Non-stabilized Nucleophiles in Cu-catalyzed Asymmetric Synthesis

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Declaration

This thesis describes research work carried out in the Chemistry Research Laboratory from October 2012 to December 2015 under the supervision of Prof. Stephen.P.Fletcher in Oxford University. The entire thesis is my own work unless stated otherwise and has not previously been submitted for any other degree at this or other universities.

Hengzhi You

August 2016

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Abstract

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This thesis describes the study of organozirconium reagents used in copper-catalyzed asymmetric synthesis. Explorations on the asymmetric allylic alkylation of linear substrates, the cyclic substrates and enantioselective desymmetrization of *meso* compounds including the oxabicyclic alkenes and *meso*-allyl substrates are reported here.

Chapter 1 has a brief overview about general methods used in asymmetric catalysis. In particular, more relevant introduction about catalytic asymmetric allylic substitution and asymmetric desymmetrization of *meso* compounds is given.

Chapter 2 describes the investigation of organozirconium reagents used in copper-catalyzed asymmetric allylic alkylation of linear substrates, and discloses a dynamic kinetic AAA system that employs cyclic allylic chlorides as substrates.

Chapter 3 presents the study on expanding the disclosed copper-catalyzed dynamic kinetic AAA chemistry by using more stabilized cyclic allylic phosphate substrates. Further exploration of its possible mechanisms uses substituted substrates, deuterated and enantiopure substrates are also discussed.

Chapter 4 demonstrates the study of organozirconium reagents used in copper-catalyzed enantioselective desymmetrization reactions. Investigation of oxabicyclic alkenes and *meso*-allyl substrates is reported.

Chapter 5 gives supporting information of this thesis.

Abbreviations

Å	Ångstrom(s)
Ac	acetyl
ACA	asymmetric conjugate addition
aq.	aqueous
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br.	broad (spectral)
brsm	based on recovered starting material
i-Bu	isobutyl
n-Bu	normal (primary) butyl
t-Bu	tertiary butyl
Bz	benzoyl
°C	degrees Celsius
cat.	catalytic
Cbz	benzyloxycarbonyl
cm^{-1}	wavenumber
Cp	cyclopentadienyl
δ	chemical shift
d	doublet (spectral)
DCM	dichloromethane
DCE	1,2-dichloroethane
dd	doublet of doublets (spectral)
ddd	doublet of doublet of doublets (spectral)
ddt	doublet of doublet of triplets (spectral)
DFT	density functional theory

DMAP	4-dimethylaminopyridine
dq	doublet of quartets (spectral)
dt	doublet of triplets (spectral)
dtd	doublet of triplet of doublets (spectral)
ee	enantiomeric excess
EI	electron ionisation
eq	equivalents
ESI	electrospray ionisation
Et	ethyl
g	gram(s)
gCOSY	gradient Correlation Spectroscopy
gHSQC	gradient Heteronuclear Single Quantum Coherence
^{1}H	proton
h	hour(s)
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	hertz
IR	infra-red
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
L	litre(s)
LFER	linear free energy relationship
µm	micrometer(s)
M	molar (moles per litre)
m	multiplet (spectral)
mbar	millibar(s)
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)

mL	millilitre(s)
mmol	millimole(s)
mol	mole(s)
M.p.	melting point
m/z	mass to charge ratio
nm	nanometre(s)
NMR	nuclear magnetic resonance
NHC	*N*-Heterocyclic Carbene
Nu	nucleophile
PG	protecting group
Ph	phenyl
ppm	parts per million
i-Pr	isopropyl
PTFE	polytetrafluoroethylene
q	quartet (spectral)
quant	quantitative
quin	quintet (spectral)
QSSR	quantitative structure selectivity relationship
R	generic organic group
RT	room temperature
s	singlet (spectral)
sat.	saturated
sxt	sextet (spectral)
t	triplet (spectral)
TBD	triazabicyclodecene
t-BuOMe	*tert*-Butyl methyl ether
td	triplet of doublets (spectral)
tdd	triplet of doublet of doublets (spectral)
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid

TFAA	trifluoroacetic anhydride
TLC	thin layer chromatography
TMG	tetramethylguanidine
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl
TS	transition state
THAB	tetrahexylammonium bromide
THF	tetrahydrofuran
UV	ultraviolet

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Chapter 1

Introduction

1.1 Asymmetric Catalysis

1.1.1 General Approaches

Since Fischer outlined the initial concept of asymmetric induction in 1894 [1]: the preferential formation in a chemical reaction of one enantiomer or diastereoisomer over the other, controlling molecular chirality has represented one of the most important roles in modern chemical science and technology (Figure **1.1**).

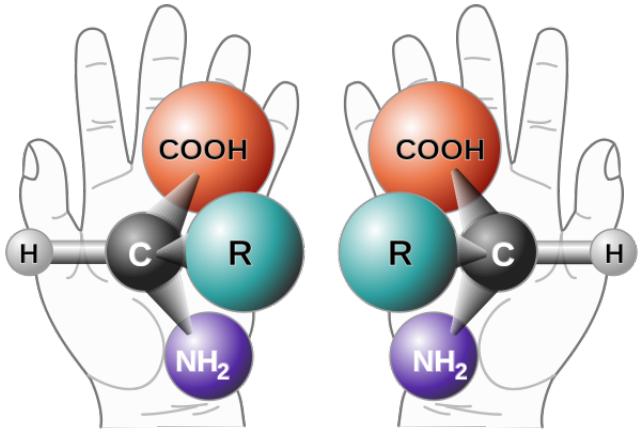

Figure 1.1 | Selected sample of molecular chirality: alpha amino acid.

General principles of asymmetric synthesis include five main strategies [1-6]: (a) Enantioselective catalysis; (b) Chiral auxiliaries; (c) Biocatalysis; (d) Chiral pool synthesis; (e) Chiral resolution.

(a) Enantioselective catalysis

Enantioselective catalysis [1-3] refers to the use of chiral coordination complexes as catalysts. It is a classical strategy used in asymmetric synthesis, which enables a broader range of transformations compared to other approaches (Figure **1.2**) [7]. The commonly used catalysts are rendered chiral by using chiral ligands, recent study also shows the possibility to employ a chiral-at-metal complexes using simple achiral ligands [8]. At the same time, the

high efficiency of enantioselective catalysts makes them the most versatile strategies used in industrial scale synthesis [3].

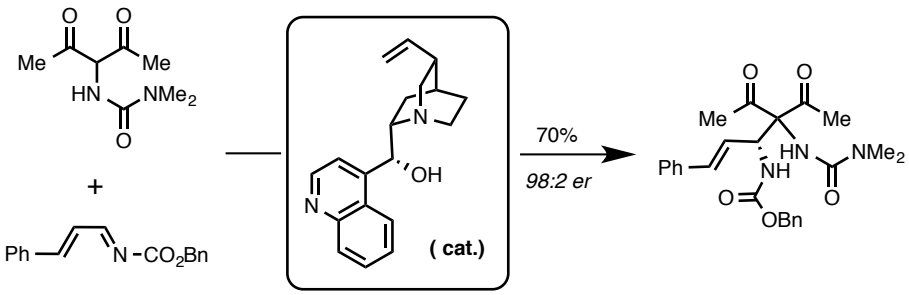

Figure 1.2 | Selected sample of enantioselective catalysis used in asymmetric synthesis.

(b) Chiral auxiliaries

A chiral auxiliary [1-4, 10] is a stereogenic group or unit that is temporarily incorporated into an organic compound in order to control the stereochemical outcome of the synthesis (Figure **1.3**) [9]. The chirality present in the auxiliary can also bias the stereoselectivity of one or more subsequent reactions [4,10].

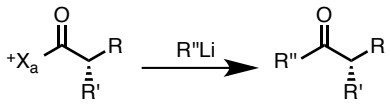

Figure 1.3 | Selected sample of chiral auxiliary used in asymmetric synthesis.

However, traditional chiral auxiliary strategies normally use a stoichiometric amount of chiral compounds, the necessity of recycling them in terms of cost efficiency and green chemistry makes it a challenging procedure in practical asymmetric synthesis [11].

(c) Biocatalysis

Biocatalysis[1-3, 5] makes use of biological materials, ranging from isolated enzymes to living cells in performing chemical transformations (Figure **1.4**) [12]. Practical asymmetric synthetic approach in industry largely relies on biochemical catalysts, since they commonly provide

excellent enantioselectivities, mild operating conditions and low environmental impact [3,11]. At the same time, the scope of these strategies employing enzymes, cell cultures, or whole microorganisms is currently quite limited because of the inherent single-handedness and specificity of biocatalysts [3, 5, 11].

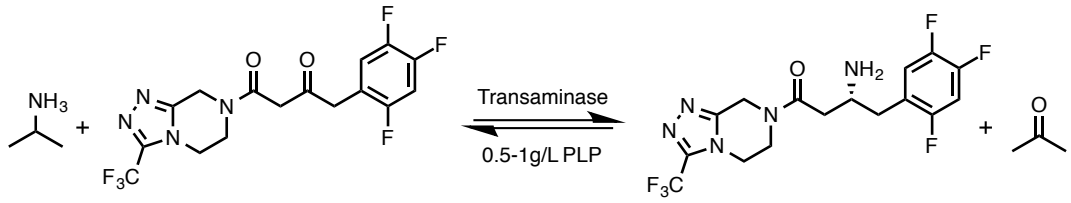

Figure 1.4 | Selected sample of biocatalyzed asymmetric synthesis.

(d) Chiral pool synthesis

Chiral pool synthesis[1-3, 13] starts the organic synthesis of a complex enantiopure chemical compound from a stock of readily available enantiopure substances (Figure **1.4**) [14]. The strategy shows a great advantage in the asymmetric synthesis of desired products, which bear a resemblance to cheap enantioenriched natural starting materials. However, the suitable enantioenriched starting materials are limited, other techniques may be more flexible and fruitful in asymmetric catalysis.

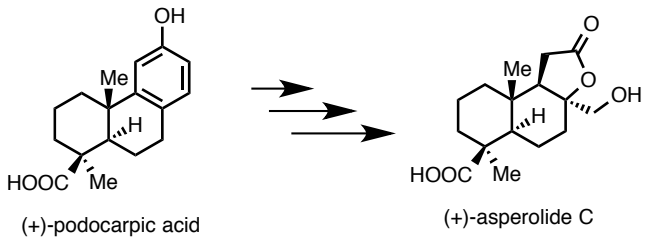

Figure 1.5 | Selected sample of chiral pool synthesis used in asymmetric synthesis.

(e) Chiral resolution

Chiral resolution [1-3, 6] is a process to separate racemic compounds into their corresponding enantiomers (Figure **1.5**) [15]. A main disadvantage here is this approach only provides up to

50% yield compared to other asymmetric synthetic methods. The widely used strategies include: resolution by crystallization, chiral derivatizing agents and chiral column chromatography. In cases when both enantiomers may find a use, such separations can be cost-effective and this may be an attractive approach to employ.

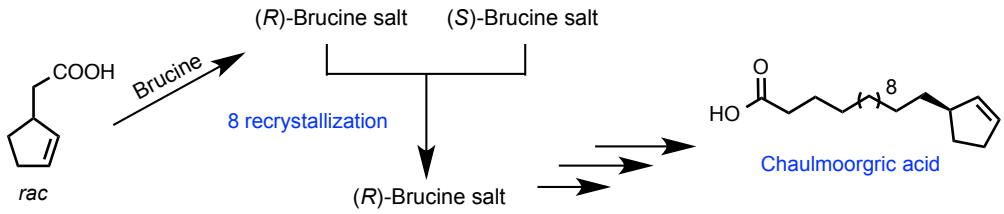

Figure 1.5 | Selected sample of chiral resolution in asymmetric synthesis.

1.1.2 Advance in using Racemic Starting Materials.

Generally, there are two main methods widely used for enantioselective catalysis in asymmetric catalysis. One prevailing strategy is generating new asymmetric centers from a prochiral molecule (Figure **1.6**, a). While many attractive methods have been proven extremely effective in synthesizing pure enantiomers, the number of viable prochiral functional groups is rather limited compared to the wide pool of racemic starting materials in nature [1, 2, 16].

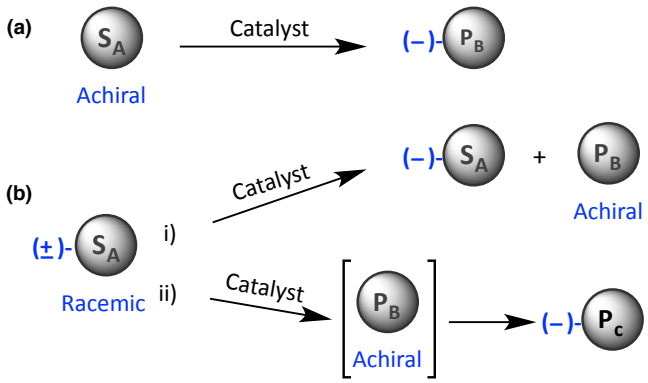

Figure 1.6 | Main strategies for enantioselective catalysis.

The advance of a developing strategy is to access the enantioenriched organic substances from a racemic mixture (Figure **1.6**, b): (i) one procedure is selectively converting one enantiomer of

the starting material into the desired product. In addition, recent released methods have been able to recycle the left achiral products back into racemic starting materials improve the efficiency of the process [16]. (ii) A second procedure is transforming both enantiomers of the racemic starting materials into designed enantioenriched products through dynamic kinetic resolution in a good yield [16].

Here we have a brief introduction about the development of this strategy: (a) Kinetic resolution (KR) & Parallel Kinetic Resolution (PKR); (b) Dynamic Kinetic Resolution (DKR); (c) Dynamic Kinetic Asymmetric Transformation (DYKAT); (d) Direct Enantioconvergent Transformation (DET) [16-19].

(a) Kinetic resolution (KR) & Parallel Kinetic Resolution (PKR)

Kinetic resolution is a classical method used in asymmetric synthesis from a racemic starting material, where the two enantiomers of the racemate react at different rates and provide the desired product in up to 50% ideal yield (Figure **1.7**). Here, the reaction rate of one enantiomer of the starting material SM_R is significantly higher than the other SM_S, thus enantioenriched product P_R is obtained and with lower reactivity of SM_S, it ideally remains unreacted.

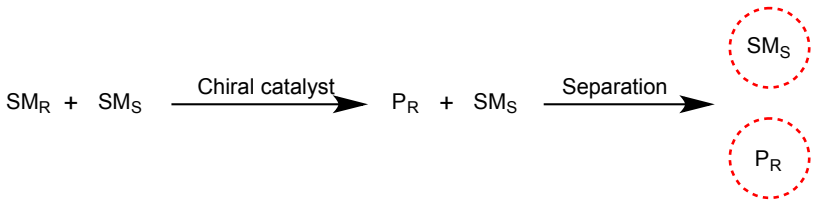

Figure 1.7 | General mechanistic pathway of kinetic solution (KR).

A large number of attractive processes have been developed, taking advantage of this kinetic preference (Figure **1.8**) [1-3,20-24]. From these, a few selected examples are highlighted: a wide variety of secondary alcohols have been resolved by Stoltz's oxidative kinetic resolution strategy, employing oxygen as oxidant, where a Pd-complex selective oxidizes

one enantiomer of starting material into an achiral ketone while leaving unreacted alcohol with high e.e. (Figure **1.8**, a) [21].

Elegant oxidative resolution of sulfoxides was demonstrated by Jackson and co-workers in 2005. The racemic sulfoxides were effectively resolved and provided highly enantioenriched starting material catalyzed by a vanadium-complex (Figure **1.8**, b) [22].

Work by Noyori and Sharpless with their co-workers in kinetic resolution merits special consideration (Figure **1.8**, c&d) [23, 24]. Both chemists, together with Knowles, were honoured with the 2001 Nobel Prize in Chemistry for their brilliant work in asymmetric catalysis. Noyori's hydrogenation of allylic alcohols with a Ru-catalyst provides reductive kinetic resolution by symmetrizing one enantiomer of substrate. Sharpless's asymmetric epoxidation and kinetic resolution enables the usage of broad substrates and the scope of these reactions as well as the ready accessibility of the catalyst components led to the wide employment of this strategy by synthetic chemists.

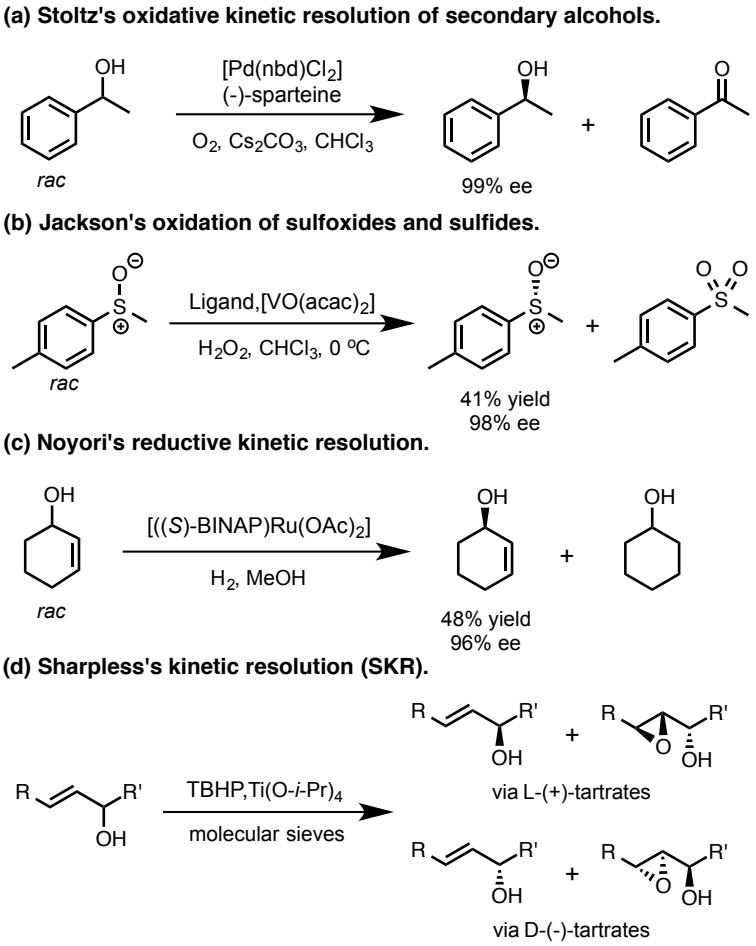

Figure 1.8 | Selected samples of kinetic resolution in asymmetric synthesis.

In comparison to Kinetic Resolution (KR), Parallel Kinetic Resolution (PKR) refers to where both enantiomers of a racemic mixture are equally reacted along two distinct pathways, so that the process provides two different diastereoisomeric products (Figure **1.9**) [25].

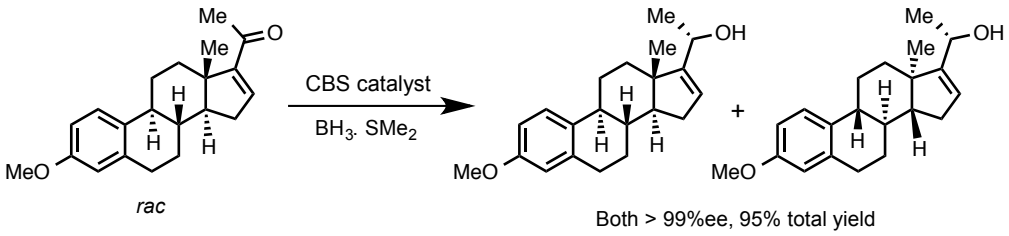

Figure 1.9 | Selected sample of Parallel Kinetic Resolution in asymmetric synthesis.

(b) Dynamic Kinetic Resolution (DKR)

To overcome the limitation of incomplete conversion of racemic starting materials in KR, elegant deracemization processes have been developed where both enantiomers of the racemic mixture were converted into single enantioenriched product. A well-established method is the Dynamic Kinetic Resolution (DKR). A DKR commonly obtains the desired enantioenriched product by racemization of the two enantiomers of the starting material (Figure **1.10**). During this process, the enantioselective reaction rate of favoured enantiomer SM_R is sufficiently faster than SM_S. Through a racemization of SM_R and SM_S, the designed high enantioselective P_R can be achieved with ideal yield.

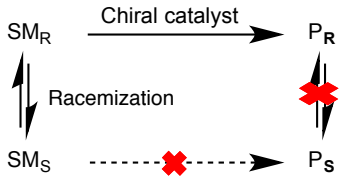

Figure 1.10 | General mechanistic pathway of dynamic kinetic solution (DKR).

The most challenging aspect of the work appears to involve the capability of a substrate to undergo facile racemization of both enantiomers in the starting materials (Figure **1.11**)[26-31]. A number of beautiful methods have been demonstrated by chemists here. One of the most popular strategies is employing substrates with a α-carboxylic moiety where racemization is accomplished via carbonyl enolization using additives such as polar solvents, bases or halide salts through a dynamic kinetic resolution (DKR) process (Figure **1.11**, a)[26, 27].

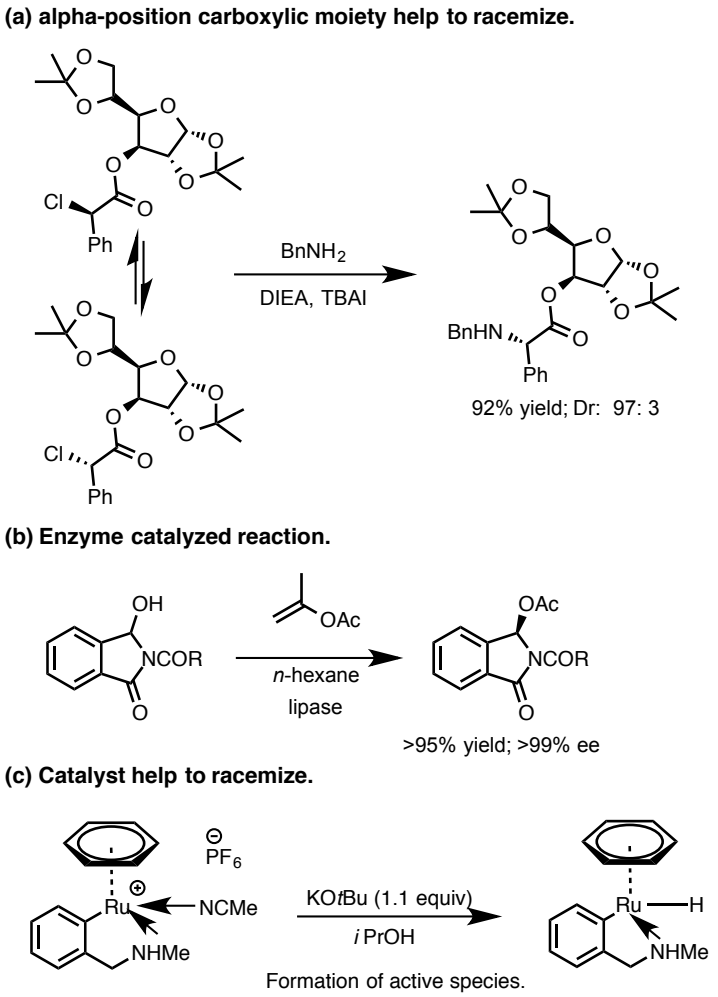

Figure 1.11 | Selected samples of dynamic kinetic resolution in asymmetric synthesis.

The use of enzymes, rather than traditional organo-or metal-catalysts, represents another attractive strategy for the DKRs, in view of mild operating condition and extremely efficient enantiomeric induction (Figure **1.11**, b) [28-30]. Here the acetylation of racemic *N*-acylhemiaminals with lipases exclusively gave the desired product in quantitative yield via DKR.

Recent development in the catalytic racemization of chiral amines and alcohols by Feringa and De Vries group with co-workers was also impressive by employing the half-sandwich cationic ruthena-and iridacycle complexes (Figure **1.11**, c) [31]. During the process, with the activation of responding complexes by KO*t*Bu, the catalysts are able to help racemize both chiral alcohols and amines.

(c) Dynamic Kinetic Asymmetric Transformation (DYKAT)

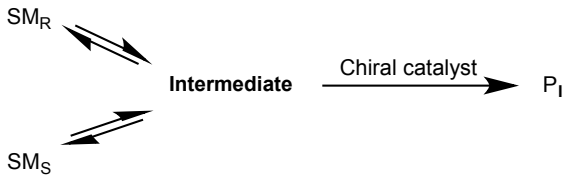

Figure 1.12 | General mechanistic pathway of DYKAT.

DYKAT is another well-established process, which converts two enantiomers of racemic mixture into a single enantioenriched products. During the process, two substrate enantiomers lose their chiral centres and are converted into an intermediate, and the subsequent enantioselective induction of the intermediate provides desired product in up to 100% yield with high enantioselectivity (Figure **1.12**).

