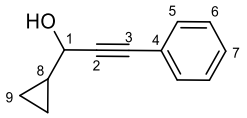


A 1000 mL round-bottomed flask was charged with a stirrer bar and cooled under nitrogen. A solution of cyclopropanemethanol (18 g, 250 mmol, 1.0 eq.) in dry dichloromethane (250 mL) prepared in a separate 500 mL round-bottomed flask was added, and the resulting solution was cooled to 0 °C in an ice bath. (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (78 mg, 0.5 mmol, 0.5 mol%) was added. Potassium bromide (2.99 g, 25 mmol, 0.1 eq.), sodium bicarbonate (52.5 g, 625 mmol, 2.5 eq.) and sodium hypochlorite (10-13% aq., 150 mL, 313 mmol, 1.25 eq.) was dissolved in distilled water (80 mL), and added slowly into reaction mixture over a period of 10 min. The resulting mixture was allowed to stir at 0 °C for 2 h. Reaction mixture was extracted with dichloromethane (3 × 150 mL). The organic layer was washed with distilled water (250 mL), dried over magnesium sulfate, filter, and concentrated under reduced pressure to give a clean oil. Crude product was purified by flash distillation (400 mmHg, 40 °C) to afford the title compound as a clean oil (53% in dichloromethane, 21.2627 g, 155 mmol, 62%).

R_f: 0.17 (10% ethyl acetate in petroleum ether).

Spectroscopic data was in agreement with literature.[194]

1-Cyclopropyl-3-phenylprop-2-yn-1-ol, 84

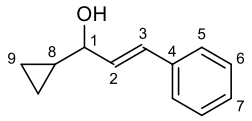


A 50 mL round-bottomed flask was charged with a stirrer bar and cooled under argon. A solution of phenylacetylene (2.2 mL, 10 mmol, 1.0 eq.) in dry tetrahydrofuran (15 mL) was added and the resultant mixture was cooled to −78 °C in a dry-ice–acetone bath. *n*-Butyllithium (12.5 mL, 1.6 M in hexane, 20 mmol, 1.0 eq.) was added dropwise over a period of 10 min. The resulting mixture was stirred at −78 °C for 1 h, then added **57** (3.0 mL, 53% in dichloromethane, 20 mmol, 1.0 eq.). Reaction mixture was slowly warmed to room temperature, and allowed to stir for 2 h. Reaction was quenched with ammonium chloride (20 mL, sat. aq.). The organic layer was extracted with ethyl acetate (3 × 50 mL), washed with ammonium chloride (100 mL sat. aq.), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil. Crude product was purified by flash column chromatography (eluent: 20% ethyl acetate in petroleum ether) to give the title compound as a pale-yellow oil (2.6679 g, 7.8 mmol, 78%).

R_f: 0.28 (30% ethyl acetate in petroleum ether).

Spectroscopic data was in agreement with literature.[195]

1-Cyclopropyl-3-phenyl-prop-2-en-1-ol, 85

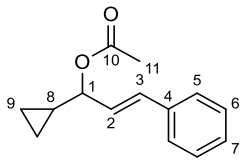


A 50 mL round-bottomed flask was charged with a stirrer bar and cooled under argon. A solution of sodium bis(2-methoxyethoxy)aluminumhydride (4.5 mL, 65% in toluene, 15 mmol, 1.5 eq.) in dry diethyl ether (10 mL) was added, and the resulting mixture was cooled to 0 °C in an ice bath. A solution of **84** (1.72 g, 10 mmol, 1.0 eq.) in dry diethyl ether (10 mL) was added dropwise over a period of 5 min. The resulting mixture was slowly warmed to room temperature, and allowed to stir for 3 h. Reaction was quenched by slowly adding hydrochloric acid (20 mL, 1 N, aq.) at 0 °C for 15 min. The resulting mixture was warmed to room temperature, extracted with diethyl ether (3 × 50 mL), washed with hydrochloric acid (50 mL, 1 N, aq.), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil. Crude product was purified by flash column chromatography (eluent: 25% ethyl acetate in petroleum ether) to give the title compound as a clean oil (600 mg, 3.4 mmol, 34%).

R_f: 0.37 (30% ethyl acetate in petroleum ether).

Spectroscopic data was in agreement with literature.[196]

1-Cyclopropyl-3-phenyl-prop-2-en-1-acetate, 86

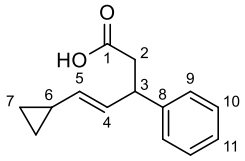


A 25 mL round-bottomed flask was charged with a stirrer bar and cooled under nitrogen. A solution of **85** (3.0 mmol, 1.0 eq.) in dry diethyl ether (5 mL) prepared in a separate 10 mL round-bottomed flask was added, and the resulting solution was cooled to 0 °C in an ice bath. 4-Dimethylaminopyridine (6 mg, 5 mol%) and pyridine (0.5 mL, 4.5 mmol, 1.5 eq.) was added. Acetic anhydride (0.6 mL, 4.5 mmol, 1.5 eq.) was added dropwise using a syringe over a period of 2 min to reaction mixture. The resulting solution was slowly warmed to room temperature, and stirred overnight for 18 h. Reaction was quenched with distilled water (20 mL). The aqueous layer was extracted with ethyl acetate (4 × 50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil. Crude product was purified by flash column chromatography (eluent: 10% ethyl acetate in petroleum ether) to yield the title compound as a pale-yellow oil (315 mg, 1.5 mmol, 49%).

R_f: 0.61 (25% ethyl acetate in petroleum ether).

Spectroscopic data was in agreement with literature.[37]

(*E*)-5-Cyclopropyl-3-phenylpent-4-enoic acid, 87

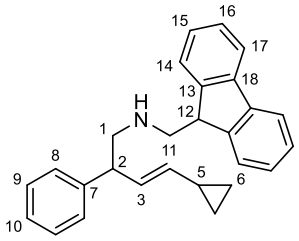


A 100 mL round-bottomed flask was charged with a stirrer bar and cooled under nitrogen. Lithium bis(trimethylsilyl)amide (30.0 mL, 1.0 M in toluene, 30.0 mmol, 3.0 eq.) was dissolved in 30 mL dry toluene. Triethyl amine (14.0 mL, 100.0 mmol, 10 eq.) was added and reaction was cooled to −78 °C in a dry-ice–acetone bath. A solution of **86** (2.16 g, 10.0 mmol, 1.0 eq.) in 10 mL dry toluene was added dropwise over a period of 10 min. Reaction was allowed to warm to room temperature, and stirred for 2 h. Upon completion, reaction was quenched with sodium hydroxide (20 mL, 5% aq.) with vigorously stirring for 30 min before diluted with diethyl ether. The aqueous layer was acidified with citric acid (1M aq.) until pH = 3, extracted with diethyl ether (4 × 50 mL), washed with brine (20 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give an orange oil. Crude product was purified by flash column chromatography (eluent: 10% ethyl acetate, 1% acetic acid in petroleum ether) to yield the title compound as a pale-yellow solid (1.68 g, 7.8 mmol, 78%).

R_f: 0.15 (25% ethyl acetate in petroleum ether).

Spectroscopic data was in agreement with literature.[37]

(*E*)-*N*-((*9H*-Fluoren-9-yl)methyl)-4-cyclopropyl-2-phenylbut-3-en-1-amine, 88

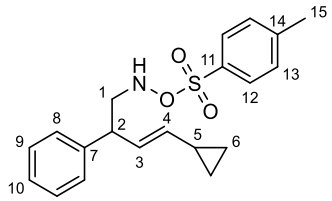


A 50 mL round-bottomed flask was charged with a stirrer bar and cooled under nitrogen. **87** (1.62 g, 7.5 mmol, 1.0 eq.) was dissolved in 10 mL dry toluene. Triethyl amine (1.3 mL, 9.0 mmol, 1.2 eq.) and diphenylphosphoryl azide (2.0 mL, 9.0 mmol, 1.2 eq.) was added. Reaction was heated at 100 °C for 1 h. Copper chloride (74 mg, 0.75 mmol, 10 mol%) and 9-fluorenylmethanol (1.77 g, 9.0 mmol, 1.2 eq.) was added, and the resultant mixture was stirred at 100 °C. After 2 h, reaction was cooled to room temperature, quenched with sodium bicarbonate (15 mL, sat. aq.), extracted with diethyl ether (3 × 50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil. Crude product was purified by flash column chromatography (eluent: 10% ethyl acetate in petroleum ether) to give the title compound as a yellow solid (1.90 g, 4.7 mmol, 62%).

R_f: 0.21 (10% ethyl acetate in petroleum ether).

Spectroscopic data was in agreement with literature.[37]

(*E*)-*N*-(4-Cyclopropyl-2-phenylbut-3-en-1-yl)-*O*-tosylhydroxylamine, 89

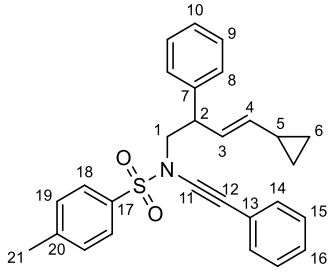


A 50 mL round-bottomed flask was charged with a stirrer bar and cooled under nitrogen. **88** (1.60 g, 3.9 mmol, 1.0 eq.) was dissolved in 10 mL dichloromethane and 10 mL diethyl amine. The resultant mixture was stirred at room temperature overnight, before concentrated under reduced pressure. Crude mixture was dissolved in 10 mL dry dichloromethane, then added triethyl amine (0.6 mL, 3.9 mmol, 1.0 eq.) and 4-toluenesulfonyl chloride (744 mg, 3.9 mmol, 1.0 eq.). Reaction was stirred at room temperature for 2 h, then quenched with citric acid (10 mL, 1 M, aq.). The aqueous layer was extracted with ethyl acetate (3 × 50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil. Crude product was purified by flash column chromatography (eluent: 5% ethyl acetate in petroleum ether) to give the title compound as a yellow solid (761 mg, 2.2 mmol, 56%).

R_f: 0.31 (20% ethyl acetate in petroleum ether).

Spectroscopic data was in agreement with literature.[37]

(*E*)-*N*-(4-Cyclopropyl-2-phenylbut-3-en-1-yl)-4-methyl-*N*-(phenylethynyl)benzenesulfonamide, 90



The title compound was prepared according to *general procedure B* using sulfonamide **89** (100 mg, 0.29 mmol, 1.0 eq.) and (bromoethynyl)benzene. **90** was afforded as an orange oil (91 mg, 0.20 mmol, 71%).

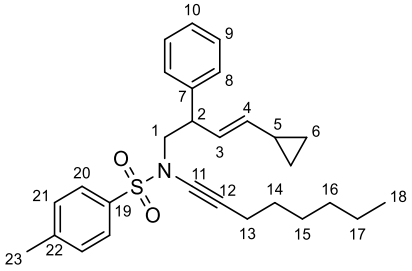
R_f: 0.26 (10% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (2H, d, *J* = 8.5 Hz, H18), 7.34–7.28 (9H, m, H8, H9, H10, H14, H15), 7.23–7.20 (3H, m, H16, H18), 5.65 (1H, dd, *J* = 15.5, 8.0 Hz, H3), 5.05 (1H, dd, *J* = 15.5, 9.0 Hz, H4), 3.75 (1H, q, *J* = 8.0 Hz, H2), 3.68–3.64 (2H, m, H1), 2.43 (3H, s, H21), 1.36–1.31 (1H, m, H5), 0.67–0.62 (2H, m, H6), 0.34–0.29 (2H, m, H6).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.5, 141.1, 137.0, 134.7, 131.4, 129.7, 128.7, 128.3, 127.9, 127.8, 127.7, 126.9, 126.8, 123.0, 82.5, 71.2, 56.2, 47.5, 21.7, 13.8, 6.7, 6.6.

Spectroscopic data was in agreement with literature.[37]

(*E*)-*N*-(4-Cyclopropyl-2-phenylbut-3-en-1-yl)-4-methyl-*N*-(oct-1-yn-1-yl)benzenesulfonamide, 91



The title compound was prepared according to *general procedure B* using sulfonamide **89** (100 mg, 0.29 mmol, 1.0 eq.) and 1-bromooct-1-yne. **91** was afforded as a yellow oil (85 mg, 0.19 mmol, 67%).

Physical State: yellow oil.

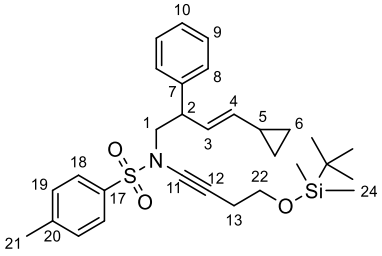
R_f: 0.36 (10% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (2H, d, *J* = 8.5 Hz, H21), 7.29–7.25 (4H, m, H8, H9), 7.21 (1H, t, *J* = 7.0 Hz, H10), 7.18 (2H, d, *J* = 8.5 Hz, H20), 5.62 (1H, dd, *J* = 15.5, 8.0 Hz, H3), 5.02 (1H, dd, *J* = 15.5, 9.0 Hz, H4), 3.67 (1H, q, *J* = 8.0 Hz, H1), 3.53 (1H, dd, *J* = 13.0, 8.5 Hz, H1), 3.48 (1H, dd, *J* = 13.0, 7.5 Hz, H2), 2.42 (3H, s, H23), 2.24 (2H, t, *J* = 7.0 Hz, H13), 1.48–1.43 (2H, m, H14), 1.36–1.24 (7H, m, H5, H15, H16, H17), 0.90 (3H, t, J = 7.5 Hz, H18), 0.68–0.63 (2H, m, H6), 0.34–0.28 (2H, m, H6).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 141.3, 136.7, 134.8, 129.5, 128.6, 128.0, 127.7, 127.0, 126.8, 73.0, 70.9, 55.9, 47.1, 31.4, 29.0, 28.5, 22.6, 21.6, 18.5, 14.1, 13.8, 6.7, 6.6.

Spectroscopic data was in agreement with literature.[37]

(*E*)-*N*-(4-((tert-Butyldimethylsilyl)oxy)but-1-yn-1-yl)-*N*-(4-cyclopropyl-2-phenylbut-3-en-1-yl)-4-methylbenzenesulfonamide, 92



The title compound was prepared according to *general procedure B* using sulfonamide **89** (100 mg, 0.29 mmol, 1.0 eq.) and ((4-bromobut-3-yn-1-yl)oxy)(tert-butyl)dimethylsilane. **92** was afforded as a yellow oil (92 mg, 0.20 mmol, 70%).

Physical State: yellow oil.

R_f: 0.36 (10% ethyl acetate in petroleum ether).

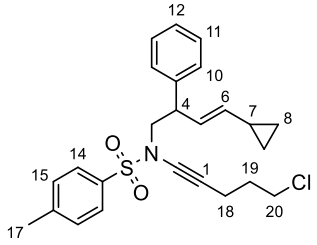
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62–7.53 (2H, m, H19), 7.25–7.03 (7H, m, H18, H8, H9, H10), 5.55 (1H, dd, *J* = 15.3, 7.9 Hz, H3), 4.95 (1H, ddd, *J* = 15.2, 8.6 Hz, H4), 3.66–3.53 (3H, m, H1, H2), 3.45 (2H, t, *J* = 4.0 Hz, H13), 2.38 (2H, t, *J* = 4.0 Hz, H22), 1.20 (1H, m, H5), 0.83 (9H, s, H25), 0.71–0.58 (2H, m, H6), 0.31–0.20 (2H, m, H6), 0.00 (6H, s, H24).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 136.7, 134.7, 129.5, 128.5, 127.9, 127.6, 126.9, 120.3, 67.7, 62.2, 60.4, 55.9, 47.1, 31.6, 25.9, 22.9, 21.6, 21.1, 18.3, 14.2, 13.7, 6.66, –5.25.

HR–MS (ESI+): calculated for $C_{30}H_{41}NO_3SSi$ $[M+H]^+$ 524.26492, found 524.26392.

IR (thin film, ν_{max}/cm^{-1}): 3004, 2928, 2857, 2253, 1663, 1598, 1494, 1453, 1364, 1185, 1168, 1092, 1019.

(*E*)-*N*-(5-Chloropent-1-yn-1-yl)-*N*-(4-cyclopropyl-2-phenylbut-3-en-1-yl)-4-methylbenzenesulfonamide, 93



The title compound was prepared with *general procedure B* using sulfonamide **89** (200 mg, 0.58 mmol, 1.0 eq.) and1-bromo-5-chloropent-1-yne (230 mg, 1.16 mmol, 2.0 eq.). Crude material was purified by flash column chromatography (eluent: 5% ethyl acetate in petroleum ether) to yield the title compound as a pale-yellow oil (198 mg, 0.51 mmol, 88%).

R_f: 0.40 (10% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67–7.50 (2H, m, H14), 7.27–7.16 (4H, m, H15,10), 7.17–7.13 (1H, m, H12), 7.13–7.06 (2H, m, H11), 5.55 (1H, dd, *J* = 15.2, 7.8 Hz, H5), 4.94 (1H, dd, *J* = 15.3, 8.7 Hz, H6), 3.66–3.53 (1H, m, H4), 3.53–3.41 (4H, m, H3,20), 2.42–2.33 (5H, m, H17,18), 1.81 (2H, p, *J* = 6.5 Hz, H19), 1.32–1.20 (1H, m, H7), 0.61–0.52 (2H, m, H8), 0.24 (2H, qd, *J* = 4.7, 3.5 Hz, H8).

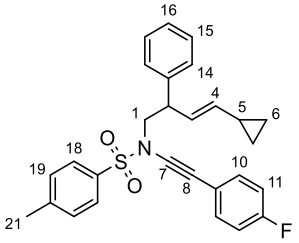
^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 141.1, 136.8, 134.6, 129.6, 128.6, 127.9, 127.6, 126.9, 126.8, 74.2, 68.7, 55.8, 47.3, 43.6, 31.4, 21.6, 15.9, 13.7, 6.6.

HR–MS (ESI+): calculated for $C_{25}H_{28}ClNO_2SNa$ $[M+Na]^+$ 464.1427, found 464.1429.

IR (thin film, ν_{max}/cm^{-1}): 2980, 2360, 2253, 2050, 1687, 1597, 1305, 1185.

Spectroscopic data was in agreement with literature.[37]

(*E*)-*N*-(4-Cyclopropyl-2-phenylbut-3-en-1-yl)-*N*-((4-fluorophenyl)ethynyl)-4-methylbenzenesulfonamide, 94



The title compound was prepared with *general procedure B* using sulfonamide **89** (170 mg, 0.50 mmol, 1.0 eq.) and 1-(bromoethynyl)-4-fluorobenzene (180 mg, 1.0 mmol, 2.0 eq.). Crude material was purified by flash column chromatography (eluent: 5% ethyl acetate in petroleum ether) to yield the title compound as a pale-yellow oil (151 mg, 0.35 mmol, 69%).

R_f: 0.35 (10% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70–7.58 (2H, m, H18), 7.29–7.17 (6H, m, H14,15,19), 7.17–7.06 (3H, m, H10,16), 6.97–6.82 (2H, m, H11), 5.57 (1H, dd, *J* = 15.2, 7.7 Hz, H3), 4.95 (1H, dd, *J* = 15.2, 8.7 Hz, H4), 3.70–3.59 (1H, m, H2), 3.59–3.50 (2H, m, H1), 2.36 (3H, s, H21), 1.35–1.21 (1H, m, 5H), 0.56 (2H, ddd, *J* = 8.4, 4.1, 2.7 Hz, H6), 0.23 (2H, tt, *J* = 4.6, 2.2 Hz, H6).

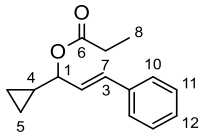
^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 161.0, 144.5, 140.9, 137.0, 134.6, 133.5, 133.4, 129.6, 128.6, 127.9, 127.7, 126.9, 126.7, 115.6, 115.3, 82.0, 70.0, 56.1, 53.4, 47.5, 21.6, 13.8, 6.6.

HR–MS (ESI+): calculated for $C_{28}H_{26}O_2NFSNa$ $[M+Na]^+$ 482.1566, found 482.1565.

IR (thin film, ν_{max}/cm^{-1}): 2980, 2360, 2237, 1736, 1662, 1598, 1508, 1453, 1364, 1293.

Spectroscopic data was in agreement with literature.[37]

(*E*)-1-Cyclopropyl-3-phenylallyl propionate, 95



To a stirred solution of 1-cyclopropyl-3-phenyl-prop-2-en-1-ol (900 mg, 5.0 mmol, 1.0 eq.) in 20 mL dichloromethane was added triethylamine (1.0 mL, 10.0 mmol, 2.0 eq.), propionic anhydride (1.1 mL, 7.5 mmol, 1.5 eq.) and 4-dimethylaminopyridine (62 mg, 0.50 mmol, 10 mol%). The resultant mixture was stirred at room temperature for two days, and quenched with 20 mL ammonium chloride (sat., aq.). The aqueous layer was extracted with diethyl ether (3 x 30 mL), washed with sodium bicarbonate (20 mL, sat., aq.) and brine (20 mL), dried over magnesium sulfate and concentrated. Crude material was used without further purification.

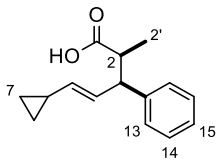
R_f: 0.78 (20% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.28 (2H, m, H10), 7.28–7.20 (2H, m, H11), 7.20–7.10 (2H, m, H12), 6.62–6.47 (1H, d, *J* = 16.0 Hz, H3), 6.14 (1H, dd, *J* = 16.0, 6.7 Hz, H2), 4.83 (1H, ddd, *J* = 8.2, 6.7, 1.2 Hz, H1), 2.31 (2H, qd, *J* = 7.5, 2.2 Hz, H7), 1.15–0.99 (4H, m, H4,8), 0.58–0.46 (2H, m, H5), 0.4–0.35 (1H, m, H5), 0.35–0.18 (1H, m, H5).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 136.4, 132.0, 128.6, 127.8, 127.0, 126.6, 78.2, 27.9, 15.0, 9.2, 3.6, 2.7.

Spectroscopic data was in agreement with literature.[37]

(*E*)-5-Cyclopropyl-2-methyl-3-phenylpent-4-enoic acid, 96



The title compound was prepared with *general procedure A* using **95** (3.20 g, 14.0 mmol, 1.0 eq.). Crude material was purified by flash column chromatography (eluent: 9% ethyl acetate, 1% acetic acid in petroleum ether) to afford the title compound as an orange needle (2.16 g, 9.5 mmol, 68%).

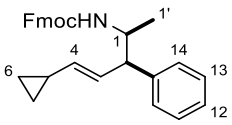
R_f: 0.12 (20% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.29 (2H, m, H13), 7.23–7.20 (3H, m, H14,15), 5.65 (1H, dd, *J* = 15.5, 7.5 Hz, H4), 5.01 (1H, dd, *J* = 15.0, 9.0 Hz, H5), 3.78 (1H, q, *J* = 8.0 Hz, H3), 2.73 (2H, d, *J* = 8.0 Hz, H2), 1.39–1.30 (1H, m, H6), 0.70–0.62 (2H, m, H7), 0.35–0.27 (2H, m, H7);

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 143.0, 135.0, 129.2, 128.6, 127.4, 126.6, 44.3, 40.7, 13.6, 6.7, 6.6.