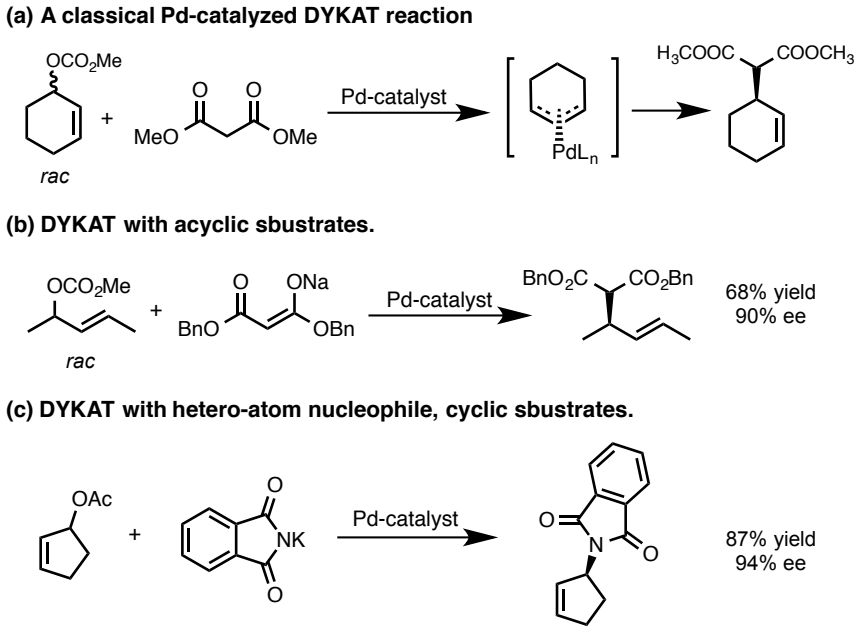

Figure 1.13 | Selected samples of Pd-catalyzed DYKAT in asymmetric synthesis.

Elegant and extensive work has been done by Trost and co-workers on the Pd-catalyzed DYKAT reactions (Figure **1.13**) [32-37]. Mechanistic studies reveal that the Pd-catalyzed DYKATs operate through a pathway where both enantiomers of the starting material are converted to a common pseudo-prochiral intermediate, and a subsequent enantioselective

step creates the new stereogenic centre (Figure **1.13**, a) [32,35-37]. A broad range of substrates and reaction partners can be used in the Pd-catalyzed DYKATs (Figure **1.13**, b&c) [32,34].

(d) Direct Enantioconvergent Transformation (DET)

A more recent concept of employing racemic substrates in forming desired enantioenriched molecular in high yield and enantioselectivity is the DET introduced by Ito and co-workers [19]. In this process, two enantiomers of the racemic starting material reacted through different pathways by a single chiral catalyst, but form the same enantioenriched product (Figure **1.14**).

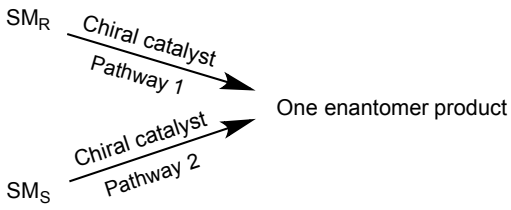

Figure 1.14 | General mechanistic pathway of DET.

As seen below (Figure **1.15**, a), in Ito's first DET reaction in 2010 [19] the (*S*)-enantiomer interacts with a borylcopper on the opposite face of the leaving alkoxy group to afford the (*S*)-product via an *anti*-S_N2' pathway. In contrast, the other enantiomer react through a *syn*-S_N2' pathway to provide the same product. A detailed mechanistic study, aided by theoretical calculations by Alexakis and co-workers (Figure **1.15**, b) [17, 38] suggested a DET pathway was occurring in the copper catalysed asymmetric allylic alkylation of cyclic allyl bromides with Grignard reagetns, leading to a complete revision of the initially proposed DYKAT mechanism.

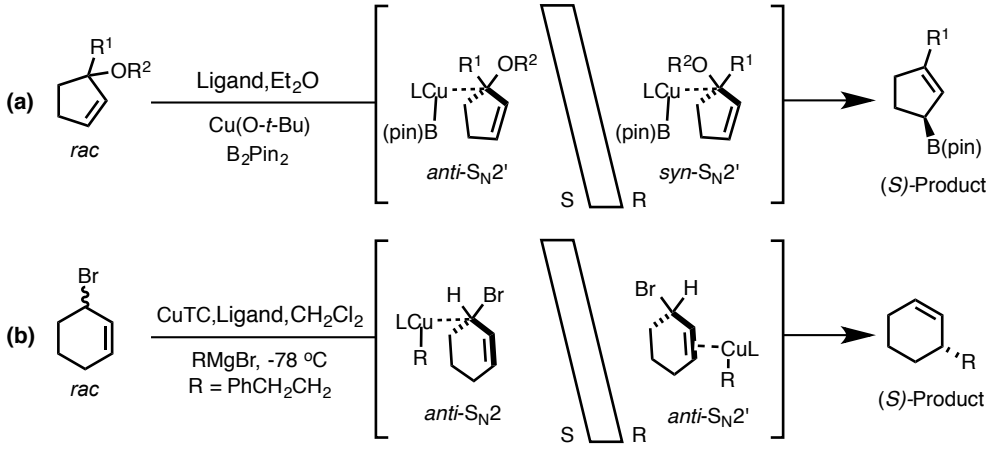

Figure 1.15 | Selected samples of DET in asymmetric synthesis.

1.2 Catalytic Asymmetric Allylic Substitution

Allylic compounds are found in many natural products, synthetically building blocks with allylic functional groups have been proven extremely important from practical, theoretical, and historical points of view [39]. Asymmetric induction in asymmetric allylic substitution is a critical dimension in modern organic synthesis. Over the past decades, catalytic asymmetric allylic substitution has emerged as a powerful tool allowing the synthesis of a broad range of Carbon-Carbon, Carbon-Oxygen, Carbon-Nitrogen, and Carbon-Sulphur bonds[40-48]. Generally, these reactions occur by one of two different mechanisms, which differ according to the nature of nucleophiles (Figure **1.16)**. With stabilized nucleophiles, defined as nucleophiles derived from conjugate acids whose $pK_a < 25$ [48], bond breaking and forming events normally occur outside the coordination sphere of the metal, and the enantioselective step is determined by nucleophiles' attack at carbon in a π-allyl-metal moiety [40-43]. In contrast, non-stabilized nucleophiles (nucleophiles derived from conjugate acids with $pK_a > 25$) normally undergo reactions where the nucleophiles directly attack the metal centre, and reductive elimination then forms the desired products [44-47].

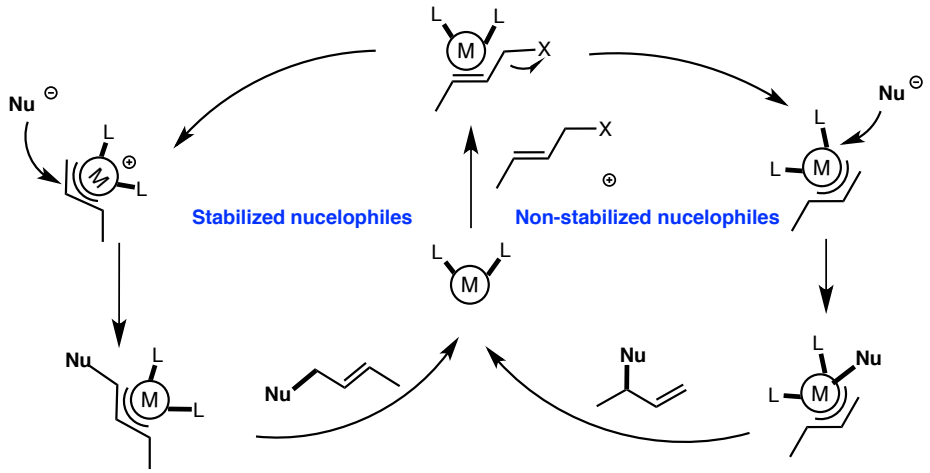

Figure 1.16 | General catalytic asymmetric allylic substitution mechanism pathway

The enantio-, stereo- and regio-selectvity observed in this processes, as well as the wide range of potential reaction partners that may be used, make such allylic alkylations an attractive strategy in modern asymmetric synthesis.

1.2.1 Stabilized Nucleophiles

Here we briefly introduce the use of stabilized nucleophiles in modern catalytic asymmetric allylic substitution reactions: (a) C-C bond formation; (b) C-O bond formation; (c) C-N bond formation; (d) C-S bond formation.

(a) C-C bond formation

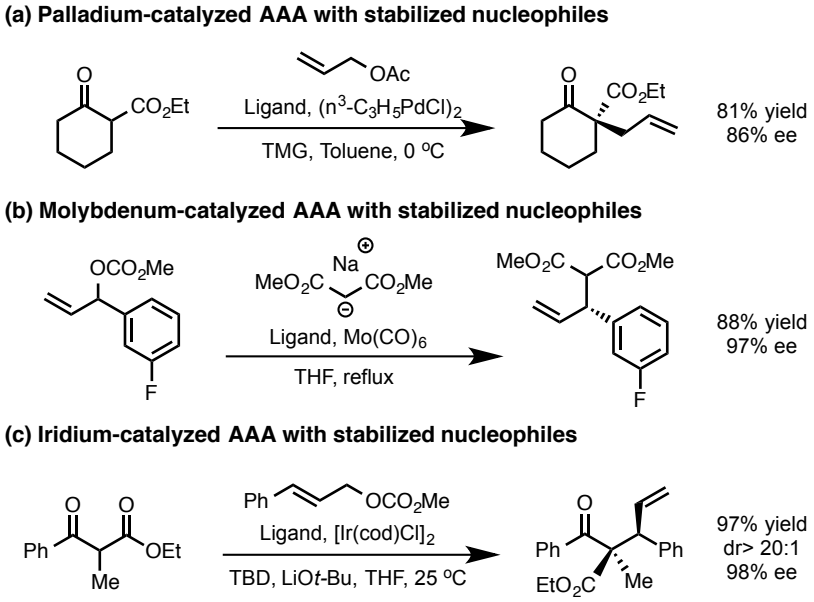

Figure 1.17 | Selected samples of stabilized nucleophiles in C-C bond formation.

AAA to form carbon-carbon bond formation has received tremendous attention in synthetic organic chemistry. A wide range of efficient methods has been released by chemists using stabilized carbon nucleophiles as shown above. Figure **1.17** a, highlights work by Trost and co-workers [32-37], where a typical Pd-catalyzed AAA reaction was used in the alkylation of β -ketoesters with its application to asymmetric synthesis of spiro-alkaloid nitramine [49].

Other metal catalysts have also been studied and Figure **1.17** b, highlights an alkylation method catalyzed by molybdenum illustrated by Merck laboratories [50]. The reaction was used to construct the stereocenters in the asymmetric synthesis of (+)-*trans*-3-hydroxymethyl-4- (3-fluorophenyl) cyclopentanone, which is an advanced intermediate of a new drug candidate. Figure **1.17** c, shows a recently developed alkylation introduced by Stoltz and co-workers [51]. The reaction involves β -ketoesters to generate vicinal quaternary and tertiary stereocentres by employing an iridium-phosphoramidite catalyst.

(b) C-O bond formation

Methodologies using stabilized nucleophiles tolerate oxygen containing functional groups are a critical area in catalytic asymmetric allylic substitutions. Synthesis of a range of biologically active molecules has demonstrated the power of this strategy in asymmetric catalysis (Figure **1.18**) [52-54]. A highlighted example is 2-bromoethanol and butadiene monoepoxide undergo a DYKAT to form an intermediate in a protein kinase C inhibitor. A classical Trost ligand here provides the reaction with a proper rate for the sufficient high regio- and enantio-selectivity of the desired product (Figure **1.18**, a) [52].

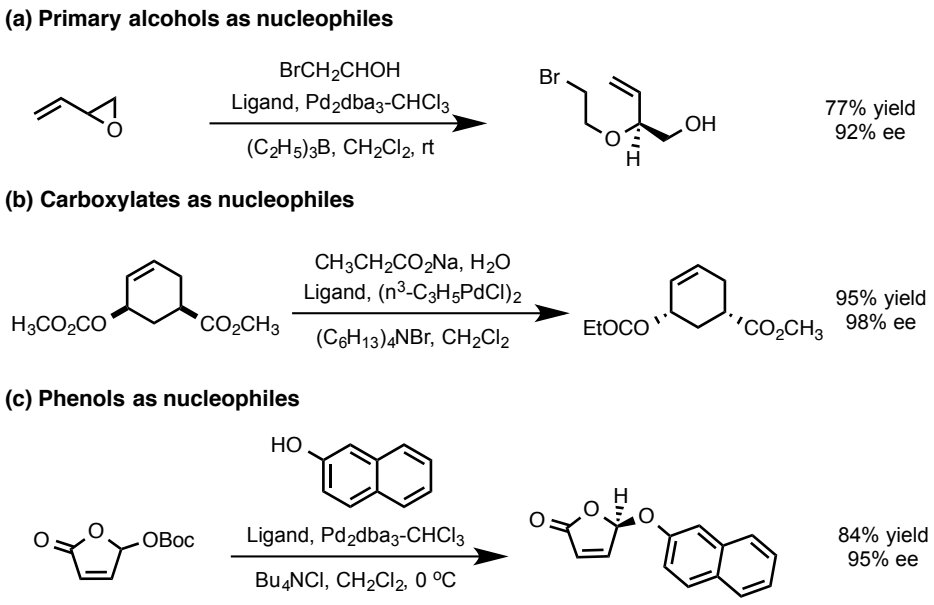

Figure 1.18 | Selected samples of stabilized nucleophiles in C-O bond formation.

A second example is the carboxylates. They are generally compatible nucleophiles for these asymmetric allylic substitutions. Here, deracemization of the 5-substituted cyclic allyl carboxylate gave a *meso*- π -allyl intermediate which is attacked by sodium propionate to obtain the desired product (Figure **1.18**, b) [53].

Phenols are widely occurring functional groups in natural products and biologically active molecules, and their use in C-O bond formation represents an attractive method in asymmetric catalysis. Here the DYKAT of butenolide with 2-naphthol afforded the desired

product with 95% ee and 84% yield which is an essential intermediate in the synthesis of brefeldin A (Figure **1.18**, c) [54].

(c) C-N bond formation

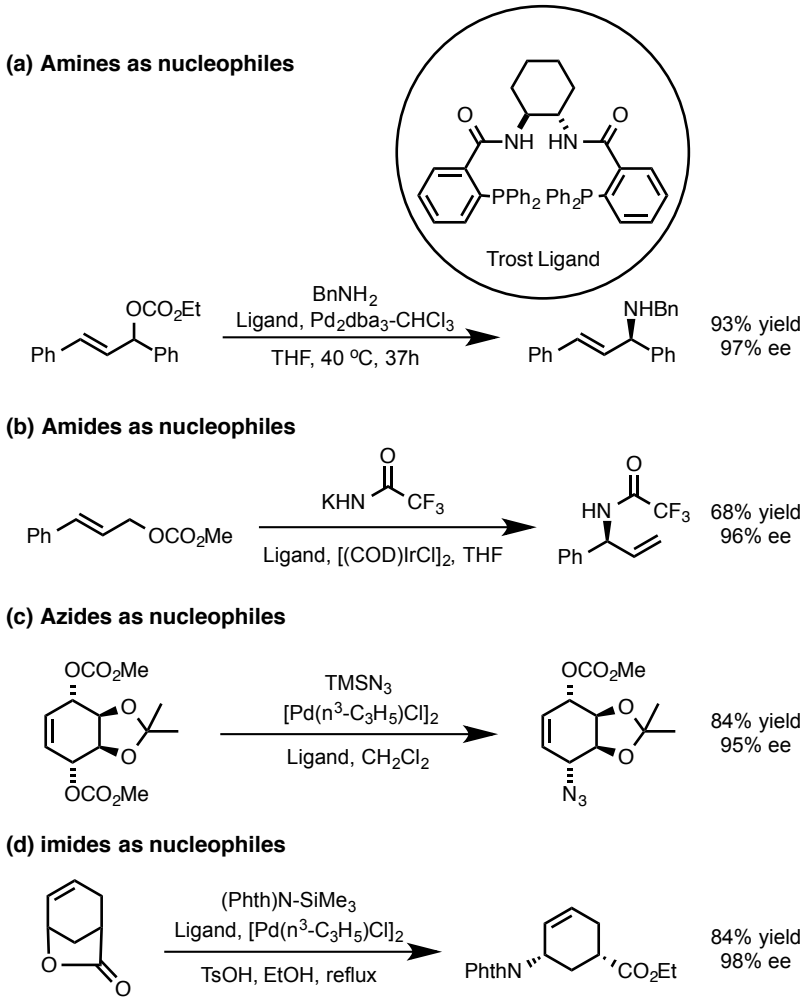

Figure 1.19 | Selected samples of stabilized nucleophiles in C-N bond formation.

Stereoselective C-N bond formation is another significant part in the asymmetric synthesis of many bioactive molecules. The advance of catalytic asymmetric substitutions with nitrogen-based nucleophiles is a powerful strategy for chemists (Figure **1.19**) [55-59].

Alkyl amines have long been one of the most attractive nucleophiles in C-N bond formation through catalytic asymmetric allylic substitution. The pioneering work was done by Hayashi and co-workers in enantioselective allylic substitution using symmetrical 1,3-

diphenylallyl and 1,3-dialkylallyl carbonates who showed that excellent yields and enantioselectivities were possible, for example see Figure **1.19**, a [55].

Neutral amides are typically less nucleophilic at N and amide anions are strong base, which might deactivate the catalyst [56]. However, as shown in the selected example reported by Hartwig and co-workers (Figure **1.19**, b) [57], by employing the potassium trifluoromethyl acetamide, the amide nucleophiles can be added using an Iridium complex to provide the desired product with good enantioexcess.

The azide functional group is another useful nitrogen nucleophile. It is easily converted into amino groups under mild reduction condition and is popular in asymmetric synthesis. Trost and Pulley demonstrated a very nice desymmetrization of *meso*-dicarbonates using $TMSN_3$ as the nucleophiles, where the method provides an efficient strategy to synthesize 1,4- or 1,2- substituted products (Figure **1.19**, c) [58].

Imides are the most common nucleophiles in catalytic asymmetric C-N bond formation; delocalization of electron density on nitrogen by the attached groups makes imides excellent stabilized nucleophiles in asymmetric catalysis (Figure **1.19**, d) [59].

(d) C-S bond formation

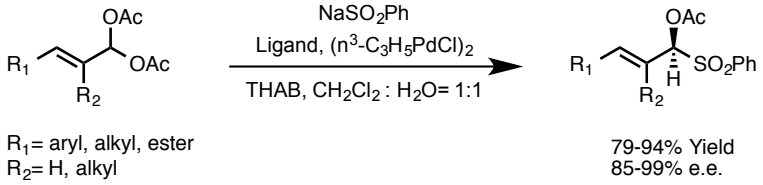

Figure 1.20 | A selected sample of stabilized nucleophiles in C-S bond formation.

Asymmetric C-S bond formation is highly desirable in modern organic synthesis. Allylic sulfones are capable of both nucleophilic and electrophilic introduction to the α-carbon. Here a selected example of sodium benzenesulfinate being used in a catalytic allylic

substitution with allylic diacetates to give the enantioenriched sulfones products is shown (Figure **1.20**) [60]. However, strategies for chiral sulphur-compounds synthesis are still challenging.

1.2.2 Non-stabilized Nucleophiles

Complementary to the use of stabilized nucleophiles, employment of non-stabilized nucleophiles represents another important area of catalytic allylic substitution. Non-stabilized nucleophiles can undergo efficient S_N2' oxidative addition and reductive elimination to form γ-substituted products with high regio- and enantio-selectivity. In contrast to stabilized nucleophiles where palladium and iridium were widely used as the metal catalysts, copper catalysts are the most intensively studied metal used here. According to the commonly accepted Cu-catalyzed enantioselective allylic substitution mechanistic pathway [44-47], the electron-deficient copper complexes will favor a faster reductive elimination to promote the γ-substituted products with desired enantioslectivity (Figure **1.21**) [45].

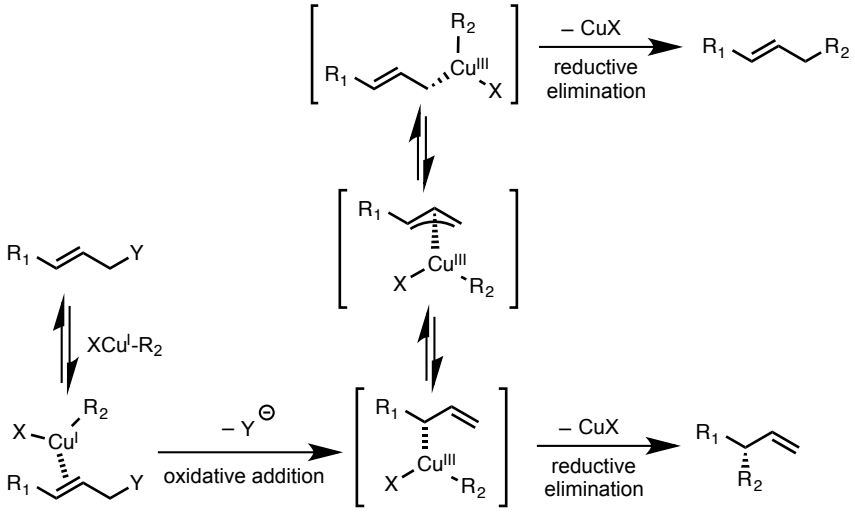

Figure 1.21 | General Cu-catalyzed allylic substitution mechanism.

Great efforts have been made in the catalytic allylic substitution systems employing: (a) Organomagnesium reagents; (b) Organozinc reagents; (c) Organoaluminum reagents; (d) Organoboron reagents; (e) Organolithium reagents.

(a) Organomagnesium reagents

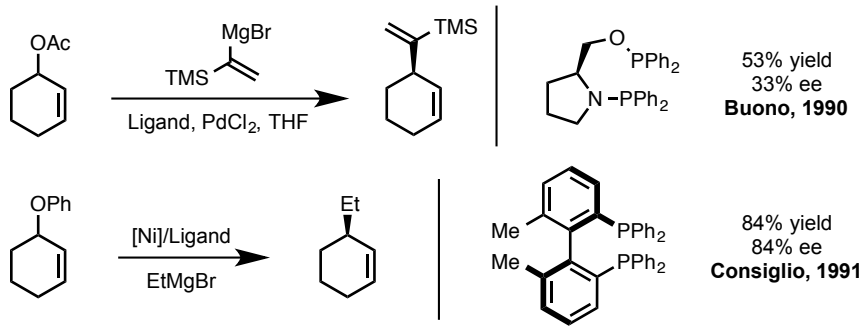

Figure 1.22 |Pioneering Ni- and Pd-catalyzed asymmetric allylic alkylation

Organomagnesium reagents are one of the most powerful tools used in non-stabilized nucleophiles in catalytic allylic substitution. Buono and co-workers reported the first Pd-catalyzed asymmetric allylic alkylation with vinylmagnesium bromide to form the desired product in 1990. Even though only moderate yield and enantioselectivity was observed, this work reveals the potential of employing organomagnesium reagents in metal-catalyzed AAA systems (Figure **1.22**) [61].

Later on, Consiglio and co-workers performed the initial exploration of asymmetric allylic alkylation using Grignard reagents involved processes catalyzed by Ni in the presence of chiral phosphine ligands [62].

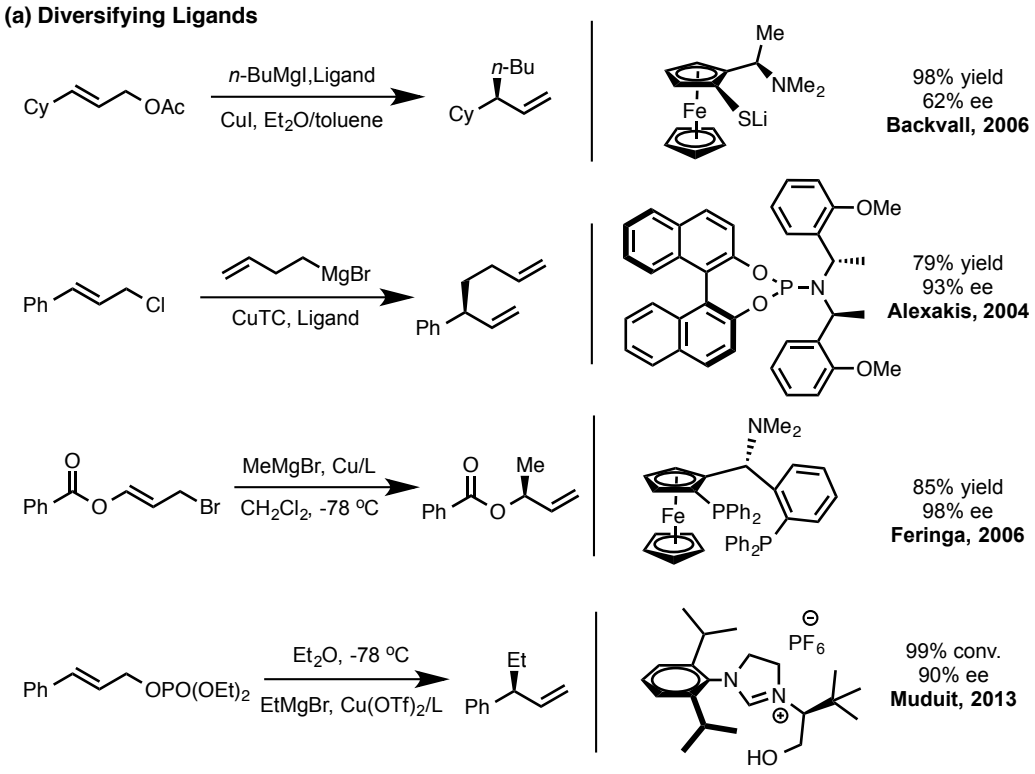

Figure 1.23(a) |Main trend of Cu-catalyzed AAA in using organomagnesium reagents

Since Backvall introduced the first Cu-catalyzed AAA reaction using alkylmagnesium reagents in 1995 [63], Cu-catalyzed AAA reactions have been intensively studied by chemists and excellent regioselectivity in the construction of stereogenic centres can be observed. Development in the Cu-catalyzed AAA reaction using organomagnesium reagents has aimed to diversify the scope of this chemistry. Various ligands and substrates now able to achieve enantioenriched products with good yields. Later on, second and third generation of copper thiolates, based on ferrocene backbones, was also demonstrated by Backvall and co-workers (Figure **1.23**, a) [64].

Alexakis and co-workers reported a series of Cu-catalyzed asymmetric allylic alkylation reactions using phosphoramidite ligands in which "Alexakis' ligand" with two methoxy groups at 2-position of the amine, provides excellent regio- and enantio-selectivity to various substrates (Figure **1.23**, a) [65].

Reactions using diphosphine ligands reported by Feringa and co-workers are also capable of catalyzing asymmetric allylic alkylation reactions and these ligands allow use of functionalized substrates bearing heteroatoms to provide the S_N2' products (Figure **1.23**, a) [66]. As recently reported by Mauduit and co-workers, NHC ligands in Cu-catalyzed AAA reactions of cinnamyl phosphate and ethyl magnesium bromide can also provide high yield, enantioselectivity, and regioselectivity (Figure **1.23**, a) [67].

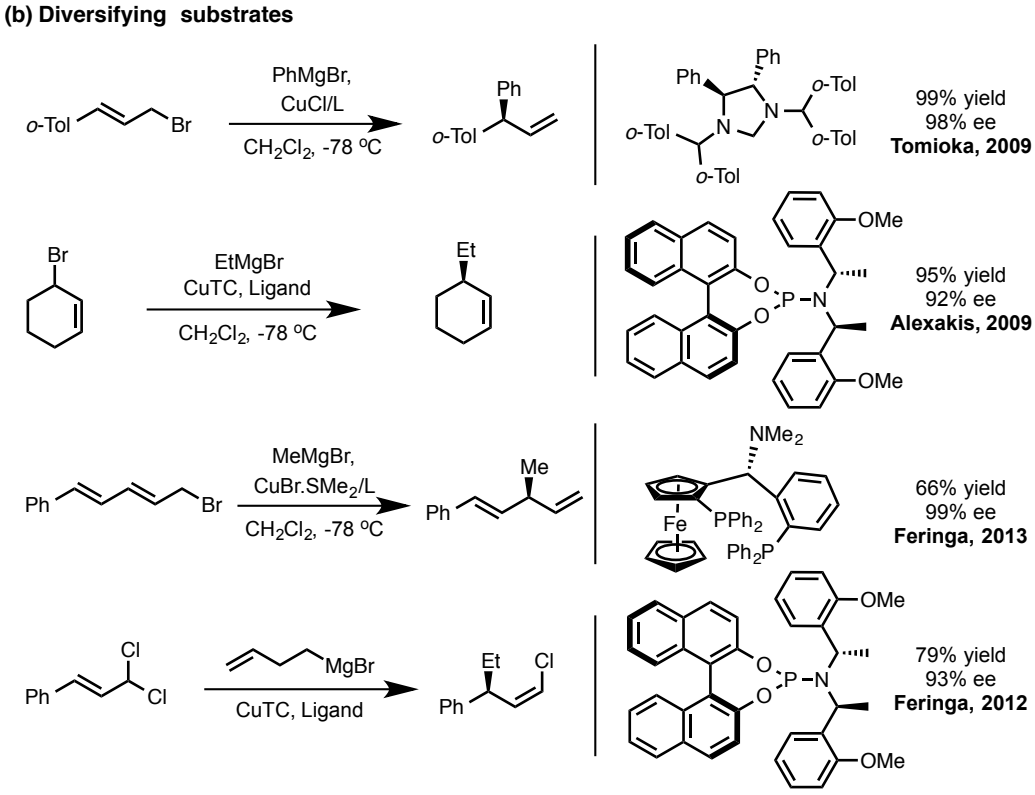

Figure 1.23(b) |Main trend of Cu-catalyzed AAA in using organomagnesium reagents

In addition to the classical cinnamyl substrates, more functionalized substrates have been extended to fertilize synthetically useful AAA approaches. Tomioka and co-workers reported highly enantio- and regioselective Cu-catalyzed AAA reaction using arylmagnesium reagents in 2009 (Figure **1.23**, b) [68].

At the same year, Alexakis reported the first example of a dynamic kinetic asymmetric allylic alkylation using non-stabilized nucleophiles; both enantiomers of the starting

material are converted into the desired product with high enantioenrichment and good yield (Figure **1.23**, b) [38]. Feringa and co-workers used organomagnesium reagents with allylic substrates bearing an extended unsaturated system (Figure **1.23**, b). Finally prochiral *gem*-dichloride substrates react with the Grignard reagents under catalytic conditions to give the functionalized products with excellent enantioselectivity and regioselectivity [69,70].

(b) Organozinc reagents

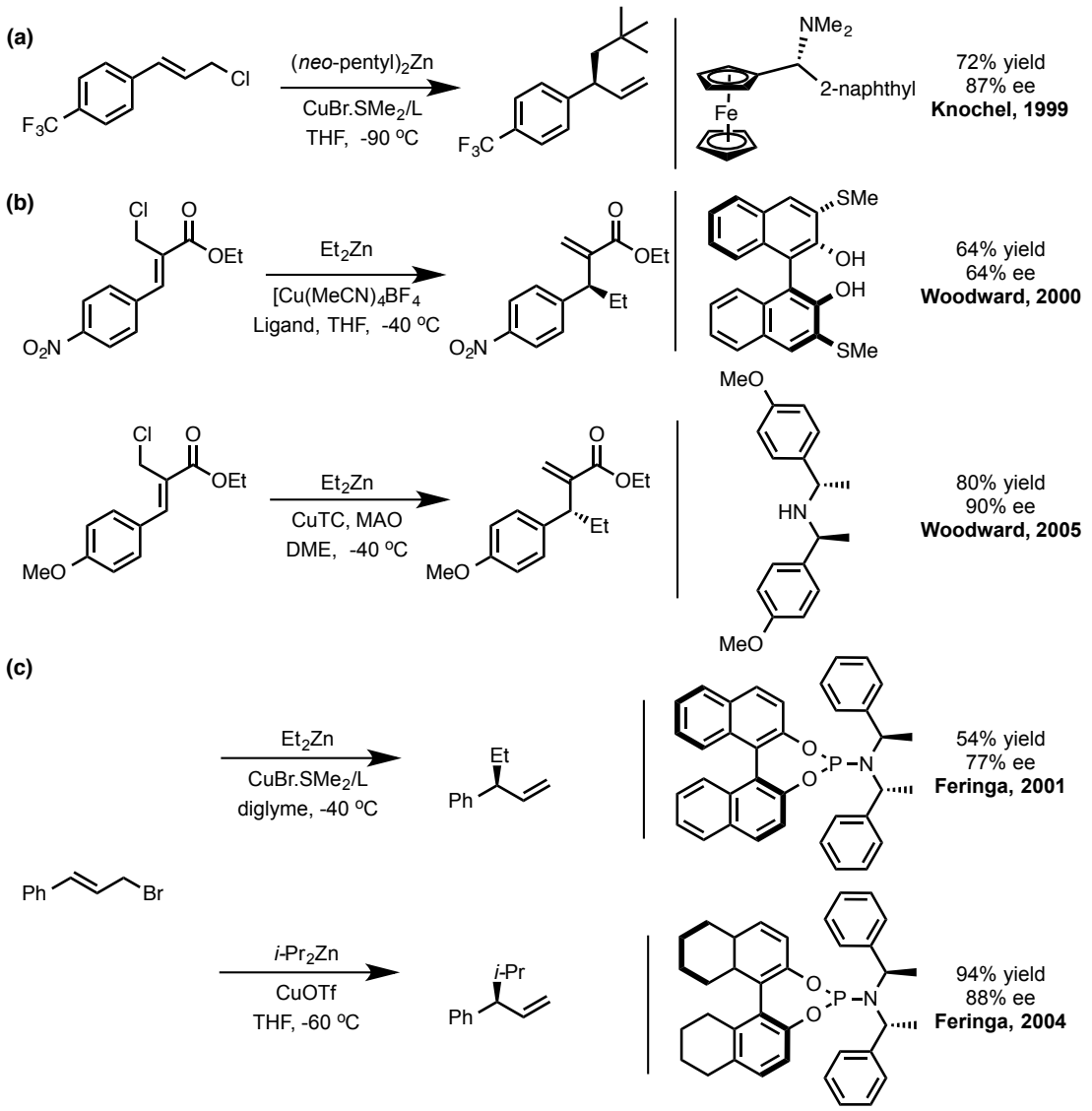

Figure 1.24(a, b, c) |Development of Cu-catalyzed AAA in using organozinc reagents

Soon after Backvall's pioneering work on Cu-catalyzed AAA with Grignard reagents [63], Knochel and co-workers developed Cu-catalyzed AAAs using organozinc reagents (Figure **1.24**, a) [71]. Exploration of this type of nucleophile in copper catalyzed asymmetric allylic alkylations has focused on developing efficient copper/ligand combinations.

Woodward and co-workers reported the asymmetric allylic substitution with diethylzinc species and substrates derived from the Morita-Baylis-Hillmann chemistry using a binaphthol ligand in 2000 (Figure **1.24**, b) [72]. Later on, further study of this type of reaction illustrated the addition of MAO (methyl aluminoxane, halide scavenger) with new sole symmetrical amine ligand led to an increased 90% e.e. of desired product [73].

Feringa and co-workers also demonstrated the use of organozinc reagents with phosphoramidite ligands in Cu-catalyzed AAA reactions (Figure **1.24**, c) [74]. The ee of these reactions was found to be dependent on a number of different factors: leaving groups, ligands, solvents, temperatures etc., and fine tuning of the reaction conditions allowed up to 88% enantioselectivity using phosphoramidite ligands in combination with CuOTf [75].

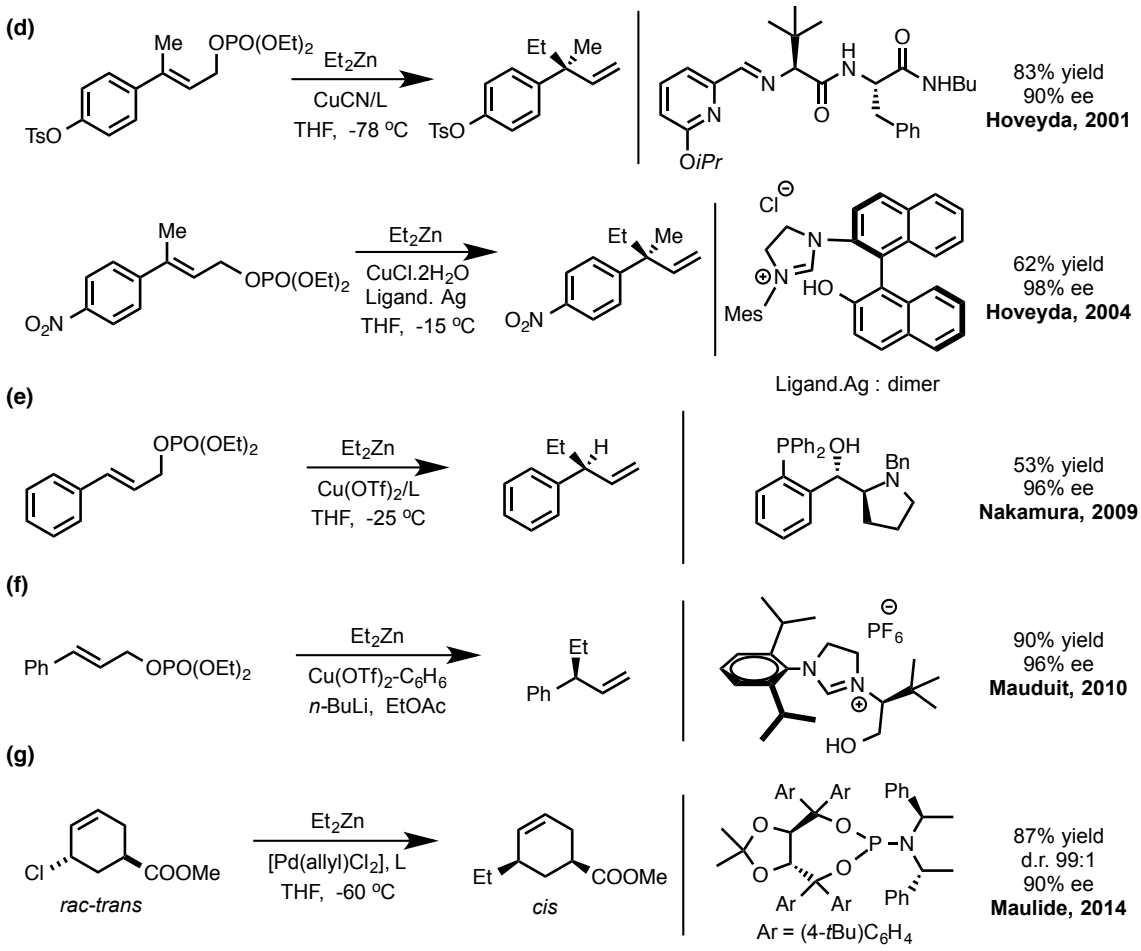

Figure 1.24(d-g) |Development of Metal-catalyzed AAA in using organozinc reagents

In the same year, Hoveyda and co-workers revealed peptide-based ligand systems to promote the asymmetric allylic alkylation of organozinc reagents with allylic phosphates (Figure **1.24**, d) and good yield and high enantioselectivity can be achieved in the formation of challenging quaternary centers [76]. Moreover, improved peptide-based ligands were later reported which allow excellent yield and enantioenrichment of the desired products [77]. One year later, another elegant system was disclosed by Hoveyda and co-workers with the promotion of the bidentate diaminocarbene-based ligands. These new catalysts are reported to be more efficient and highly selective than the peptide-type ligands [78]. Beautiful further generations of such NHC ligands were also reported by Hoveyda group, enabling efficient asymmetric arylation with arylzinc reagents[79, 80].

Design of new ligand systems and expanding of reaction scope, new metal catalysts have been developed recently (Figure **1.23**, e-g). For example, Nakamura and co-workers' amino hydroxyl phosphine ligands [81]; Mauduit and co-workers' hydroxyalkyl NHC ligands both provide high yield and enantioselctivity of the products [82]. Work by Maulide and co-workers reported Pd-catalyzed AAA using organozinc reagents in 2014 where use of racemic *trans*-cyclohexenyl allylic susbtrates reacts with Et_2Zn, to provide excellent diastereo- and enantio-selectivity of exclusively *cis* products [83].

(c) Organoaluminum reagents

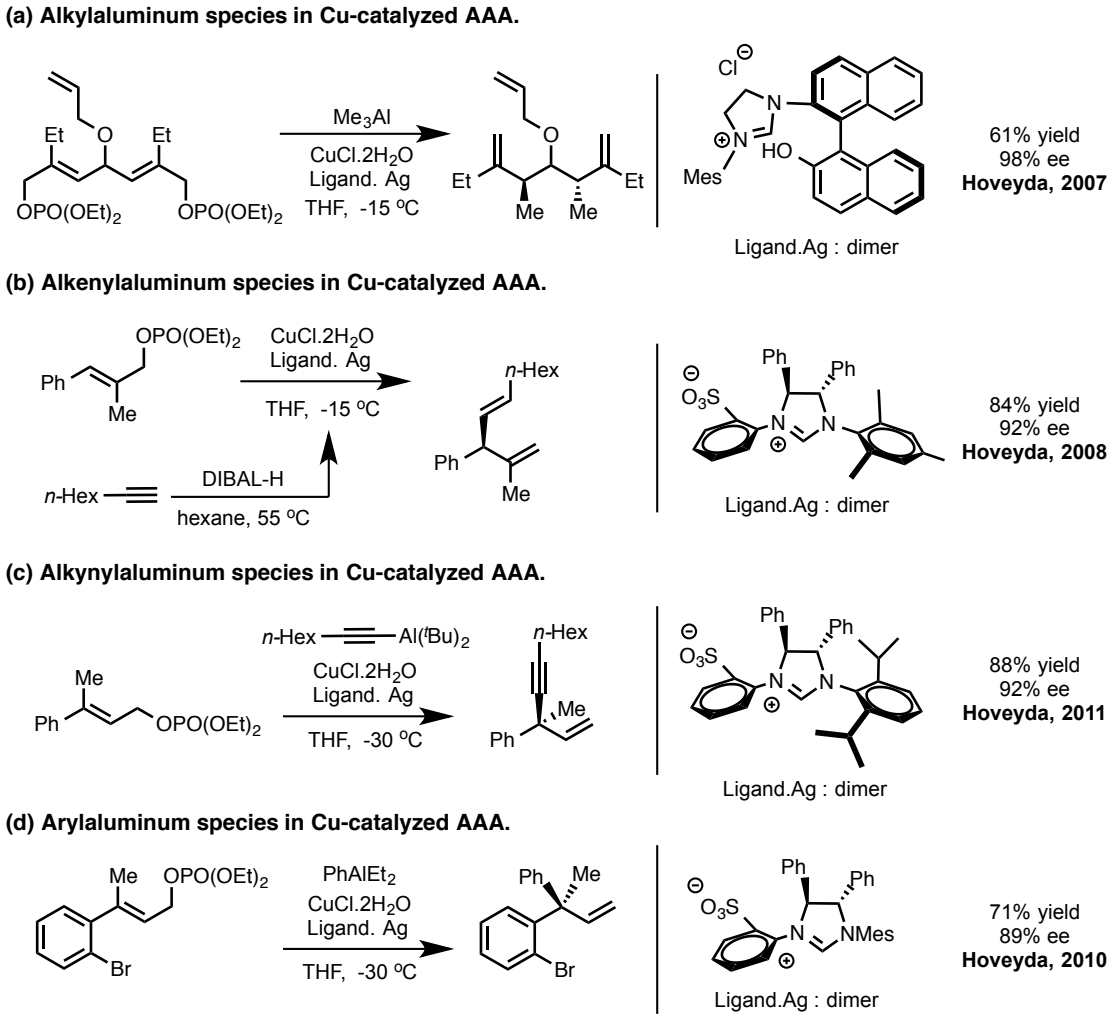

Figure 1.25 |Catalytic asymmetric allylic substitution using organoaluminum reagents

Compared to more widely used organomagnesium and organozinc reagents, organoaluminum reagents are less frequently used as non-stabilized nucleophiles. However, elegant work in this area by Hoveyda and co-workers demonstrates that organoaluminum reagents can provide superior results to organozincs in Cu-catalyzed asymmetric substitution of allylic phosphates as $AlMe_3$ was observed to give better results than Me_2Zn (Figure **1.25**, a) [84].

Later, alkenylaluminum reagents, generated in situ from an alkyne and DIBAL-H, were shown to be capable of allylic substitution catalyzed by Cu-NHC complexes (Figure **1.25**, b) [85]. The ability to employ either (*E*)-or (*Z*)-type of alkenylaluminum reagents was demonstrated in the study of hydroalumination of phenylacetylene derivatives under different reaction conditions [86].

With these successes in hand, the Hoveyda group investigated alkynylaluminum reagent addition to form quaternary stereocenters, where impressive chemoselectivities were observed with a variety of alkynylaluminums (Figure **1.25**, c) [87]. To full elaborate on the organoaluminum reagents system, Hoveyda and co-workers also examined the possibility of using arylaluminum species in the catalytic asymmetric allylic substitutions (Figure **1.25**, d). Overall, it is impressive to see that such a broad scope of substrates are useful for these reactions with interesting arylaluminum reagents, especially in the construction of challenging quaternary stereocenters [88].

(d) Organoboron reagents

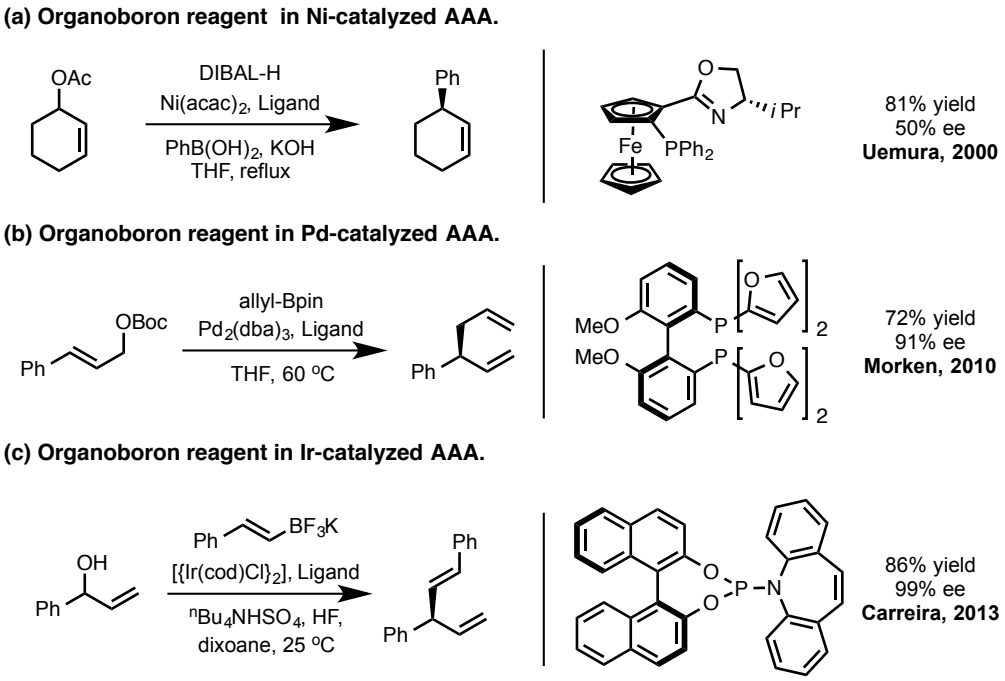

Figure 1.26 (a-c) |Catalytic asymmetric allylic substitution using organoboron reagents

Organoboron reagents represent one of the most diverse non-stabilized nucleophiles in reactions with different metal catalysts. The first catalytic asymmetric allylic substitution employing organoboron reagents was reported by Uemura and co-workers using Ni as the metal catalyst [89]. In these reactions, the lower nucleophilicity of the organoboron reagents compared to classical non-stabilized nucleophiles required the addition of base, and the reaction operated at reflux in THF (Figure **1.26**, a).

Recently, Pd-catalyzed asymmetric allylic substitution was also reported, Morken and co-workers illustrate an elegant strategy employing allylic carbonates and the organoboron species to deliver the desired enantiomerically enriched vicinal π-π products in good yields (Figure **1.26**, b) [90]. Expansion of this chemistry to form all-carbon quaternary centers was reported later by the same group [91].

Carreira and co-workers proposed the first Ir-catalyzed asymmetric allylic alkylation with allylic alcohols and the alkenylborates in 2013. The $^{n}Bu_4NHSO_4$ was demonstrated to help activate the allylic alcohol and dissolve the borate salt to facilitate phase-transfer in the

catalytic process [92]. Following this, the Carreira group further expanded the scope of reacting partners by using of alkynyltrifluoroborates later [93].

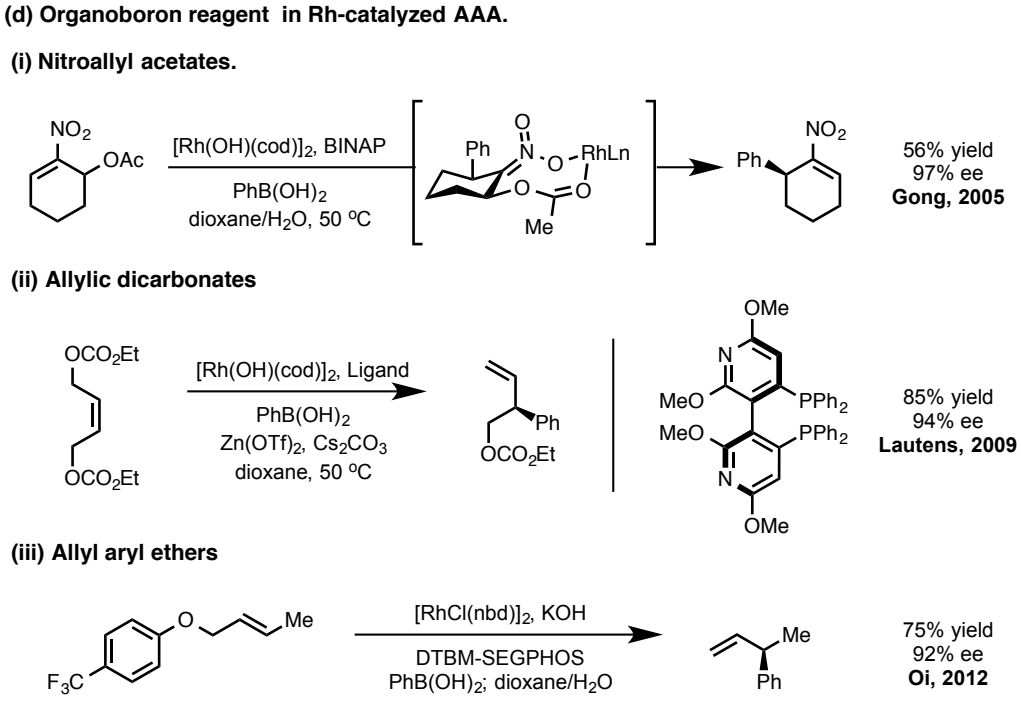

Figure1.26 (d) |Catalytic asymmetric allylic substitution using organoboron reagents

Rhodium is one of the most used metal catalysts with organoboron reagents in catalytic asymmetric allylic substitutions. Following previous related studies on 1,4-additions, Gong and co-workers disclosed Rh-catalyzed asymmetric allylic substitution with nitroallyl acetate and $PhB(OH)_2$ (Figure **1.26** (d), i) [94]. During this process, β-elimination of the acetate group in the 1,4-addition addition enolate intermediate proceeds to give the final product.