Spectroscopic data was in agreement with literature.[37]

(*9H*-Fluoren-9-yl)methyl ((*E*)-5-cyclopropyl-3-phenylpent-4-en-2-yl)carbamate, 96a

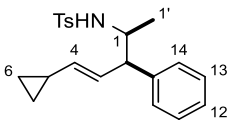


To a stirred solution of **96a** (2.16 g, 10.0 mmol, 1.0 eq.) in 20 mL toluene was added triethylamine (2.1 mL, 15.0 mmol, 1.5 eq.) and diphenylphosphoryl azide (2.6 mL, 12.0 mmol, 1.2 eq.). The resultant mixture was stirred at 100 °C for 2 h, then added copper chloride (99 mg, 1.0 mmol, 10 mol%) and 9-fluorenylmethanol (2.35 g, 12.0 mmol, 1.2 eq.). After 3 h, reaction was cooled down to room temperature and quenched with 15 mL sodium bicarbonate (sat., aq.). The aqueous layer was extracted by diethyl ether (3 x 25 mL), dried over magnesium sulfate and concentrated under reduced pressure. Crude material was purified by flash column chromatography (eluent: 10% ethyl acetate in petroleum ether) to afford the title compound as a yellow solid (2.50 g, 5.3 mmol, 53%).

R_f: 0.23 (20% ethyl acetate in petroleum ether).

Spectroscopic data was in agreement with literature.[37]

(*E*)-*N*-(5-Cyclopropyl-3-phenylpent-4-en-2-yl)-4-methylbenzenesulfonamide, 96b



96a (2.50 g, 5.3 mmol, 1.0 eq.) was dissolved in 20 mL dichloromethane and 20 mL diethylamine. The resultant suspension was stirred at room temperature overnight until complete consumption of starting material, and concentrated under reduced pressure. The dark yellow residue was dissolved in 30 mL dichloromethane, then added triethylamine (0.8 mL, 5.3 mmol, 1.0 eq.) and 4-toluenesulfonyl chloride (1.01 g, 5.3 mmol, 1.0 eq.). The resultant mixture was stirred at room temperature for 5 h, before quenched with citric acid (1 M, aq.). The aqueous layer was extracted by ethyl acetate (3 x 30 mL), washed with brine (50 mL), dried over magnesium sulfate and concentrated. The crude material was purified by flash column chromatography to yield the title compound as a yellow oil (822 mg, 2.2 mmol, 42%).

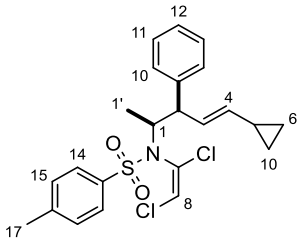
R_f: 0.26 (20% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, CDCl3): δ 7.70 (2H, d, *J* = 8.5 Hz, HTs), 7.32–7.20 (5H, m, H12,13,14), 7.06 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.49 (1H, dd, *J* = 15.0, 8.0 Hz, H3), 4.97 (1H, dd, *J* = 15.0, 9.0 Hz, H4), 4.35 (1H, s, *NH*), 3.32 (1H, q, *J* = 8.0 Hz, H1), 3.22–3.12 (1H, m, H2), 2.44 (3H, s, H*TsCH*$_3$), 1.37–1.29 (1H, m, H5), 0.73–0.63 (2H, m, H6), 0.37–0.27 (2H, m, H6).

^{13}C NMR (100 MHz, CDCl3): δ 143.5, 140.9, 137.4, 136.9, 129.7, 128.9, 127.5, 127.2, 127.1, 126.9, 48.3, 47.7, 21.6, 13.7, 6.8.

Spectroscopic data was in agreement with literature.[37]

_N_-((_E_)-5-Cyclopropyl-3-phenylpent-4-en-2-yl)-_N_-((_E_)-1,2-dichlorovinyl)-4-methylbenzenesulfonamide, 97



The title compound was prepared using *general procedure D* using **96b** (822 mg, 2.2 mmol, 1.0 eq.). Crude material was purified by flash column chromatography to yield the title compound as an orange oil (870 mg, 1.8 mmol, 84%).

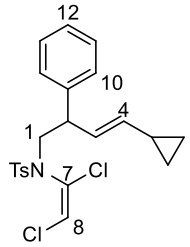
R_f: 0.45 (10% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85–7.75 (2H, m, H14), 7.31–7.10 (7H, m, H15,10,11,12), 6.54–6.42 (1H, m, H8), 5.63 (1H, dd, *J* = 15.0, 10.0 Hz, H3), 5.13–5.01 (0.5H, m, H4), 4.81–4.67 (0.5H, m, H4), 4.33–4.26 (1H, m, H1), 3.85–3.70 (1H, m, H2), 2.43 (3H, s, H17), 1.38–1.13 (4H, m, H1',5), 0.68–0.57 (2H, m, H6), 0.34–0.19 (2H, m, H6).

^{13}C NMR (100 MHz, CDCl3): δ 144.5, 144.3, 143.0, 137.9, 137.4, 136.6, 129.7, 128.7, 128.6, 128.2, 126.5, 125.0, 124.7, 123.2, 122.9, 63.7, 60.8, 53.4, 51.9, 21.8, 15.9, 15.5, 13.9, 6.6, 6.5.

Spectroscopic data was in agreement with literature.[37]

_N_-((_E_)-4-Cyclopropyl-2-phenylbut-3-en-1-yl)-_N_-((E)-1,2-dichlorovinyl)-4-methylbenzenesulfonamide, 97a



The title compound was prepared with *general procedure D* using sulfonamide **89** (120 mg, 0.35 mmol, 1.0 eq.). Crude material was purified by flash column chromatography (eluent: 5% ethyl acetate in petroleum ether) to give the title compound as a pale-yellow oil (156 mg, 0.35 mmol, 98%).

R_f: 0.61 (5% ethyl acetate in petroleum ether).

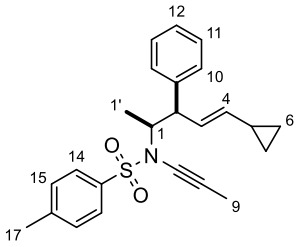
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (2H, d, J = 8.0 Hz, Ts*H*), 7.27–7.15 (4H, m, HTs,11), 7.16–7.09 (2H, m, H12), 7.06 (2H, d, *J* = 7.5 Hz, H10), 6.32 (1H, s, H8), 5.51 (1H, s, H3), 4.92 (1H, dd, *J* = 15.3, 8.7 Hz, H4), 3.61 (1H, s, H2), 3.38 (1H, s, H1), 3.19 (1H, s, H1), 2.35 (3H, s, TsC*H*$_3$), 1.32–1.05 (1H, m, H5), 0.63–0.51 (2H, m, H6), 0.22 (2H, t, *J* = 6.4, 3.2 Hz, H6).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.5, 141.2, 137.0, 129.6, 128.6, 128.5, 127.8, 126.8, 121.0, 53.4, 53.1, 47.3, 21.6, 13.7, 6.5.

HR–MS (ESI+): calculated for $C_{22}H_{23}O_2NCl_2NaS$ $[M+Na]^+$ 458.0719, found 458.0718.

IR (thin film, ν_{max}/cm^{-1}): 3084, 3027, 2925, 2360, 2341, 1664, 1452, 1403, 1292, 1090.

_N_-((_E_)-5-Cyclopropyl-3-phenylpent-4-en-2-yl)-4-methyl-_N_-(prop-1-yn-1-yl)benzenesulfonamide, 98



The title compound was prepared with *general procedure E* using **97** (232 mg, 0.49 mmol, 1.0 eq.). Crude material was purified by flash column chromatography (eluent: 5% ethyl acetate in petroleum ether) to yield the title compound as a pale-yellow solid (145 mg, 0.49 mmol, 98%).

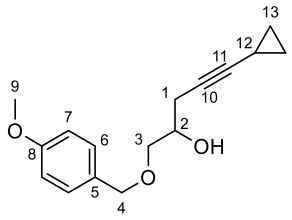
R_f: 0.35 (10% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (2H, d, *J* = 8.5 Hz, H14), 7.24–7.21 (2H, m, H10), 7.19–7.17 (3H, m, H)11,12, 7.11 (2H, d, *J* = 8.5 Hz, H15), 5.62 (1H, dd, *J* = 15.0, 9.5 Hz, H3), 5.03 (1H, dd, *J* = 15.0, 8.5 Hz, H4), 4.30 (1H, dq, *J* = 10.0, 6.5 Hz, H1), 3.35 (1H, dd, *J* = 10.0, 9.5 Hz, H2), 2.38 (3H, s, H9), 1.92 (3H, s, Ts*CH*$_3$), 1.37–1.30 (1H, m, H5), 1.22 (3H, d, *J* = 6.5 Hz, H1'), 0.69–0.60 (2H, m, H6), 0.35–0.24 (2H, m, H6).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 142.4, 137.1, 135.8, 129.4, 128.5, 127.9, 127.6, 127.1, 126.5, 69.1, 68.3, 59.5, 54.2, 21.7, 17.6, 13.8, 6.7, 6.6, 3.6.

Spectroscopic data was in agreement with literature.[37]

5-Cyclopropyl-1-((4-methoxybenzyl)oxy)pent-4-yn-2-ol, 101



An oven dried 100 mL round-bottomed flask was charged with a stirrer bar and cooled under argon. Cyclopropylacetylene (2.0 mL, 24.0 mmol, 1.2 eq.) was dissolved in 20 mL anhydrous tetrahydrofuran, cooled to −78 °C in a dry-ice–acetone bath. *n*-Butyllithium (13.8 mL, 1.6 M in hexane, 24.0 mmol, 1.2 eq.) was added dropwise over a period of 10 min. The resulting mixture was stirred at −78 °C for 1 h, then added 18 (3.88 g, 20.0 mmol, 1.0 eq.) and boron trifluoride diethyl etherate (3.8 mL, 24.0 mmol, 1.2 eq.) dropwise using a syringe over a period of 10 min. The resultant mixture was stirred at −78 °C for a further 3 h, before quenched with ammonium chloride (25 mL, sat., aq.).

The resulting mixture was slowly warmed to room temperature, extracted with diethyl ether (3 × 50 mL), washed with brine (50 mL, sat., aq.), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil. Crude product was purified by flash column chromatography (eluent: 10% ethyl acetate in petroleum ether) to give the title compound as a clean oil (3.76 g, 14.4 mmol, 72%).

R_f: 0.27 (20% ethyl acetate in petroleum ether).

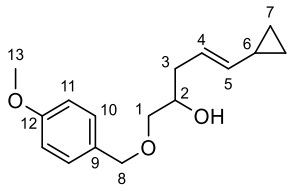
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (2H, d, *J* = 8.5 Hz, H7), 6.88 (2H, d, *J* = 8.5 Hz, H6), 4.49 (2H, s, H4), 3.91–3.85 (1H, m, H2), 3.80 (3H, s, H9), 3.55 (1H, dd, *J* = 9.5, 4.0 Hz, H3), 3.43 (1H,

dd, *J* = 9.5, 6.5 Hz, H3), 2.42–2.31 (2H, m, H1), 1.23–1.15 (1H, m, H12), 0.73–0.67 (2H, m, H13), 0.63–0.57 (2H, m, H13).

^{13}C NMR (100 MHz, CDCl3): δ 159.8, 130.5, 129.9, 114.3, 86.3, 73.5, 73.2, 71.4, 69.6, 55.8, 24.4, 8.5, 0.0.

Spectroscopic data was in agreement with literature.[37]

(*E*)-5-Cyclopropyl-1-((4-methoxybenzyl)oxy)pent-4-en-2-ol, 102



An oven dried 100 mL round-bottomed flask was charged with a stirrer bar and cooled under argon. Lithium aluminum hydride (4.0 M in diethyl ether, 3.0 mL, 12.0 mmol, 1.0 eq.) was suspended in 10 mL anhydrous dioxane. A solution of **101** (3.12 g, 12.0 mmol, 1.0 eq.) in 10 mL dioxane was added dropwise over a period of 10 min. The resultant mixture was stirred at 100 °C for 40 h, and allowed to cool to room temperature. Sodium bicarbonate (20 mL, sat., aq.) was added slowly. The aqueous layer was extracted with ethyl acetate (3 × 20 mL), washed with brine (50 mL, sat., aq.), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil. Crude product was purified by flash column chromatography (eluent: 10% ethyl acetate in petroleum ether) to give the title compound as a clean oil (2.20 g, 8.4 mmol, 70%).

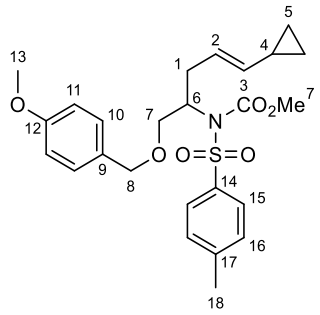
R_f: 0.48 (30% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, CDCl3): δ 7.26 (2H, d, *J* = 8.5 Hz, H11), 6.89 (2H, d, *J* = 8.5 Hz, H10), 5.48 (1H, dt, *J* = 15.5 and 7.0 Hz, H4), 5.04 (1H, dd, *J* = 15.5 and 8.5 Hz, H5), 4.48 (2H, s, H8), 3.83–3.77 (1H, m, H2), 3.81 (3H, s, H13), 3.47 (1H, dd, *J* = 9.5, 3.5 Hz, H1), 3.33 (1H, dd, *J* = 9.5 and 7.5 Hz, H1), 2.19–2.16 (2H, m, H3), 1.40–1.31 (1H, m, H6), 0.72–0.60 (2H, m, H7), 0.38–0.27 (2H, m, H7).

^{13}C NMR (100 MHz, CDCl3): δ 159.3, 137.5, 130.2, 129.4, 122.9, 113.9, 73.6, 73.0, 70.1, 55.3, 36.7, 13.6, 6.6, 6.5.

Spectroscopic data was in agreement with literature.[37]

Methyl (*E*)-(5-cyclopropyl-1-((4-methoxybenzyl)oxy)pent-4-en-2-yl)(tosyl)carbamate, 103



A 50 mL round-bottomed flask was charged with a stirrer bar and cooled under nitrogen. **102** (2.0 g, 7.6 mmol, 1.0 eq.) was dissolved in 10 mL anhydrous tetrahydrofuran. A solution of methyl tosylcarbamate (1.76 g, 7.7 mmol, 1.1 eq.) in 5 mL tetrahydrofuran was added, followed by addition of diisopropyl azodicarboxylate (1.8 mL, 9.1 mmol, 1.2 eq.) dropwise over a period of 5 min. A solution of triphenylphosphine (2.60 g, 9.9 mmol, 1.3 eq.) in 10 mL tetrahydrofuran was added, and the resultant mixture was stirred at room temperature overnight. After 20 h, reaction was concentrated under reduced pressure. Crude product was purified by flash column chromatography (eluent: 10% ethyl acetate in petroleum ether) to give the title compound as a clean oil (1.91 g, 4.0 mmol, 53%).

R_f: 0.50 (20% ethyl acetate in petroleum ether).

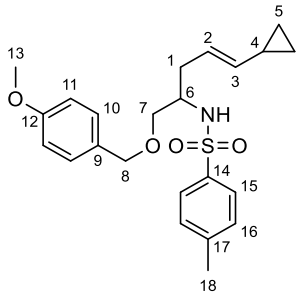
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (2H, d, *J* = 8.5 Hz, H16), 7.18–7.13 (4H, m, H15, H11), 6.84 (2H, d, *J* = 8.5 Hz, H10), 5.41 (1H, dt, *J* = 15.0, 7.5 Hz, H2), 5.03 (1H, dd, *J* = 15.0, 8.5 Hz, H3), 4.82–4.75 (1H, m, H6), 4.49 (1H, d, *J* = 11.5 Hz, H8), 4.37 (1H, d, *J* = 11.5 Hz, H8), 3.86 (1H, d,

J = 9.5 Hz, H7), 3.80 (3H, s, H13), 3.60 (3H, s, H7), 3.57 (1H, dd, *J* = 9.5, 5.5 Hz, H7), 2.54 (1H, dt, *J* = 14.0, 8.5 Hz, H1), 2.41 (1H, dd, *J* = 14.0, 7.0 Hz, H1), 2.38 (3H, s, H18), 1.35–1.26 (1H, m, H4), 0.69–0.59 (2H, m, H5), 0.35–0.25 (2H, m, H5).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 152.6, 143.9, 137.7, 137.1, 130.2, 129.4, 128.9, 128.8, 123.2, 113.7, 72.5, 69.6, 58.9, 55.3, 53.2, 33.6, 21.6, 13.5, 6.5.

Spectroscopic data was in agreement with literature.[37]

(*E*)-*N*-(5-Cyclopropyl-1-((4-methoxybenzyl)oxy)pent-4-en-2-yl)-4-methylbenzenesulfonamide, 103a



An oven dried 50 mL round-bottomed flask was charged with a stirrer bar and cooled under nitrogen. **103** (1.91 g, 4.0 mmol, 1.0 eq.) was dissolved in 20 mL methanol. Potassium carbonate (2.70 g, 20.0 mmol, 5.0 eq.) was added and the resultant mixture was stirred at room temperature overnight. After 40 h, reaction was diluted with distilled water (20 mL), extracted with dichloromethane (3 × 20 mL), washed with brine (50 mL, sat., aq.), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil. Crude product was purified by flash column chromatography (eluent: 10% ethyl acetate in petroleum ether) to give the title compound as a clean oil (1.04 g, 2.6 mmol, 65%).

R_f: 0.39 (20% ethyl acetate in petroleum ether).

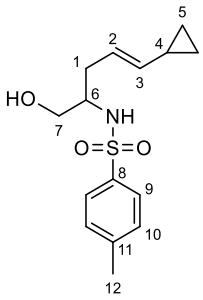
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (2H, d, *J* = 8.5 Hz, H16), 7.25 (2H, d, *J* = 8.5 Hz, H15), 7.16 (2H, d, *J* = 8.5 Hz, H11), 6.86 (2H, d, *J* = 8.5 Hz, H10), 5.13 (1H, dt, *J* = 15.5, 7.5 Hz, H1), 4.89 (1H, dd, *J* = 15.5, 8.5 Hz, H2), 4.73 (1H, d, *J* = 7.5 Hz, *NH*), 4.33 (1H, d, *J* = 11.5 Hz, H8), 4.30

(1H, d, *J* = 11.5 Hz, H8), 3.81 (3H, s, H13), 3.40 (1H, dd, *J* = 9.0, 3.5 Hz, H7), 3.34–3.27 (1H, m, H6), 3.24 (1H, dd, *J* = 9.0, 5.0 Hz, H7), 2.41 (3H, s, H18), 2.22–2.09 (2H, m, H4), 1.25–1.17 (1H, m, H4), 0.67–0.59 (2H, m, H5), 0.28–0.21 (2H, m, H5).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 143.2, 138.2, 137.9, 130.0, 129.6, 129.3, 127.2, 122.3, 113.8, 72.8, 70.4, 55.3, 53.2, 35.3, 21.5, 13.6, 6.6, 6.5.

Spectroscopic data was in agreement with literature.[37]

(*E*)-*N*-(5-Cyclopropyl-1-hydroxypent-4-en-2-yl)-4-methylbenzenesulfonamide, 104



A 25 mL round-bottomed flask was charged with a stirrer bar and cooled under nitrogen. **103a** (1.00 g, 2.1 mmol, 1.0 eq.) was dissolved in 9.0 mL dichloromethane and 1.0 mL pH 7 buffer. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (953 mg, 4.2 mmol, 2.0 eq.) was added. The resultant mixture was stirred at 0 °C for 4 h, then concentrated under reduced pressure. Crude mixture was diluted with distilled water (10 mL), extracted with dichloromethane (3 × 20 mL), washed with distilled water (20 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a dark brown oil. The flask was evacuated, backfilled with nitrogen for three times. 10 mL methanol was added to dissolve the residue, followed by addition of potassium carbonate (1.45 g, 10.5 mmol, 5.0 eq.). Reaction was stirred at room temperature for 2 h, then diluted with distilled water (10 mL), extracted with dichloromethane (3 × 20 mL), washed with brine (10 mL, sat., aq.), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a brown oil. Crude product was purified by flash column chromatography (eluent: 10% ethyl acetate in petroleum ether) to give the title compound as a brown oil (403 mg, 1.3 mmol, 65%).

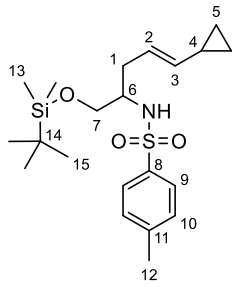
R_f: 0.50 (25% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, CDCl3): δ 7.76 (2H, d, *J* = 8.5 Hz, H10), 7.31 (2H, d, *J* = 8.5 Hz, H9), 5.04 (1H, dt, *J* = 15.0, 7.0 Hz, H2), 4.92 (1H, dd, *J* = 15.0, 8.5 Hz, H3), 4.81 (1H, d, *J* = 7.0 Hz, N*H*), 3.60 (1H, dd, *J* = 11.5, 4.0 Hz, H7), 3.53 (1H, dd, *J* = 11.5, 5.5 Hz, H7), 3.24–3.15 (1H, m, H6), 2.43 (3H, s, H12), 2.24–2.01 (2H, m, H1), 1.24–1.15 (1H, m, H4), 0.69–0.61 (2H, m, H5), 0.31–0.24 (2H, m, H5).

^{13}C NMR (100 MHz, CDCl3): δ 143.7, 138.9, 137.4, 129.8, 127.4, 122.0, 64.8, 55.4, 34.9, 21.7, 13.7, 6.7, 6.7.

Spectroscopic data was in agreement with literature.[37]

(*E*)-*N*-(1-((*tert*-Butyldimethylsilyl)oxy)-5-cyclopropylpent-4-en-2-yl)-4-methylbenzenesulfonamide, 105



An oven dried 25 mL round-bottomed flask was charged with a stirrer bar and cooled under nitrogen. **104** (400 mg, 1.4 mmol, 1.0 eq.) was dissolved in 10 mL anhydrous dichloromethane, then added imidazole (143 mg, 2.1 mmol, 1.5 eq.) and *tert*-butyldimethylchlorosilane (316 mg, 2.1 mmol, 1.0 eq.). The resultant mixture was stirred at room temperature for 2 h, before quenched with ammonium chloride (10 mL, sat., aq.). The aqueous layer was extracted with dichloromethane (3 × 20 mL), washed with brine (20 mL, sat., aq.), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil. Crude product was purified by flash column chromatography (eluent: 25% ethyl acetate in petroleum ether) to give the title compound as a clean oil (209 mg, 0.5 mmol, 39%).

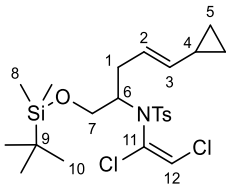
R_f: 0.50 (25% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (2H, d, *J* = 8.5 Hz, H10), 7.29 (2H, d, *J* = 8.5 Hz, H9), 5.17 (1H, dt, *J* = 15.0, 7.5 Hz, H2), 4.91 (1H, dd, *J* = 15.0, 8.5 Hz, H3), 4.69 (1H, d, *J* = 7.5 Hz, N*H*), 3.53 (1H, dd, *J* = 10.0, 3.5 Hz, H7), 3.35 (1H, dd, *J* = 10.0, 5.0 Hz, H7), 3.23–3.16 (1H, m, H6), 2.42 (3H, s, H12), 2.20–2.08 (2H, m, H1), 1.28–1.19 (1H, m, H4), 0.84 (9H, s, H15), 0.67–0.62 (2H, m, H5), 0.29–0.25 (2H, m, H5), –0.02 (3H, H13), –0.03 (3H, H13).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 138.2, 138.1, 129.7, 127.3, 122.7, 63.8, 54.8, 35.0, 26.0, 21.6, 18.4, 13.7, 6.6, 6.6, –5.4.