Later, Lautens and co-workers demonstrated an Rh-catalyzed asymmetric arylation reaction with the allylic dicarbonates in 2009 (Figure **1.26** (d), ii) [95]. The author proposed a mechanism where the products distribution is dictated by competing rates of reductive elimination versus isomerization and may depend on the species coordinated to σ-enyl complex. Oi and co-workers used allyl aryl ethers as electrophiles in Rh-catalyzed

asymmetric allylic substitution with various arylboronic acids in 2012 (Figure **1.26** (d), iii) [96]. The group suggested critical beta aryloxy elimination is the stereo-determining step to deliver the desired products.

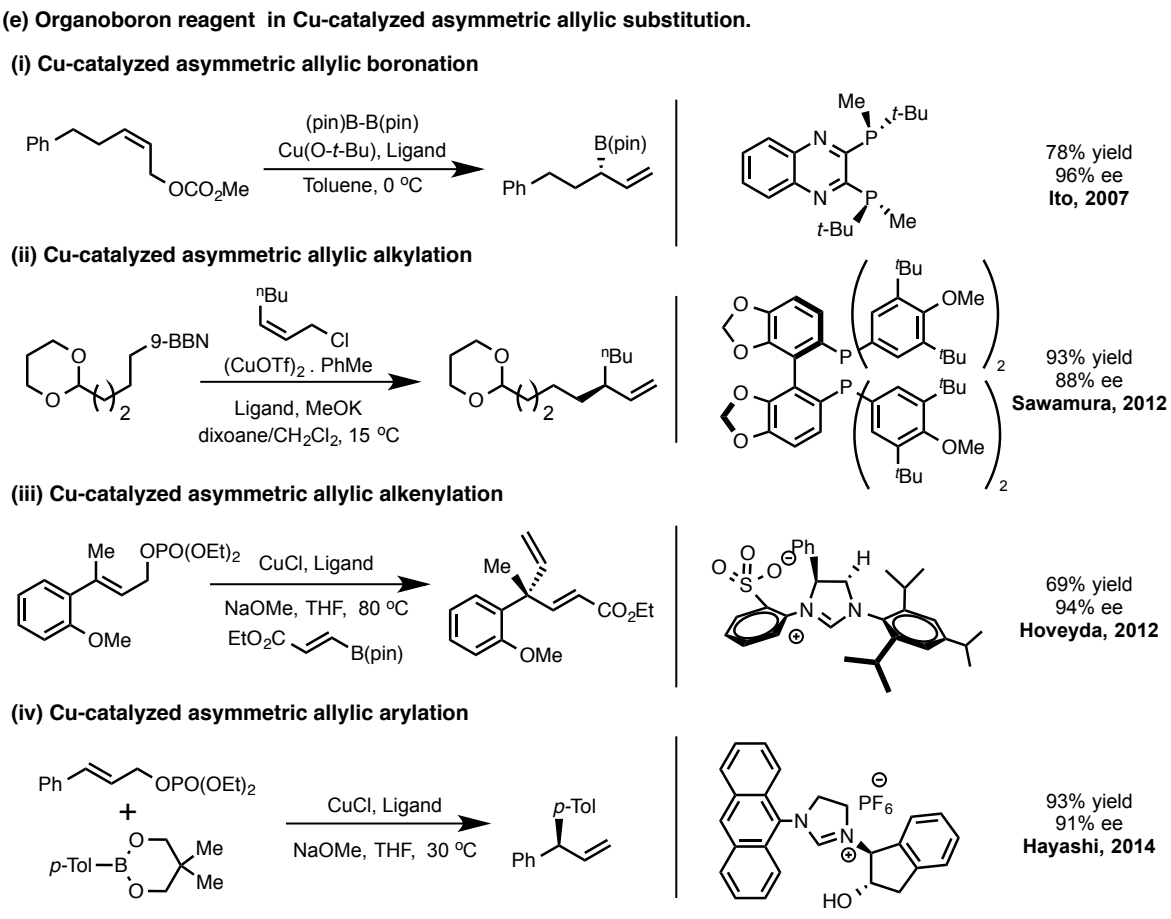

Figure1.26 (e) |Catalytic asymmetric allylic substitution using organoboron reagents

Copper catalyst is another metal catalyst widely used in the asymmetric allylic substitutions employing organoboron reagents. The pioneering work by Ito involves a copper-catalyzed asymmetric allylic substitution with diboron nucleophiles and allylic carbonates to provide allylboronate products in good yield and high enantioselectivity (Figure **1.26** (e), i) [97].

Afterwards, this organoboron chemistry was expanded by using a broad range of carbon-based boron nucleophiles to form different allylic bonds. In 2012, Sawamura and co-

workers reported the first copper-catalyzed enantioselective allylic alkylation using unactivated alkylborons (Figure **1.26** (e), ii) [98]. The allylic chloride and the alkylborane substrate react under Cu-catalysis with the DTBM-SEGPHOS ligand, to provide designed products in excellent yield with high regio- and enantio-selectivity.

Based on the successful development of aluminum reagents used in copper-catalyzed AAA systems, Hoveyda and co-workers also studied the alkenylboron reagents in this system (Figure **1.26** (e), iii) [99]; allylic phosphates react with alkenylboronate esters under Cu-catalysis with NHC ligands, to offer good yield and high enantio- and regio-selectivity of the products, and further extended scope using allenylboron reagents was released soon after [100].

In 2014, Hayashi and co-workers reported another copper-catalyzed asymmetric allylic arylation strategy using arylboron reagents (Figure **1.26** (e), iv) [101]. A broad range of arylboron reagents was employed, reacted with substituted allylic phosphate substrates, to construct the quaternary stereocenters in desired molecules.

(e) Organolithium reagents

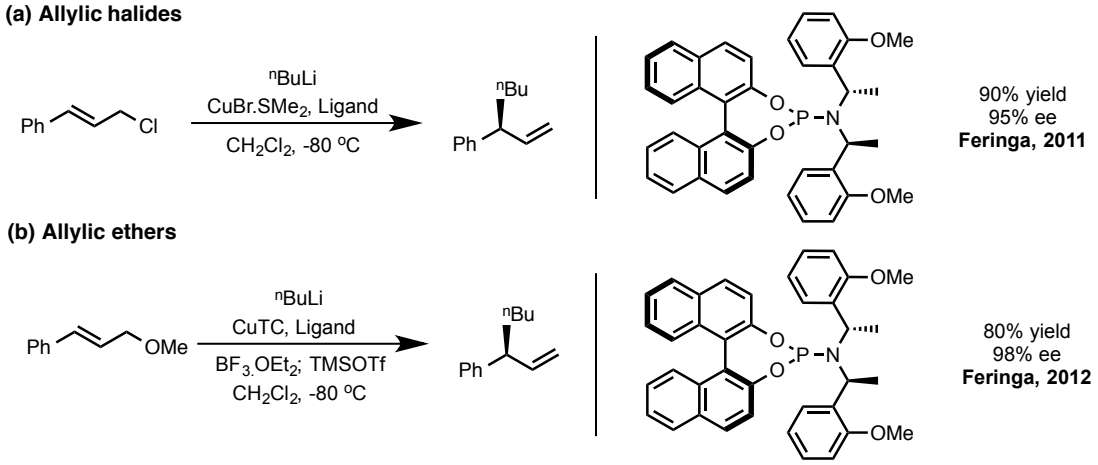

Figure 1.27 |Catalytic asymmetric allylic substitution using organolithium reagents

Due to the high reactivity of organolithium reagents, their employment as non-stabilized nucleophiles in catalytic asymmetric substitutions remains challenging. Pioneering work was done by Feringa and co-workers in 2011, which involves slow addition of organolithium reagents to a dichloromethane solution of allylic chloride in the presence of phosphoramidite ligands to give desired products in excellent yield and enantio-, and region-selectivity (Figure **1.27**, a) [102]. Soon after, an extension of this chemistry was reported using allylic ether substrates with a Lewis acid additive (Figure **1.27**, b) [103].

1.3 Catalytic Asymmetric Desymmetrization of *meso*-compounds

Catalytic asymmetric desymmetrization is a powerful and general synthetic strategy used in the asymmetric catalysis [104]. The nature of these achiral *meso*-compounds enables the enantioselective differentiation of its two symmetry related enantiotopic groups, provides means to achieve full conversion of the starting materials into the desired enantioriched products. Moreover, the asymmetric desymmetrization intermediates/products can contain useful functional groups, which offer the possibility to construct multiple stereogenic centres simultaneously in the designed molecules. Elegant work towards catalytic asymmetric desymmetrization has been developed by chemists to accomplish the goal of synthesising various enantioenriched materials from simple small compounds to complex bioactive nature products. Here, we have a brief introduction to the most popular substrates used in this chemistry: oxabicyclic compounds and *meso*-allyl compounds.

1.3.1 Oxabicyclic Compounds

Oxabicyclic compounds have a naphthalene-like skeleton, which exists in a broad range of bioactive molecules [108, 109] and are common starting materials in catalytic asymmetric desymmetrizations. The transition-metal-catalyzed asymmetric ring opening of oxabicyclic

alkenes, named asymmetric ring opening (ARO) reactions, are an attractive strategy in the formation of (a) carbon-carbon bond and (b) carbon-heteroatom bond [110-112].

(a) Carbon-carbon bond formation

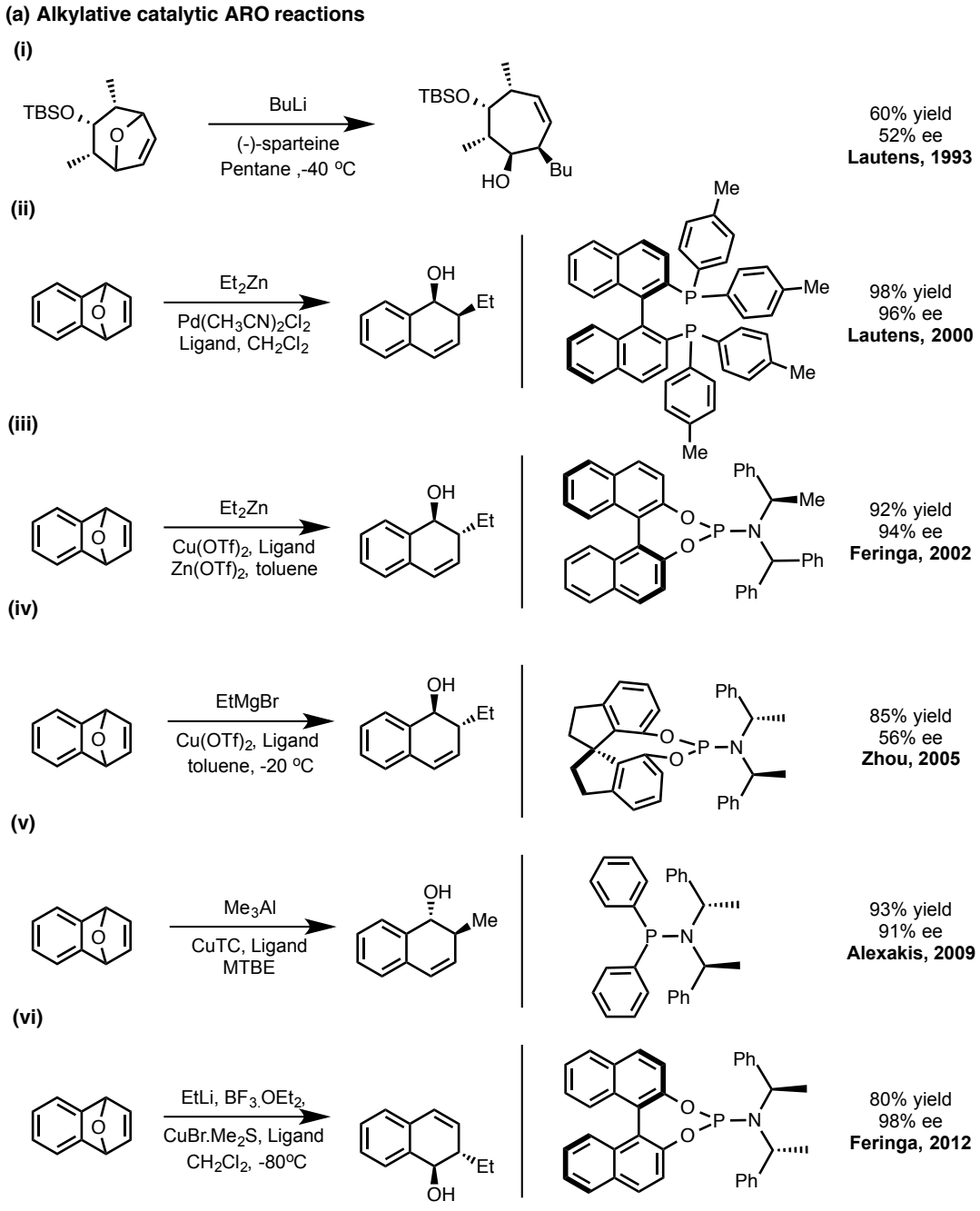

Figure1.28 (a) |Catalytic ARO reactions: carbon-carbon bond formation.

The asymmetric carbon-carbon bond formation stands in the heart of modern organic synthesis. The first alkylative catalytic asymmetric desymmetrization of an oxabicycle was reported by Lautens and co-workers in 1993 (Figure **1.28** (a), i) [113]. Employment of BuLi, catalyzed by substoichiometric amounts of sparteine led to 60% yield and 52% enantioselectivity of a complex desired product. Years later, a Pd-catalyzed enantioselective asymmetric ring opening reaction of oxabicycle substrates was reported by the same group (Figure **1.28** (a), ii) [114]. The reaction uses organozinc reagents, and the excellent yields, enantioselectivity of products and broad functional group tolerance make it an attractive strategy in asymmetric catalysis.

In 2002, Feringa and co-workers extended this chemistry by a highly enantioselective asymmetric ring opening reaction using a copper-phosphoramidite catalyst (Figure **1.28** (a), iii) [115] which gave *anti*-products arising from endo attack of dialkylzinc reagent, complementary to the palladium-catalyzed reactions.

Later, Zhou and co-workers revealed a method using Grignard reagents in 2005 (Figure **1.28** (a), iv) [116]. Even though the results are moderate, the easy-access simple Grignard reagents illustrate a potential approach in this enantioselective asymmetric ring opening system.

Recently, advance of this chemistry using organoaluminum and organolithium reagents was found to be viable by the Alexakis and Feringa Groups separately (Figure **1.28** (a), v&vi) [117,118]. Both of these methods are highly efficient, and gave *anti* isomers with excellent enantioselectivity and yields.

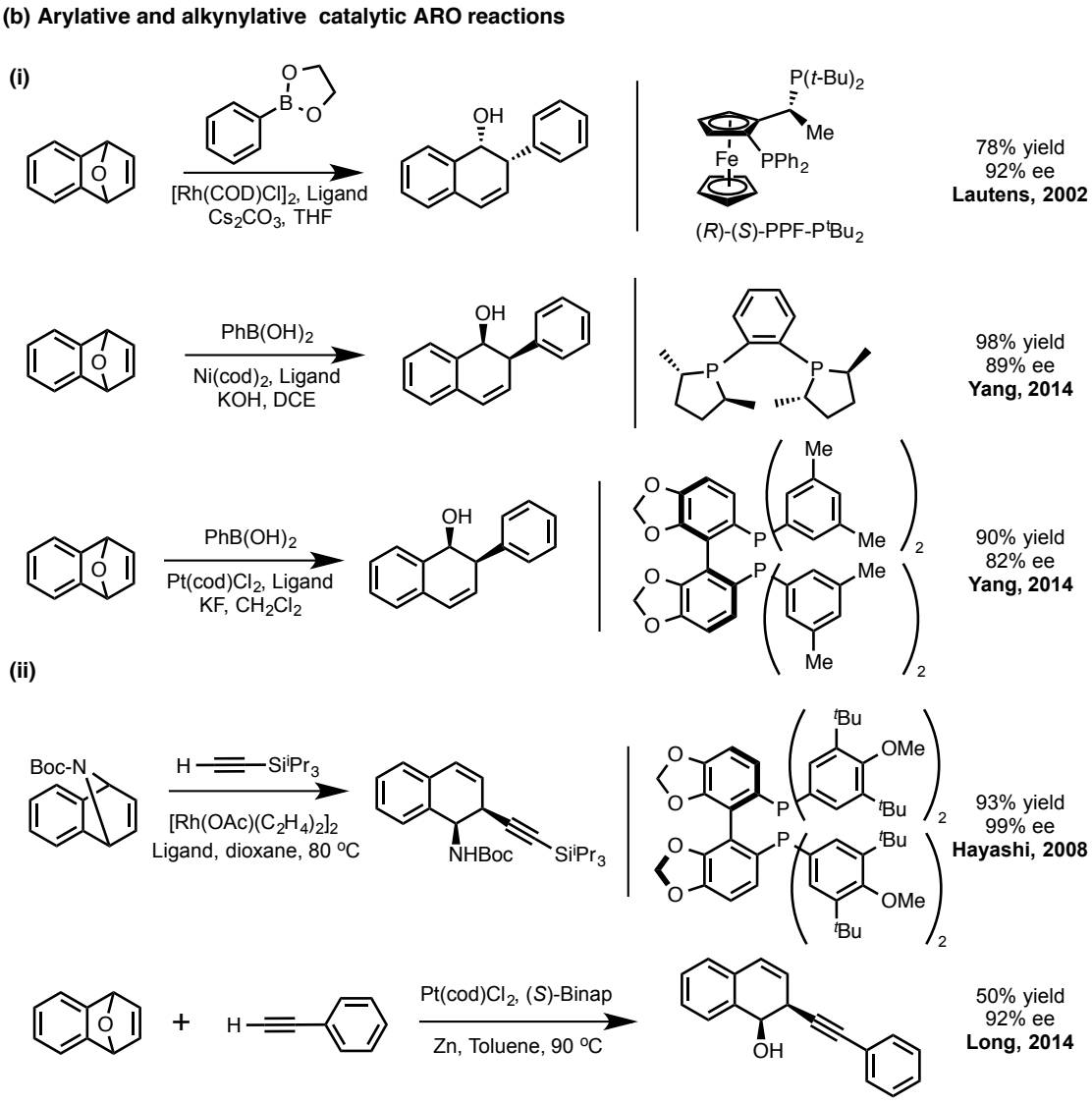

Figure1.28 (b) |Catalytic ARO reactions: carbon-carbon bond formation.

Inspired by the alkylative catalytic asymmetric ring opening reactions, the possibility of other types of carbon-carbon bond formation was also studied (Figure **1.28**, b). A rhodium-catalyzed enantioselective ARO reaction using organoboron reagent was reported by Lautens and co-workers in 2002 (Figure **1.28** (b), i) [119]. Recently, Yang and co-workers disclosed two versatile and highly efficient methods using arylboronic acids catalyzed by nickel and platinum respectively [120,121]. Both methods tolerate a wide variety of arylboronic acids and provide good to excellent enantioenrichment to the desired products under mild conditions.

Another type of carbon-carbon formation by the catalytic asymmetric ring opening reaction of oxabicyclic compounds involves alkynes (Figure **1.28** (b), ii). In 2008, Hayashi and co-workers reported a highly enantioselective alkynylation of azabenzonorbornadienes by use of a sterically bulky silylacetylene and rhodium catalyst [122]. The reaction demonstrates that yield and enantioselectivity of the products are strongly dependent on the steric bulk of the terminal alkynes. The Long group developed a platinum-catalyzed ARO reaction of oxabenzonorbornadiene with terminal aromatic alkynes in 2014 [123]. This method provides an alternative approach to synthesize enantiomerically enriched chiral derivatives of the naphthalene skeleton.

(b) Carbon-heteroatom bond formation

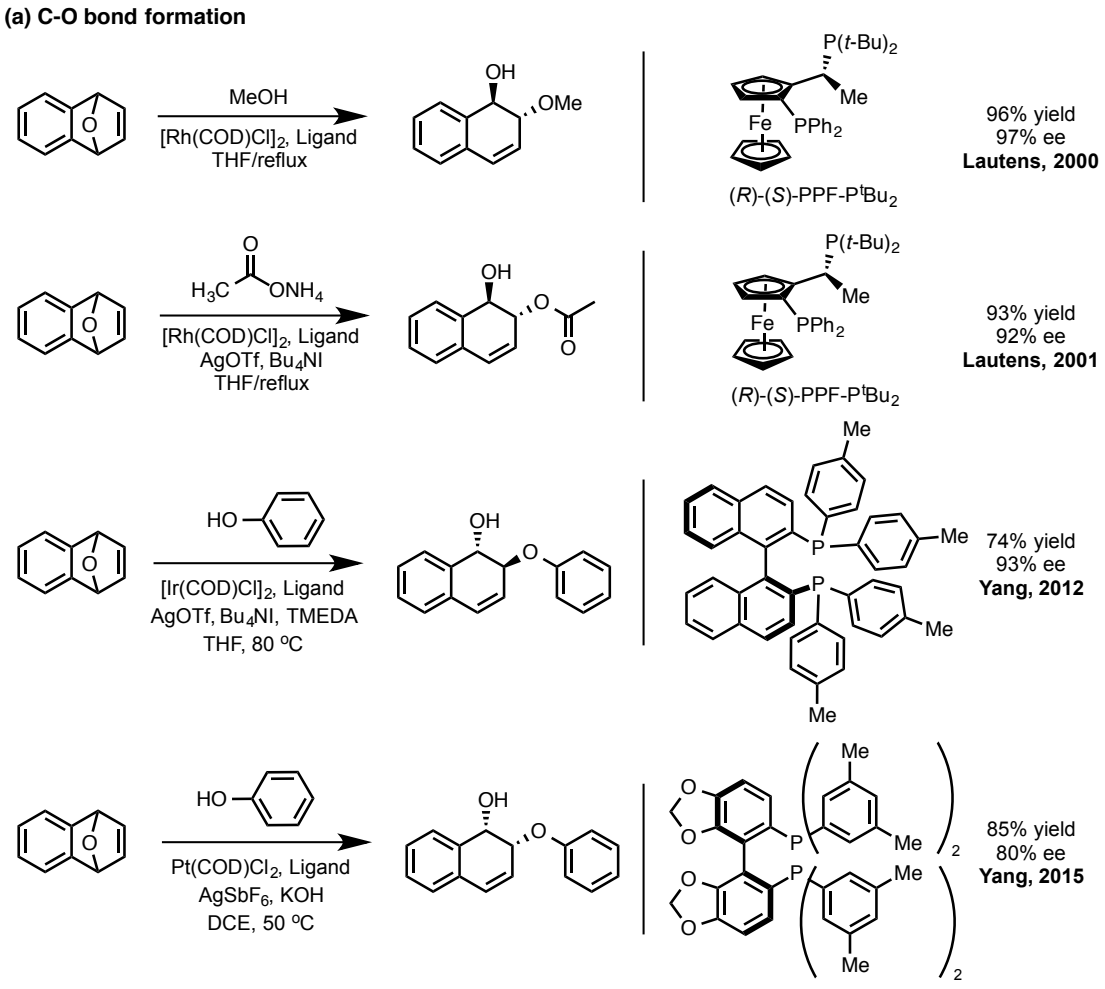

Figure1.29 (a) |Catalytic ARO reactions: carbon-heteroatom bond formation.

Carbon-heteroatom bond formation consists another important area in the catalytic asymmetric ring opening reactions. The pioneering work was done by Lautens and co-workers to develop a rhodium-catalyzed enantioselective ARO reaction using alcohol nucleophiles to provide new C-O bonds (Figure **1.29**, a) [124].

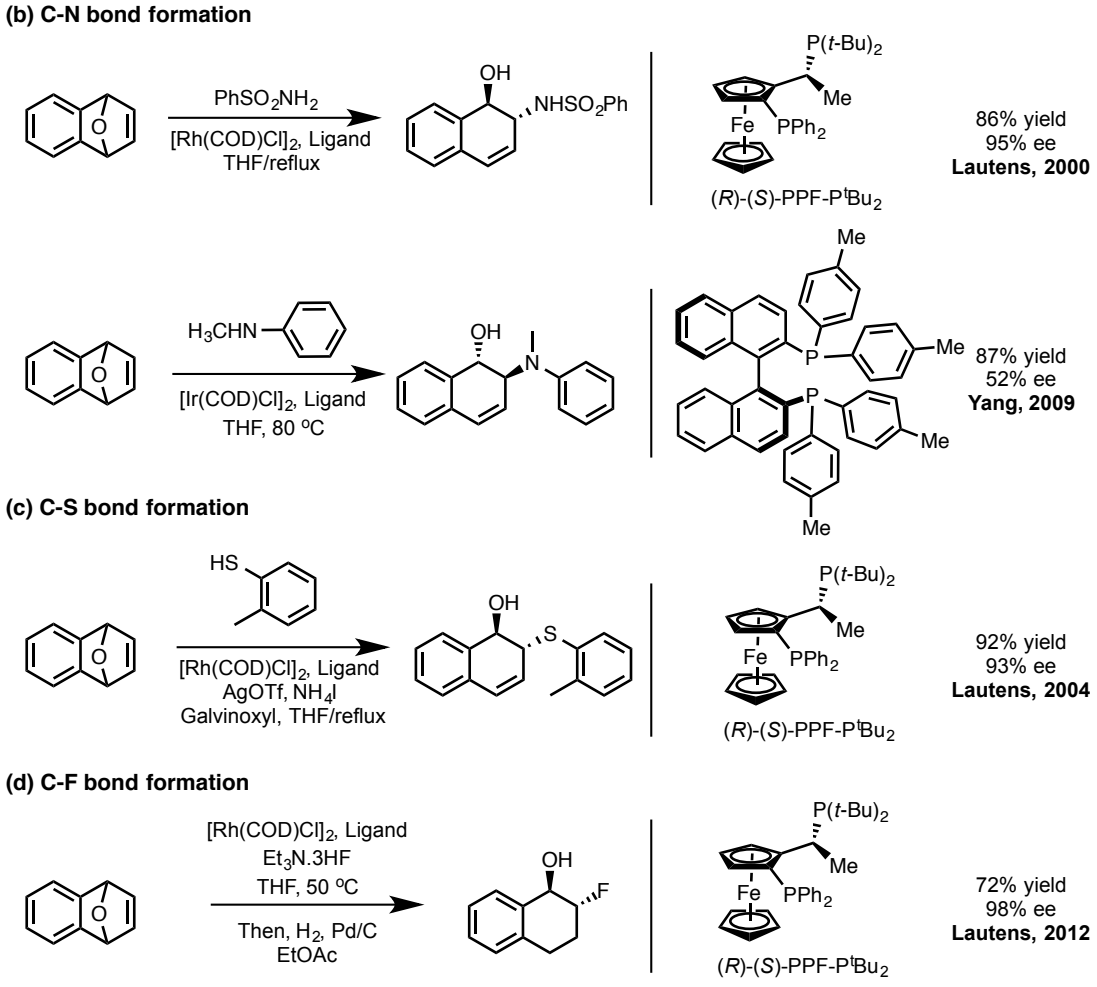

Figure1.29 (b-d) |Catalytic ARO reactions: carbon-heteroatom bond formation.