Spectroscopic data was in agreement with literature.[37]

_N_-((_E_)-1-((_tert_-Butyldimethylsilyl)oxy)-5-cyclopropylpent-4-en-2-yl)-_N_-((_E_)-1,2-dichlorovinyl)-4-methylbenzenesulfonamide, 106



An oven dried 3.5 mL vial was charged with a stirrer bar and cooled under argon. **105** (200 mg, 0.50 mmol, 1.0 eq.) was dissolved in anhydrous dimethylformamide (0.4 mL). Cesium carbonate (480 mg, 1.5 mmol, 3.0 eq.) and trichloroethylene (150 µL, 1.5 mmol, 3.0 eq.) was added. The resultant mixture was heated to 50 °C and stirred overnight. After 20 h, reaction was diluted with distilled water (2.0 mL), extracted with ethyl acetate (3 × 5 mL), washed with brine (5 mL, sat., aq.), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil. Crude product was purified by flash column chromatography (eluent: 10% ethyl acetate in petroleum ether) to give the title compound as a clean oil (123 mg, 0.30 mmol, 59%).

R_f: 0.81 (10% ethyl acetate in petroleum ether).

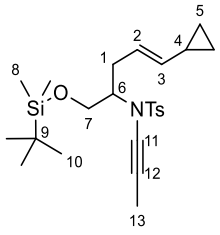
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (2H, d, *J* = 8.0 Hz, Ts*H*), 7.31 (2H, d, *J* = 8.0 Hz, Ts*H*), 6.57–6.52 (1H, m, H12), 5.45–5.34 (1H, m, H2), 5.11–4.80 (1H, m, H4), 3.85–3.52 (2H, m, H6, H7),

2.59–1.96 (5H, m, TsCH_3, H1), 1.32–1.10 (1H, m, H4), 0.89–0.80 (9H, m, H10), 0.66–0.59 (2H, m, H5), 0.29–0.20 (2H, m, H5), 0.05–0.10 (6H, m, H8);

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4, 137.3, 136.8, 129.7, 128.6, 123.7, 123.0, 123.0, 63.9, 63.8, 32.1, 25.9, 21.8, 18.3, 13.7, 6.5, 6.5, –5.4, –5.6.

Spectroscopic data was in agreement with literature.[37]

(*E*)-*N*-(1-((*tert*-Butyldimethylsilyl)oxy)-5-cyclopropylpent-4-en-2-yl)-4-methyl-*N*-(prop-1-yn-1-yl)benzenesulfonamide, 107



An oven dried 7.0 mL vial was charged with a stirrer bar and cooled under argon. **106** (100 mg, 0.20 mmol, 1.0 eq.) was dissolved in 2.0 mL anhydrous tetrahydrofuran, and the resultant mixture was cooled to −78 °C in a dry-ice–acetone bath. Phenyl lithium (2.0 M in dibutyl ether, 220 µL, 0.44 mmol, 2.2 eq.) was added dropwise over a period of 15 min. The resultant mixture was stirred at −78 °C for 2 h, before iodomethane (15 µL, 0.24 mmol, 1.2 eq.) was added. Reaction was allowed to warm to room temperature and stirred for a further 2 h. Upon completion, reaction was quenched with distilled water (2.0 mL), diluted with diethyl ether (5.0 mL), extracted with diethyl ether (3 × 5 mL), washed with brine (5 mL, sat., aq.), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil. Crude product was purified by flash column chromatography (eluent: 5% ethyl acetate in petroleum ether) to give the title compound as a clean oil (56 mg, 0.13 mmol, 63%).

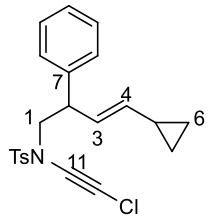
R_f: 0.60 (10% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (2H, d, *J* = 8.5 Hz, Ts*H*), 7.29 (2H, d, *J* = 8.5 Hz, Ts*H*), 5.12 (1H, dt, *J* = 15.0, 7.0 Hz, H2), 4.93 (1H, d, *J* = 15.0, 8.5 Hz, H3), 3.84 (1H, dq, *J* = 9.0, 6.0 Hz, H6), 3.62 (1H, dd, *J* = 10.5, 6.0 Hz, H7), 3.54 (1H, dd, *J* = 10.5, 6.0 Hz, H7), 2.41 (3H, s, TsCH_3), 2.29–2.22 (1H, m, H1), 2.16–2.10 (1H, m, H1), 1.90 (3H, s, H13), 1.13 (1H, m, H4), 0.85 (9H, s, H10), 0.64–0.56 (2H, m, H5), 0.28–0.20 (2H, m, H5), 0.00 (6H, s, H8).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 137.3, 136.4, 129.6, 127.8, 123.0, 69.2, 67.4, 63.9, 61.8, 32.7, 25.9, 21.8, 18.4, 13.7, 6.6, 3.6, –5.4.

Spectroscopic data was in agreement with literature.[37]

(*E*)-*N*-(Chloroethynyl)-*N*-(4-cyclopropyl-2-phenylbut-3-en-1-yl)-4-methylbenzenesulfonamide, 108



The title compound was prepared with *general procedure E* using **97a** (100 mg, 0.29 mmol, 1.0 eq.). Crude material was used without further purification.

R_f: 0.89 (10% ethyl acetate in petroleum ether).

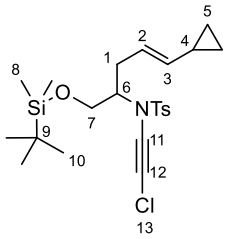
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51–7.35 (2H, m, Ts*H*), 7.15–6.95 (5H, m, Ts*H*, H8, H10), 6.95–6.93(2H, m, H9), 5.36 (1H, dd, *J* = 15.3, 7.9 Hz, H3), 4.91–4.61 (1H, dd, *J* = 7.9, 6.6 Hz, H4), 3.45–3.35 (1H, m, H2), 3.30 (2H, d, *J* = 8.3 Hz, H1), 2.21 (3H, s, TsC*H*$_3$), 1.18–0.97 (1H, m, H5), 0.51–0.27 (2H, m, H6), 0.15–0.02 (2H, m, H6).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 137.8, 129.6, 129.6, 127.7, 122.2, 76.7, 63.8, 61.9, 32.7, 25.8, 21.6, 18.3, 13.5, –5.6.

HR–MS (ESI+): calculated for $C_{22}H_{22}O_2SNClNa$ $[M+Na]^+$ 422.0949, found 422.0952.

IR (thin film, ν_{max}/cm^{-1}): 2242, 1598, 1493, 1452, 1427, 1329, 1159, 1093, 1054, 1020.

(*E*)-*N*-(1-((*tert*-Butyldimethylsilyl)oxy)-5-cyclopropylpent-4-en-2-yl)-*N*-(chloroethynyl)-4-methylbenzenesulfonamide, 110



The title compound was prepared with *general procedure E* using **106** (100 mg, 0.21 mmol, 1.0 eq.). Crude material was used without further purification.

R_f: 0.85 (10% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84–7.67 (2H, m, Ts*H*), 7.35–7.25 (2H, m, Ts*H*), 5.08 (1H, dt, *J* = 14.5, 7.1 Hz, H4), 5.00–4.86 (1H, dd, *J* = 8.5, 7.1 Hz, H5), 3.83 (1H, dq, *J* = 8.8, 5.8 Hz, H2), 3.67–3.50 (2H, m, H1), 2.43 (3H, s, TsC*H*$_3$), 2.27 (1H, ddd, *J* = 14.0, 6.9, 5.6 Hz, H3), 2.14 (1H, ddd, *J* = 14.4, 8.5, 7.1 Hz, H3), 1.12 (1H, dt, *J* = 8.3, 4.8 Hz, H6), 0.84 (9H, s, Si*tBu*), 0.60 (2H, ddd, *J* = 8.1, 3.5, 2.2 Hz, H7), 0.37–0.12 (2H, m, H7), 0.00 (6H, d, *J* = 1.6 Hz, SiC*H*$_3$).

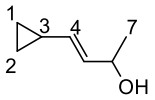
^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 137.8, 135.7, 129.6, 127.7, 122.2, 76.8, 76.7, 63.8, 61.9, 60.9, 53.4, 32.7, 25.8, 25.8, 21.6, 18.3, 13.5, 6.5, 6.4, –5.6.

HR–MS (ESI+): calculated for $C_{23}H_{34}O_3NClNaSSi$ $[M+Na]^+$ 490.1610, found 490.1609.

IR (thin film, ν_{max}/cm^{-1}): 2324, 2260, 1780, 1632, 1427, 1326, 1259, 1053.

6.3.2 Synthesis of Enyne substrates

(*E*)-4-Cyclopropylbut-3-en-2-ol, 136a



To a stirred solution of ethynylcyclopropane (1.65 g, 25.0 mmol, 1.0 eq.) in 50 mL anhydrous tetrahydrofuran at −78 °C, was added n-butyllithium (2.5 M in hexane, 10.0 mL, 25.0 mmol, 1.0 eq.) dropwise over a period of 20 min. The resultant mixture was stirred at −78 °C for 30 min, then added acetaldehyde (1.10 g, 25.0 mmol, 1.0 eq.) and stirred at room temperature for 3 h. Solvent was removed under reduced pressure, and the orange residue was dissolved in 50 mL anhydrous diethyl ether at 0 °C. Lithium aluminum hydride (4.0 M in dibutyl ether, 25.0 mL, 100.0 mmol, 4.0 eq.) was carefully added. The resultant suspension was allowed to warm to room temperature and stirred overnight, before quenched with 100 mL Rochelle's salt (sat., aq.). The aqueous layer was extracted with diethyl ether (3 x 50 mL), washed with water (50 mL), dried over magnesium

sulfate and concentrated under reduced pressure. Crude material was used without further purification.

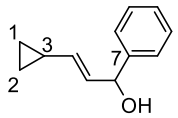
R_f: 0.46 (5% ethyl acetate in petroleum ether)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.53 (1H, dd, *J* = 15.3, 6.8 Hz, H5), 5.10 (1H, dd, *J* = 15.4, 8.8 Hz, H4), 4.26–4.05 (1H, m, H6), 1.22–1.14 (3H, s, C*H*$_3$), 0.94–0.71 (1H, m, H3), 0.65 (2H, ddd, *J* = 8.1, 3.4, 2.1 Hz, H1), 0.30 (2H, td, *J* = 4.4, 1.7 Hz, H2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.0, 132.1, 69.1, 23.6, 13.5, 7.0.

Spectroscopic data was in agreement with literature.[15]

(*E*)-3-Cyclopropyl-1-phenylprop-2-en-1-ol, 136b



To a stirred solution of ethynylcyclopropane (1.65 g, 25.0 mmol, 1.0 eq.) in 50 mL anhydrous tetrahydrofuran at −78 °C, was added *n*-butyllithium (2.5 M in hexane, 10.0 mL, 25.0 mmol, 1.0 eq.) dropwise over a period of 20 min. The resultant mixture was stirred at −78 °C for 30 min, then added benzaldehyde (4.0 mL, 25.0 mmol, 1.0 eq.) and stirred at room temperature for 3 h. Solvent was removed under reduced pressure, and the orange residue was dissolved in 50 mL anhydrous diethyl ether at 0 °C. Lithium aluminum hydride (4.0 M in dibutyl ether, 25.0 mL, 100.0 mmol, 4.0 eq.) was carefully added. The resultant suspension was allowed to warm to room temperature and stirred overnight, before quenched with 100 mL Rochelle's salt (sat., aq.). The aqueous layer was extracted with diethyl ether (3 x 50 mL), washed with water (50 mL), dried over magnesium sulfate and concentrated under reduced pressure. Crude product was purified by flash column

chromatography (eluent: 20% ethyl acetate in petroleum ether) to yield the title compound as a clean oil (4.0 g, 22.8 mmol, 91%).

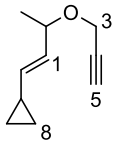
R_f: 0.40 (5% ethyl acetate in petroleum ether)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.25 (3H, m, H8, H10), 7.23–7.05 (2H, m, H9), 5.65 (1H, d, *J* = 7.0 Hz, H5), 5.19 (1H, dd, *J* = 15.2, 8.9 Hz, H4), 5.06 (1H, dd, *J* = 7.1, 2.8 Hz, H6), 1.41–1.26 (1H, m, H3), 0.71–0.59 (2H, m, H2), 0.38–0.26 (2H, m, H1).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 136.6, 129.9, 128.5, 127.5, 126.2, 99.9, 75.1, 13.5, 6.9.

Spectroscopic data was in agreement with literature.[197]

(*E*)-(3-(prop-2-yn-1-yloxy)but-1-en-1-yl)cyclopropane, 137



The title compound was prepared with *general procedure G* using **136a** (17 mg, 0.15 mmol, 1.0 eq.) and propargylic bromide (24 mg, 0.20 mmol, 1.33 eq.). Crude material was purified by flash column chromatography (eluent: 3% ethyl acetate in petroleum ether) to yield the title compound as a yellow oil (18 mg, 0.08 mmol, 50%).

R_f: 0.30 (10% ethyl acetate in petroleum ether).

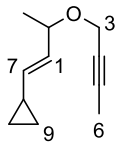
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.29 (dd, *J* = 15.1, 8.2 Hz, 1H, H2), 5.12 (dd, *J* = 15.3, 8.7 Hz, 1H, H6), 4.07 (dd, *J* = 15.6, 2.1 Hz, 1H, H3), 3.99–3.86 (m, 2H. H2,3), 2.31 (t, *J* = 2.4 Hz, 1H, H5), 1.41–1.21 (m, 1H, H7), 1.21 (d, *J* = 6.4 Hz, 3H, C*H*$_3$), 0.74–0.56 (m, 2H, H8), 0.32 (dt, *J* = 4.8, 2.9 Hz, 2H, H8).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 127.2, 79.9, 75.3, 73.6, 55.3, 24.5, 15.8, 7.5.

HR–MS (ESI+): calculated for $C_{10}H_{15}O$ $[M+H]^+$ 151.1123, found 151.1119.

IR (thin film, ν_{max}/cm^{-1}): 3015, 2925, 2857, 2342, 1724, 1260, 1027, 801..

(*E*)-(3-(But-2-yn-1-yloxy)but-1-en-1-yl)cyclopropane, 138



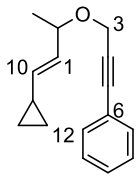
The title compound was prepared with *general procedure G* using **136a** (168 mg, 1.50 mmol, 1.0 eq.) and 1-bromobut-2-yne (160 µL, 2.3 mmol, 1.5 eq.). Purification by flash column chromatography (eluent: 5% ethyl acetate in petroleum ether) afforded the title compound (227 mg, 1.43 mmol, 93%) as a yellow oil. Spectroscopic data agrees with literature.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.38–5.20 (1H, m, H1), 5.10 (1H, dd, *J* = 15.3, 8.7 Hz, H7), 4.02 (1H, dq, *J* = 17.3, 2.4 Hz, H2), 3.86 (2H, ddd, *J* = 14.1, 7.2, 2.2 Hz, H3), 1.86 (3H, s, C*H*$_3$), 1.31 (1H, app dq, *J* = 8.4, 3.9 Hz, H8), 1.25–1.11 (3H, t, *J* = 4.8 Hz, H6), 0.77–0.54 (2H, m, H9), 0.31 (2H, tdd, *J* = 7.3, 5.4, 3.2 Hz, H9).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6, 128.6, 81.6, 76.7, 75.7, 55.4, 21.6, 15.6, 13.3, 6.9, 3.9.

Spectroscopic data was in agreement with literature.[15]

(*E*)-(3-((4-Cyclopropylbut-3-en-2-yl)oxy)prop-1-yn-1-yl)benzene, 139



The title compound was prepared with *general procedure G* using **136a** (30 mg, 0.20 mmol, 1.0 eq.) and (3-bromoprop-1-yn-1-yl)benzene (30 mg, 0.30 mmol, 1.0 equiv.). The product was purified by flash chromatography (eluent: 5% ethyl acetate in petroleum ether) to yield the title compound (16 mg, 0.78 mmol, 36%) as an orange oil.

R_f: 0.35 (10% ethyl acetate in petroleum ether).

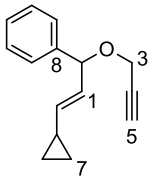
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.29 (2H, m, H7), 7.26–7.20 (3H, m, H8, H9), 5.34 (1H, dd, *J* = 15.3, 8.2 Hz, H1), 5.16 (1H, dd, *J* = 15.3, 8.7 Hz, H10), 4.30 (1H, d, *J* = 15.6 Hz, H3), 4.17 (1H, d, *J* = 15.6 Hz, H3), 3.98 (1H, dd, *J* = 8.2, 6.3 Hz, H2), 1.44–1.25 (1H, m, H11), 1.22 (3H, d, *J* = 6.3 Hz, CH3), 0.74–0.55 (2H, m, H12), 0.33 (2H, tt, *J* = 4.6, 3.0 Hz, H12).

^{13}C NMR (100 MHz, CDCl3): δ 138.0, 131.7, 130.1, 128.4, 128.2, 122.8, 85.8, 76.7, 75.4, 55.5, 21.6, 13.3 7.0, 6.8.

HR–MS (ESI+): calculated for $C_{16}H_{18}ONa$ $[M+Na]^+$ 249.1250, found 249.1251.

IR (thin film, ν_{max}/cm^{-1}): 2926, 1662, 157, 1489, 1471, 1438, 1369, 1067.

(*E*)-(3-Cyclopropyl-1-(prop-2-yn-1-yloxy)allyl)benzene, 140



The title compound was prepared with *general procedure G* using **136b** (174 mg, 1.00 mmol, 1.0 eq.) and propargylic bromide (180 mg, 1.50 mmol, 1.5 eq.). The crude product was purified by flash chromatography (eluent: 3% ethyl acetate in petroleum ether) to yield the title compound (160 mg, 1.11 mmol, 75%) as a yellow oil.

R_f: 0.31 (10% ethyl acetate in petroleum ether).

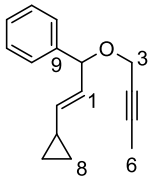
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18–7.09 (2H, m, H10), 7.08–6.99 (3H, m, H9, H11), 5.42 (1H, dd, *J* = 15.3, 7.7 Hz, H1), 5.06 (1H, dd, *J* = 15.3, 8.9 Hz, H6), 4.73 (1H, d, *J* = 7.7 Hz, H2), 3.98–3.84 (2H, m, H3), 2.19 (1H, t, *J* = 2.4 Hz, H5), 1.22–1.04 (1H, m, H6), 0.58–0.42 (2H, m, H7), 0.22–0.12 (2H, m, H7).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7, 138.5, 132.6, 128.4, 128.1, 127.1, 126.5, 83.2, 80.9, 55.1,13.5, 6.9.

HR–MS (ESI+): calculated for $C_{15}H_{16}ONa$ $[M+Na]^+$ 235.1099, found 235.1099.

IR (thin film, ν_{max}/cm^{-1}): 3005, 1719, 1600, 1493, 1450, 1269, 1175, 1064, 1025, 964.

(*E*)-(1-(But-2-yn-1-yloxy)-3-cyclopropylallyl)benzene, 141



The title compound was prepared with *general procedure G* using **136b** (174 mg, 1.00 mmol, 1.0 eq.) and 1-bromobut-2-yne (200 mg, 1.50 mmol, 1.5 eq.). The crude product was purified by flash column chromatography to yield the title compound (202 mg, 0.88 mmol, 88%) as a yellow oil.

R_f: 0.25 (10% ethyl acetate in petroleum ether).

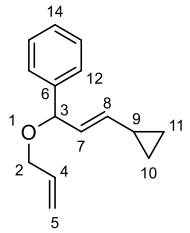
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.21 (3H, m, H12, H13), 7.19 (2H, m, H11), 5.57 (1H, dd, *J* = 15.4, 7.5 Hz, H1), 5.18 (1H, dd, *J* = 15.3, 8.8 Hz, H7), 4.83 (1H, d, *J* = 7.5 Hz, H2), 3.98 (2H, m, H3), 1.78 (3H, t, *J* = 2.3 Hz, H6), 1.44–1.24 (1H, m, H7), 0.63 (2H, dt, *J* = 8.2, 2.6 Hz, H8), 0.44–0.21 (2H, m, H8).

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.0, 138.0, 128.4, 127.5, 126.9, 82.1, 80.8, 75.3, 55.6, 14.1, 13.5, 6.9, 3.7.

HR–MS (ESI+): calculated for $C_{16}H_{18}ONa$ $[M+Na]^+$ 249.1249, found 249.1251.

IR (thin film, ν_{max}/cm^{-1}): 3005, 2921, 2854, 1663, 1493, 1451, 1357, 1155, 1135, 1023, 962.

(*E*)-(1-(allyloxy)-3-cyclopropylallyl)benzene, 143



The title compound was prepared with *general procedure G* using **136b** (174 mg, 1.00 mmol, 1.0 eq.) and 3-bromoprop-1-ene (180 mg, 1.50 mmol, 1.5 eq.). The crude product was purified by flash column chromatography to yield the title compound (75 mg, 0.35 mmol, 35%) as a yellow oil.

R_f: 0.18 (10% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.27 (4H, m, H12,13), 7.22–7.10 (1H, m, H14), 5.86 (1H, ddt, *J* = 17.3, 10.4, 5.6 Hz, H4), 5.64–5.43 (1H, m, H7), 5.28–5.01 (3H, m, H3,5), 4.67 (1H, dd, *J*

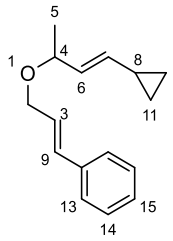
= 7.5, 1.0 Hz, H8), 3.88 (2H, qdt, *J* = 12.8, 5.5, 1.5 Hz, H2), 1.35–1.24 (1H, m, H9), 0.76–0.52 (2H, m, H10), 0.40–0.17 (2H, m, H11).

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 137.3, 135.0, 128.4, 128.3, 127.4, 126.8, 116.8, 81.7, 68.9, 13.5, 6.9.

HR–MS (ESI+): calculated for $C_{15}H_{18}O$ $[M+H]^+$ 215.1436, found 215.1425.

IR (thin film, ν_{max}/cm^{-1}): 2950, 2896, 1777, 1027, 1165, 951.

((*E*)-3-(((*E*)-4-cyclopropylbut-3-en-2-yl)oxy)prop-1-en-1-yl)benzene, 144



The title compound was prepared with *general procedure G* using **136a** (30 mg, 0.20 mmol, 1.0 eq.) and (*E*)-(2-bromovinyl)benzene (27 mg, 0.15 mmol, 1.5 eq.). The crude product was purified by flash column chromatography to yield the title compound (30 mg, 0.13 mmol, 67%) as a pale-yellow oil.

R_f: 0.18 (10% ethyl acetate in petroleum ether).