Soon after, carboxylate nucleophiles were also employed by the same group [125] and during the process, it was found that a protic additive is essential to induce the desired product, and an intriguing halide effect on the rhodium catalyst was observed. The recent developments of enantioselective ARO chemistry to form C-O bonds were reported by Yang and co-workers [126, 127]. In 2009, the Yang group revealed an iridium-catalyzed enantioselective ARO reaction with phenols to afford *trans*-products in high yield and

good enantioselectivity. Later, *cis*-products were reported by the same group using a platinum-catalyzed asymmetric ring opening procedure.

C-N bonds formation is a significant area for chemists in the syntheses of bioactive molecules. Early work was again first reported by Lautens and co-workers in 2000 using rhodium catalysis with benzene sulfonamide (Figure **1.29**, b) [124]. The Yang group also showed Iridium-catalyzed asymmetric ring opening reactions of oxabicyclic alkenes with secondary amine nucleophiles [128].

C-S bonds formation in catalytic AROs has also been studied, the selected example was reported by Lautens group, reported in 2004 (Figure **1.29**, c) [129], again using a well established rhodium catalyst system to produce sulphide derivatives of the dihydronaphthalene scaffold with good yield and high enantioselectivity.

Recently, an impressive breakthrough in aliphatic C-F bond formation from oxabicyclic alkenes was reported by the same group (Figure **1.29**, d) [130]. Organofluorine compounds are widely used in pharmaceuticals, agrochemicals and other modern chemistry application. This method employs triethylamine trihydrofluoride as nucleophile, and provides an efficient and highly enantioselective fluorination strategy.

1.3.2 *meso*-Allyl Compounds

Enantioselective desymmetrization of prochiral *meso*-allyl compounds (Figure **1.30**) is another interesting extension of catalytic asymmetric allylic substitution chemistry (see **chapter 1.2**). This strategy provides an alterative route in synthesizing enantioenriched products with ideal yields complement to the dynamic kinetic resolution [26-31] and DYKAT methods [32-37].

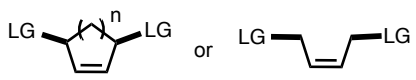

Figure 1.30 | *meso*-Allyl compounds.

However, enantioselective desymmetrization of *meso*-allyl compounds is also challenging due to more complex possible reaction pathways with its two enantiotopic allylic functional groups (Figure **1.31**). Taking the example of a 1,4 *meso*-allyl substrate, the allylic displacement may occur via an S_N2 or S_N2' reaction pathway, with overall retention or inversion in both cases. In particular, in the case of S_N2 substitution, where new allylic derivatives are obtained, a second allylic substitution may take place, which will enhance the complexity of the products and makes the reaction challenging.

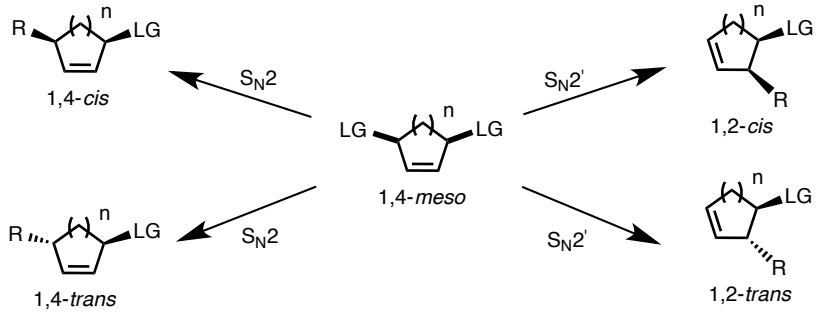

Figure 1.31 | Reaction pathways of 1,4 *meso*-Allyl compound.

Here we have a brief introduction to the enantioselective desymmetrization of *meso*-allyl compounds which divided into two main parts: (a) enantioselective desymmetrization of *meso*-allyl compounds by stabilized nucleophiles; (b) enantioselective desymmetrization of *meso*-allyl compounds by non-stabilized nucleophiles.

(a) Stabilized nucleophiles

Among well-known desymmetrization strategies, palladium-catalyzed enantioselective desymmetrization of *meso*-allyl compounds is one of the most widely used methods to employ stabilized nucleophiles [40-43]. A typical Pd-catalyzed desymmetrization pathway usually involves the complexation of palladium-ligand catalyst with *meso*-allyl starting material, followed by ionization of leaving groups and nucleophilic addition, which are essential enantiodeterming steps of the process. Finally, decomplexation gives the desired products (Figure **1.32**).

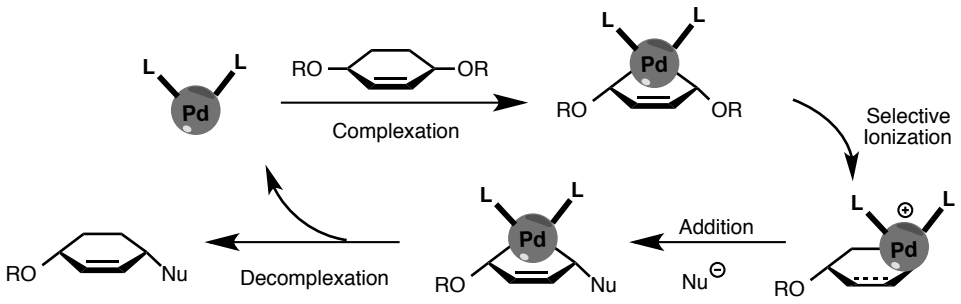

Figure 1.32 | A typical Pd-catalyzed desymmetrization pathway

Highlighted is the well-established and systematic work by Trost and co-workers (Figure **1.33**). In 1992, Trost group reported a modular approach for ligand design for Pd-catalyzed asymmteric allylic alkylations [131]. 2-Methylcyclohexane-1, 3-dione was used as the nucleophile with DBU as base to give the monoalkylation product in good yield and excellent enantioselectivity.

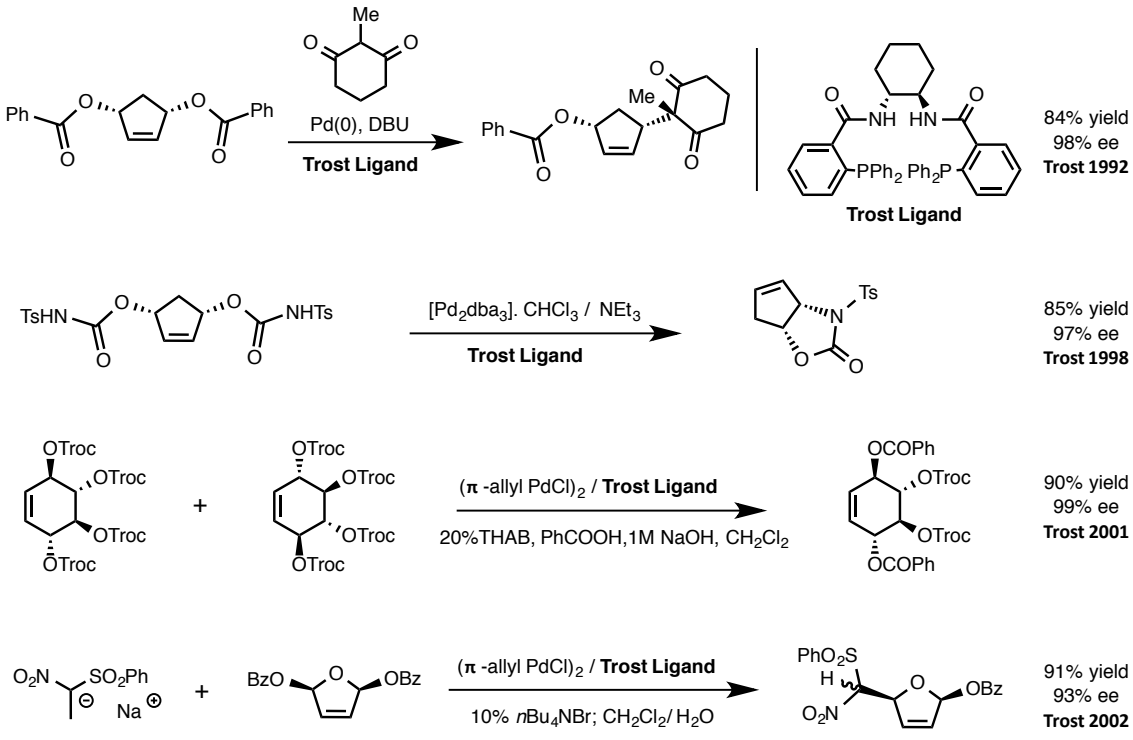

Figure1.33 | Desymmetrization of *meso*- allyl substrates by stabilized nucleophiles

Later on, an intramolecular reaction was revealed by using the internal *N*-functional group as nucleophile to produce bicyclic products [132]. Application of this Pd-catalyzed desym-

metrization chemistry was used in the synthesis of aminocyclohexitol of hygromycin A [34]. In 2002, another enantioselective desymmetrization method was developed by Trost group in the synthesis of *C-2-epi*-Hygromycin. In the reaction, the *meso*-dihydrofuran substrate was catalyzed by Pd-Ligand complex to afford the furan moiety of *C-2-epi*-Hygromycin with excellent yield and enantioselectivity [133].

(b) Non-stabilized nucleophiles

In contrast to stabilized nucleophiles, employment of non-stabilized nucleophiles in the enantioselective desymmetrization of *meso*-allyl substrates is more challenging. Non-stabilized nucleophiles generally involve a different reaction pathway where during the reaction, nucleophiles will attach directly to the metal center in the intermediates. And the functional group tolerance profile of these nucleophiles tends to differentiate them from stabilized ones.

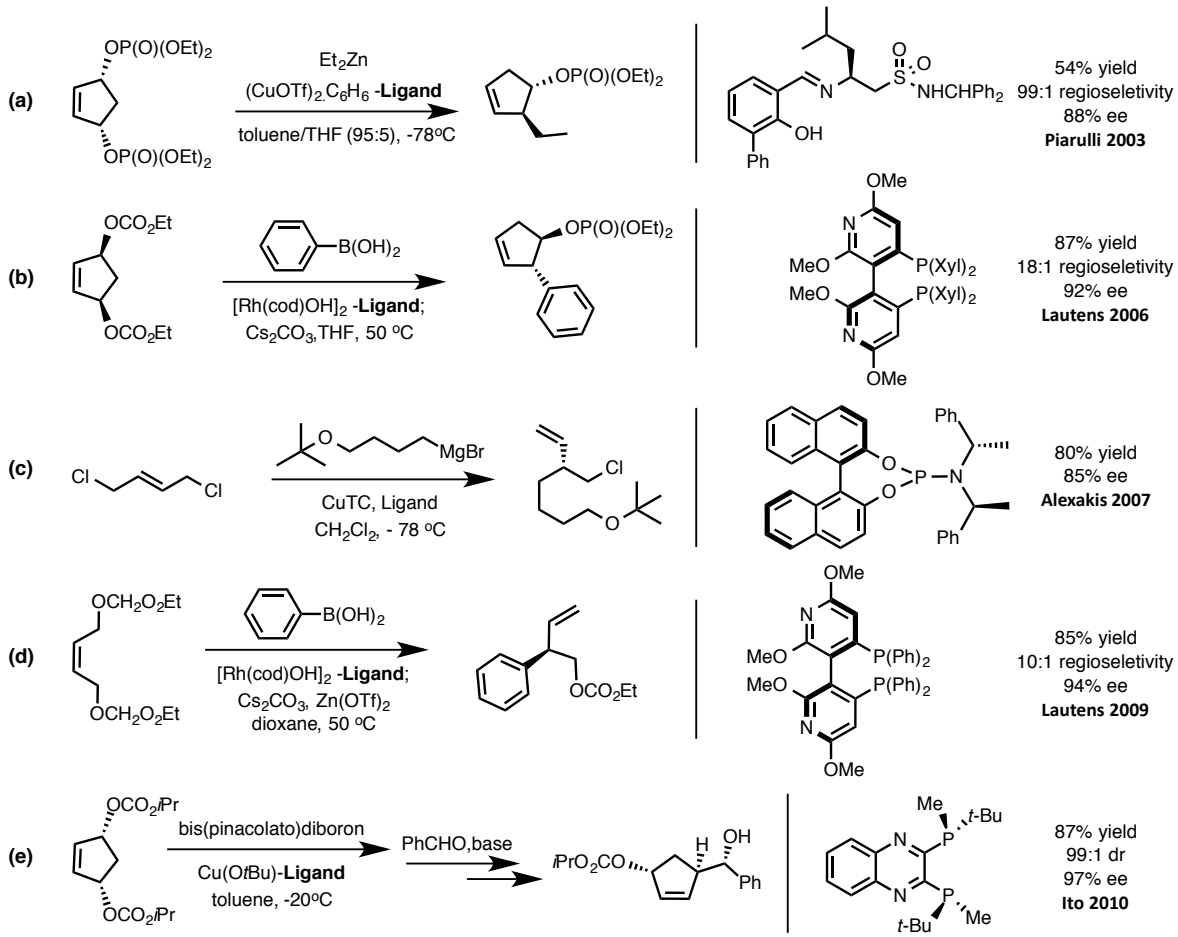

Figure1.34 | Desymmetrization of *meso*- allyl substrates by non-stabilized nucleophiles

Early highlighted work was done by Piarulli, Feringa and co-workers in Cu-catalyzed highly regio-, diastereo-, and enantio-selective dsymmetriztion of *meso*-cyclic allylic *bis*-diethyl phosphates with organozinc reagents (Figure **1.34**, a) [134, 135].

Later, based on previous excellent studies on catalyltic asymmetric desymmetrization of oxabicycle substrates, the Lautens group reported an Rh-catalyzed asymmetric allylic substitution of arylboronic acid with *meso*-cyclic allylic dicarbonates in 2006 (Figure **1.34**, b) [136]. One year after, Alexakis and co-workers reported the desymmetrization reaction using difunctionalized allylic substrates, where 1,4-*bis*-halo-2-butenes is coupled with Grignard reagents (Figure **1.34**, c) [138]. The formed products not only provide the

constructed enantioenriched stereocenters, but the double bound and the residual halide offer opportunities for further transformation in the synthesis.

In 2009, a further extension of the reported Rh catalyzed desymmetrization chemistry [136] was developed by Lautens group with its capability to use acyclic substrates (Figure **1.34**, d) [137]. Then, a recent exploration of the desymmetrization reaction was reported by Ito group in developing a copper-catalyzed asymmetric borylation and stereoselective aldehyde allylation with *meso*-2-alkene-1, 4-diol derivatives (Figure **1.34**, e) [139]. And the method was further employed in an efficient synthesis of desired molecules with multiple chiral centers.

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Chapter 2

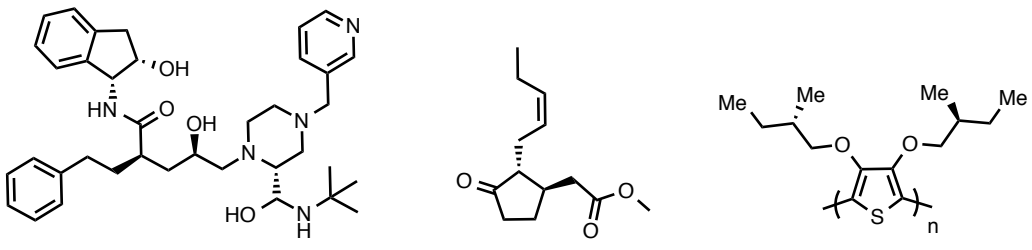
Non-stabilized nucleophiles in Cu-catalyzed dynamic kinetic asymmetric allylic alkylation

2.1 Overview

This chapter fully describes the study of copper-catalyzed dynamic kinetic asymmetric allylic alkylation using organozirconium reagents. Exploration of a copper-catalyzed asymmetric allylic alkylation with linear substrates and then cyclic substrates is reported. The research revealed a powerful method to form highly enantioenriched products from racemic starting material in good yields under mild reaction condition. The reactions can be performed on gram scales, and have been used in the asymmetric synthesis of biologically active natural products. Its mechanistic pathway was also tested, and studies indicate that the reaction proceeds through a rapidly isomerizing intermediate, which leads to a dynamic kinetic asymmetric (DYKAT) process. We anticipate this approach will be a valuable complement to existing asymmetric catalytic methods and inspire future studies in the development of dynamic kinetic asymmetric transformation using non-stabilized nucleophiles.

2.2 Introduction

The development of new reactions forming asymmetric carbon– carbon bonds has enabled chemists to synthesize a broad range of important carbon-containing molecules, including pharmaceutical agents, fragrances and polymers and three selected examples are shown in Figure **2.1** [1].



Indinavir, Merck — **Pharmaceutical agents**

Hedione — **Fragrances**

Polythiophene — **Materials**

Figure 2.1 | Selected applications of asymmetric catalysis.

Over the past decades, a number of strategies for generating single enantiomer compounds using enantioselective catalysis have emerged and become embraced by the synthetic community. In general, there are two main solutions: the first strategy is generating a chiral product by a selective reaction, which introduces asymmetry to a prochiral substrate (Figure **2.2**). This prochiral approach has proven important in the development of catalytic asymmetric reactions, despite the rather limited availability of prochiral substrates when compared to chiral substrates exist in nature [2-12].

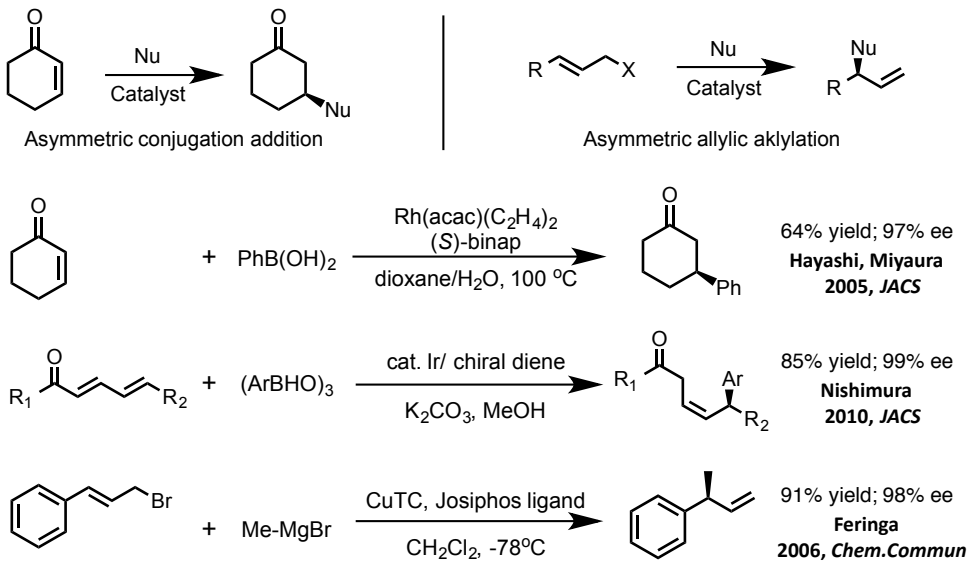


Figure 2.2 | Selected examples of asymmetric catalysis from prochiral substrates.

The second widely used strategy is to start from a racemic mixture of chiral starting materials.

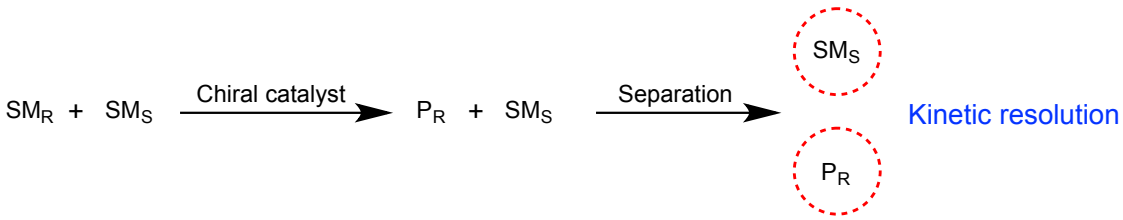


Figure 2.3 | Asymmetric catalysis from a racemic mixture: Kinetic resolution

Here the catalyst selectively reacts with one of the two enantiomers allowing differentiation (or resolution) of the enantiomers, but the yield is necessarily limited to 50%, as the undesired

enantiomer remains as starting material (Figure **2.3**). Noteworthy examples include Noyori and co-workers reductive resolution and Stoltz and co-worker's oxidative resolution (Figure **2.4**) [13-17].

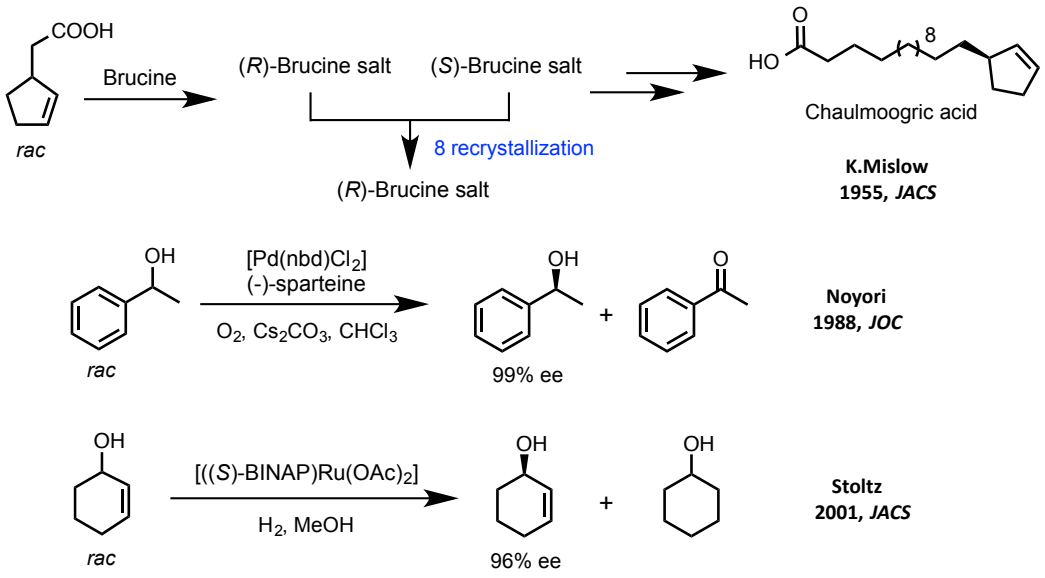


Figure 2.4 | Selected examples of kinetic resolution from racemic mixtures.

An efficient variation of this second strategy is to couple enantiomer differentiation with interconversion of the enantiomers, commonly called dynamic kinetic resolution. This strategy allows yields of more than 50% from chiral starting materials (Figure **2.5**) [18-21].

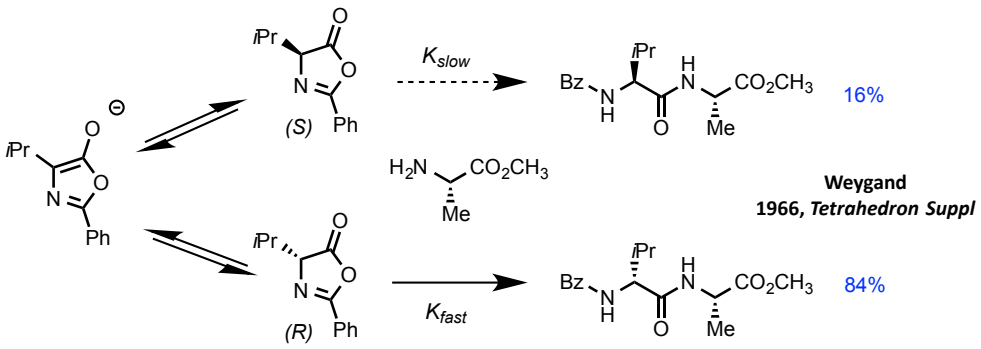


Figure 2.5 | Example of a dynamic kinetic resolution.