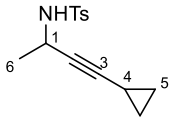
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.21 (5H, m, H13,14,15), 6.71 (1H, d, *J* = 16.0 Hz, H9), 6.24 (1H, ddt, *J* = 18.6, 15.9, 6.0 Hz, H3), 5.38 (1H, dd, *J* = 15.4, 7.9 Hz, H6), 5.08 (1H, dd, *J* = 15.4, 8.7 Hz, H7), 4.17–4.09 (1H, app. m, H4), 3.93 (1H, d, *J* = 12.7, Hz, H2), 3.86–3.75 (1H, app. m, H2), 1.40–1.07 (1H, m, H8), 0.80 (3H, ddd, *J* = 12.9, 10.9, 5.4 Hz, H5), 0.66 (2H, dt, *J* = 8.2, 1.5 Hz, H11), 0.40–0.22 (2H, m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.9, 136.7, 131.8, 129.4, 128.6, 128.5, 127.7, 126.7, 126.5, 126.1, 70.7, 21.7, 13.3, 6.8.

HR–MS (ESI+): calculated for $C_{16}H_{21}O$ $[M+H]^+$ 229.1592, found 222.1578.

IR (thin film, ν_{max}/cm^{-1}): 3081, 3026, 2924, 1944, 1724, 1664, 1495, 1314, 1099, 982.

_N_-(4-Cyclopropylbut-3-yn-2-yl)-4-methylbenzenesulfonamide, 148a



The title compound was prepared with *general procedure H* using *N*-methylidene-4-methylbenzenesulfonamide (986 mg, 5.00 mmol, 1.0 equiv.) and ethynylcyclopropane (710 mg, 6.00 mmol, 1.2 equiv.). Purification by flash chromatography afforded the title compound (500 mg, 1.67 mmol, 33%) as a white solid.

R_f: 0.17 (10% ethyl acetate in petroleum ether).

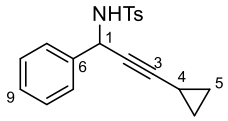
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72–7.65 (2H, m, Ts*H*), 7.27–7.21 (2H, m, Ts*H*), 4.75 (1H, d, *J* = 8.5 Hz, N*H*), 4.06 (1H, qd, *J* = 7.0, 1.7 Hz, H1), 2.36 (3H, s, TsCH_3), 1.29 (3H, d, *J* = 6.9 Hz, H6), 0.94–0.82 (1H, m, 4H), 0.58–0.47 (2H, m, H5), 0.28–0.18 (2H, m, H5).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.3, 144.8, 133.2, 130.7, 88.2, 78.3, 42.6, 22.7, 22.5, 15.4, 8.8.

HR–MS (ESI+): calculated for $C_{14}H_{17}O_2NNaS$ $[M+Na]^+$ 286.0872, found 286.0873.

IR (thin film, ν_{max}/cm^{-1}): 3266, 2242, 1598, 1426, 1329, 1157, 1092.

_N_-(3-Cyclopropyl-1-phenylprop-2-yn-1-yl)-4-methylbenzenesulfonamide, 148b



The title compound was prepared with *general procedure H* using *N*-benzylidene-4-methylbenzenesulfonamide (1.36 g, 5.20 mmol, 1.0 eq.) and ethynylcyclopropane (730 mg, 6.24 mmol, 1.2 eq.). Purification by flash column chromatography afforded the title compound as a white solid (1.33 g, 79%).

R_f: 0.50 (25% ethyl acetate in petroleum ether).

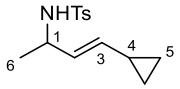
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (2H, d, J = 8.3 Hz, Ts*H*), 7.44–7.32 (2H, m, Ts*H*), 7.27 – 7.11 (5H, m, H7, H8, H9), 5.19 (1H, d, *J* = 9.0 Hz, HNH), 4.74 (1H, d, *J* = 9.0 Hz, H1), 2.37 (3H, s, TsC*H*$_3$), 0.96 (1H, tt, *J* = 8.3, 5.0 Hz, H4), 0.63–0.51 (2H, m, H5), 0.35–0.21 (2H, m, H5).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 138.8, 138.4, 130.2, 129.4, 129.0, 128.2, 128.0, 91.1, 77.5, 72.6, 50.2, 22.3, 8.8.

HR–MS (ESI+): calculated for $C_{19}H_{19}O_2NNaS$ $[M+Na]^+$ 348.1029, found 348.1029.

IR (thin film, ν_{max}/cm^{-1}): 3285, 2242, 1598, 1327, 1159.

(*E*)-*N*-(4-Cyclopropylbut-3-en-2-yl)-4-methylbenzenesulfonamide, 149a



The title compound was prepared with *general procedure F* using **148a** (500 mg, 1.90 mmol, 1.0 eq.) and lithium aluminum hydride (4.0 M in diethyl ether, 0.5 mL, 3.8 mmol, 2.0 eq.) in refluxing tetrahydrofuran. The crude product was used without further purification.

R_f: 0.15 (10% ethyl acetate in petroleum ether).

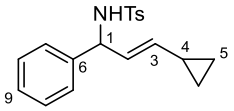
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60–7.49 (2H, m, Ts*H*), 7.10–7.01 (2H, m, Ts*H*), 5.02 (1H, dd, *J* = 15.3, 6.5 Hz, H2), 4.68 (1H, dd, *J* = 15.3, 8.9 Hz, H3), 4.17 (1H, d, *J* = 7.3 Hz, NH), 3.65 (1H, q, *J* = 6.6 Hz, H1), 2.22 (3H, s, TsCH_3), 1.04–0.97 (1H, m, H4), 0.95 (3H, d, *J* = 6.7 Hz, H6), 0.48–0.36 (2H, m, H5), 0.01 (2H, dt, *J* = 6.2, 4.4 Hz, H5).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 138.2, 135.7, 129.5, 128.1, 127.2, 51.3, 22.0, 21.5, 13.1, 6.5.

HR–MS (ESI+): calculated for $C_{14}H_{19}O_2NNaS$ $[M+Na]^+$ 288.1029, found 288.1030.

IR (thin film, ν_{max}/cm^{-1}): 3277, 2927, 1666, 1495, 1325, 1158, 1094.

(*E*)-*N*-(3-Cyclopropyl-1-phenylallyl)-4-methylbenzenesulfonamide, 149b



The title compound was prepared with *general procedure F* using **148b** (1.33 g, 4.10 mmol, 1.0 eq.) and lithium aluminum hydride (4.0 M in diethyl ether, 2.0 mL, 8.20 mmol, 2.0 eq.) in refluxing tetrahydrofuran. Crude material was used without further purification.

R_f: 0.49 (25% ethyl acetate in petroleum ether).

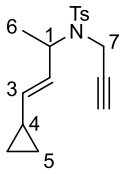
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (2H, d, *J* = 8.3 Hz, Ts*H*), 7.55 (2H, d, *J* = 8.3 Hz, Ts*H*), 7.29–7.19 (2H, m, H7), 7.16–6.96 (3H, m, H8, H9), 5.39 (1H, dd, *J* = 15.1, 6.9 Hz, H2), 4.90–4.82 (2H, m, H3, N*H*), 4.62 (1H, d, *J* = 7.0 Hz, H1), 2.33 (3H, s, TsCH_3), 1.21–1.13 (1H, m, H4), 0.63–0.49 (2H, m, H5), 0.18–0.13 (2H, m, H5).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.4, 141.8, 138.6, 136.5, 129.1, 128.8, 128.6, 126.9, 125.8, 121.1, 57.2, 20.0, 14.6, 6.9.

HR–MS (ESI+): calculated for $C_{19}H_{21}O_2NNaS$ $[M+Na]^+$ 350.1185, found 350.1185.

IR (thin film, ν_{max}/cm^{-1}): 3775, 3356, 3260, 3028, 2922, 2852, 2233, 1659, 1301.

(*E*)-*N*-(4-cyclopropylbut-3-en-2-yl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide, 150



The title compound was prepared with *general procedure F* using **149a** (28 mg, 0.10 mmol, 1.0 eq.) and propargylic bromide (18 mg, 0.15 mmol, 1.5 eq.). Purification by flash column chromatography afforded the title compound as an orange oil (12 mg, 0.03 mmol, 29%).

R_f: 0.39 (10% ethyl acetate in petroleum ether).

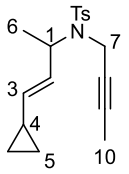
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.4 Hz, Ts*H*), 7.23–7.17 (m, 2H, Ts*H*), 5.34 (dd, *J* = 15.5, 5.5 Hz, H2), 4.94 (dd, *J* = 15.5, 8.7 Hz, 1H, H3), 4.41 (qdd, *J* = 7.0, 5.3, 1.6 Hz, 1H, H1), 4.05 (dd, *J* = 18.5, 2.5 Hz, 1H, H7), 3.84 (dd, *J* = 18.5, 2.5 Hz, 1H, H7), 2.35 (s, 3H, TsC*H*$_3$), 2.08 (t, *J* = 2.5 Hz, 1H, H9), 1.54–1.48 (m, 1H, H4), 1.17 (d, *J* = 6.4 Hz, 3H, H6), 0.60 (dt, *J* = 8.1, 2.1 Hz, 2H, H5), 0.27–0.19 (m, 2H, H5).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 143.1, 137.9, 129.5, 127.9, 126.2, 80.4, 72.1, 54.5, 36.1, 32.1, 22.7, 18.0, 6.73.

HR–MS (ESI+): calculated for $C_{17}H_{21}O_2NNaS$ $[M+Na]^+$ 326.1185, found 326.1185.

IR (thin film, ν_{max}/cm^{-1}): 3291, 3024, 2925, 2855, 2360, 2117, 1447, 1349, 1162, 1117, 956, 814.

(*E*)-*N*-(But-2-yn-1-yl)-*N*-(4-cyclopropylbut-3-en-2-yl)-4-methylbenzenesulfonamide, 151



The title compound was prepared with *general procedure F* using **149a** (28 mg, 0.10 mmol, 1.0 eq.) and 1-bromobut-2-yne (10 mg, 0.075 mmol, 1.5 eq.). Purification by flash column chromatography afforded the title compound as an orange oil (12 mg, 0.04 mmol, 78%).

R_f: 0.42 (10% ethyl acetate in petroleum ether).

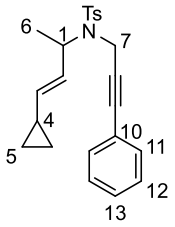
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62–7.53 (2H, m, Ts*H*), 7.07–7.03 (2H, m, Ts*H*), 5.19 (1H, dd, *J* = 15.5, 5.6 Hz, H2), 4.78 (1H, dd, *J* = 15.5, 8.7 Hz, H3), 4.33–4.20 (1H, m, H1), 3.88–3.75 (1H, m, H7), 3.64 (1H, dq, *J* = 18.2, 2.3 Hz, H7), 2.20 (3H, s, TsCH_3), 1.46 (3H, t, *J* = 2.4 Hz, H10), 1.07 (1H, dtd, *J* = 11.5, 7.6, 3.9 Hz, H4), 1.00 (3H, d, *J* = 6.9 Hz, H6), 0.48–0.39 (2H, m, H5), 0.13–0.00 (2H, m, H5).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 138.2, 129.2, 128.0, 126.6, 79.9, 76.7, 75.5, 54.4, 32.7, 21.5, 18.1, 13.4, 6.7, 3.4.

HR–MS (ESI+): calculated for $C_{18}H_{23}O_2NNaS$ $[M+Na]^+$ 340.1342, found 340.1343.

IR (thin film, ν_{max}/cm^{-1}): 3735, 3291, 3024, 2925, 2855, 2360, 2117, 1716, 1662, 1541, 1305, 1162.

(*E*)-*N*-(3-cyclopropylbut-2-en-1-yl)-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide, 152



The title compound was prepared with *general procedure F* using **149a** (28 mg, 0.10 mmol, 1.0 eq.) and (3-bromoprop-1-yn-1-yl)benzene (29 mg, 0.15 mmol, 1.5 eq.). Purification by flash column chromatography afforded the title compound as an orange oil (30 mg, 0.64 mmol, 64%).

R_f: 0.38 (10% ethyl acetate in petroleum ether).

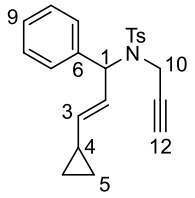
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80–7.69 (m, 2H, Ts*H*), 7.29–7.10 (m, 7H, H10–13, Ts*H*), 5.43 (dd, *J* = 15.5, 5.6 Hz, 1H, H2), 4.97 (dd, *J* = 15.4, 8.8 Hz, 1H, H3), 4.51 (dq, *J* = 7.0, 5.4 Hz, 1H, H1), 4.26 (d, *J* = 18.6 Hz, 1H, H7), 4.12 (d, *J* = 18.6 Hz, 1H, H7), 2.29 (s, 3H, TsC*H*$_3$), 1.25–1.16 (m, 1H, H4), 1.16 (s, 3H, H6), 0.66–0.52 (m, 2H, H5), 0.31–0.15 (m, 2H, H5).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.9, 138.4, 137.2, 131.4, 129.3, 128.2, 128.1, 127.6, 126.6, 122.7, 85.8, 84.1, 54.5, 33.0, 21.4, 18.1, 13.5, 6.8.

HR–MS (ESI+): calculated for $C_{23}H_{25}O_2NNaS$ $[M+Na]^+$ 402.1498, found 402.1501.

IR (thin film, ν_{max}/cm^{-1}): 3004, 2449, 1662, 1334, 1160, 1093, 1010, 907.

(*E*)-*N*-(3-cyclopropyl-1-phenylallyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide, 153



The title compound was prepared with *general procedure F* using **149b** (32 mg, 0.10 mmol, 1.0 eq.) and propargylic bromide (16 mg, 0.15 mmol, 1.5 eq.). Purification by flash column chromatography afforded the title compound as an orange oil (28 mg, 0.66 mmol, 66%).

R_f: 0.50 (10% ethyl acetate in petroleum ether).

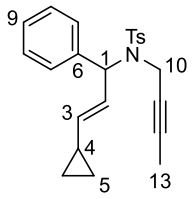
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67–7.50 (m, 2H, Ts*H*), 7.28–6.88 (m, 7H, H7,8,9, Ts*H*), 5.61 (dd, *J* = 15.2, 8.5 Hz, 1H, H2), 5.27 (dd, *J* = 8.5, 2.5 Hz, 1H, H3), 4.86–4.66 (m, 1H, H1), 3.87 (dd, *J* = 18.5, 2.5, 1H, H10), 3.55 (dd, *J* = 18.5, 2.5 Hz, 1H, H10), 2.21 (s, 3H, TsC*H*$_3$), 1.84 (t, *J* = 2.5 Hz, 1H, H12), 1.28–0.98 (m, 1H, H4), 0.50–0.35 (m, 2H, H5), 0.16–0.00 (m, 2H, H5).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 139.6, 138.7, 137.7, 129.1, 128.4, 127.9, 123.5, 122.8, 81.2, 72.6, 69.8, 63.9, 57.9, 32.7, 11.6, 7.2.

HR–MS (ESI+): calculated for $C_{22}H_{24}O_2NS$ $[M+H]^+$ 366.1528, found 366.1518.

IR (thin film, ν_{max}/cm^{-1}): 3060, 3004, 2538, 1934, 1851, 1186, 1161, 1018, 898.

(*E*)-*N*-(But-2-yn-1-yl)-*N*-(3-cyclopropyl-1-phenylallyl)-4-methylbenzenesulfonamide, 154



The title compound was prepared with *general procedure F* using **149n** (16 mg, 0.05 mmol, 1.0 eq.) and 1-bromobut-2-yne (10 mg, 0.075 mmol, 1.5 eq.). Purification by flash column chromatography afforded the title compound as an orange oil (12 mg, 0.067 mmol, 67%).

R_f: 0.47 (10% ethyl acetate in petroleum ether).

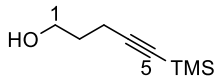
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63–7.55 (2H, m, Ts*H*), 7.20–7.12 (2H, m, Ts*H*), 7.12–7.07 (2H, m, H7), 7.04–6.99 (3H, m, H8, H9), 5.62 (1H, dd, *J* = 15.2, 8.5 Hz, H2), 5.28 (1H, d, *J* = 8.5 Hz, H1), 4.78 (1H, dd, *J* = 15.3, 8.5 Hz, H3), 3.92 (1H, dq, *J* = 11.4, 2.4 Hz, H10), 3.50 (1H, dq, *J* = 18.2, 2.4 Hz, H10), 2.22 (3H, s, TsC*H*$_3$), 1.38 (3H, t, *J* = 2.4 Hz, H13), 1.15–1.04 (1H, m, H4), 0.50–0.37 (2H, m, H5), 0.00 (2H, dqq, *J* = 9.5, 4.8, 2.7, 2.2 Hz, H5).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 139.2, 137.9, 129.2, 128.9, 128.3, 128.1, 127.8, 127.5, 123.0, 80.7, 74.9, 63.0, 34.3, 21.5, 13.2, 6.7, 6.3, 3.3.

HR–MS (ESI+): calculated for $C_{23}H_{26}NO_2S$ $[M+H]^+$ 380.1684, found 380.1675.

IR (thin film, ν_{max}/cm^{-1}): 3735, 3268, 3030, 2922, 2842, 2380, 1541, 1329, 1154.

5-(Trimethylsilyl)pent-4-yn-1-ol, 155a



To a stirred solution of 3-butyn-1-ol (422 mg, 5.0 mmol, 1.0 eq.) in 20 mL anhydrous tetrahydrofuran at −78 °C was added *n*-butyllithium (1.18 M in hexane, 9.3 mL, 10.0 mmol, 2.0 eq.) dropwise over 20 min. After stirring at −78 °C for 1 h, trimethylsilyl chloride (1.09 g, 10.0 mmol, 2.0 eq.) was added. The resultant suspension was warmed to room temperature and stirred for a further 1 h, before poured into 20 mL hydrochloric acid (1N, aq.) and 20 mL diethyl ether. Reaction mixture was stirred at room temperature overnight until complete consumption of starting material. The aqueous layer was extracted with diethyl ether (3 x 20 mL), washed with brine (20 mL), dried over magnesium sulfate and concentrated. Crude product was purified by flash column chromatography (eluent: 100% dichloromethane) to yield the title compound as a clean oil (780 mg, 5.0 mmol, >98%).

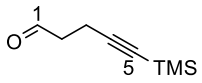
R_f: 0.66 (30% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (2H, t, *J* = 8.0 Hz, H1), 2.37 (2H, t, *J* = 8.0 Hz, H3), 1.79 (2H, q, *J* = 8.0 Hz, H2), 0.16 (9H, s, SiCH_3).

^{13}C NMR (100 MHz, CDCl3): δ 106.7, 84.6, 60.8, 31.0, 16.0, 0.0.

Spectroscopic data was in agreement with literature.[14]

5-(Trimethylsilyl)pent-4-ynal, 155b



Oxalyl chloride (438 mg, 3.45 mmol, 1.5 eq.) was dissolved in anhydrous dichloromethane at −78 °C. Dimethyl sulfoxide (449 mg, 5.75 mmol, 2.5 eq.) was added dropwise, and the resultant mixture was stirred at −78 °C for 15 min, before a solution of **155a** (350 mg, 2.30 mmol, 1.0 eq.) in dichloromethane was added. After stirring at −78 °C for further 60 min, trimethylamine (1.59 mL, 11.5 mmol, 5.0 eq.) was added. Reaction mixture was warmed to room temperature and stirred until complete consumption of starting material, then participated between dichloromethane and water. The aqueous layer was extracted with dichloromethane, washed in tandem with 20 mL hydrochloric acid (1 N, aq.), 15 mL sodium carbonate (sat., aq.) and 30 mL brine, dried over magnesium sulfate and concentrated. Crude material was purified by flash column chromatograph (eluent: 50% ethyl acetate in petroleum ether) to give the title compound as a clean oil (182 mg, 1.38 mmol, 60%). Spectroscopic data was in agreement with literature.

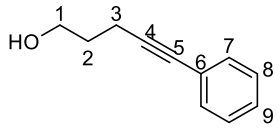
R_f: 0.60 (25% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.65 (1H, t, *J* = 1.2 Hz, H1), 1.22–1.05 (2H, m, H2), 0.79–0.63 (2H, m, H3), 0.00 (6H, d, *J* = 1.1 Hz, HSiCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.5, 107.6, 81.3, 41.0, 17.0, 0.0.

Spectroscopic data was in agreement with literature.[198]

5-Phenylpent-4-yn-1-ol, 155c



A 100 mL round-bottomed flask was charged with a stirrer bar and cooled under argon. Tetrakis(triphenylphosphine)palladium (185 mg, 0.16 mmol, 0.8 mol%) and copper iodide (61 mg, 0.32 mmol, 1.6 mol%) was suspended in anhydrous triethylamine (56 mL, 400.0 mmol, 20.0 eq.) A solution of pent-4-yn-1-ol (1.9 mL, 20.0 mmol, 1.0 eq.) and iodobenzene (4.5 mL, 40.0 mmol, 2.0 eq.) in 10 mL anhydrous tetrahydrofuran was added into reaction mixture dropwise over a period of 20 min. The resultant mixture was stirred at room temperature overnight. After 16 h, reaction was filtered through Celite with diethyl ether, concentrated under reduced pressure, and purified by flash column chromatography (eluent: 20% ethyl acetate in petroleum ether) to yield the title compound as a yellow oil (2.93 g, 18.2 mmol, 91%).

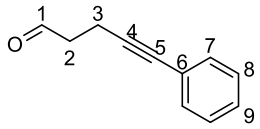
R_f: 0.15 (20% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.28 (1H, m, H7), 7.27–7.10 (3H, m, H8, H9), 3.74 (2H, t, *J* = 6.2 Hz, H3), 2.46 (2H, t, J = 6.9 Hz, H2), 1.86–1.73 (2H, q, J = 6.4 Hz, H1).

^{13}C NMR (100 MHz, CDCl3): δ 131.5, 128.2, 127.7, 123.7, 89.3, 81.1, 61.8, 31.3, 16.0.

Spectroscopic data was in agreement with literature.[199]

5-Phenylpent-4-ynal, 155d



A 100 mL round-bottomed flask was charged with a stirrer bar and cooled under argon. Anhydrous dimethyl sulfoxide (3.1 mL, 43.8 mmol, 2.5 eq.) was dissolved in 20 mL anhydrous dichloromethane. Reaction was cooled to −78 °C in a dry-ice–acetone bath and added oxalyl chloride (2.3 mL, 26.3 mmol, 1.5 eq.) dropwise over a period of 10 min. The resultant mixture was stirrer at −78 °C for 30 min, then slowly warmed to −40 °C in a dry-ice–acetonitrile bath. A solution of **155c** (2.80 g, 17.5 mmol, 1.0 eq.) in 20 mL dichloromethane was added, and reaction mixture was immediately warmed to room temperature. After 1 h, anhydrous trimethylamine (12.2 mL, 87.5 mmol, 5.0 eq.) was added. Reaction was allowed to stir at room temperature for a further 4 h, before quenched with distilled water (25 mL). The aqueous layer was extracted with dichloromethane (50 mL), washed with brine (30 mL, sat., aq.), hydrochloric acid (20 mL, 1N, aq.), sodium hydroxide (20 mL, 1M, aq.), bleach (20 mL), dried over magnesium sulfate, filtered, and concentrated to give a red oil. Purification with flash column chromatography (eluent: 50% dichloromethane in pentane) afforded the title compound as a red oil (1.64 g, 10.5 mmol, 60%).

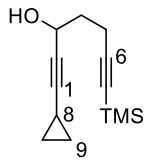
R_f: 0.79 (35% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (1H, d, *J* = 1.2 Hz, H1), 7.35–7.26 (2H, m, H7), 7.27–7.11 (3H, m, H8, H9), 2.73 – 2.60 (4H, m, H2, H3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.4, 131.5, 128.2, 123.3, 102.2, 89.4, 87.7, 42.6, 12.7.

Spectroscopic data was in agreement with literature.[200]

1-Cyclopropyl-7-(trimethylsilyl)hepta-1,6-diyn-3-ol, 156a



The title compound was prepared with *general procedure H* using **155b** (600 mg, 3.90 mmol, 1.0 eq.) and cyclopropyl acetylene (0.4 mL, 4.68 mmol, 1.2 eq.). Crude material was purified by flash column chromatography (eluent: 10% diethyl ether in petroleum ether) to yield the title compound as a pale-yellow oil (598 mg, 2.73 mmol, 70%).

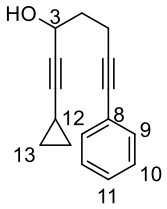
R_f: 0.43 (10% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.55–4.23 (1H, m, H3), 2.38–2.16 (2H, m, H4), 1.77–1.62 (2H, m, H5), 1.02–0.91 (1H, m, H8), 0.65–0.47 (4H, m, H9), 0.10 (9H, s, SiC*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): 106.2, 65.8, 61.6, 41.2, 36.6, 28.9, 22.5, 15.2, 11.3, 8.2, 0.0.

Spectroscopic data was in agreement with literature.[14]

1-Cyclopropyl-7-phenylhepta-1,6-diyn-3-ol, 156b



A 100 mL round-bottomed flask was dried in oven overnight, charged with a stirrer bar, evacuated and backfilled with argon for three times. Ethynylcyclopropane (1.0 mL, 12.0 mmol, 1.2 eq.) was dissolved in 20 mL anhydrous tetrahydrofuran at −78 °C in a dry-ice–acetone bath. n-Butyl lithium (1.18 M in hexane, 9.2 mL, 11.0 mmol, 1.1 eq.) was added dropwise over a period of 20 min and the resultant mixture was stirred at −78 °C for 15 min. A solution of **155c** (1.60 g, 10.0 mmol, 1.0 eq.) in 10 mL tetrahydrofuran was added dropwise over a period of 10 min. Reaction was allowed to warm to room temperature and stirred for a further 2 h.

Upon completion, reaction was quenched with ammonium chloride (20 mL, sat., aq.) extracted with ethyl acetate (3 × 50 mL), washed with brine (30 mL, sat., aq.), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil. Purification with flash column chromatography afforded the title compound as a yellow oil (1.68 g, 7.5 mmol, 75%).

R_f: 0.53 (25% ethyl acetate in petroleum ether).

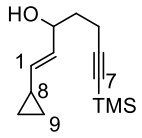
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.26 (2H, m, H10), 7.26–7.13 (3H, m, H9, H11), 4.47 (1H, td, *J* = 6.4, 1.7 Hz, H3), 2.60–2.42 (2H, m, H5), 1.94–1.84 (2H, m, H4), 1.23–1.14 (1H, m, H12), 0.74–0.66 (2H, m, H13), 0.66–0.59 (2H, m, H13).

^{13}C NMR (100 MHz, $CDCl_3$): δ 132.2, 128.8, 128.3, 124.3, 89.9, 89.6, 81.8, 76.3, 62.2, 37.5, 16.1, 8.9, 0.0.

HR–MS (ESI+): calculated for $C_{16}H_{17}O$ $[M+H]^+$ 225.1201, found 225.1191.

IR (thin film, ν_{max}/cm^{-1}): 3394, 2980, 2359, 2240, 1736, 1598, 1571, 1490, 1442, 1374, 1243, 1155, 1056.

(*E*)-1-Cyclopropyl-7-(trimethylsilyl)hept-1-en-6-yn-3-ol, 157



The title compound was prepared with *general procedure F* using **156a** (129 mg, 0.60 mmol, 1.0 eq.). Crude material was purified by flash column chromatography (eluent: 20% diethyl ether in petroleum ether) to yield the title compound as a clean oil (120 mg, 0.53 mmol, 88%).

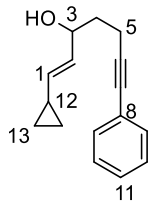
R_f: 0.53 (25% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.53 (1H, dd, *J* = 15.4, 7.1 Hz, H1), 5.19 (1H, dd, *J* = 15.4, 8.8 Hz, H2), 4.16 (1H, m, H3), 2.31 (2H, m, H4), 1.78–1.65 (2H, m, H5), 1.42–1.32 (1H, m, H8), 0.71–0.61 (2H, m, H9), 0.36–0.24 (2H, m, H9), 0.14 (9H, s, SiCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 136.3, 129.6, 106.9, 85.1, 71.9, 35.8, 16.3, 13.4, 6.8, 0.1.

Spectroscopic data was in agreement with literature.[14]

(*E*)-1-Cyclopropyl-7-phenylhept-1-en-6-yn-3-ol, 158



The title compound was prepared by *general procedure F* using **156b** (300 mg, 1.20 mmol, 1.0 eq.) and Red-Al (1.80 mmol, 1.5 eq.). The crude product was of sufficient purity to be used directly without further purification.

R_f: 0.42 (10% ethyl acetate in petroleum ether).

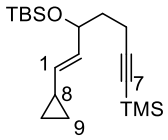
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.27 (2H, m, H9), 7.23–7.14 (3H, m, H10, 11), 5.50 (1H, dd, *J* = 15.3, 7.1 Hz, H2), 5.16 (1H, dd, *J* = 15.3, 8.9 Hz, H1), 4.24–4.04 (1H, m, H3), 2.43 (2H, t, *J* = 7.1 Hz, H4), 2.29 (1H, br, O*H*), 1.81–1.59 (2H, m, H5), 1.40–1.20 (1H, m, H12), 0.78–0.56 (2H, m, H13), 0.31 (2H, m, H13).

^{13}C NMR (100 MHz, $CDCl_3$): δ 128.5, 128.4, 122.2, 101.9, 88.9, 83.5, 80.3, 62.3, 61.9, 39.7, 12.2, 11.0, 0.0.

HR–MS (ESI+): calculated for $C_{16}H_{18}ONa$ $[M+Na]^+$ 249.1255, found 249.1235.

IR (thin film, ν_{max}/cm^{-1}): 3089, 2706, 2645, 2312, 1698, 1686, 1450, 1471.

(*E*)-*tert*-Butyl((1-cyclopropyl-7-(trimethylsilyl)hept-1-en-6-yn-3-yl)oxy)dimethylsilane, 159



The title compound was prepared with *general procedure I* using **157** (110 mg, 0.50 mmol, 1.0 eq.) and *tert*-butyldimethylsilyl chloride (115 mg, 0.75 mmol, 1.5 eq.). Crude material was purified by flash column chromatography (eluent: 2% ethyl acetate in petroleum ether) to yield the title compound as a clean oil (190 mg, 0.50 mmol, >98%).

R_f: 0.89 (15% ethyl acetate in petroleum ether).

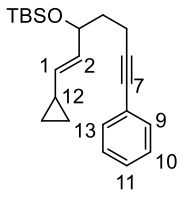
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.30 (1H, dd, *J* = 15.3, 6.9 Hz, H2), 4.96 (1H, dd, *J* = 15.3, 8.7 Hz, H2), 4.02 (1H, tdd, *J* = 7.1, 5.5, 1.1 Hz, H3), 2.23–1.99 (2H, m, H4), 1.61–1.44 (2H, m, H5), 1.28–1.14 (1H, m, H8), 0.74 (9H. s, Si*tBu*), 0.59–0.46 (2H, m, H9), 0.30–0.16 (2H, m, H9), 0.00 (9H, s, SiCH_3), –0.10 (6H, d, *J* = 10.6 Hz, SiCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.4, 130.3, 107.3, 84.4, 76.5, 71.9, 36.9, 25.8, 18.1, 15.9, 13.0, 6.4, 0.3, 0.0, –4.3.

HR–MS (ESI+): calculated for $C_{19}H_{36}ONaSi_2$ $[M+Na]^+$ 359.2197, found 359.2197.

IR (thin film, ν_{max}/cm^{-1}): 3007, 2956, 2929, 2857, 2360, 2175, 1667, 1472, 1361, 1249, 1083, 1047.

(*E*)-*tert*-Butyl((1-cyclopropyl-7-phenylhept-1-en-6-yn-3-yl)oxy)dimethylsilane, 160



The title compound was prepared with *general procedure I* using **158** (200 mg, 0.80 mmol, 1.0 eq.). Purification by flash chromatography afforded the title compound (226 mg, 0.62 mmol, 78%) as a yellow oil.

R_f: 0.90 (25% ethyl acetate in petroleum ether).

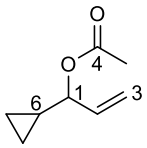
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.27 (2H, m, H13), 7.27–7.12 (3H, m, H10, 11), 5.44 (1H, dd, *J* = 15.3, 6.9 Hz, H2), 5.11 (1H, dd, *J* = 8.6, 1.0 Hz, H1), 4.26–4.08 (1H, m, H3), 2.50–2.24 (2H, m, H4), 1.85–1.55 (2H, m, H5), 1.35–1.25 (1H, m, H12), 0.82 (9H, s, Si*tBu*), 0.69–0.60 (2H, m, H13), 0.45–0.07 (2H, m, H13), 0.05 (3H, s, Si*CH*$_3$), –0.06 (3H, s, SiC*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.7, 131.5, 130.5, 128.2, 127.5, 90.2, 80.7, 72.2, 37.2, 25.9, 18.2, 15.5, 13.2, 6.5, □□□□□□□□□□□

HR–MS (ESI+): calculated for $C_{22}H_{32}ONaSi$ $[M+Na]^+$ 363.2116, found 363.2115.

IR (thin film, ν_{max}/cm^{-1}): 3082, 2006, 2856, 2308, 1666, 1598, 1490, 1471, 1252, 1079, 1052.

1-Cyclopropylallyl acetate, 161



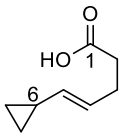
To a stirred solution of vinylmagnesium bromide (14.3 mL, 1.0 M in THF, 14.3 mmol, 1.0 eq.) in 50 mL anhydrous diethyl ether at 0 °C was added cyclopropanecarbaldehyde (1.0 g, 14.3 mmol, 1.0 eq.) dropwise. After stirring at 0 °C for 30 min, pyridine (1.4 mL, 17.2 mmol, 1.2 eq.) and acetic anhydride (1.8 mL, 17.2 mmol, 1.2 eq.) was added. The resultant mixture was warmed to room temperature and stirred for a further 3 h, before quenched by 2 mL methanol. Reaction mixture was participated between 50 mL diethyl ether and 50 mL water. The aqueous layer was extracted with diethyl ether (3 x 50 mL), washed with hydrochloric acid (50 mL, 1 N, aq.) and brine (50 mL), dried over magnesium sulfate and concentrated. Crude material was purified by flash column chromatography (eluent: 5% diethyl ether in petroleum ether) to afford the title compound as a clean oil (1.89 g, 13.6 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83 (1H, dd, *J* = 17.3, 10.5, Hz, H2), 5.26 (1H, d, *J* = 17.3 Hz, H3), 5.15 (1H, d, *J* = 10.5 Hz, H3), 4.74–4.64 (1H, m, H1), 2.07 (3H, s, H5), 1.08–1.02 (1H, m, H6), 0.59–0.50 (2H, m, H7), 0.43–0.78 (1H, m, H7), 0.33–0.27 (1H, m, H7).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 135.6, 116.5, 78.6, 21.3, 14.6, 3.5, 2.5.

Spectroscopic data was in agreement with literature.[37]

(*E*)-5-Cyclopropylpent-4-enoic acid, 162



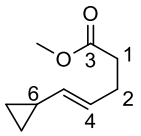
The title compound was prepared with *general procedure A* using **161** (1.40 g, 10.0 mmol, 1.0 eq.). Crude material was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.34 (1H, dt, *J* = 15.4, 6.7 Hz, H4), 4.87 (1H, dd, *J* = 15.2, 8.6 Hz, H4), 2.25 (2H, dd, *J* = 7.6, 6.9 Hz, H2), 2.22–2.09 (2H, m, H3), 1.44–0.97 (1H, m, H6), 0.67–0.31 (2H, m, H7), 0.16 (2H, m, H7).

^{13}C NMR (100 MHz, $CDCl_3$): δ 179.8, 135.5, 125.3, 34.2, 27.5, 13.5, 6.5.

Spectroscopic data was in agreement with literature.[37]

Methyl (*E*)-5-cyclopropylpent-4-enoate, 163



To a stirred solution of **162** (1.08 g, 7.8 mmol, 1.0 eq.) in 20 mL anhydrous dimethylformamide at 0 °C was added potassium carbonate (3.25 g, 38.0 mmol, 5.0 eq.) and iodomethane (1.5 mL, 23.4 mmol, 3.0 eq.). The resultant mixture was allowed to warm to room temperature and stirred for 2 h. Reaction mixture was participated between 20 mL sodium bicarbonate (sat., aq.) and 20 mL diethyl ether. The aqueous layer was extracted with diethyl ether (3 x 20 mL), washed with water and brine (1:1, 3 x 20 mL), dried over magnesium sulfate and concentrated under reduced pressure. Crude material was purified by flash column chromatography (eluent: 10% diethyl ether in petroleum ether) to yield the title compound as an orange oil (839 mg, 5.5 mmol, 71%).

R_f: 0.75 (20% ethyl acetate in petroleum ether).

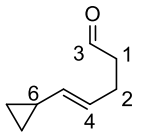
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.47–5.29 (1H, dt, *J* = 15.2, 8.4 Hz, H4), 4.90 (1H, ddt, *J* = 15.2, 8.6 Hz, H5), 3.55 (3H, s, OC*H*$_3$), 2.31–2.22 (2H, m, H1), 2.19 (2H, s, H2), 1.22 (1H, dddd, *J* = 13.2, 10.2, 8.2, 4.8 Hz, H6), 0.63–0.43 (2H, m, H7), 0.34–0.12 (2H, m, H7).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 135.3, 125.7, 51.5, 34.2, 27.8, 13.5, 6.4.

HR–MS (ESI+): calculated for $C_9H_{14}O_2Na$ $[M+Na]^+$ 177.0888, found 177.0886.

IR (thin film, ν_{max}/cm^{-1}): 3727, 3012, 2925, 2850, 2360, 2341, 1731, 1680, 1504, 1256, 1173, 1092.

(*E*)-5-Cyclopropylpent-4-enal, 164



To a stirred solution of **163** (796 mg, 5.2 mmol, 1.0 eq.) in 20 mL anhydrous dichloromethane at −78 °C was added diisobutylaluminium hydride (1.0 M in henxane, 7.7 mL, 7.7 mmol, 1.5 eq.) slowly over a period of 20 min. The resultant mixture was stirred at −78 °C for 20 min, before quenched with 20 mL Rochelle's salt (sat., aq.). After stirring at −78 °C for 1 h, the resultant suspension was allowed to slowly warm to room temperature and stirred for a further 2 h. The aqueous layer was extracted with dichloromethane (3 x 25 mL), dried over sodium sulfate, and concentrated under reduced pressure. Crude product was used without further purification.

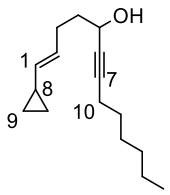
R_f: 0.46 (10% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (1H, t, *J* = 1.7 Hz, H3), 5.42 (1H, dt, *J* = 15.2, 6.6 Hz, H4), 4.94 (1H, dd, *J* = 15.2, 8.6 Hz, H5), 2.18–1.81 (2H, m, H1), 1.70–1.43 (2H, m, H2), 0.88–0.73 (1H, m, H6), 0.64–0.44 (2H, m, 7H), 0.32–0.17 (2H, m, H7).

HR–MS (ESI+): calculated for $C_8H_{13}O$ $[M+H]^+$ 125.0962, found 124.0888.

IR (thin film, ν_{max}/cm^{-1}): 3081, 2981, 2722, 2360, 2341, 2238, 1724, 1666, 1599, 1442, 1368, 1232, 1169, 1115, 1090.

(*E*)-1-Cyclopropyltridec-1-en-6-yn-5-ol, 165



The title compound was prepared with *general procedure H* using **164** (125 mg, 1.00 mmol, 1.0 eq.) and oct-1-yne (177 mg, 1.20 mmol, 1.2 eq.). Crude material was purified by flash column chromatography to yield the title compound as a clean oil (140 mg, 0.54 mmol, 54%).

R_f: 0.60 (20% ethyl acetate in petroleum ether).

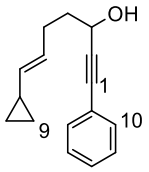
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.44 (1H, dt, *J* = 15.3, 6.8 Hz, H2), 4.95 (1H, dd, *J* = 15.3, 8.6 Hz, H1), 4.30 (1H, qt, *J* = 6.4, 1.8 Hz, H5), 2.20–2.03 (4H, m, H3,10), 1.74–1.55 (2H, m, H4), 1.47–1.36 (2H, m, H11), 1.34–1.12 (7H, m, H8,12,13,14), 0.82 (3H, t, *J* = 6.9 Hz, H15), 0.64–0.50 (2H, m, H9), 0.24 (2H, m, H9).

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.8, 126.9, 85.8, 81.1, 62.3, 37.9, 31.3, 28.6, 28.5, 28.2, 22.6, 18.7, 14.1, 13.5, 6.4.

HR–MS (ESI+): calculated for $C_{33}H_{56}O_3Na_2$ $[2M+H+Na+MeOH]^+$ 575.3688, found 575.3327.

IR (thin film, ν_{max}/cm^{-1}): 3081, 3006, 2929, 2857, 2387, 2234, 1742, 1640, 1045, 1018.

(*E*)-7-Cyclopropyl-1-phenylhept-6-en-1-yn-3-ol, 166



The title compound was prepared with *general procedure H* using **164** (125 mg, 1.00 mmol, 1.0 eq.) and phenylacetylene (110 mg, 1.20 mmol, 1.2 eq.). Crude material was purified by flash column chromatography (eluent: 10% ethyl acetate in petroleum ether) to give the title compound as a yellow oil (133 mg, 0.59 mmol, 59%).

R_f: 0.52 (20% ethyl acetate in petroleum ether).

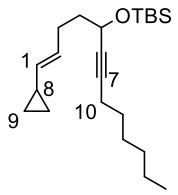
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.31 (2H, m, H10), 7.31–7.15 (3H, m, H11,12), 5.57–5.35 (1H, m, H6), 5.06–4.90 (1H, m, H7), 4.69–4.47 (1H, m, H2), 2.23–2.05 (2H, m, H3), 1.84–1.69 (2H, m, H4), 1.32–1.21 (1H, m, H8), 0.65–0.47 (2H, m, H9), 0.25 (2H, m, H9).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.1, 132.1, 131.7, 128.8, 128.4, 126.7, 122.6, 89.9, 85.1, 62.5, 37.7, 28.2, 13.6, 6.4.

HR–MS (ESI+): calculated for $C_{34}H_{43}O_4Na$ $[2M+Na]^+$ 538.3059, found 538.3081.

IR (thin film, ν_{max}/cm^{-1}): 3080, 3004, 2925, 2851, 2360, 2340, 1665, 1598, 1489, 1442, 1333, 1044.

(*E*)-*tert*-Butyl((1-cyclopropyltridec-1-en-6-yn-5-yl)oxy)dimethylsilane, 167



The title compound was prepared with *general procedure I* using **165** (140 mg, 0.54 mmol, 1.0 eq.) and *tert*-butyldimethylsilyl chloride (122 mg, 0.81 mmol, 1.5 eq.). Crude material was purified by flash column chromatography (eluent: 5% ethyl acetate in petroleum ether) to yield the title compound as a clean oil (74 mg, 0.26 mmol, 42%).

R_f: 0.75 (10% ethyl acetate in petroleum ether).

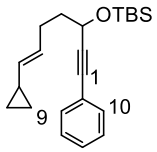
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.49–5.33 (1H, m, H2), 4.91 (1H, dd, *J* = 15.2, 8.6 Hz, H1), 4.31–4.17 (1H, m, H5), 2.11 (2H, td, *J* = 7.0, 2.0 Hz, H3), 2.08–1.99 (2H, m, H10), 1.62 (2H, tdd, *J* = 8.4, 7.6, 6.3 Hz, H4), 1.47–1.35 (2H, m, H11), 1.34–1.26 (1H, m, H8), 1.26–1.00 (9H, m, H12,13,14,15), 0.82 (9H, s, Si*tBu*), 0.66–0.54 (2H, m, H9), 0.31–0.17 (2H, m, H9), 0.09 (3H, s, SiCH_3), 0.00 (3H, s, SiCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 133.2, 126.2, 83.6, 80.8, 61.5, 37.9, 30.3, 27.6, 27.5, 27.3, 24.8, 21.6, 17.7, 17.2, 13.0, 12.5, 5.3, 0.0, -5.4, -5.9.

HR–MS (ESI+): calculated for $C_{22}H_{41}OSi$ $[M+H]^+$ 349.2927, found 349.2922.

IR (thin film, ν_{max}/cm^{-1}): 3655, 2957, 2929, 2857, 2360, 2341, 1462, 1388, 1360, 1258, 1089.

(*E*)-*tert*-Butyl((7-cyclopropyl-1-phenylhept-6-en-1-yn-3-yl)oxy)dimethylsilane, 168



The title compound was prepared with *general procedure I* using **166** (80 mg, 0.30 mmol, 1.0 eq.) and *tert*-butyldimethylsilyl chloride (76 mg, 0.45 mmol, 1.5 eq.). Crude material was purified by flash column chromatography (eluent: 5% ethyl acetate in petroleum ether) to yield the title compound as a pale-yellow oil (112 mg, 0.30 mmol, >98%).

R_f: 0.81 (15% ethyl acetate in petroleum ether).

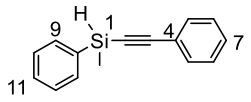
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.18 (2H, m, H10), 7.19–7.10 (3H, m, H11,12), 5.38 (1H, dt, *J* = 15.2, 6.8 Hz, H7), 4.87 (1H, dt, *J* = 15.2, 8.5 Hz, H6), 4.42 (1H, t, *J* = 6.5 Hz, H3), 2.14–1.86 (2H, m, H4), 1.78–1.59 (2H, m, H5), 1.20 (1H, m, H8), 0.81 (9H, s, Si*tBu*), 0.57–0.43 (2H, m, H9), 0.17 (2H, m, H9), 0.05 (3H, s, SiC*H*$_3$), 0.04 (3H, s, SiC*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.6, 131.5, 128.2, 128.1, 127.0, 123.2, 91.1, 84.2, 62.8, 38.6, 28.3, 25.9, 25.9, 18.3, 13.6, 6.39, –4.3, –4.9.

HR–MS (ESI+): calculated for $C_{22}H_{33}OSi$ $[M+H]^+$ 341.2301, found 341.2296.