The use of stabilized nucleophiles (pKa<25, where Ka is the acid dissociation constant) in palladium-catalyzed asymmetric allylic alkylation reactions has proved to be extremely

versatile in these processes [22, 23]. These reactions are dynamic kinetic asymmetric transformations (DYKATs). In a classical DYKAT mechanism，both enantiomers of the starting material are converted into the same designed enantiomer of product in quantitative yield through a common π-allyl intermediate (Figure **2.6**, a).

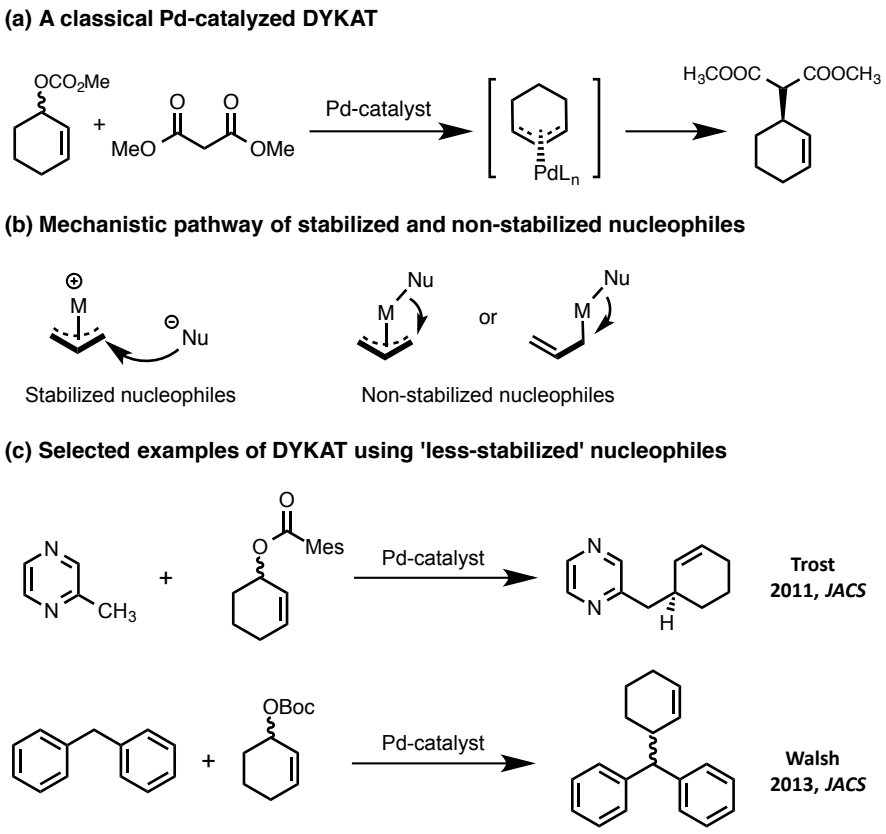


Figure 2.6 | DYKAT in allylic substitution.

However, the use of non-stabilized nucleophiles in such reactions is a long-standing research challenge. A significant factor to consider is the different mechanistic pathway between stabilized and non-stabilized nucleophiles: Compared to a π-allyl-Pd intermediate where the enantioselectivity determining step involves attack at carbon with stabilized nucleophiles, non-stabilized nucleophiles normally first bind to the metal centre followed by reductive elimination to form the key bond (Figure **2.6**, b). Tremendous effort has been taken to broaden the scope of DYKAT to non-stabilized nucleophiles. We are now pleased to see efficient and interesting 'less-stabilized' partners being used in achieving the desired products from the

racemic starting materials both in an enantioselective and non-enantioselective fashion (Figure **2.6**, c) [24-27].

2.3 Prochiral substrates: linear allylic substrates

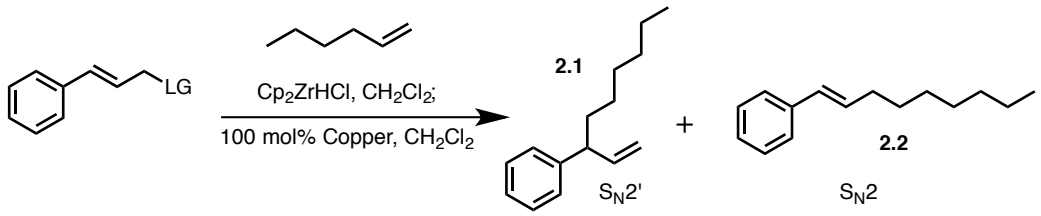
Copper is among the most readily available and the cheapest metals for catalysis, it is also a widely used efficient metal catalyst in employing non-stabilized nucleophiles for asymmetric catalysis reactions [6,7]. Alkylzirconium nucleophiles had been used within our group in a copper-catalyzed highly enantioselective conjugate addition at room temperature with tolerance to a broad variety of functional groups [28-31]. We then sought to explore the performance of these reagents with another series of related prochiral substrates: allylic substrates.

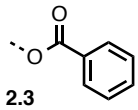
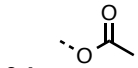
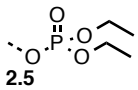
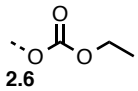
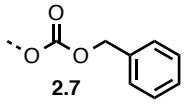
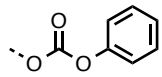
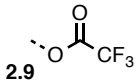
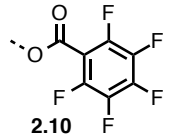
The pioneering work of employing alkylzirconium reagents in a copper catalyzed allylic alkylation reaction was reported in 1992 by Bruce H. Lipshutz *et al* [32]. It is worth to note the major selectivity issue in metal-catalyzed asymmetric allylic alkylation (AAA), involves controlling preference for S_N2 / S_N2' substitution (Figure **2.7**). The control of its regioselectivity as well as control of enantioselectivity in S_N2' substitution makes the development of AAA chemistry a long-standing challenge.

Figure 2.7 | S_N2' and S_N2 substitution in asymmetric allylic alkylation.

We began by exploring the coupling of linear allylic substrates with 1-hexene catalyzed by $CuBr.SMe_2$ and CuCN separately (Table **2.1**). A wide variety of leaving groups were tested to find the proper active substrates suitable for the alkylzirconium reagent system. A high yield was achieved when the bromo-substrate **2.11** was employed combined with a moderate S_N2' selectivity (Table **2.1**, entries 9 and 18). At the same time, substrates **2.5** and **2.9** were also

Table 2.1l Selected exploration experiments: Allylic substrates in racemic reaction [a]



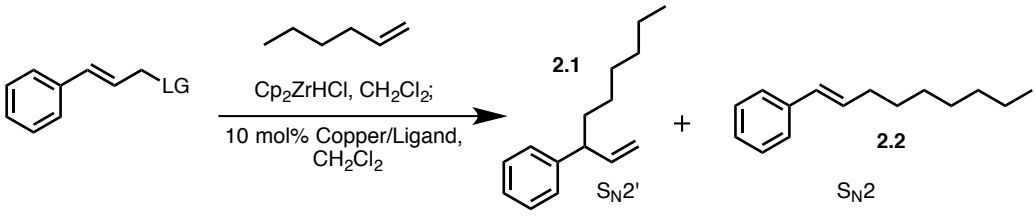
LG	Entry	Copper	Yield [b]	2.1 : 2.2 [c]	Entry	Copper	Yield [b]	2.1 : 2.2 [c]
 **2.3**	1[d]	CuBr•SMe$_2$	ND[e]	ND	10	CuCN	ND	ND
 **2.4**	2 [f]	CuBr•SMe$_2$	ND	ND	11	CuCN	ND	ND
 **2.5**	3	CuBr•SMe$_2$	64%	71 : 29	12	CuCN	70%	91 : 9
 **2.6**	4	CuBr•SMe$_2$	ND	ND	13	CuCN	ND	ND
 **2.7**	5	CuBr•SMe$_2$	ND	ND	14	CuCN	ND	ND
 **2.8**	6	CuBr•SMe$_2$	ND	ND	15	CuCN	ND	ND
 **2.9**	7	CuBr•SMe$_2$	ND	ND	16	CuCN	43%	93 : 7
 **2.10**	8	CuBr•SMe$_2$	ND	ND	17	CuCN	ND	ND
2.11	9	CuBr•SMe$_2$	95%	86 : 14	18	CuCN	84%	75 : 25

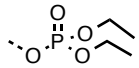
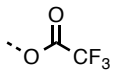
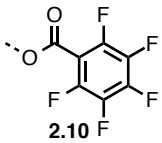
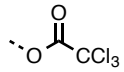
[a] Reaction conditions: exploration was performed for the AAA of linear allylic substrates (1 equiv.) and 1-Hexene (2.5 equiv.), Cp_2ZrHCl (2 equiv.),Copper source (100 mol%);
[b] Isolated yield in flask;
[c] Ratio of **2.1** : **2.2** determined by NMR analysis;
[d] Further optimization adding TMSCl (1 equiv.) and changing the solvent into Et_2O was done seperately without achieving the product.
[e] Formation was not observed.
[f] Further optimization adding TMSCl (1 equiv.) was done without achieving the product.

observed to give a moderate yield with a high S_N2' selectivity when catalyzed by CuCN (Table **2.1**, entries 12 and 16). These results indicated an activated leaving group is essential to conduct the allylic alkylation reaction employing alkylzirconium reagents.

After a quick screen of suitable linear substrates under racemic reaction conditions, the performance of these substrates was examined in an asymmetric procedure (Table **2.2**). (t-BuCN)$_2$Cu.OTf was used as a general copper salt as it was found to be air stable and easy to handle.

Table 2.2 | Selected exploration experiments: Allylic substrates in asymmetric reaction [a]



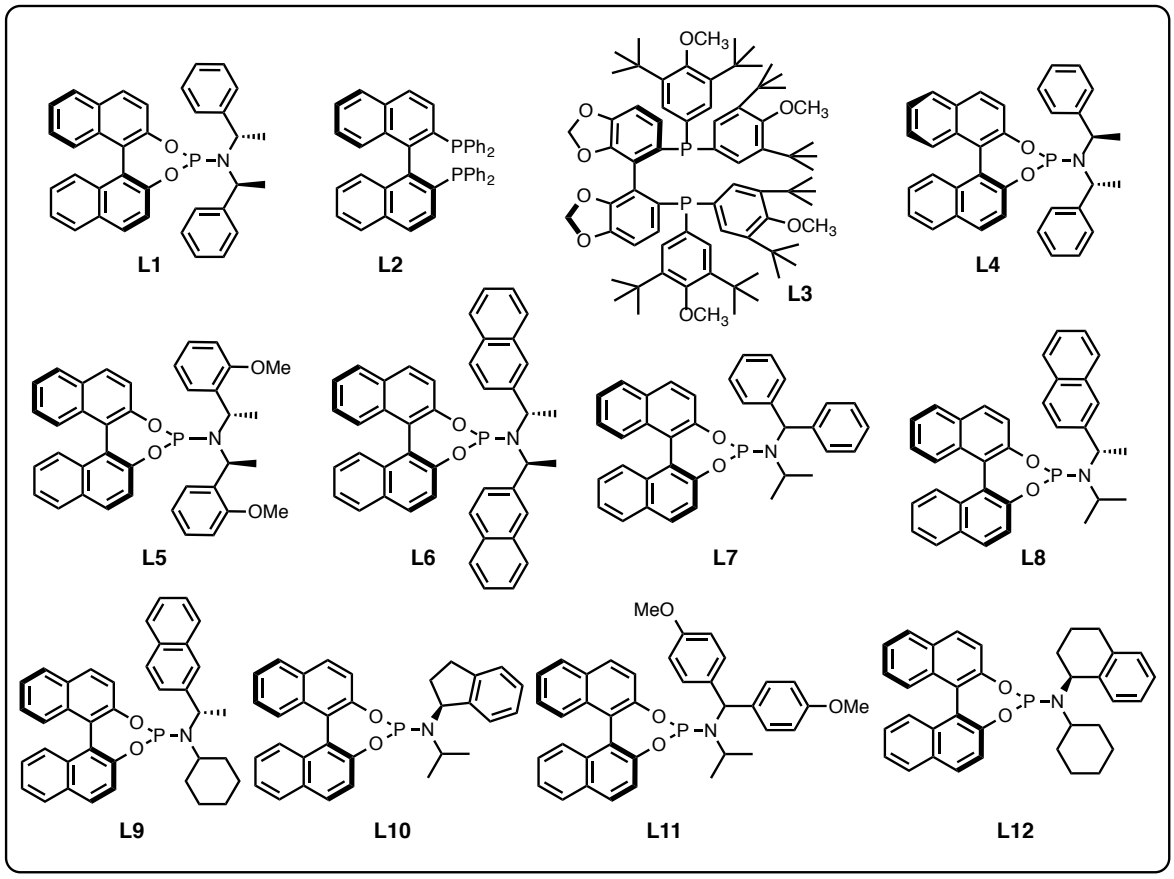
LG	Entry	Copper	Ligand	Yield [b]	2.1 : 2.2 [c]	ee [d]
2.4	1	(tBuCN)$_2$Cu • OTf	**L1**	ND [e]	ND	ND
	2	(tBuCN)$_2$Cu • OTf	**L2**	ND	ND	ND
	3	(tBuCN)$_2$Cu • OTf	**L3**	ND	ND	ND
 **2.5**	4	(tBuCN)$_2$Cu • OTf	**L7**	34%	48 : 52	15%
	5	(tBuCN)$_2$Cu • OTf	**L2**	15%	1 : 99	35%
	6	(tBuCN)$_2$Cu • OTf	**L3**	23%	1 : 99	21%
 **2.9**	7	(tBuCN)$_2$Cu • OTf	**L4**	27%	90 : 10	40%
	8	(tBuCN)$_2$Cu • OTf	**L2**	ND	ND	ND
	9	(tBuCN)$_2$Cu • OTf	**L3**	ND	ND	ND
 **2.10**	10	(tBuCN)$_2$Cu • OTf	**L1**	ND	ND	ND
	11	(tBuCN)$_2$Cu • OTf	**L2**	ND	ND	ND
	12	(tBuCN)$_2$Cu • OTf	**L3**	ND	ND	ND
2.11	13	(CuOTf)$_2$ • C_6H_6	**L1**	21%	72 : 28	3%
	14	(CuOTf)$_2$ • C_6H_6	**L2**	17%	74 : 26	3%
	15	(CuOTf)$_2$ • C_6H_6	**L3**	50%	78 : 22	25%
 **2.12**	16	(tBuCN)$_2$Cu • OTf	**L1**	ND	ND	NH_2D
	17	(tBuCN)$_2$Cu • OTf	**L2**	ND	ND	ND
	18	(tBuCN)$_2$Cu • OTf	**L3**	ND	ND	ND

[a] Reaction conditions: exploration was performed for the AAA of linear allylic substrates (1 equiv.) and 1-Hexene (2.5 equiv.), Cp_2ZrHCl (2 equiv.),Copper source/Ligand (10 mol%);
[b] Isolated yield in flask;
[c] Ratio of **2.1** : **2.2** determined by NMR analysis;
[d] Enantioselectivity was determined by derivatization of the related product in HPLC;
[e] Formation was not observed.

Here, the regioselectivity and enantioselectivity were examined in combination with two main ligand families; phosphoramidite and bisphosphine ligands. To our delight, the employment of substrate **2.9** in the presence of phorsphoramidite ligands led to a high regioselectivity despite low yield (27%) and ee (40%) (Table **2.2**, entry 7). This motivated us to expand reaction

screening to related substrates **2.10** and **2.12**. However, we didn't observe any product formation in both cases. Additionally, the classical substrates **2.5** and **2.11**, which proved to be efficient allylic starting materials in previously non-asymmetric reactions seemed not ideal when chiral ligands were used. It is worth noting an intriguing result, where use of bisphosphine ligands with substrate **2.5** was observed to give exclusive S_N2 substitution, illustrating the importance of ligand effects on the regioselectivity of AAA reactions.

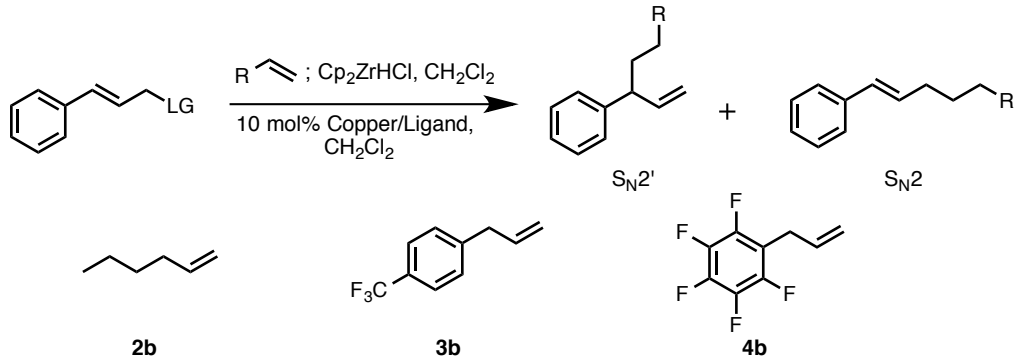
Chapter 2: Ligand Pool



Further exploration on the effect of copper source and additional ligands was performed later. In improving the efficiency of these reaction optimization experiments, alkenes **2b**, **3b**, and **4b** were tested. These are more convenient for reaction screening as the enantiomeric excess of the products can be determined by HPLC without derivatization (**4b**). Different copper sources were examined with a linear allylic chloride (Table **2.3**, entries 1-6). Among the results, CuTC gave high yield with reasonable S_N2'selectivity (85:15, entry 3). Based on this, a group of

phosphoramidite ligands were studied using CuTC (Table **2.3**, entries 7-10), but no experiments gave >10% ee.

Table 2.3 | Further exploration experiments: Allylic substrates in asymmetric reaction [a]



Entry	LG	R	Copper	Ligand	Yield(%) [b]	S_N2' : S_N2 [c]	ee (%) S_N2' [d]
1	Cl	**2b**	$CuBr.SMe_2$	**L1**	16	85:15	25
2	Cl	**2b**	CuI	**L1**	10	66:34	35
3	Cl	**2b**	CuTC	**L1**	93	85:15	0
4	Cl	**3b**	CuCl/ AgOTf	**L1**	95	36: 64	0
5	Cl	**4b**	CuCl	**L1**	78	93:7	3
6	Cl	**4b**	CuCN	**L1**	75	95:5	0
7	Cl	**4b**	CuTC	**L10**	> 80	91:9	9
8	Cl	**4b**	CuTC	**L7**	> 80	97:3	7
9	Cl	**4b**	CuTC	**L11**	> 80	97:3	9
10	Cl	**4b**	CuTC	**L12**	> 80	97:3	0
11	$OC(O)CF_3$	**4b**	CuI	**L1**	~ 5	97:3	75
12	$OC(O)CF_3$	**4b**	CuTC	**L1**	> 80	96:4	5
13	$OC(O)CF_3$	**4b**	$CuBr.SMe_2$	**L1**	> 80	95:5	9
14	$OC(O)CF_3$	**4b**	CuCl/ AgOTf	**L1**	~40	95:5	24
15 [e]	$OC(O)CF_3$	**4b**	CuI	**L1**	~80	94:6	0
16	$OP(O)(OEt)_2$	**4b**	CuI	**L1**	> 80	80:20	3
17	$OP(O)(OEt)_2$	**4b**	CuTC	**L1**	> 80	75:25	3
18	$OP(O)(OEt)_2$	**4b**	$CuBr.SMe_2$	**L1**	> 80	76:25	5
19	$OP(O)(OEt)_2$	**4b**	CuCl/ AgOTf	**L1**	> 80	67:33	17
20	$OP(O)(OEt)_2$	**4b**	CuCN	**L1**	> 80	92:8	0

[a] Reaction conditions: exploration was performed for the AAA of linear allylic substrates (1 equiv.) and alkene (2.5 equiv.), Cp_2ZrHCl (2 equiv.),Copper source/Ligand (10 mol%);
[b] Yields are estimated by NMR analysis.
[c] Ratio of **S_N2' : S_N2** determined by NMR analysis;
[d] Enantioselectivity was dermined either directly or by derivatization of the related product in HPLC
[e] Reflux overnight

Expanded copper source screening was also performed with substrates **2.5** and **2.9** (Table **2.3**, entries 11-20). Even though high S_N2'selectivity was observed in the case of substrates **2.9**, the yields vary and no good enantioselectivity was observed (Table **2.3**, entries 11-15). Specifically, CuI used to give 75% ee at room temperature but with low (5%) yield, however

refluxing conditions improved the yield to ~80% with the complete loss of enantioselectivity (entry 15). In the case of phosphate-substrates **2.5**, generally good yield was found but the regio- and enantioselectivity are modest. Clearly, this research illustrated the complexity of copper-catalyzed asymmetric allylic alkylation with linear substrates. After these efforts, we decided to move on and turn our focus to cyclic examples, which are racemic substrates that present their own difficulties.

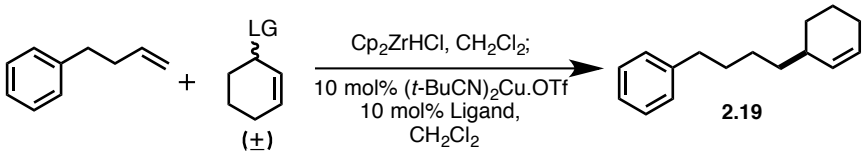
2.4 Racemic substrates: cyclic allylic substrates exploration.

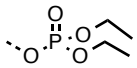
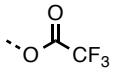
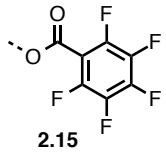
The exploration of dynamic kinetic processes that are copper-catalyzed is challenging compare to the classical Pd-catalyzed counterparts, as non-stabilized organometallic reagents are typically very reactive, hindering the isolation of intermediates and characterization of its pathways. Generally, copper-catalyzed allylic alkylations are accepted to operate via regio-specific *anti*-addition mechanisms: selective rate determining S_N2' oxidative additions give copper (III) intermediates, and the following fast reductive elimination forms the desired final product [6, 7]. The key distinction between Cu-catalyzed AAA and Pd-catalyzed AAA is the lack of an efficient σ - to π - isomerization [33] in the case of copper, so that if reductive elimination is fast, a π -allyl-Cu species will not form and reactions involving racemic starting materials will lead to racemic products.

Cu-catalyzed AAA on prochiral materials, where selective oxidative addition occurs on one enantiotopic face of the substrate, can be achieved [6,7,33,34]. However, the generally accepted Cu-catalyzed mechanisms would seem to preclude efficient asymmetric reactions with chiral racemic substrates, where addition would be controlled by the stereogenic centre of the substrate, not the catalyst [33]. We note that racemization of enantiopure starting materials during Cu-catalyzed allylic alkylation has been reported, suggesting the possibility of generating useful π -allyl-Cu species and DYKATs [35]. Building on this work, promising initial results have been obtained with Grignard reagents [36], but despite extensive examination, and the

elucidation of interesting mechanistic pathways, generally useful procedures have not emerged [37,38].

Table 2.4 | Selected exploration experiments: Cyclic allylic substrates [a]



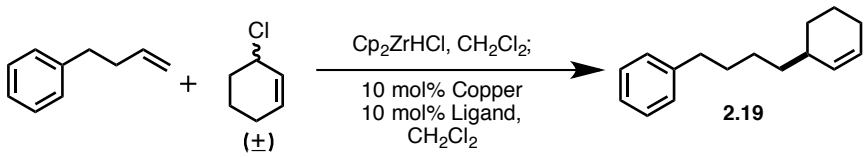
LG	Entry	Ligand	Yield [b]	ee [c]
 **2.13**	1	**L7**	good	4%
	2	**L2**	good	1%
	3	**L3**	good	10%
 **2..14**	4	**L1**	medium	20%
	5	**L2**	medium	5%
	6	**L3**	medium	10%
 **2.15**	7	**L1**	low	7%
	8	**L2**	low	10%
	9	**L3**	low	ND
---Br **2.16**	10 [d]	**L1**	good	55%
	11	**L2**	good	3%
	12	**L3**	good	4%
--Cl **2.17**	13	**L1**	good	71%
	14	**L2**	good	1%
	15	**L3**	good	35%

[a] Reaction conditions: exploration was performed for the AAA of cyclic allylic substrates (1 equiv.) and alkene (2.5 equiv.), Cp_2ZrHCl (2 equiv.),Copper source/Ligand (10 mol%);
[b] Crude yield estimated by NMR;
[c] Enantioselectivity was dermined by HPLC;
[d] When reaction performed at 0°C, 65%ee was observed.

Based on the previous results from the exploration of linear allylic substrates, we investigated the copper-catalyzed AAA reaction of racemic cyclic substrates. The initial reaction employed the phosphoramidite ligands and diphosphine ligands as chiral ligands, which have previously proved very powerful in asymmetric carbon-carbon bond formation [39,40]. The enantioselectivity of the reaction was explored by the coupling of 4-phenyl-1-butene with allylic leaving groups that had proven efficient with linear substrates, using (*t*-BuCN)$_2$Cu.OTf as the catalyst (Table **2.4**). A general higher efficiency was found employing the phosphoramidite ligands compared to bisphosphine ligands. To our delight, the enantioselectivity improved to 55% when the

allylic bromide was used as the leaving group, (substrate **2.16**, entry 10, Table **2.4**). It demonstrates the significant effect of reactivity of the substrates and leaving groups in developing a successful AAA method. In spite of the moderate enantiomeric excess achieved, the completion time of the bromide reaction was less than 20 mins (as followed by NMR spectroscopy) and the enantioselectivity improved to 65% at 0 ºC. In consideration that such a rapid reaction rate was not sufficient to provide a highly enantioselective product, it motivated us to explore the system using the less activated allylic chloride as leaving group (entry 13, Table **2.4**). To our delight, the enantioselectivity of a less reactive allyl chloride **2.17** improved the results to 71% ee with 86% yield (entry 13, Table **2.4**).

Table 2.5 | Selected optimization experiments: Copper & Ligands [a]



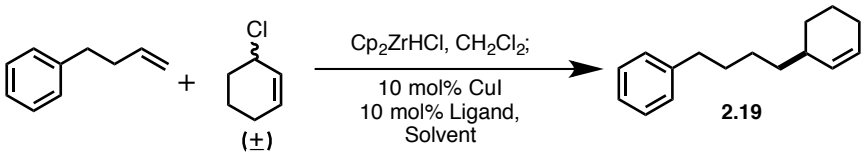
Entry	Copper	Ligand	ee [b]	Entry	Copper	Ligand	ee [b]
1	CuCl	**L1**	49%	15	$CuCl/AgClO_4$	**L1**	59%
2	$CuCl_2$	**L1**	47%	16	$CuCl/AgBF_4$	**L1**	69%
3	$CuCl_2 \cdot 2H_2O$	**L1**	23%	17	$CuCl_2/AgBF_4$	**L1**	17%
4	CuBr	**L1**	73%	18	$CuCl/AgSO_3CF_3$	**L1**	71%
5	$CuBr_2$	**L1**	37%	19	$CuCl_2/AgSO_3CF_3$	**L1**	7%
6	$CuBr \cdot SMe_2$	**L1**	51%	20	$(tBuCN)_2Cu \cdot OTf$	**L1**	71%
7	CuI	**L1**	89%	21	$(tBuCN)_2Cu \cdot OTf$	**L2**	1%
8	CuI [c]	**L1**	87%	22	$(tBuCN)_2Cu \cdot OTf$	**L3**	35%
9	$(CuI)_4 \cdot 3SMe_2$	**L1**	85%	23	CuI	**L4**	73%
10	$Cu(OAc)_2$	**L1**	37%	24	CuI	**L5**	61%
11	$Cu(OTf)_2$	**L1**	71%	25	CuI	**L6**	87%
12	CuTC	**L1**	40%	26	CuI	**L7**	89%
13	$CuCl/SbF_6Ag$	**L1**	51%	27	CuI	**L8**	85%
14	$CuCl/AgNTf_2$	**L1**	21%	28	CuI	**L9**	89%

[a] Reaction conditions: exploration was performed for the AAA of cyclic allylic chlorides (1 equiv.) and alkene (2.5 equiv.), Cp_2ZrHCl (2 equiv.),Copper source/Ligand (10 mol%), Full converstion was observed in all cases shown;
[b] Enantioselectivity was determined by HPLC;
[c] CuI, 99.99% purity ;

We then explored the effect of different combinations of copper sources with different phosphoramidite ligand catalysts in this system (Table **2.5**). Surprisingly, usage of the simple inorganic copper salts was found to be very successful (entries 1-12, Table **2.5**). Particularly

excellent enantioselectivity was observed when CuI was used (89% ee, entry 7, Table **2.5**). Another noteworthy phenomenon is that copper(II) species were found to perform well in catalysing the reactions (entries 2,3,5,11; Table **2.5**). This is quite rare as in classical copper-catalyzed AAA reactions copper(I) species are generally used [6,7]. Here, we assume that the copper(II) species undergoes reduction step to copper(I) during the procedure. At the same time more activated copper(I) species seemed to led to better enantioselectivity, so we examined the combination of copper and silver sources (filtering off the AgCl byproduct) to produce more activated copper species (entries 13-19, Table **2.5**). These results show the counter ion of copper has a significant effect on enantioselectivity, but none of these salts gave higher levels of enantioselectivity than simple copper iodide. With CuI as our optimized copper source, the enantiomeric outcome of the reaction was then studied in the presence of different selected popular phosphoramidite ligands (entries 20-28, Table **2.5**). In stark contrast to bisphosphine ligands, all the phosphoramidite ligands gave good to excellent enantioselectivity, in particular, ligands **L1**, **L7**, **L9** all induced up to 89% enantioexcess.

Table 2.6 | Selected optimization experiments: Solvent [a]

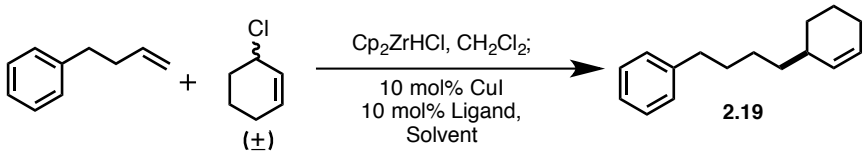


Entry	Solvent	Ligand	ee [b]	Entry	Solvent	Ligand	ee [b]
1	CH_2Cl_2	**L1**	89%	10	CH_2Cl_2	**L7**	89%
2	Et_2O	**L1**	63%	11	Et_2O	**L7**	67%
3	THF	**L1**	43%	12	THF	**L7**	43%
4	Hexane	**L1**	63%	13	Hexane	**L7**	67%
5	2-Me-THF	**L1**	33%	14	2-Me-THF	**L7**	35%
6	*t*-BuOMe	**L1**	53%	15	*t*-BuOMe	**L7**	61%
7	$CHCl_3$	**L1**	93%	16	$CHCl_3$	**L7**	91%
8	Toluene	**L1**	37%	17	Toluene	**L7**	39%
9	1,2-Dichloroethane	**L1**	85%	18	1,2-Dichloroethane	**L7**	87%

[a] Reaction conditions: exploration was performed for the AAA of cyclic allylic chlorides (1 equiv.) and alkene (2.5 equiv.), Cp_2ZrHCl (2 equiv.),CuI/Ligand (10 mol%), good to Full converstion was observed in all cases shown;
[b] Enantioselectivity was dermined by HPLC;

Considering the easy access of Ligands **L1** and **L7** and their efficiency in catalysing the reaction, we chose to use both ligands with CuI to further optimize the conditions when testing solvent effects (Table **2.6**). It appears that the enantioselectivity observed in formation of **2.19** is generally slight better when using ligand **L7** compared to ligand **L1**. Moreover, coordinating solvents such as THF and Et_2O gave only moderate ee (entries 2,3,5,6; Table **2.6**). While using $CHCl_3$, excellent enantioselectivity (up to 93%) was observed at room temperature in the presence of ligand **L1** (entry 7, Table **2.6**).

Table 2.7 | Selected optimization experiments: other related factors [a]

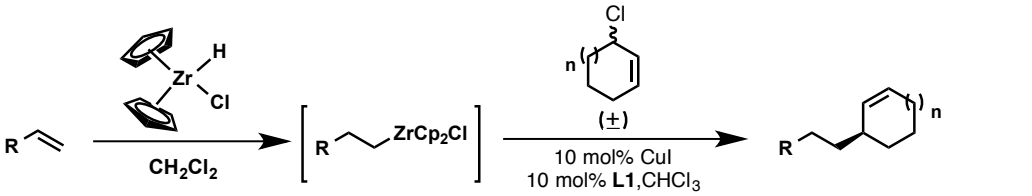


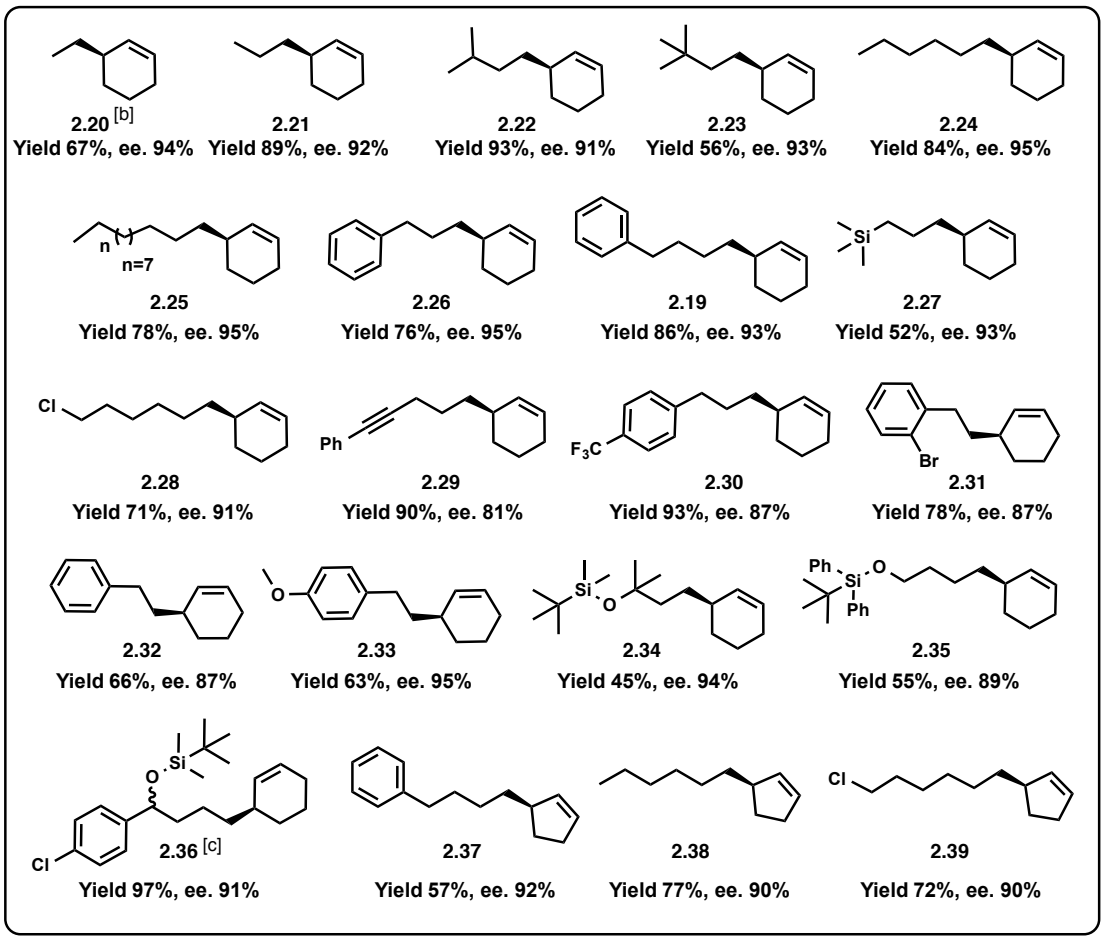
Entry	Solvent	CH_2Cl_2:Solvent	CuI:Ligand	Ligand	Temp.	ee [b]
1	$CHCl_3$	0.2ml : 1ml	0.1 eq : 0.12eq	**L7**	RT	91%
2	$CHCl_3$	0.2ml : 0.4ml	0.1 eq : 0.1eq	**L7**	RT	91%
3	$CHCl_3$	0.2ml : 2.2ml	0.1 eq : 0.1eq	**L7**	RT	91%
4	$CHCl_3$	0.2ml : 0.4ml	0.1 eq : 0.1eq	**L7**	0°C	93%
5	$CHCl_3$	0.2ml : 0.4ml	0.1 eq : 0.1eq	**L7**	60°C	77%
6	CH_2Cl_2	0.2ml : 0.4ml	0.1 eq : 0.1eq	**L7**	0°C	91%
7	CH_2Cl_2	0.2ml : 0.4ml	0.1 eq : 0.1eq	**L1**	0°C	93%
8	$CHCl_3$	0.2ml : 0.4ml	0.1 eq : 0.1eq	**L1**	RT	93%
9	$CHCl_3$	0.2ml : 0.4ml	0.1 eq : 0.1eq	**L1**	0°C	95%

[a] Reaction conditions: exploration was performed for the AAA of cyclic allylic chlorides (1 equiv.) and alkene (2.5 equiv.), Cp_2ZrHCl (2 equiv.),CuI/Ligand (10 mol%), good to Full converstion was observed in all cases shown;
[b] Enantioselectivity was dermined by HPLC;

Further optimization by examining other factors was performed (Table **2.7**). An excess of ligand catalyst loading did not improve the enantioselectivity observed (entry 1, Table **2.7**). A more concentrated reaction increased yield with the same enantioselectivity of the product (entries 2,3, Table **2.7**). Reactions at different temperatures employing ligands **L1** and **L7** showed a slight improvement of enantioexcess when reactions were performed at lower temperature, while higher temperature led reduced enantioselectivity. In consideration of operational convenience, a final optimized condition was selected: CuI and ligand **L1** in chloroform at room temperature.

Table 2.8 | Selected dynamic kinetic AAA with alkylzirconium nucleophiles generated from alkenes [a]





[a] Reaction conditions: AAA of cyclic allylic chlorides (1 equiv.) and alkene (2.5 equiv.), Cp_2ZrHCl (2 equiv.),CuI/**L1** (10 mol%); room temprerature overnight ; argon atmosphere; Yield refers to pure isolated compounds; Enantioselectivity was either dermined directly by HPLC or on the corresponding expoxides by gas chromatography using a chiral stationary phase.
[b] Absolute configuration refers to the reported same compound in literature [41].
[c] Starting materials use racemic alkene.

The scope of the alkyl-coupling partners was investigated using a variety of simple gaseous alkenes (giving products **2.20**–**2.22**) and unfunctionalized primary alkenes (**2.23**–**2.25**) (Table **2.8**). High yields and consistently high enantioselectivities were obtained. Functionalized alkenes (**2.26**–**2.37**) were also examined: halogens, alkynes, aromatic rings, ethers, protected alcohols, trifluoromethyl groups and preformed stereogenic centres were all found to be compatible with the procedure. Electron rich alkenes such as allylsilane (to give **2.27**) and

styrenes (to give **2.31**–**2.33**) also work well. We also examined the use of 5-membered rings with this procedure; we found that it is suitable for the direct preparation of highly enantioenriched cyclopentenes (**2.37**–**2.39**) from an easily prepared racemic 5-membered allylchloride.

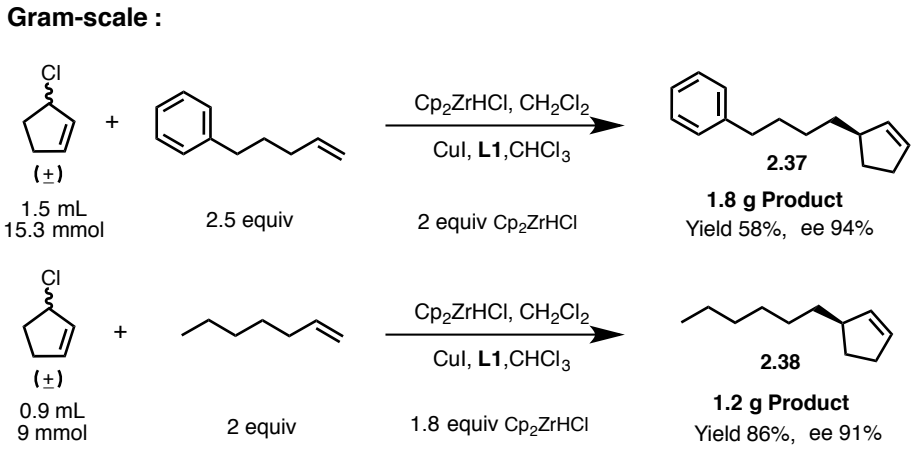


Figure 2.8 | Scale-up reactions of dynamic kinetic Cu-catalyzed AAA [42]**.**

To probe practical aspects of this chemistry, scale-up reactions were performed (Figure **2.8**). Despite excellent conversion (90%), the yield of **2.37** on a 15 mmol scale was low because the product and the residual alkene have similar polarities and boiling points, complicating isolation. Even so, we were easily able to obtain more than 1.8 g of pure **2.37** (58% yield, 94% e.e.). When 1-hexene was used (to give **2.38**), we arbitrarily reduced the ratio of alkene and Schwartz reagent used (to 2 and 1.8 equiv. respectively) and observed improved yield (86% yield, 91% e.e., 1.2 g) relative to using our standard test conditions (Table **2.8**).

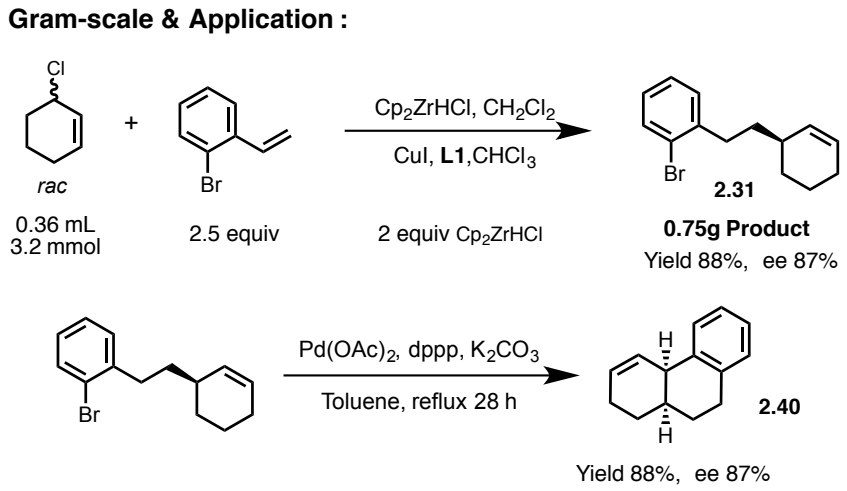


Figure 2.9 | Application of the method to access tricyclic structures.

Functionalized **2.31** containing a bromide (Figure **2.9**) was also synthesized on a preparative scale (88% yield, 87% e.e., 0.75 g) and a subsequent Heck reaction to provide *cis*-fused tricycle **2.40** (88% yield) demonstrates that these reactions can be used to rapidly access complex molecular frameworks.

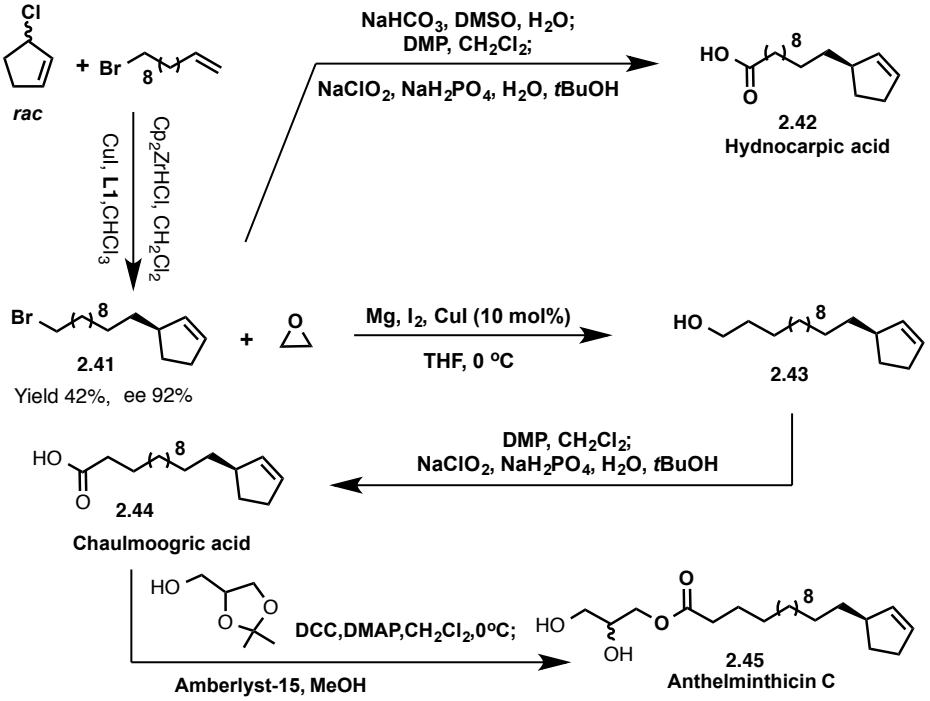


Figure 2.10 | Application of the method to access natural products [42].

Contributed by Dr. Mireia Sidera, application of this method in inducing rapid access to important structural motifs was also performed for asymmetric syntheses of biologically active cyclopentene-containing natural products (Figure **2.10**) [42]. This approach provides short, straightforward, flexible syntheses compared to those previously reported procedures [43], and will facilitate the study of structural analogues. Hydnocarpic acid (**2.42**) and chaulmoogric acid (**2.43**) are leprosy treatments used in ancient and traditional medicine: in both cases, the cyclopentenyl ring is a requirement for biological activity. Hydnocarpic acid is believed to act by blocking the activity of biotin or inhibiting microbial biotin synthesis [44], while the activity of chaulmoogric acid is probably due to incorporation into the cell wall lipids of Mycobacterium leprae [45]. Recent reports show that chaulmoogric acid and anthelminthicin C (**2.44**) significantly inhibit Mycobacterium tuberculosis growth with minimum inhibitory concentration values of 9.82 and 4.38 mM, respectively [46]. Anthelminthicin C has also recently been found to inhibit *para*-aminobenzoic acid biosynthesis (pABAB) [46]; inhibitors of pABAB are important leads for the development of new antibiotics, as this pathway is not found in humans [46].

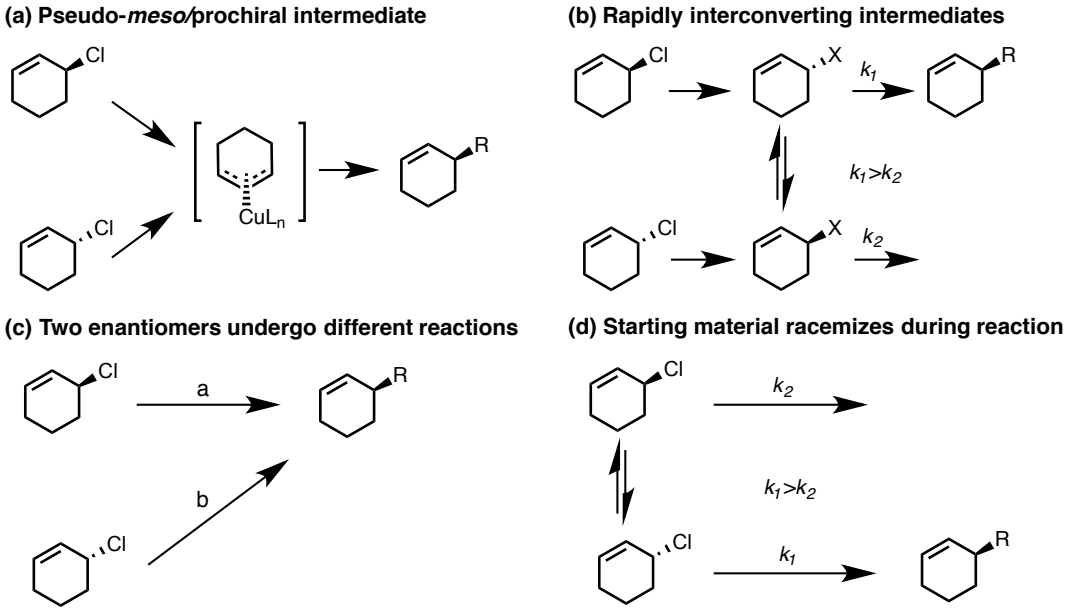


Figure 2.11 | Mechanistic possibilities.

A mechanism study was performed here, based on the previous reaction reported [36,37,38] and above exploration with this copper-catalyzed asymmetric catalysis on racemic cyclic substrates, it seems a DYKAT mechanism is occurring by one of the four following pathways (Figure **2.11**): (a) the reaction proceeds through a pseudo-*meso*-Cu intermediate similar to the classical Pd-intermediates in the stabilized nucleophiles; (b) A related scenario, where the reaction goes through a rapid interconverting intermediates derived from the cyclic allylic chloride (such as σ -allyl-Cu species), and one enantiomer of it undergoes the selective reaction; (c) the two enantiomers of cyclic allylic chloride undergo different reaction pathways, but both giving the same product (an enantio-convergent transformation [37]); (d) the cyclic allylic chloride racemizes during the reaction and the asymmetric allylic alkylation is selectively for one of the enantiomers of the starting material.

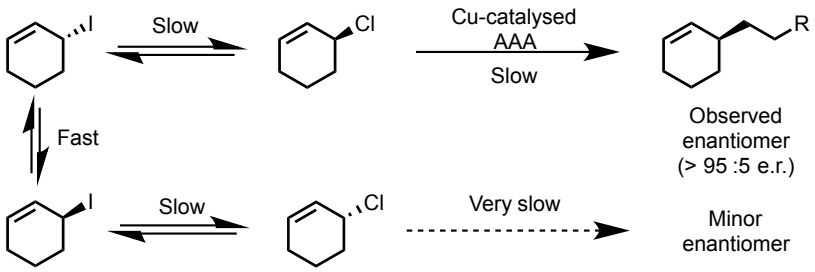
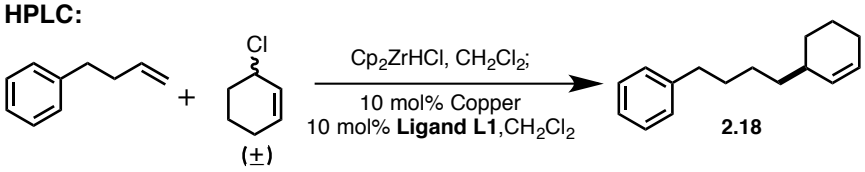


Figure 2.12 | Proposed mechanism for the copper-catalyzed AAA DYKAT reaction.

In collaboration with Emeline Rideau, and Mireia Sidera, a detailed NMR spectroscopy study of the reaction [46] was performed and a proposed mechanism is shown here (Figure **2.12**): the cyclic allylic chlorides racemize through a *syn*-S_N2' displacement via an allylic iodide intermediate, and selective asymmetric allylic alkylation of one of the enantiomers of cyclic allylic chloride gives the product with high enantiomeric excess.