IR (thin film, ν_{max}/cm^{-1}): 3081, 2954, 2928, 2856, 2360, 1744, 1599, 1360, 1091.

Methyl(phenyl)(phenylethynyl)silane, 183



The title compound was prepared with *general procedure G* using chloro(methyl)(phenyl)silane (300 µL, 2.00 mmol, 1.0 eq.) and ethynylbenzene (240 µL, 2.20 mmol, 1.1 eq.). Purification by flash column chromatography afforded the title compound as a clean oil (440 mg, 2.00 mmol, >98%).

R_f: 0.95 (5% dichloromethane in petroleum ether).

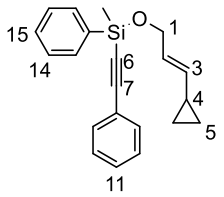
1H NMR (400 MHz, $CDCl_3$): δ 7.72–7.51 (2H, m, H5), 7.49–7.37 (2H, m, H9), 7.42–7.28 (3H, m, H6, H7), 7.30–7.17 (3H, m, H10, H11), 4.71 (d, *J* = 3.9 Hz, Si*H*), 0.49 (3H, d, *J* = 3.9 Hz, SiC*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.4, 132.1, 129.9, 128.3, 128.1, 128.0, 127.9, 122.6, 108.0, 88.9, –3.5.

HR–MS (ESI+): calculated for $C_{15}H_{14}Si$ $[M]^+$ 222.1592, found 222.1578.

IR (thin film, ν_{max}/cm^{-1}): 3068, 2360, 2158, 159, 1488, 1428, 1251, 1219.

(*E*)-((3-Cyclopropylallyl)oxy)(methyl)(phenyl)(phenylethynyl)silane, 184



(*E*)-3-Cyclopropylprop-2-en-1-ol (148 mg, 1.50 mmol, 1.5 eq.), **183** (222 mg, 1.00 mmol, 1.0 eq.) and dichloro(*p*-cymene)ruthenium (6.0 mg, 1 mol%) were stirred at 0 °C. After 1 h, the reaction mixture was diluted with 2 mL petroleum ether/diethyl ether (3:1), flushed through a pad of Celite, and concentrated. Purification by flash column chromatography afforded the title compound (232 mg, 0.73 mmol, 73%) as a colorless oil.

R_f: 0.27 (10% dichloromethane in petroleum ether).

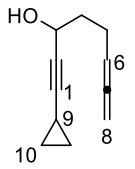
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75–7.56 (2H, m, H9), 7.54–7.41 (2H, m, H13), 7.39–7.29 (3H, m, H10, H11), 7.28–7.23 (3H, m, H14, H15), 5.60 (1H, d, *J* = 15.2 Hz, H3), 5.11 (1H, dt, *J* = 15.2, 8.8 Hz, H2), 4.24–4.16 (1H, m, H1), 4.12 (1H, dd, *J* = 12.5, 6.1 Hz, H1), 1.35–1.20 (1H, m, H4), 0.65–0.55 (2H, m, H5), 0.49 (3H, s, SiC*H*$_3$), 0.31–0.19 (2H, m, H5).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 135.8, 134.7, 132.8, 130.8, 129.7, 128.9, 126.4, 123.1, 107.6, 90.6, 77.3, 65.3, 14.0, 7.3, 0.0.

HR–MS (ESI+): calculated for $C_{21}H_{22}Si$ $[M]^+$ 318.1440, found 318.1430.

IR (thin film, ν_{max}/cm^{-1}): 3853, 3726, 3628, 2980, 2360, 2341, 2158, 1669.

1-Cyclopropyl-7λ^5-octa-6,7-dien-1-yn-3-ol, 218



The title compound was prepared with *general procedure G* using 5λ5-hexa-4,5-dienal (710 mg, 7.40 mmol, 1.0 eq.) and ethynylcyclopropane (753 μL, 8.88 mmol, 1.2 eq.). Crude material was purified by flash column chromatography (eluent: 10% ethyl acetate in petroleum ether) to yield the title compound as an orange oil (860 mg, 4.59 mmol, 66%).

R_f: 0.36 (10% ethyl acetate in petroleum ether).

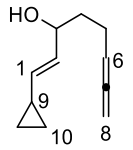
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.95 (1H, p, *J* = 6.7 Hz, H8), 4.51 (2H, dt, *J* = 6.7, 3.3 Hz, H6, H8), 4.31–4.13 (1H, m, H3), 2.03–1.92 (2H, m, 4H), 1.68–1.50 (3H, m, H5, H9), 0.63–0.51 (2H, m, H10), 0.48 (2H, m, H10).

^{13}C NMR (100 MHz, $CDCl_3$): δ 209.1, 89.8, 76.8, 75.9, 67.7, 62.9, 37.8, 25.0, 24.5, 8.9.

HR–MS (ESI+): calculated for $C_{11}H_{15}O$ $[M+H]^+$ 163.1117, found 163.1118.

IR (thin film, ν_{max}/cm^{-1}): 3201, 3004, 2860, 2220, 1958, 1259, 1002, 953.

(*E*)-1-Cyclopropyl-7λ^5-octa-1,6,7-trien-3-ol, 219



The title compound was prepared with *general procedure F* using **218** (400 mg, 2.30 mmol, 1.0 eq.). Crude material was purified by flash column chromatography (eluent: 10% ethyl acetate in petroleum ether) to yield the title compound as an orange oil (335 mg, 1.91 mmol, 83%).

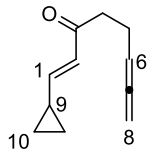
R_f: 0.35 (10% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.48 (1H, dd, *J* = 15.3, 7.2 Hz, H6), 5.18–5.00 (2H, m, H1, H2), 4.61 (2H, dt, *J* = 6.7, 3.3 Hz, H8), 4.02 (1H, q, *J* = 6.3 Hz, H3), 2.11–1.89 (2H, m, H4), 1.65–1.47 (2H, m, H5), 1.31 (1H, qt, *J* = 8.6, 4.8 Hz, H9), 0.72–0.55 (2H, m, H10), 0.37–0.20 (2H, m, H10).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.5, 136.2, 130.2, 99.9, 89.6, 75.1, 36.3, 24.2, 13.4, 6.8.

Spectroscopic data was in agreement with literature.[42]

(*E*)-1-cyclopropyl-7λ^5-octa-1,6,7-trien-3-one, 219a



219 (10 mg, 0.06 mmol, 1.0 eq.) and Dess–Martin periodinane (45 mg, 0.07 mmol, 1.2 eq.) were stirred in 1.0 mL dichloromethane at 0 °C. After 2 h, the reaction mixture was quenched with 0.5 mL sodium bicarbonate (sat., aq.), extracted with diethyl ether (3 x 2.0 mL), and concentrated. Purification by flash column chromatography afforded the title compound (36 mg, 0.05 mmol, 79%) as a pale-yellow oil.

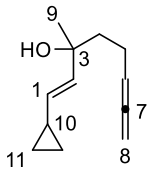
R$_f$: 0.45 (10% diethyl ether in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.25 (dd, *J* = 15.6, 9.5 Hz, 1H, H1), 6.15 (d, *J* = 15.6 Hz, 1H, H2), 5.10 (q, *J* = 9.5, 6.5 Hz, 1H, H6), 4.62 (dd, *J* = 6.8, 3.5 Hz, 2H, H8), 2.55 (dt, *J* = 7.8, 6.8 Hz, 2H, H4), 2.23 (ddt, *J* = 10.8, 6.2, 3.5 Hz, 2H, H5), 1.58–1.39 (m, 1H, H9), 1.04–0.79 (m, 2H, H10), 0.67–0.51 (m, 2H, H10).

^{13}C NMR (100 MHz, $CDCl_3$): δ 209.2, 199.4, 154.4, 126.4, 89.2, 39.1, 31.5, 21.0, 14.6, 8.9.

Spectroscopic data was in agreement with literature.[42]

(*E*)-1-cyclopropyl-3-methyl-7λ^5-octa-1,6,7-trien-3-ol, 222



219a (36 mg, 0.05 mmol, 1.0 eq.) and methylmagnesium bromide (3.0 M in diethyl ether, 10 µL, 0.06 mmol, 1.2 eq.) were stirred in 5.0 mL tetrahydrofuran at 0 °C. After 2 h, the reaction mixture was slowly warmed to room temperature, quenched with 2.0 mL ammonium chloride (sat., aq.), extracted with diethyl ether (3 x 5.0 mL), and concentrated. Purification by flash column chromatography afforded the title compound (31 mg, 0.04 mmol, 87%) as a pale-yellow oil.

R$_f$: 0.42 (20% diethyl ether in petroleum ether).

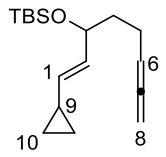
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.51 (d, J = 15.2 Hz, 1H, H2), 5.12 (dd, *J* = 15.2, 7.0 Hz, 1H, H1), 4.65–4.85 (m, 3H, H6,8), 3.72–3.58 (br, O*H*), 2.41 (t, J = 7.0 Hz, 2H, H4), 1.98 (dtt, *J* = 13.2, 6.7, 3.2 Hz, 2H, H5), 1.45–1.24 (m, 1H, H10), 1.23 (s, 3H, H9), 0.72–0.56 (m, 2H, H11), 0.41–0.22 (m, 2H, H11).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.1, 138.0, 132.4, 82.5, 75.8, 39.9, 30.0, 21.3, 18.6, 9.8.

HR–MS (ESI+): calculated for $C_{12}H_{19}O$ $[M+H]^+$ 179.1439, found 179.1442.

IR (thin film, ν_{max}/cm^{-1}): 3222, 2908, 2031, 1856, 1659, 1325, 1003, 954.

(*E*)-*tert*-butyl((1-cyclopropyl-7λ^5-octa-1,6,7-trien-3-yl)oxy)dimethylsilane, 223



The title compound was prepared with *general procedure I* using **219** (10 mg, 0.06 mmol, 1.0 eq.) and *tert*-butyldimethylsilyl chloride (15 mg, 0.09 mol, 1.5 eq.). Crude material was purified by flash column chromatography (eluent: 5% diethyl ether in petroleum ether) to yield the title compound as a yellow oil (17 mg, 0.09 mmol, >98%).

R_f: 0.84 (20% ethyl acetate in petroleum ether).

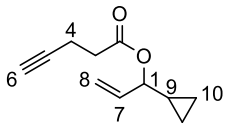
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.41–5.30 (app. m, 1H, H2), 5.14–5.01 (m, 2H, H1,6), 4.64 (dt, *J* = 6.7, 3.3 Hz, 1H, H3), 4.17–3.95 (app. m, 2H, H8), 2.21–1.89 (m, 4H, H4,5), 1.52–1.46 (m, 1H, H9), 0.86 (s, 9H, Si*tBu*), 0.71–0.60 (m, 2H, H10), 0.39–0.25 (m, 2H, H10), 0.05 (s, 6H, SiC*H$_3$*).

^{13}C NMR (100 MHz, $CDCl_3$): δ 209.5, 134.2, 132.2, 89.3, 74.0, 70.8, 43.3, 28.5, 24.0, 18.7, 10.77, 7.3, –4.0.

HR–MS (ESI+): calculated for $C_{17}H_{30}OSiNa$ $[M+Na]^+$ 301.1964, found 301.1963.

IR (thin film, ν_{max}/cm^{-1}): 3112, 2856, 2224, 1460, 1217, 1181, 1142, 1073, 960, 948.

1-Cyclopropylallyl pent-4-ynoate, 231



1-Cyclopropylprop-2-en-1-ol (1.7 mL, 10.0 mmol, 1.0 eq.) and pent-4-ynoic acid (1.19 g, 12.0 mmol, 1.2 eq.) were stirred in 50 mL dichloromethane at 0 °C. *N*,*N*'-Dicyclohexylcarbodiimide (2.47 g, 12.0 mmol, 1.2 eq.) and 4-dimethylaminopyridine (122 mg, 1.0 mmol, 10 mol%) were carefully added to the reaction mixture. After 1 h, reaction was slowly warmed to room temperature and was allowed to stir for a further 16 hours. Upon completion, reaction was quenched with 20 mL ammonium chloride (sat., aq.), extracted with dichloromethane (3 x 30 mL), and concentrated. Purification by flash column chromatography afforded the title compound (1.78 mg, 10.0 mmol, >98%) as a clean oil.

R_f: 0.87 (25% diethyl ether in petroleum ether).

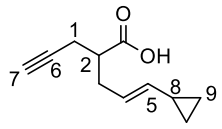
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78 (ddd, *J* = 17.3, 10.5, 5.9 Hz, 1H, H7), 5.22 (d, *J* = 17.3 Hz, 1H, H8), 5.10 (d, *J* = 10.5 Hz, 1H, H8), 4.68 (dd, *J* = 8.6, 5.9 Hz, 1H, H1), 2.62–2.42 (m, 4H, H3,4), 1.91 (t, *J* = 2.5 Hz, 1H, H6), 0.99–0.86 (m, 1H, H9), 0.61–0.44 (m, 2H, H10), 0.39–0.17 (m, 2H, H10).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 136.8, 121.1, 85.2, 79.9, 69.8, 33.6, 14.5, 3.4, 0.4.

HR–MS (ESI+): calculated for $C_{11}H_{14}O_2Na$ $[M+Na]^+$ 201.0886, found 201.0888.

IR (thin film, ν_{max}/cm^{-1}): 3649, 3301, 3085, 2925, 2360, 2122, 1731, 1424, 1368, 1251, 1166, 950.

(*E*)-5-cyclopropyl-2-(prop-2-yn-1-yl)pent-4-enoic acid, 232



The title compound was prepared by *general procedure A* using **231** (178 mg, 1.00 mmol, 1.0 eq.). Purification by flash column chromatography afforded the title compound (157 mg, 0.88 mmol, 88%) as a pale-yellow oil.

R_f: 0.35 (25% ethyl acetate in petroleum ether).

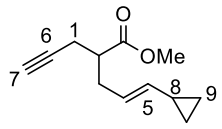
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.35 (dt, *J* = 15.0, 7.4 Hz, 1H, H4), 5.02 (dd, *J* = 15.2, 8.7 Hz, 1H, Hg), 2.62–2.53 (m, 1H, H2), 2.53–2.23 (m, 4H, H1,3), 1.94 (t, *J* = 2.6 Hz, 1H, H7), 1.39–1.05 (m, 1H, H8), 0.70–0.52 (m, 2H, H9), 0.26 (dt, *J* = 6.4, 4.4 Hz, 2H, H9).

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.9, 122.2, 84.6, 70.1, 44.5, 39.8, 34.3, 20.8, 13.9, 6.5.

HR–MS (ESI+): calculated for $C_{11}H_{13}O_2$ $[M–H]^-$ 177.0921, found 177.0918.

IR (thin film, ν_{max}/cm^{-1}): 3801, 3301, 3082, 2980, 2670, 2360, 2341, 2121, 1707, 1507, 1394, 1072, 962.

Methyl (*E*)-5-cyclopropyl-2-(prop-2-yn-1-yl)pent-4-enoate, 233



232 (178 mg, 1.0 mmol, 1.0 eq.) were stirred in 10 mL methanol at 0 °C. *N*,*N*'-Dicyclohexylcarbodiimide (247 mg, 1.2 mmol, 1.2 eq.) and 4-dimethylaminopyridine (12 mg, 1.0 mmol, 10 mol%) were carefully added to the reaction mixture. After 1 h, reaction was slowly warmed to room temperature and was allowed to stir for a further 16 hours. Upon completion, reaction was quenched with 10 mL ammonium chloride (sat., aq.), extracted with dichloromethane (3 x 15 mL), and concentrated. Purification by flash column chromatography afforded the title compound (191 mg, 1.0 mmol, >98%) as a clean oil.

R_f: 0.86 (25% diethyl ether in petroleum ether).

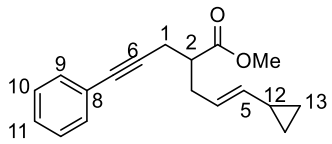
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.40 (dt, *J* = 15.0, 7.3 Hz, 1H, H4), 5.06 (dd, *J* = 15.1, 8.6 Hz, 1H, H5), 3.72 (app. t, *J* = 1.3 Hz, 3H, OC*H*$_3$), 2.63 (app. pd, *J* = 6.8, 1.8 Hz, 1H, H2), 2.55–2.27 (m, 4H, H1,4), 2.00 (t, *J* = 2.7 Hz, 1H, H7), 1.42–1.30 (m, 1H, H8), 0.68 (dt, *J* = 6.0, 5.1 Hz, 2H, H9), 0.37–0.29 (m, 2H, H9).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.3, 139.6, 123.0, 84.8, 70.3, 50.8, 45.5, 32.7, 20.8, 12.4, 6.0.

HR–MS (ESI+): calculated for $C_{12}H_{17}O_2$ $[M+H]^+$ 193.1223, found 193.1225.

IR (thin film, ν_{max}/cm^{-1}): 3298, 3004, 2951, 1735, 1665, 1437, 1368, 1192, 1167, 962.

Methyl (*E*)-5-cyclopropyl-2-(3-phenylprop-2-yn-1-yl)pent-4-enoate, 234



233 (19 mg, 0.10 mmol, 1.0 eq.), copper iodide (0.4 mg, 0.002 mol, 2 mol%), and tetrakis(triphenylphosphine)palladium(0) (1.2 mg, 0.001 mmol, 1 mol%) were stirred in 1.0 mL triethylamine at 0 °C. Iodobenzene (24 µL, 0.20 mmol, 2.0 eq.) was carefully added to the reaction mixture. After 1 h, reaction was slowly warmed to room temperature and was allowed to stir for a further 16 hours. Upon completion, reaction was extracted with diethyl ether (3 x 5 mL), and concentrated. Purification by flash column chromatography afforded the title compound (18 mg, 1.0 mmol, 69%) as a pale-yellow oil.

R_f: 0.33 (25% diethyl ether in petroleum ether).

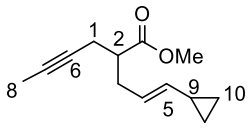
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.26 (m, 2H, H10), 7.22–7.15 (m, 3H, H9,11), 5.43 (dt, *J* = 15.2, 8.4 Hz, 1H, H4), 5.01 (dd, *J* = 15.2, 8.6 Hz, 1H, H5), 3.64 (s, 3H, OC*H*$_3$), 2.65–2.55 (m, 3H, H1,2), 2.42–2.25 (m, 2H, H3), 1.27–1.09 (m, 1H, H12), 0.66–0.51 (m, 2H, H13), 0.29–0.17 (m, 1H, H13).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 137.4, 132.2, 128.5, 126.6, 125.6, 122.2, 88.7, 82.1, 51.7, 42.5, 34.1, 21.3, 13.5, 8.3.

HR–MS (ESI+): calculated for $C_{18}H_{21}O_2$ $[M+H]^+$ 269.1536, found 269.1537.

IR (thin film, ν_{max}/cm^{-1}): 2950, 1735, 1367, 1255, 1166, 1099, 952, 914.

Methyl (*E*)-2-(3-cyclopropylallyl)hex-4-ynoate, 235



233 (19 mg, 0.10 mmol, 1.0 eq.) and iodomethane (12 µL, 0.20 mmol, 2.0 eq.) were stirred in 2.0 mL tetrahydrofuran at –78 °C. Lithium bis(trimethylsilyl)amide (1.0 M in toluene, 120 µL, 0.24 mmol, 1.2 eq.) was carefully added to the reaction mixture. After 30 min, reaction was slowly warmed to room temperature and was allowed to stir for a further 2 hours. Upon completion, reaction was quenched with ammonium chloride (2.0 mL), then extracted with diethyl ether (3 x 5 mL), and concentrated. Purification by flash column chromatography afforded the title compound (17 mg, 0.16 mmol, 80%) as a clean oil.

R_f: 0.48 (10% diethyl ether in petroleum ether).

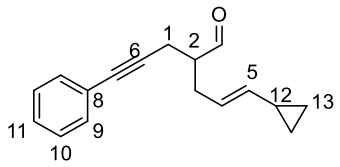
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.26 (dt, *J* = 15.0, 7.4 Hz, 1H, H4), 4.90 (dd, *J* = 15.2, 8.4 Hz, 1H, H5), 3.56 (d, *J* = 5.3 Hz, 3H, OC*H*$_3$), 2.56–2.35 (m, 3H, H2, H1), 2.28–2.13 (m, 2H, H3), 1.63 (t, *J* = 2.5 Hz, 3H, H8), 1.23–1.14 (m, 1H, H9), 0.57–0.44 (m, 2H, H10), 0.25–0.10 (m, 2H, H10).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 135.2, 125.2, 76.0, 51.6, 44.7, 34.9, 33.5, 22.0, 14.0, 6.9, –1.8.

HR–MS (ESI+): calculated for $C_{13}H_{18}O_2Na$ $[M+Na]^+$ 229.1205, found 229.1204.

IR (thin film, ν_{max}/cm^{-1}): 2922, 2118, 1736, 1434, 1367, 1192, 1166, 1099, 1045, 1020, 962.

(*E*)-5-cyclopropyl-2-(3-phenylprop-2-yn-1-yl)pent-4-enal, 236



The title compound was prepared by *general procedure F* using **234** (27 mg, 0.10 mmol, 1.0 eq.) and diisobutylaluminium hydride (1.0 M in hexane, 150 µL, 0.15 mmol, 1.5 eq.). Purification by flash column chromatography afforded the title compound (24 mg, 0.05 mmol, 49%) as a pale-yellow oil.

R_f: 0.65 (10% ethyl acetate in petroleum ether).

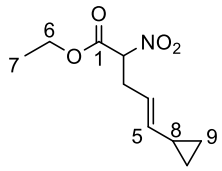
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (d, *J* = 1.3 Hz, 1H, C*H*O), 7.45–7.22 (m, 2H, H10), 7.22–7.18 (m, 3H, H9,11), 5.39 (dt, *J* = 14.7, 7.1 Hz, 1H, H4), 5.05 (dd, *J* = 15.2, 8.6 Hz, 1H, H5), 2.72–2.50 (m, 2H, H1), 2.44 (dt, *J* = 13.4, 6.7 Hz, 1H, H2), 2.57–2.19 (m, 2H, H3), 1.39–1.05 (m, 1H, H12), 0.72–0.53 (m, 2H, H13), 0.27 (dt, *J* = 6.4, 3.4 Hz, 2H, H13).

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.0, 137.8, 131.6, 128.4, 127.8, 132.4, 122.7, 86.4, 82.5, 48.9, 32.2, 20.8, 14.9, 9.3.

HR–MS (ESI+): calculated for $C_{17}H_{19}O_2$ $[M+H]^+$ 239.1430, found 239.1429.

IR (thin film, ν_{max}/cm^{-1}): 3003, 2914, 2729, 2360, 1725, 1655, 1598, 1440, 1047, 963.

Ethyl (*E*)-5-cyclopropyl-2-nitropent-4-enoate, 239



Triphenylphosphine (131 mg, 0.50 mmol, 0.5 eq.), tris(dibenzylideneacetone) dipalladium(0) (103 mg, 0.10 mmol, 10 mol%), and triethylamine (280 µL, 2.0 mmol, 2.0 eq.) were placed in a 21 mL vial and stirred for 30 minutes at room temperature. A solution of (*E*)-3-cyclopropylallyl methyl carbonate (156 mg, 1.0 mmol, 1.0 eq.) and ethyl 2-nitroacetate (160 mg, 1.2 mmol, 1.2 eq.) in 5.0 mL tetrahydrofuran was added dropwise. The reaction mixture was stirred at room temperature overnight for 24 hours, before concentrated under reduced pressure. Purification by flash column chromatography afforded the title compound (213 mg, 1.0 mmol, >98%) as a pale-yellow oil.

R_f: 0.62 (25% ethyl acetate in petroleum ether).

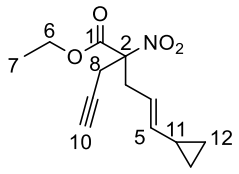
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.33 (dt, *J* = 14.6, 7.1 Hz, 1H, H4), 5.10 (d, *J* = 8.8 Hz, 1H, H5), 5.07–5.02 (app. M, 1H, H2), 4.22 (q, *J* = 7.1 Hz, 2H, H6), 2.91–2.69 (m, 2H, H3), 1.37–1.10 (m, 5H, H7,8), 0.69–0.56 (m, 2H, H9), 0.27 (ddd, *J* = 6.0, 5.0, 3.9 Hz, 2H, H9).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 140.5, 119.3, 88.6, 61.3, 27.7, 15.0, 13.6, 9.2.

HR–MS (ESI+): calculated for $C_{10}H_{15}NO_4Na$ $[M+Na]^+$ 236.0898, found 236.0898.

IR (thin film, ν_{max}/cm^{-1}): 3649, 3084, 2971, 2360, 2341, 1748, 1559, 1465, 1337, 1300, 1096, 1049.

Ethyl (*E*)-5-cyclopropyl-2-nitro-2-(prop-2-yn-1-yl)pent-4-enoate, 242



The title compound was prepared by *general procedure G* using **239** (213 mg, 1.0 mmol, 1.0 eq.) and propargylic bromide (187 mg, 1.5 mmol, 1.5 eq.). Purification by flash column chromatography afforded the title compound (105 mg, 0.42 mmol, 42%) as a pale-yellow oil.

R_f: 0.54 (25% ethyl acetate in petroleum ether).

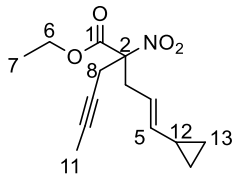
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.23 (dt, *J* = 14.6, 7.1 Hz, 1H, H4), 5.12–4.97 (app. m, 1H, H2), 4.92 (dd, *J* = 9.3, 5.5 Hz, 1H, H5), 3.95 (q, *J* = 7.1 Hz, 2H, H6), 2.81–2.65 (m, 4H, H3,8), 1.88 (app. s, 1H, H10), 1.40–1.11 (app. m, 4H, H7,11), 0.56–0.49 (m, 2H, H12), 0.21–0.13 (m, 2H, H12).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 140.9, 118.7, 89.1, 62.3, 60.0, 58.9, 38.3, 32.2, 14.5, 12.4, 6.2.

HR–MS (ESI+): not found.

IR (thin film, ν_{max}/cm^{-1}): 3295, 3005, 2361, 1750, 1666, 1560, 1370, 1022, 954.

Ethyl (*E*)-2-(3-cyclopropylallyl)-2-nitrohex-4-ynoate, 243



242 (25 mg, 0.10 mmol, 1.0 eq.) and anhydrous potassium carbonate (27 mg, 0.20 mmol, 2.0 eq.) were placed in a 14 mL vial in 2.0 mL dimethylformamide. A solution of iodomethane (28 mg, 2.0 mmol, 2.0 eq.) in 2.0 mL dimethylformamide was added dropwise. The reaction mixture was stirred at room temperature overnight for 16 hours, before concentrated under reduced pressure. Purification by flash column chromatography afforded the title compound (27 mg, 0.10 mmol, >98%) as a pale-yellow oil.

R_f: 0.46 (10% ethyl acetate in petroleum ether).

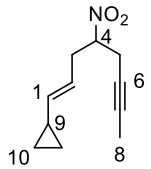
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19 (dt, *J* = 14.7, 7.2 Hz, 1H, H4), 5.08 (dd, *J* = 15.2, 8.5 Hz, 1H, H5), 4.20 (q, *J* = 7.1 Hz, 2H, H6), 2.99–2.83 (m, 4H, H3,8), 1.69 (t, *J* = 2.6 Hz, 3H, H11), 1.35–1.25 (m, 1H, H12), 1.23 (t, *J* = 7.1 Hz, 3H, H7), 0.62 (dt, *J* = 7.9, 2.1 Hz, 2H, H13), 0.27 (dt, *J* = 4.6, 1.9 Hz, 2H, H13).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 141.5, 128.5, 117.5, 95.4, 79.9, 72.4, 62.3, 34.6, 26.1, 15.5, 9.7, 2.1.

HR–MS (ESI+): calculated for $C_{14}H_{20}NO_4$ $[M+H]^+$ 266.1387, found 266.1380.

IR (thin film, ν_{max}/cm^{-1}): 3384, 3091, 3009, 2341, 1635, 1428, 1085, 1051.

(*E*)-(4-Nitrooct-1-en-6-yn-1-yl)cyclopropane, 244



243 (27 mg, 0.10 mmol, 1.0 eq.), and sodium chloride (116 mg, 0.20 mmol, 2.0 eq.) were dissolved in 2.0 mL dimethyl sulfoxide. The resultant mixture was sealed in a 14 mL vial and heated at 150 °C for 3 days, before concentrated under reduced pressure. Purification by flash column chromatography afforded the title compound (15 mg, 0.08 mmol, 79%) as a pale-yellow oil.

R_f: 0.38 (10% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.29 (dt, *J* = 14.7, 7.2 Hz, 1H, H2), 5.03 (dd, *J* = 15.3, 8.6 Hz, 1H, H1), 4.45 (tt, *J* = 6.9, 6.2 Hz, 1H, H4), 2.75–2.65 (m, 2H, H3), 2.61–2.43 (m, 2H, H5), 1.70 (t, *J* = 2.4 Hz, 3H, H8), 1.38–1.10 (m, 1H, H9), 0.70–0.50 (m, 2H, H10), 0.27 (app. d, *J* = 5.0 Hz, 2H, H10).

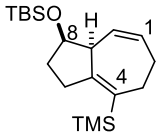
^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9, 119.5, 87.7, 79.2, 73.6, 35.8, 23.1, 13.5, 6.4, 3.4.

HR–MS (ESI+): calculated for $C_{11}H_{15}NO_2Na$ $[M+Na]^+$ 216.1000, found 216.1002.

IR (thin film, ν_{max}/cm^{-1}): 3299, 3002, 2391, 1685, 1550, 1241, 962.

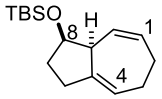
6.3.3 [5+2] Cycloisomerization products

tert-Butyldimethyl(((1*R*,8a*S*)-4-(trimethylsilyl)-1,2,3,5,6,8a-hexahydroazulen-1-yl)oxy)silane, _anti_-197



The title compound was prepared with *general procedure C* using **159** (20 mg, 0.08 mmol, 1.0 eq.). Purification by flash column chromatography lead to desilylation product **197a**.

tert-Butyl(((1*R*,8a*S*)-1,2,3,5,6,8a-hexahydroazulen-1-yl)oxy)dimethylsilane, _anti_-197a



R_f: 0.76 (7.5% dichloromethane in petroleum ether).

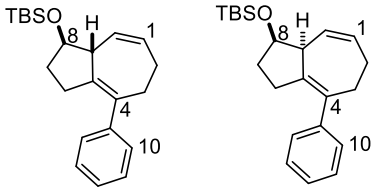
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80–5.59 (m, 2H, H1,9), 5.53 (d, *J* = 5.3 Hz, 2H, H4), 4.21 (dt, *J* = 5.7, 4.4 Hz, 1H, H8), 3.44 (dd, *J* = 5.7, 1.4 Hz, 1H, H8a), 2.45 (m, 1H, H2), 2.38–2.06 (m, 4H, H2,3), 2.01 (m, 2H, H6), 1.68–1.48 (m, 2H, H7), 0.82 (s, 9H, Si*tBu*), 0.00 (s, 6H, SiC*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): 141.2, 137.5, 129.7, 121.0, 75.8, 46.9, 34.2, 30.6, 26.5, 25.9, 18.2, –4.5, –4.8.

HR–MS (ESI+): calculated for $C_{16}H_{29}OSi$ $[M+H]^+$ 265.1909, found 265.1912.

IR (thin film, ν_{max}/cm^{-1}): 2952, 2930, 2857, 2360, 2341, 1720, 1463, 1408, 1361, 1225, 1189, 1048.

***tert*-Butyldimethyl(((1*R*,8a*S*)-4-phenyl-1,2,3,5,6,8a-hexahydroazulen-1-yl)oxy)silane, *anti*-198 and *tert*-butyldimethyl(((1*R*,8a*R*)-4-phenyl-1,2,3,5,6,8a-hexahydroazulen-1-yl)oxy)silane, *syn*-198**



The title compound was prepared with *general procedure C* using **160** (20 mg, 0.08 mmol, 1.0 eq.). Purification by flash column chromatography yielded the title compound as a yellow oil (18 mg, 0.07 mmol, 90%, 1:1 *d.r.*).

R_f: 0.60 (*anti*-**198**, 7.5% dichloromethane in petroleum ether); 0.62 (*syn*-**198**, 7.5% dichloromethane in petroleum ether).

^{1}H NMR (*anti*-**198**, 400 MHz, $CDCl_3$): δ 7.26–7.16 (m, 2H, H10), 7.14–7.02 (m, 3H, H11,12), 5.71 (app. dq, *J* = 11.5, 2.0 Hz, 1H, H1), 5.63–5.52 (app. m, 1H, H9), 4.22 (dt, *J* = 6.2, 4.7 Hz, 1H, H8), 3.62 (dd, *J* = 6.2, 2.5 Hz, 1H, H8a), 3.04–2.88 (m, 2H, H6), 2.33–2.17 (m, 4H, H2,3), 1.58–1.46 (m, 2H, H7), 0.83 (s, 9H, Si*tBu*), 0.09 (s, 3H, SiCH_3), –0.03 (s, 3H, SiCH_3).

^{1}H NMR (*syn*-**198**, 400 MHz, $CDCl_3$): δ 7.26–7.16 (m, 2H, H10), 7.14–7.02 (m, 3H, H11,12), 5.61–5.49 (app. m, 1H, H9), 5.53–5.46 (app. m, 1H, H1), 3.85 (dt, *J* = 7.5, 2.4 Hz, 1H, H8), 3.42–3.36 (app. m, 1H, H8a), 2.99–2.82 (m, 2H, H6), 2.51–2.32 (m, 2H, H2), 2.15–2.05 (m, 2H, H3), 1.70 (ddt, *J* = 11.6, 6.5, 5.2 Hz, 2H, H7), 0.83 (s, 9H, Si*tBu*), 0.09 (s, 3H, SiCH_3), –0.04 (s, 3H, SiCH_3).

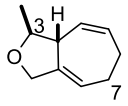
^{13}C NMR (*anti*-**198**,100 MHz, $CDCl_3$): δ 145.9, 133.2, 129.0, 127.9, 127.8, 123.9, 79.2, 74.8, 51.1, 46.2, 35.4, 32.6, 30.5, 27.3, 24.6, 17.6, –4.2.

^{13}C NMR (*syn*-**198**,100 MHz, $CDCl_3$): δ 146.0, 142.8, 134.0, 131.2, 128.3, 127.8, 80.4, 75.2, 49.2, 46.0, 33.9, 32.7, 29.3, 28.7, 18.0, 17.3, –4.3.

HR–MS (ESI+): calculated for $C_{22}H_{32}ONaSi$ $[M+Na]^+$ 363.2116, found 363.2115.

IR (thin film, ν_{max}/cm^{-1}): 3726, 3060, 3027, 2953, 2856, 2360, 2341, 1718, 1598, 1493, 1471, 1462, 1389, 1254, 1168, 1092.

(3*S*,3a*R*)-3-methyl-3,3a,6,7-tetrahydro-1*H*-cyclohepta[*c*]furan, *syn*-192



The title compound was prepared with *general procedure C* using **137** (17 mg, 0.10 mmol, 1.0 eq.). Crude material was purified by flash column chromatography (eluent: 5% ethyl acetate in petroleum ether) to yield the title compound as a pale-yellow oil (7 mg, 0.04 mmol, 40%).

R_f: 0.35 (25% ethyl acetate in petroleum ether).

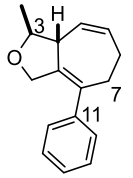
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85–5.71 (app. m, 1H, H4), 5.44–5.39 (app. m, 1H, H8), 5.40 (dt, *J* = 10.7, 2.2 Hz, 1H, H5), 4.37–4.27 (m, 2H, H10), 4.22 (dq, *J* = 6.0, 1.5 Hz, 1H, H3), 4.20–4.14 (app. m, 1H, H3a), 2.29–2.13 (m, 2H, H6), 2.12–1.97 (m, 2H, H7), 1.27 (d, *J* = 6.0 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.9, 130.2, 128.3, 118.8, 73.3, 49.1, 45.7, 27.1, 25.5, 17.9.

HR–MS (ESI+): calculated for $C_{10}H_{14}ONa$ $[M+Na]^+$ 173.0942, found 173.0944.

IR (thin film, ν_{max}/cm^{-1}): 3406, 2928, 3102, 1722, 1600, 1447, 1265, 1178, 1030.

(3*S*,3a*R*)-3-Dethyl-8-phenyl-3,3a,6,7-tetrahydro-1H-cyclohepta[c]furan, *syn*-193



The title compound was prepared with *general procedure C* using **139** (13 mg, 0.04 mmol, 1.0 eq.). Purification by flash column chromatography (eluent: 10% diethyl ether in petroleum ether) afforded the title compound as a yellow oil (12 mg, 0.04 mmol, 95%).

R_f: 0.48 (25% ethyl acetate in petroleum ether).

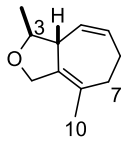
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (dd, *J* = 8.3, 7.0 Hz, 2H, H13), 7.12–7.04 (m, 3H, H12, H14), 5.80–5.63 (m, 1H, H4), 5.34 (dt, *J* = 11.1, 1.9 Hz, 1H, H5), 4.34–4.13 (m, 2H, H1), 3.60 (1H, d, *J* = 9.6 Hz, 1H, H3), 3.26 (dd, *J* = 10.3, 2.7 Hz, 1H, H3a), 2.95–2.71 (m, 2H, H6), 2.40–2.26 (m, 2H, H7), 1.31 (3H, d, *J* = 6.0 Hz, HCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 140.9, 132.7, 131.1, 127.1, 126.5, 125.9, 81.8, 70.5, 56.3, 49.1, 32.8, 27.3, 18.8.

HR–MS (ESI+): calculated for $C_{16}H_{18}ONa$ $[M+Na]^+$ 249.1249, found 249.1251.

IR (thin film, ν_{max}/cm^{-1}): 2927, 1722, 1598, 1493, 1447, 1266, 1178, 1030.

(3*S*,3a*R*)-3,8-Dimethyl-3,3a,6,7-tetrahydro-1*H*-cyclohepta[c]furan, *syn*-194



The title compound was prepared with *general procedure C* using **138** (9 mg, 0.04 mmol, 1.0 eq.). Purification by flash chromatography (eluent: 10% diethyl ether in petroleum ether) afforded the title compound (9 mg, 0.04 mmol, >98%) as a yellow oil.

R_f: 0.28 (10% ethyl acetate in petroleum ether).

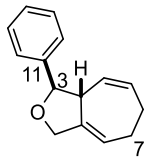
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80–5.64 (app. m, 1H, H5), 5.39–5.33 (app. m, 1H, H6), 4.41–4.13 (m, 2H, H1), 3.53 (d, *J* = 10.0 Hz, 1H, H3), 3.05 (dd, *J* = 9.9, 5.0 Hz, 1H, H3a), 2.36–2.21 (m, 2H, H7), 1.96–1.73 (m, 2H, H8), 1.50 (s, 3H, H10), 1.26 (d, *J* = 5.9 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.6, 128.5, 127.1, 125.8, 81.6, 70.5, 68.7, 48.4, 32.5, 20.8, 16.1.

HR–MS (ESI+): calculated for $C_{11}H_{16}ONa$ $[M+Na]^+$ 187.1099, found 187.1098.

IR (thin film, ν_{max}/cm^{-1}): 2924, 2854, 2361, 2341, 1724, 1453, 1376, 1260, 1026.

(3*R*,3a*R*)-3-Phenyl-3,3a,6,7-tetrahydro-1*H*-cyclohepta[c]furan, *syn*-195



The title compound was prepared with *general procedure C* using **140** (12 mg, 0.04 mmol, 1.0 eq.). Purification by flash chromatography (eluent: 5% diethyl ether in petroleum ether) afforded the title compound (12 mg, 0.04 mmol, >98%) as a yellow oil.

R_f: 0.40 (25% ethyl acetate in petroleum ether).

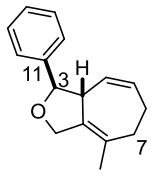
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.31 (m, 2H, H13), 7.24–7.13 (m, 3H, H12, H14), 5.84–5.71 (app. m, 1H, H4), 5.54 (dt, *J* = 7.0, 4.7 Hz, 1H, H5), 5.48 (t, *J* = 10.7 Hz, 1H, H8), 5.14–5.06 (m, 1H, H1), 4.47–4.39 (m, 1H, H1), 4.35 (d, *J* = 8.9 Hz, 1H, H3), 3.52 (dd, *J* = 8.9, 3.1 Hz, 1H, H3a), 2.14–1.99 (m, 2H, H6), 1.29–1.17 (m, 2H, H7).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 129.8, 127.7, 126.8, 125.7, 118.9, 86.2, 70.9, 67.1, 48.8, 37.7, 24.6, 22.7.

HR–MS (ESI+): calculated for $C_{15}H_{16}ONa$ $[M+Na]^+$ 235.1099, found 235.1099.

IR (thin film, ν_{max}/cm^{-1}): 2927, 1722, 1598, 1493, 1447, 1266, 1178, 1030.

(3*R*,3a*R*)-8-Methyl-3-phenyl-3,3a,6,7-tetrahydro-1*H*-cyclohepta[c]furan, *syn*-196



The title compound was prepared with *general procedure C* using **141** (13 mg, 0.04 mmol, 1.0 eq.). Purification by flash column chromatography (eluent: 10% diethyl ether in petroleum ether) afforded the title compound (13 mg, 0.04 mmol, >98%) as a yellow oil.

R_f: 0.45 (25% ethyl acetate in petroleum ether).

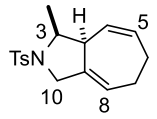
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.31 (m, 2H, H13), 7.26–7.14 (m, 3H, H12, H14), 5.73 (dd, *J* = 11.1, 5.4 Hz, 1H, H4), 5.50–5.42 (app. m, 1H, H5), 4.59 (d, *J* = 10.8 Hz, 1H, H3), 4.41–4.33 (m, 2H, H1), 3.47 (dd, *J* = 10.5, 5.1 Hz, 1H, H3a), 2.44–2.19 (m, 2H, H6), 1.96–1.81 (m, 2H, H7), 1.50 (s, 3H, C*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.2, 135.0, 133.4, 130.0, 128.6, 127.8, 127.1, 125.8, 87.6, 71.0, 49.5, 44.4, 32.2, 26.0.

HR–MS (ESI+): calculated for $C_{16}H_{18}ONa$ $[M+Na]^+$ 249.1249, found 249.1251.

IR (thin film, ν_{max}/cm^{-1}): 3026, 2851, 1600, 1494, 1449, 1373, 1334, 1133, 1054, 1026, 967.

(3*S*,3aS)-3-Methyl-2-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*c*]pyrrole, *anti*-199



The title compound was prepared with *general procedure C* using **150** (16 mg, 0.06 mmol, 1.0 eq.). Purification by flash column chromatography (eluent: 5% diethyl ether in petroleum ether) afforded to title compound as a pale-yellow oil (8 mg, 0.03 mmol, 50%).

R_f: 0.36 (10% diethyl ether in petroleum ether).

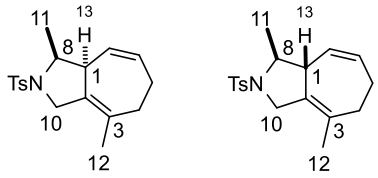
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.3 Hz, 2H, Ts*H*), 7.25 (d, *J* = 8.0 Hz, 2H, Ts*H*), 5.68 (dt, *J* = 10.9, 2.9 Hz, 1H, H4), 5.43 (app. dh, *J* = 5.2, 2.3 Hz, 1H, H8), 5.27 (dt, *J* = 10.8, 2.3 Hz, 1H, H5), 4.04 (d, *J* = 13.9 Hz, 1H, H10), 3.58 (d, *J* = 14.0 Hz, 1H, H10), 3.32 (d, *J* = 9.2 Hz, 1H, H3a), 2.82 (dq, *J* = 9.6, 6.0 Hz, 1H, H3), 2.36 (s, 3H, TsC*H*$_3$), 2.35–2.23 (m, 1H, H6), 2.17 (ddt, *J* = 10.2, 7.7, 2.8 Hz, 1H, H6), 1.98–1.88 (m, 2H, H7), 1.43 (d, *J* = 6.1 Hz, 3H, C*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2, 137.4, 132.7, 131.5, 130.0, 128.9, 127.3, 121.7, 65.2, 52.8, 48.9, 26.4, 25.5, 22.0, 19.8.

HR–MS (ESI+): calculated for $C_{17}H_{21}NO_2NaS$ $[M+Na]^+$ 326.1191, found 326.1190.

IR (thin film, ν_{max}/cm^{-1}): 3023, 2924, 2851, 1598, 1456, 1343, 1167, 1093, 1049, 862.

(3*S*,3a*S*)-3,8-dimethyl-2-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*c*]pyrrole, *anti*-200 and (3*S*,3a*R*)-3,8-dimethyl-2-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*c*]pyrrole, *syn*-200



The title compound was prepared with *general procedure C* using **151** (8 mg, 0.03 mmol, 1.0 eq.). Purification by flash column chromatography (eluent: 5% diethyl ether in petroleum ether) afforded to title compound as a yellow oil (6 mg, 0.02 mmol, 74%, 1:1 *d.r.*).

R_f: 0.42 (*anti*-**200**, 10% ethyl acetate in petroleum ether), 0.40 (*syn*-**200**, 10% ethyl acetate in petroleum ether).

^{1}H NMR (*anti*-**200**, 400 MHz, $CDCl_3$): δ 7.67–7.59 (m, 2H, Ts*H*), 7.27–7.22 (m, 2H, Ts*H*), 5.60 (ddd, *J* = 10.9, 6.0, 4.8 Hz, 1H, H6), 5.23 (dd, *J* = 10.9, 7.0 Hz, 1H, H7), 4.06 (d, *J* = 13.6 Hz, 1H, H10), 3.52 (d, *J* = 13.8 Hz, 1H, H10), 3.31–3.22 (m, 1H, H1), 2.74 (dq, J = 9.3, 6.1 Hz, 1H, H8), 2.36 (s, 3H, TsCH_3), 2.35–2.26 (app. m, 1H, H5), 2.20 (ddt, *J* = 11.6, 5.9, 2.8 Hz, 1H, H5), 1.96 (d, *J* = 2.5 Hz, 1H, H4), 1.85–1.75 (app, m, 1H, H4), 1.51 (s, 3H, H12), 1.42 (d, *J* = 6.1 Hz, 3H, H11).

^{1}H NMR (*syn*-**200**, 400 MHz, $CDCl_3$): δ 7.70–7.61 (m, 2H, Ts*H*), 7.29–7.20 (m, 2H, Ts*H*), 5.73 (ddd, *J* = 11.3, 7.0, 4.6 Hz, 1H, H6), 5.60 (dd, *J* = 11.3, 7.0 Hz, 1H, H7), 3.90 (d, *J* = 7.9 Hz, 1H, H10), 3.52 (d, *J* = 13.8 Hz, 1H, H10), 3.31–3.22 (m, 1H, H1), 2.74 (dq, J = 9.3, 6.1 Hz, 1H, H8), 2.36 (s, 3H, TsCH_3), 2.24–2.14 (app. m, 1H, H5), 2.00–1.90 (app. m, 1H, H5), 1.85–1.75 (app, m, 1H, H4), 1.50 (d, *J* = 6.0 Hz, 1H, H4), 1.42 (s, 3H, H12), 1.00 (d, *J* = 6.1 Hz, 3H, H11).

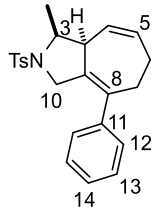
^{13}C NMR (*anti*-**200,** 100 MHz, $CDCl_3$): δ 143.5, 132.3, 131.9, 129.7, 129.6, 129.1, 128.9, 128.0, 76.7, 62.7, 53.3, 48.8, 32.0, 25.6, 21.5, 19.7.

^{13}C NMR (*syn*-**200,** 100 MHz, $CDCl_3$): δ 133.5, 131.4, 129.6, 129.0, 128.0, 126.5, 123.9, 123.0, 63.2, 59.7, 52.8, 48.7, 33.1, 27.2, 21.3, 19.9.

HR–MS (ESI+): calculated for $C_{18}H_{23}O_2NNaS$ $[M+Na]^+$ 340.1342, found 340.1343.

IR (thin film, ν_{max}/cm^{-1}): 3852, 3421, 3005, 2852, 2361, 1653, 1447, 1380, 1164.

(3*S*,3a*S*)-3-Methyl-8-phenyl-2-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[c]pyrrole, *anti*-201



The title compound was prepared with *general procedure C* using **152** (38 mg, 0.10 mmol, 1.0 eq.). Purification by flash column chromatography (eluent: 5% diethyl ether in petroleum ether) afforded to title compound as a pale-yellow oil (36 mg, 0.09 mmol, 94%).

R_f: 0.45 (10% diethyl ether in petroleum ether).

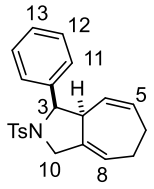
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.3 Hz, 2H, Ts*H*), 7.24 (d, *J* = 7.8 Hz, 2H, Ts*H*), 7.18 (d, *J* = 8.0 Hz, 2H, H12), 7.04–6.95 (m, 2H, H13,14), 5.61–5.51 (app. m, 1H, H5), 5.20 (dd, *J* = 10.8, 1.7 Hz, 1H, H4), 3.94 (d, *J* = 14.7 Hz, 1H, H10), 3.59 (d, *J* = 14.4 Hz, 1H, H10), 3.51–3.43 (m, 1H, H3a), 2.88 (dq, *J* = 8.5, 6.1 Hz, 1H, H3), 2.77 (t, *J* = 11.7 Hz, 2H, H7), 2.37 (s, 3H, TsCH_3), 2.27–2.14 (m, 2H, H6), 1.44 (d, *J* = 6.1 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 142.5, 135.5, 134.5, 132.7, 131.0, 129.6, 128.4, 128.0, 127.8, 127.0, 126.9, 61.8, 54.8, 48.4, 32.0, 24.4, 22.5, 19.3.

HR–MS (ESI+): calculated for $C_{23}H_{25}O_2NNaS$ $[M+Na]^+$ 402.1498, found 402.1501

IR (thin film, ν_{max}/cm^{-1}): 3699, 3034, 3001, 2922, 2851, 2360, 2016, 1714, 1360, 1165, 962.

(3*R*,3a*S*)-3-phenyl-2-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*c*]pyrrole, *anti*-202



The title compound was prepared with *general procedure C* using **153** (10 mg, 0.03 mmol, 1.0 eq.). Purification by flash column chromatography (eluent: 5% diethyl ether in petroleum ether) afforded to title compound as a pale-yellow oil (9 mg, 0.03 mmol, 90%).

R_f: 0.58 (25% diethyl ether in petroleum ether).

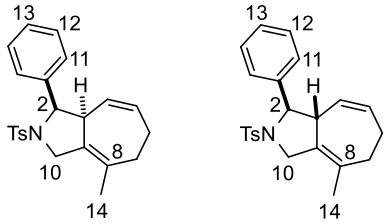
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.20 (m, 4H, Ts*H*, H11), 7.19–7.13 (m, 5H, Ts*H*, H12,13), 5.64 (dd, *J* = 11.4, 5.9 Hz, 1H, H4), 5.54–5.50 (app. m, 1H, H8), 5.26 (dt, *J* = 11.0, 2.1 Hz, 1H, H5), 4.24 (d, *J* = 13.9 Hz, 1H, H10), 3.89 (d, *J* = 13.9 Hz, 1H, H10), 3.82 (d, *J* = 9.7 Hz, 1H, H3), 3.70–3.63 (m, 1H, H3), 2.34 (s, 3H, TsCH_3), 2.33–2.12 (m, 2H, H6), 2.04–1.90 (m, 2H, H7).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 139.2, 136.5, 133.8, 131.9, 129.3, 128.3, 128.1, 127.9, 127.7, 127.6, 122.2, 69.9, 55.2, 51.7, 26.9, 25.2, 21.5.

HR–MS (ESI+): calculated for $C_{22}H_{24}O_2NS$ $[M+H]^+$ 366.1528, found 366.1518.

IR (thin film, ν_{max}/cm^{-1}): 3693, 3028, 2834, 1598, 1462, 1350, 1208, 1094, 1031, 913.

(3*R*,3a*S*)-8-methyl-3-phenyl-2-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*c*]pyrrole, *anti*-203 and (3*R*,3a*R*)-8-methyl-3-phenyl-2-tosyl-1,2,3,3a,6,7-hexahydrocyclohepta[*c*]pyrrole, *syn*-203



The title compound was prepared with *general procedure C* using **154** (10 mg, 0.03 mmol, 1.0 eq.). Purification by flash column chromatography (eluent: 5% diethyl ether in petroleum ether) afforded to title compound as a yellow oil (10 mg, 0.03 mmol, >98%, 1:1 *d.r.*).

R_f: 0.47 (*syn*-**203**, 10% ethyl acetate in petroleum ether), 0.45 (*anti*-**203**, 10% ethyl acetate in petroleum ether).

^{1}H NMR (*anti*-**203**, 400 MHz, $CDCl_3$): δ 7.50–7.33 (m, 2H, Ts*H*), 7.27–7.22 (m, 3H, Ts*H*, H11), 7.17 (m, 3H, H12, H13), 5.54 (dd, *J* = 10.8, 6.6 Hz, 1H, H4), 5.24 (dt, *J* = 11.0, 2.7 Hz, 1H, H5), 4.23 (d, *J* = 13.8 Hz, 1H, H2), 3.85–3.78 (app. m, 1H, H10), 3.74 (d, *J* = 9.3 Hz, 1H, H10), 3.70–3.64 (app. m, 1H, H3), 2.38–2.30 (app. m, 1H, H6), 2.34 (s, 3H, TsCH_3), 2.13 (ddd, *J* = 13.0, 6.3, 3.0 Hz, 1H, H6), 2.04–1.92 (app. m, 1H, H7), 1.86–1.75 (app. m, 1H, H7), 1.57 (s, 3H, H14).

^{1}H NMR (*syn*-**203**, 400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 9.6 Hz, 2H, Ts*H*), 7.25–7.15 (m, 3H, Ts*H*, H11), 7.00–6.90 (m, 3H, H12, H13), 5.76 (dd, *J* = 9.2, 7.0 Hz, 1H, H4), 5.42 (dt, *J* = 9.0, 2.5 Hz, 1H, H5), 4.17 (d, *J* = 14.5 Hz, 1H, H2), 4.08–4.08 (app. m, 1H, H10), 3.73 (d, *J* = 10.5 Hz, 1H, H10), 3.71–3.65 (app. m, 1H, H3), 2.42–2.39 (app. m, 1H, H6), 2.36 (s, 3H, TsCH_3), 2.25–2.18 (app. m, 1H, H6), 2.02–1.89 (app. m, 1H, H7), 1.87–1.77 (app. m, 1H, H7), 1.36 (s, 3H, H14).

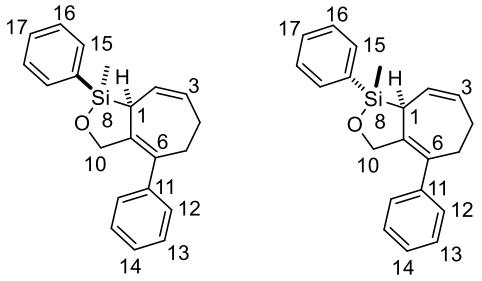
^{13}C NMR (*anti*-**203**, 100 MHz, $CDCl_3$): δ 143.4, 139.8, 132.8, 131.1, 129.8, 129.4, 129.3, 128.3, 128.2, 127.9, 127.8, 127.7, 76.7, 71.3, 53.3, 51.6, 32.2, 25.7, 21.5.

^{13}C NMR (*syn*-**203**, 100 MHz, $CDCl_3$): δ 144.1, 139.3, 132.8, 131.1, 129.4, 129.3, 127.9, 127.8, 127.7, 125.0, 124.9. 122.2, 70.5, 53.8, 51.6, 51.0, 31.3, 26.0, 21.0.

HR–MS (ESI+): calculated for $C_{23}H_{26}NO_2S$ $[M+H]^+$ 380.1684, found 380.1675.

IR (thin film, ν_{max}/cm^{-1}): 3694, 3028, 2922, 2851, 2360, 1736, 1598, 1494, 1165.

(1*R*,8a*S*)-1-Methyl-1,4-diphenyl-3,5,6,8a-tetrahydro-1*H*-cyclohepta[*c*][1,2]oxasilole, *anti*-206 and (1*S*,8a*S*)-1-methyl-1,4-diphenyl-3,5,6,8a-tetrahydro-1*H*-cyclohepta[*c*][1,2]oxasilole, *syn*-206



The title compound was prepared with *general procedure C* using **184** (10 mg, 0.03 mmol, 1.0 eq.). ^{1}H NMR indicated the formation of the title product in >98% yield.

Purification by flash column chromatography (eluent: 5% dichloromethane in petroleum ether) afforded to title compound as a yellow oil (2 mg, 0.01 mmol, 20%, *syn*-**206** only).

R_f: 0.15 (*syn*-**206** and *anti*-**206**, 5% dichloromethane in petroleum ether)

^{1}H NMR (*syn*-**206**, 400 MHz, $CDCl_3$): δ 7.42–7.35 (m, 2H, Ph*H*), 7.21–7.16 (m, 4H, Ph*H*), 7.12–6.92 (m, 4H, Ph*H*), 5.71–5.57 (app. m, 1H, H2), 5.37–5.26 (app. m, 1H, H3), 4.25 (d, *J* = 9.8 Hz, H10), 4.23 (d, *J* = 8.1 Hz, 1H, H10), 3.91–3.80 (app. m, 1H, H1), 3.06–2.93 (m, 2H, H4), 2.90–2.73 (m, 2H, H5), 2.02 (s, 3H, C*H*$_3$).

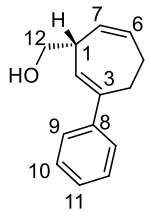
^{1}H NMR (*anti*-**206**, 400 MHz, $CDCl_3$): δ 7.42–7.35 (m, 2H, Ph*H*), 7.21–7.16 (m, 4H, Ph*H*), 7.12–6.92 (m, 4H, Ph*H*), 5.75–5.58 (app. m, 1H, H2), 5.47–5.38 (app. m, 1H, H3), 4.25 (d, *J* = 9.8 Hz, H10), 4.23 (d, *J* = 8.1 Hz, 1H, H10), 3.91–3.80 (app. m, 1H, H1), 3.06–2.93 (m, 2H, H4), 2.90–2.73 (m, 2H, H5), 2.02 (s, 3H, C*H*$_3$).

^{13}C NMR (*syn*-**206** and *anti*-**206**, 100 MHz, $CDCl_3$): δ 133.9, 132.9, 132.7, 129.9, 129.5, 129.3, 126.9, 126.6, 126.1, 125.9, 125.1, 122.7, 44.3, 41.5, 33.7, 33.1, 28.4, –0.5, –2.7, –4.7.

HR–MS (ESI+): calculated for $C_{21}H_{22}Si$ $[M]^+$ 318.1440, found 318.1430.

IR (thin film, ν_{max}/cm^{-1}): 3070, 2961, 2925, 2853, 2360, 2361, 1733, 1594, 1261, 1125, 1066, 1028, 788.

(*R*)-(3-Phenylcyclohepta-2,6-dien-1-yl)methanol, 207



206 (20 mg , 0.06 mmol, 1.0 eq.) as a solution in $CDCl_3$ was added a solution of TBAF (60 µL, 1.0 M in THF, 2.0 eq.) in a sealed NMR tube. The resultant mixture was left still at room temperature overnight, before concentrated under reduced pressure. Purification by flash column chromatography (eluent: 5% dichloromethane in petroleum ether) afforded to title compound as a pale-yellow oil (15 mg, 0.05 mmol, 75%, 92% *ee*).

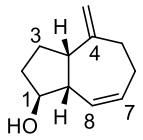
R_f: 0.58 (10% diethyl ether in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.28 (m, 2H, H10), 7.27–7.21 (m, 2H, H9), 7.19–7.12 (m, 1H, H11), 5.89 (d, *J* = 4.4 Hz, 1H, H2), 5.81–5.67 (app. m, 1H, H6), 5.46 (dd, *J* = 11.3, 3.0 Hz, 1H, H7), 3.74–3.62 (m, 2H, H12), 3.52–3.38 (br, 1H, O*H*), 2.92 (dt, *J* = 7.7, 3.6 Hz, 1H, H1), 2.60–2.53 (m, 2H, H4), 2.29–2.18 (m, 2H, H5),

^{13}C NMR (100 MHz, $CDCl_3$): δ 131.5, 129.0, 128.4, 128.2, 126.7, 125.7, 122.6, 67.0, 42.0, 29.7, 27.4.

Spectroscopic data was in agreement with literature.[201]

(1*S*,3a*S*,8a*S*)-4-methylene-1,2,3,3a,4,5,6,8a-octahydroazulen-1-ol, (*S*,*S*,*S*)-220



The title compound was prepared with *general procedure C* using **219** (20 mg, 0.12 mmol, 1.0 eq.). Purification by flash column chromatography (eluent: 10% diethyl ether in petroleum ether) afforded to title compound as a pale-yellow oil (12 mg combined, 0.07 mmol, 62%, 1:0.8 *d.r.* to (*R*,*R*,*S*)-**220**).

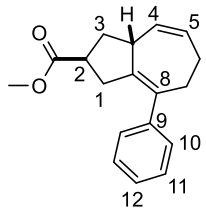
R_f: 0.20 ((*S*,*S*,*S*)-**220** and (*R*,*R*,*S*)-**220**, 10% diethyl ether in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.59–5.48 (m, 1H, H8), 5.28 (dt, *J* = 12.2, 1.6 Hz, 1H, H7), 4.73 (*d*, J = 1.0 Hz, 1H, C=CH_2), 4.69 (d, *J* = 1.5 Hz, 1H, C=CH_2), 4.02 (dt, *J* = 5.9, 4.4 Hz, 1H, H1), 3.08 (q, *J* = 8.4 Hz, 1H, H8a), 2.69 (app. s, 1H, H3a), 2.36–2.16 (m, 3H, H5,6), 2.01 (dddd, *J* = 13.4, 9.8, 6.0, 4.0 Hz, 1H, H3), 1.96–1.79 (m, 1H, H3), 1.95–1.90 (m, 1H, H6), 1.74–1.57 (m, 2H, H2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 129.3, 127.8, 110.9, 79.1, 51.7, 45.6, 34.4, 33.1, 30.9, 26.5.

Spectroscopic data was in agreement with literature.[42]

Methyl (2*S*,3a*R*)-8-phenyl-1,2,3,3a,6,7-hexahydroazulene-2-carboxylate, *syn*-245



The title compound was prepared with *general procedure C* using **234** (13 mg, 0.05 mmol, 1.0 eq.). Purification by flash column chromatography (eluent: 10% diethyl ether in petroleum ether) afforded to title compound as a pale-yellow oil (5 mg, 0.02 mmol, 40%).

R_f: 0.32 (25% diethyl ether in petroleum ether).

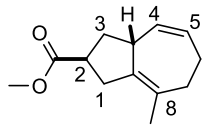
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.30 (m, 2H, H11), 7.28–7.19 (m, 3H, H10,12), 5.69–5.62 (m, 1H, H4), 5.43 (dt, *J* = 7.4, 0.6 Hz, 1H, H5), 3.84–3.72 (app. m, 1H, H3a), 3.66 (s, 3H, OCH_3), 3.02 (ddt, *J* = 15.4, 11.5, 2.6 Hz, 1H, H2), 2.90–2.81 (m, 2H, H6), 2.64–2.41 (m, 2H, H1), 2.35–2.22 (m, 2H, H7), 1.71–1.83 (m, 2H, H3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 143.9, 141.4, 133.1, 131.8, 130.4, 129.2, 127.8, 127.5, 126.1, 49.7, 42.5, 40.6, 39.0, 36.6, 26.8.

HR–MS (ESI+): calculated for $C_{18}H_{21}O_2$ $[M+H]^+$ 269.1536, found 269.1537.

IR (thin film, ν_{max}/cm^{-1}): 2950, 2893, 1736; 1434, 1203, 1196, 1055, 962.

Methyl (2*S*,3a*R*)-8-methyl-1,2,3,3a,6,7-hexahydroazulene-2-carboxylate, *syn*-246



The title compound was prepared with *general procedure C* using **235** (21 mg, 0.10 mmol, 1.0 eq.). Purification by flash column chromatography (eluent: 10% diethyl ether in petroleum ether) afforded to title compound as a pale-yellow oil (8 mg, 0.04 mmol, 36%).

R_f: 0.45 (25% diethyl ether in petroleum ether).

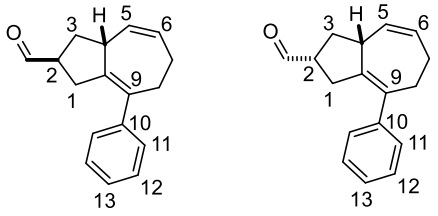
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.70–5.63 (m, 1H, H4), 5.52 (app. d, *J* = 11.0 Hz, 1H, H5), 3.71 (s, 3H, OC*H*$_3$), 3.55 (td, *J* = 8.4, 4.0 Hz, 1H, H3a), 2.80–2.60 (m, 3H, H1,2), 2.30–2.20 (m, 2H, H6), 1.80–1.71 (m, 2H, H7), 1.70 (s, 3H, C*H*$_3$), 1.37–1.24 (m, 2H, H3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 137.4, 132.2, 129.4, 127.8, 55.0, 44.7, 41.2, 38.6, 35.2, 31.2, 27.3, 22.0.

HR–MS (ESI+): calculated for $C_{13}H_{18}O_2Na$ $[M+Na]^+$ 229.1205, found 229.1204.

IR (thin film, ν_{max}/cm^{-1}): 2969, 2911, 1749, 1434, 1270, 1202, 1134, 1006, 962, 891.

(2S,3aR)-8-phenyl-1,2,3,3a,6,7-hexahydroazulene-2-carbaldehyde, *syn*-247 and (2R,3aR)-8-phenyl-1,2,3,3a,6,7-hexahydroazulene-2-carbaldehyde, *anti*-247



The title compound was prepared with *general procedure C* using **236** (24 mg, 0.10 mmol, 1.0 eq.). Purification by flash column chromatography or exposure to air resulted in rapid decomposition of the title compound, thus full characterization was not obtained.

R_f: N/A.

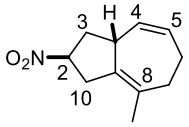
^{1}H NMR (*syn*-**247** and *anti*-**247** as 1:1 mixture, 400 MHz, $CDCl_3$): δ 9.55 (d, *J* = 3.5, 2.2 Hz, 0.5H, C*H*O), 9.53 (d, *J* = 2.2 Hz, 0.5H, C*H*O), 7.35–7.22 (m, 2H, H12), 7.20–7.08 (m, 3H, H,11,13), 5.61–5.49 (m, 1H, H5), 5.47–5.40 (dd, *J* = 11.4, 1.9 Hz, 0.5H, H6), 5.40–5.25 (dd, *J* = 11.4, 1.8 Hz, 0.5H, H6), 3.75 (app. s, 1H, H3a), 3.04–2.88 (m, 1H, H1), 2.79–2.68 (m, 1H, H1), 2.66–2.49 (m, 1H, H2), 2.44–2.08 (m, 4H, H7,8), 1.84–1.58 (m, 2H, H3).

^{13}C NMR (100 MHz, $CDCl_3$): N/A.

HR–MS (ESI+): calculated for $C_{17}H_{19}O_2$ $[M+H]^+$ 239.1430, found 239.1429.

IR (thin film, ν_{max}/cm^{-1}): N/A

(2*S*,3a*R*)-8-methyl-2-nitro-1,2,3,3a,6,7-hexahydroazulene, *syn*-248



The title compound was prepared with *general procedure C* using **244** (19 mg, 0.10 mmol, 1.0 eq.). 1H NMR indicated a quantitative yield was achieved upon completion, followed by rapid decomposition. Purification by flash column chromatography or exposure to air resulted in rapid decomposition of the title compound, thus isolated yield was not reported.

R_f: 0.36 (10% ethyl acetate in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75–5.63 (m, 1H, H5), 5.48 (dd, *J* = 13.1, 11.0 Hz, 1H, H4), 4.92 (tt, *J* = 6.1, 2.8 Hz, 1H, H2), 4.79 (ddd, *J* = 10.3, 9.0, 7.8 Hz, 1H, H3a), 3.86 (app. s, 1H, H10), 3.65 (app. s, 1H, H10), 2.91–2.81 (m, 1H, H6), 2.75 (ddt, *J* = 13.8, 8.5, 2.5 Hz, 1H, H6), 2.37–2.25 (m, 1H, H7), 2.18–2.06 (m, 1H, H7), 2.00–1.87 (m, 2H, H3), 1.70 (s, 3H, C*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): 134.3, 132.9, 131.6, 131.1, 130.2, 84.8, 40.5, 38.6, 36.7, 31.0, 25.1.

HR–MS (ESI+): calculated for $C_{11}H_{15}NO_2Na$ $[M+Na]^+$ 216.1000, found 216.1002.

IR (thin film, ν_{max}/cm^{-1}): 3284, 3009, 2825, 2260, 2141, 1472, 1264, 1200, 862, 878.

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