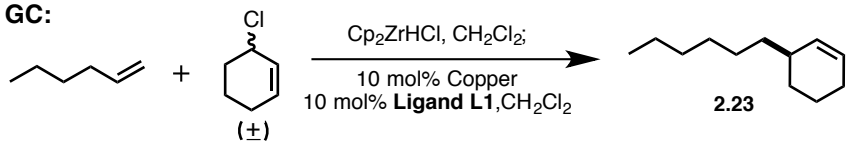
Table 2.9 | Mechanism: HPLC&GC enantioexcess study [a]

HPLC:



Time	(Cu.OTf).Ph	CuI	CuCl	CuCl/$AgSbF_6$
5 min	65 % ee	-75 % ee	-19 % ee	17 % ee
10 min	69 % ee	-57 % ee	45 % ee	21 % ee
15 min	71 % ee	3 % ee	48 % ee	19 % ee
20 min	70 % ee	0 % ee	53 % ee	23 % ee
30 min	73 % ee	17 % ee	49 % ee	23 % ee
50 min	69 % ee	49 % ee	63 % ee	36 % ee
100 min	69 % ee	69 % ee	59 % ee	13 % ee
140 min	73 % ee	75 % ee	55 % ee	3 % ee
overnight	73 % ee	87 % ee	49 % ee	17% ee

GC:



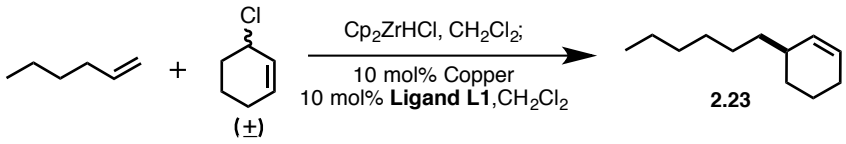
Time	(Cu.OTf).Ph	CuI	CuCl	CuCl/$AgSbF_6$
5 min	84 % ee			
10 min	85 % ee	71 % ee	81 % ee	63 % ee
30 min	83 % ee	71 % ee	82 % ee	71 % ee
2 h		85 % ee	68 % ee	77 % ee
4 h		93 % ee		
overnight	83 % ee	95 % ee	54 % ee	

[a] Reaction conditions: exploration was performed for the AAA of cyclic allylic chlorides (1 equiv. 1mmol) and alkene (2.5 equiv.), Cp_2ZrHCl (2 equiv.),CuI/Ligand (10 mol%) in 2.5 mL CH_2Cl_2, good to Full converstion was observed in all cases shown; Enantioselectivity was determined by HPLC/GC.

The enantiomeric excess of products formed as a function of time using different copper salts was also followed (Table **2.9**). Clearly, we can see that when different copper source are employed, the reactions might go through a distinct mechanistic pathways as vastly different results are obtained when using CuOTf and Copper halides. In particular, in case of the copper halide catalyzed reactions: reactions using CuCl show a decrease in enantioselectivity over time. We speculate that when CuCl is used, the rapidly reacting enantiomer of cyclic allylic chloride is consumed, without a fast-enough racemization, the reaction with the minor

enantiomer becomes significant and reduces the enantioselectivity of product as time progress; When CuI is used, the initial reaction rate is slow, and the enantioselectivity of the product increases with time suggesting a more enantioselective system is generated as the reaction progress. At least part of the role of CuI is to racemize the cyclic allylic chloride via an allylic iodide intermediate, but the identity of the proposed highly enantioselective catalyst is unclear. Both CuCl and CuI give lower initial values of enantioexcess than are observed at later stages of the CuI-catalyzed reaction. It may be that copper aggregates containing both 'Cl' and 'I' are more selective than those containing only one halogen. An experiment performed using 10% Ligand **L1** with 5% CuCl and 5% CuI ambiguously gave the product **2.18** with 90% e.e. (rather than 95% e.e.) at completion. Alternatively, salt effects may increase the e.e. of product as time progresses by favoring the formation of more highly enantioselective copper-ligand complexes; the reaction produces Cp_2ZrCl_2, which may also affect the relative solubility of other reaction components.

Table 2.10 | Mechanism: Following the ee of the allylic chloride starting material in time [a]



Time	CuCl/ *S*-L1	CuCl/ *S*-L1 (2nd run)	CuCl/ *S*-L1(3rd run)	CuCl/ *R*-L1
10 min	0 % ee	0 % ee	0 % ee	0 % ee
1 h	7 % ee	7 % ee	0 % ee	-7 % ee
2 h	13 % ee	11 % ee	11 % ee	-15 % ee

[a] Reaction conditions: exploration was performed for the AAA of cyclic allylic chlorides (1 equiv. 0.4mmol) and alkene (2.5 equiv.), Cp_2ZrHCl (2 equiv.),CuI/Ligand (10 mol%) in 0.8 mL CH_2Cl_2, good to Full converstion was observed in all cases shown; Enantioselectivity was determined by GC.

The e.e of racemic cyclic allylic chloride was also analyzed during the reaction (Table **2.10**) even though the cyclic allylic chloride is very reactive, at least 11% e.e. of the initially racemic starting material was observed rapid, careful work up of the reaction (see **5.3** in experimental section) followed by gas chromatography analysis, supporting our proposed mechanism. We were unable to make an enantiomerically enriched allylic chloride starting material.

2.5 Future Work

Interesting future work may include further extension of this chemistry to structurally more challenging reaction partner such as linear substrates or substrates bearing functional moieties, other types of nucleophiles in forming more diverse bonds etc. It is also very attractive for the exploration of this new chemistry's mechanism as well as its application in the synthesis of other bioactive or natural products/ precursors.

2.6 Conclusions

To conclude, A Cu-catalyzed dynamic kinetic asymmetric allylic alkylation has been reported here using alkyl zirconium reagents. The method provides efficient synthetic routes for the construction of enantiomerically enriched centres in designed molecules. The reaction tolerates a variety of functional groups and operates under convenient conditions. Its applications were performed on gram scales in the asymmetric synthesis of complex molecular skeletons and biologically active cyclopentene natural products. Additionally, the mechanistic studies reveal a dynamic kinetic transformation operates via racemization of the starting material.

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Chapter 3

Cu-catalyzed Dynamic Kinetic Asymmetric Allylic Alkylation of Racemic Phosphates Using Organozirconium species

3.1 Overview

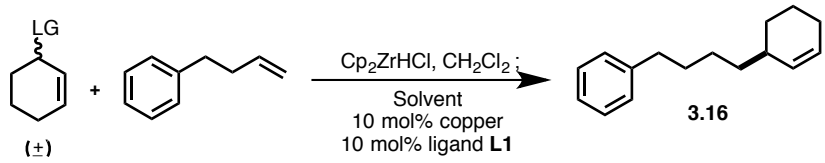
This chapter describes the expansion of copper-catalyzed dynamic kinetic asymmetric allylic alkylation chemistry (See **Chapter 2**), here the study of less reactive racemic substrates than allyl chlorides was performed, and a new process developed using allylic phosphates. This new process constitutes a significant achievement as phosphates are more general compatible with other functional groups, but they are also more chemically stable and allowed a series of interesting mechanistic experiments to be performed.

3.2 Introduction

To broaden the synthetic utility of previously reported copper-catalyzed DYCAT AAA and gain more insight of its interesting mechanism, we have focused our attention on expanding more stable and general substrates, which can be employed in this chemistry. New procedures allowing the use of less reactive electrophiles would be desirable because these would (i) be more chemically stable; (ii) be less prone to isomerization during formation or routine manipulations; (iii) would avoid the use of halogenating reagents which are generally aggressive and incompatible with many functional groups. Allylic alcohol derivatives are good candidates here, since they are general functional group that exists in natural products and various chemical intermediates in organic synthesis[1].

3.3 Development of the Methodology

Table 3.1| Selected optimization experiments: LGs& copper source [a]

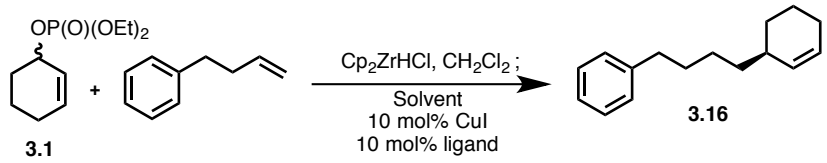


Entry	LG	Solvent	Copper source	Convension (%) [b]	ee (%) [c]
1	OAc	$CHCl_3$	CuI	_ [d]	_[d]
2	O_2CCF_3	$CHCl_3$	CuI	35	45
3	OPiv	$CHCl_3$	CuI	<10	-85
4	$OP(O)(OEt)_2$	$CHCl_3$	CuI	>95	40
5	OAc	CH_2Cl_2	CuTC	_[d]	_[d]
6	O_2CCF_3	CH_2Cl_2	CuTC	25	15
7	OPiv	CH_2Cl_2	CuTC	_[d]	_[d]
8	$OP(O)(OEt)_2$	CH_2Cl_2	CuTC	>95	5
9	$OP(O)(OEt)_2$	CH_2Cl_2	CuI	>95	38
10	$OP(O)(OEt)_2$	CH_2Cl_2	CuCl	>95	3
11	$OP(O)(OEt)_2$	CH_2Cl_2	CuBr	>95	26
12	$OP(O)(OEt)_2$	CH_2Cl_2	CuCl/ AgOTf	>95	33
13	$OP(O)(OEt)_2$	CH_2Cl_2	CuCl/ $AgNTf_2$	>95	33
14	$OP(O)(OEt)_2$	CH_2Cl_2	CuCl/ $AgSbF_4$	>95	2
15	$OP(O)(OEt)_2$	CH_2Cl_2	CuCl/ $AgBF_4$	>95	21

[a] Reaction conditions: optimization was performed for the AAA of racemic materials bearing different leaving groups (1 equiv.) and 4-phenyl-1-butene (2.5 equiv.), Cp_2ZrHCl (2 equiv.).
[b] Conversion was determined by HPLC with relative NMR analysis.
[c] Enantiomeric excess (e.e.) was determined by HPLC.
[d] Formation was not observed.

Our initial optimization of the reaction started with asymmetric allylic alkylation of various racemic allylic alcohol derivatives (Table **3.1**). The reactions were performed under the previously described conditions for cyclic allylic chlorides: 10 mol% CuI, 10 mol% **L1** in chloroform [2]. We didn't observe the desired product with the cyclic allylic acetate (Table **3.1**, entry 1). Both the trifluoroacetate and pivalate derivatives performed poorly in terms of conversions under these conditions (Table **3.1**, entries 2-3), while an allylic phosphate gave the product with complete conversion despite moderate ee (40% ee, Table **3.1**, entry 4), and similar results were obtained with CH_2Cl_2 (Table **3.1**, entry 9). We explored other copper sources (Table **3.1**, entries 8–15) and although CuOTf and $CuNTf_2$ gave comparable yields to CuI (Table **3.1**, entries 12 and 13), CuI was still found to provide the highest enantioselectivity.

Table 3.2 | Selected optimization experiments: ligands& solvents [a]



Entry	Solvent	Ligand	ee (%)[b]	Entry	Solvent	Ligand	ee (%)
1	CH_2Cl_2	**L1**	38	16	Et_2O	**L15**	7
2	CH_2Cl_2	**L2**	7	17	THF	**L15**	2
3	CH_2Cl_2	**L3**	3	18	Hexane	**L15**	3
4	CH_2Cl_2	**L4**	9	19	Toluene	**L15**	2
5	CH_2Cl_2	**L5**	_ [c]	20	CH_2Cl_2	**L16**	81
6	CH_2Cl_2	**L6**	41	21	CH_2Cl_2	**L17**	-27
7	CH_2Cl_2	**L7**	48	22	CH_2Cl_2	**L18**	41
8	CH_2Cl_2	**L8**	47	23	CH_2Cl_2	**L19**	45
9	CH_2Cl_2	**L9**	9	24	CH_2Cl_2	**L20**	73
10	CH_2Cl_2	**L10**	3	25	CH_2Cl_2	**L21**	-23
11	CH_2Cl_2	**L11**	21	26	CH_2Cl_2	**L22**	27
12	CH_2Cl_2	**L12**	21	27	$CHCl_3$	**L16**	85
13	CH_2Cl_2	**L13**	51	28	CCl_4	**L16**	_ [c]
14	CH_2Cl_2	**L14**	41	29	CH_2ClCH_2Cl	**L16**	57
15	CH_2Cl_2	**L15**	55	30	1,2,4-trichloro-benzene	**L16**	_ [c]

[a] Reaction conditions: optimization was performed for the AAA of racemic allylic phosphate (1 equiv.) and 4-phenyl-1-butene (2.5 equiv.), Cp_2ZrHCl (2 equiv.).
[b] Enantiomeric excess (e.e.) was determined by HPLC.
[c] Formation was not observed.

With ~40% ee in hand we attempted to obtain high levels of enantioselectivity by testing a battery of ligands. A brief screen of different phosphoramidite backbones and bisphosphine ligands were evaluated (Table **3.2**, entries 1-5), as these types of ligands have proven effective in a broad range of copper-catalyzed reactions [3]. BINOL backbones turned out to be best for this type of ligands in the reaction, and ligands with different amine moieties were then studied. Reactions with varying electronic and steric properties of ligands related to **L8** (Table **3.2**, entries 6-11) did not provide higher enantioselectivity, but later on, we found amines containing a chiral bicyclic-substituent were particularly selective (Table **3.2**, entries 20–24). Ligand **L16** gave the highest ee (81%, Table **3.2**, entry 20). However, its diastereomer **L17** gave very low ee and afforded the opposite enantiomer of product (entry 21). The same effect was observed with isomeric ligands **L20** and **L21** (Table **3.2**, entries 24, 25). These results suggest the BINOL backbone dictates the absolute configuration of the major enantiomer. We

also examined the effect of different solvents and found that the non-chlorinated solvents examined (Table **3.2**, entries 16-19) gave the products in essentially racemic form. Chloroform gave **3.16** with slightly better results (85% ee, Table **3.2**, entry 27) but some chlorinated solvents – CCl_4, dichloroethane and 1,2,4-trichlorobenzene – either gave no product or lower ee (entries 28–30).

Chapter 3: Ligand Pool

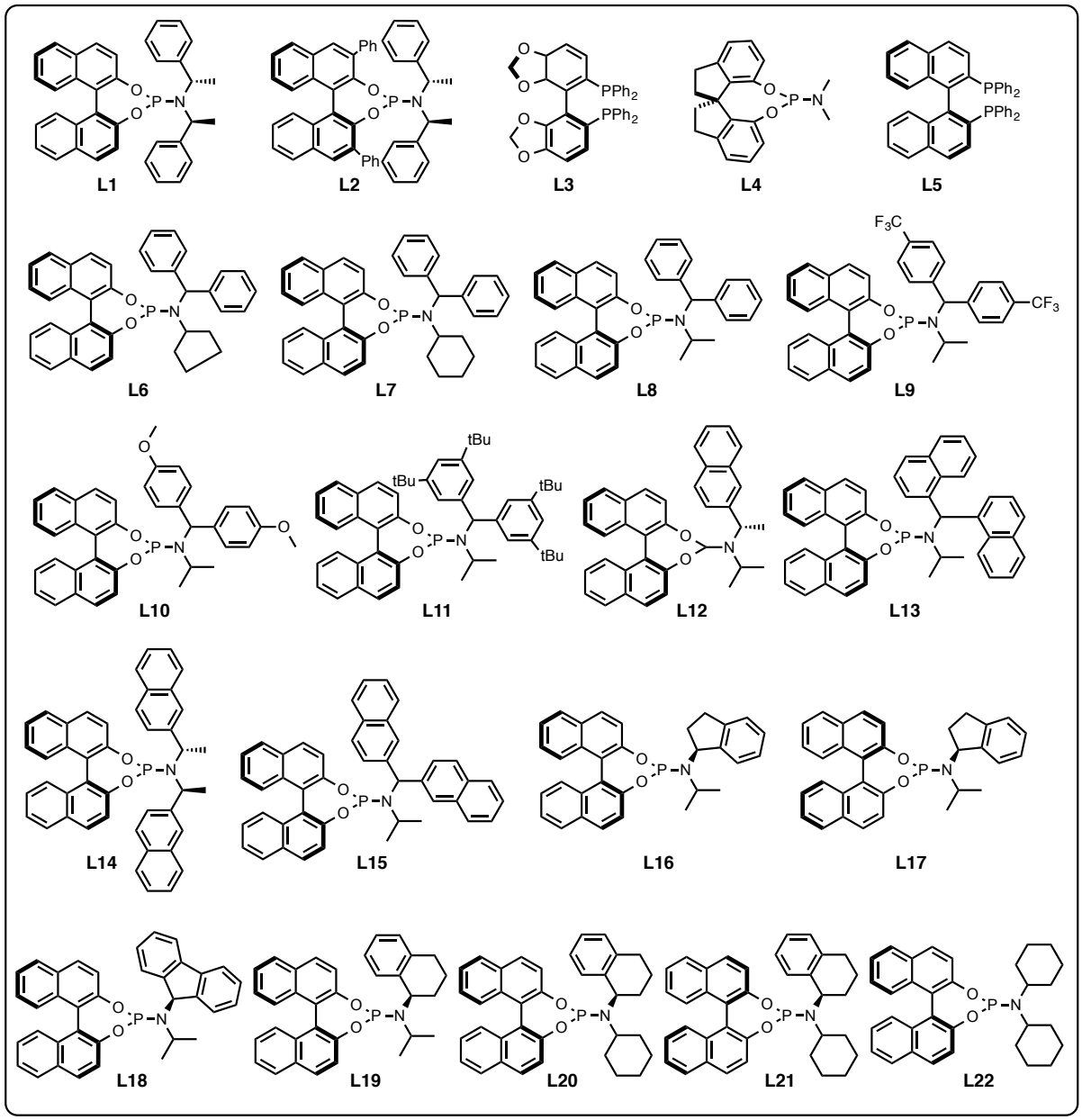
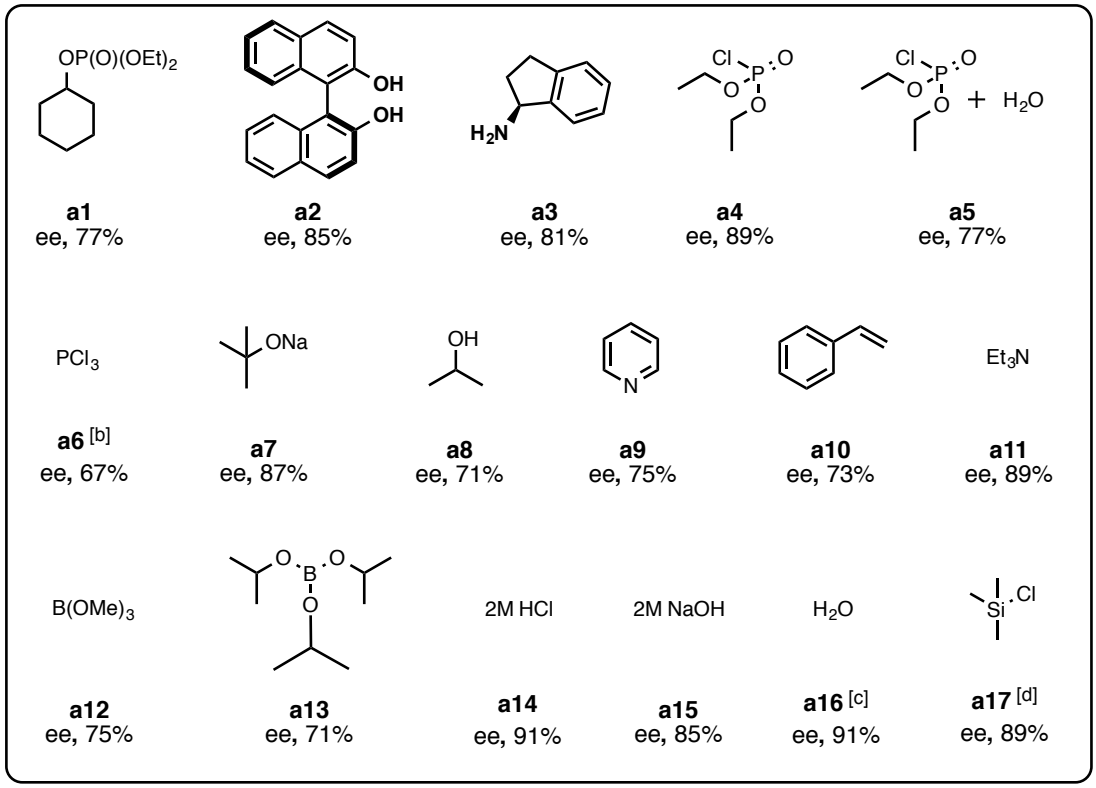


Table 3.3 I Selected optimization experiments: Additives [a]



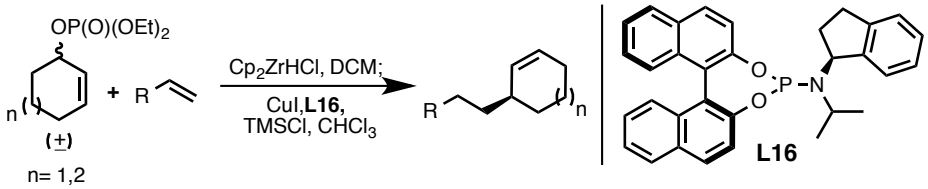
[a] Reaction conditions: optimization was performed for the AAA of racemic allylic phosphate (1 equiv.) and 4-phenyl-1-butene (2.5 equiv.), Cp_2ZrHCl (2 equiv.), CuI (10 mol%), ligand **L16** (10 mol%), additive (20 mol%) in $CHCl_3$; Enantiomeric excess (e.e.) was determined by HPLC.
[b] Additive **a6** was added in 10 mol%.
[c] Additive **a16** was added in 5 mol%, 10 mol%, 20 mol%, 30 mol%, 100 mol%, 200 mol%, 500 mol% with results: 83% ee, 85% ee, 91% ee, 83% ee, No product, No product, No product.
[d] Additive **a17** was added in 20 mol%, 50 mol%, 100 mol%, 150 mol%, 500 mol% with results: 81% ee, 75% ee, 89% ee, 85% ee, 80 % ee.

While we were able to obtain 85% ee, the procedure did not seem very robust and we sometimes saw higher or lower ee values. Since traces of saturated phosphate **a1** (1.4%) were observed in the racemic allylic phosphate starting material by high resolution NMR spectroscopic analysis, we suspected that an impurity was causing these variations and tested the presence of several additives that we imagined could contaminate the reaction mixture (such as BINOL **a2**; an enantiopure amine **a3** or $ClP(O)(OEt)_2$ **a4**; Table **3.3**) or acting as an acid, base or radical trap [4]. Interestingly, the presence of many additives had no detrimental effect on the ee. The use of 20 mol% $ClP(O)(OEt)_2$ **a4** increased the ee to 89% as did Et_3N **a11**. After substantial experimentation we found that a range of additives (**a4, a11**, **a14**, **a16**, **a17**) provided good enantioselectivity. Overall, out of concern for robustness; yield and ease of

operation, the best procedure was addition of TMSCl **a17**, where 1 equiv. of the additive reproducibly gave product **3.16** in 80% yield and 89% ee.

3.4 Generality of the Methodology

Table 3.4l Selected copper-catalyzed dynamic kinetic AAA of racemic phosphates [a]



Entry	Phosphate	Alkene	Product	Yield [b]; ee [c]
1	OP(O)(OEt)$_2$ **3.1**		3.17	95%; 85%
2	OP(O)(OEt)$_2$ **3.1**	n=7	n=7 **3.18**	77%; 92%
3	OP(O)(OEt)$_2$ **3.1**	Cl	Cl **3.19**	44%; 75%
4	OP(O)(OEt)$_2$ **3.1**	Si	Si **3.20**	28%; 93%
5	OP(O)(OEt)$_2$ **3.1**		**3.21**	91%; 81%
6	OP(O)(OEt)$_2$ **3.1**	F_3C	F_3C **3.22**	86%; 65%
7	OP(O)(OEt)$_2$ **3.2**		**3.23**	65%; 90%

[a] Reaction conditions: alkenes react with the Schwartz reagent (Cp_2ZrHCl) in CH_2Cl_2 to generate alkylzirconocene species in situ which undergo AAA with racemic cyclic allylic phosphate. Cp, cyclopentadienyl. Conditions: 2.5 equiv. alkene; 2 equiv. Cp_2ZrHCl, 10 mol% CuI, 10 mol% ligand **L16**, room temperature overnight, argon atmosphere.
[b] Yield refers to pure isolated compounds.
[c] Enantiomeric excess was either determined directly by high-performance liquid chromatography, or the corresponding epoxides by gas chromatography, using a chiral non-racemic stationary phase.

With optimal conditions in hand, we probed the reaction scope by employing a variety of alkenes. Good yield and high enantioselectivity was obtained when primary simple alkenes were used (Table **3.4**, entries 1 and 2). The presence of more elaborate functional groups containing halogen, electron rich allylsilane, aromatic rings and trifluoromethyl groups were also tested (entries 3-6). We found that in some cases caused the ee dropped. The highest ee (93%, entry 4) was obtained when using allylsilane, although the yield (28%) was low in this case. Using a seven-membered allyl phosphate, we were pleased to observe the formation of **3.23** in good yield (65%) with excellent enantioselectivity (90% ee, entry 7). This is truly remarkable result when compared to our previously described system using racemic allyl chloride and ligand **L1**. In which, the use of 7-membered rings provided very low ee's, so the ability to employ 7-membered ring substrates here extends the synthetic viability of the AAA chemistry.

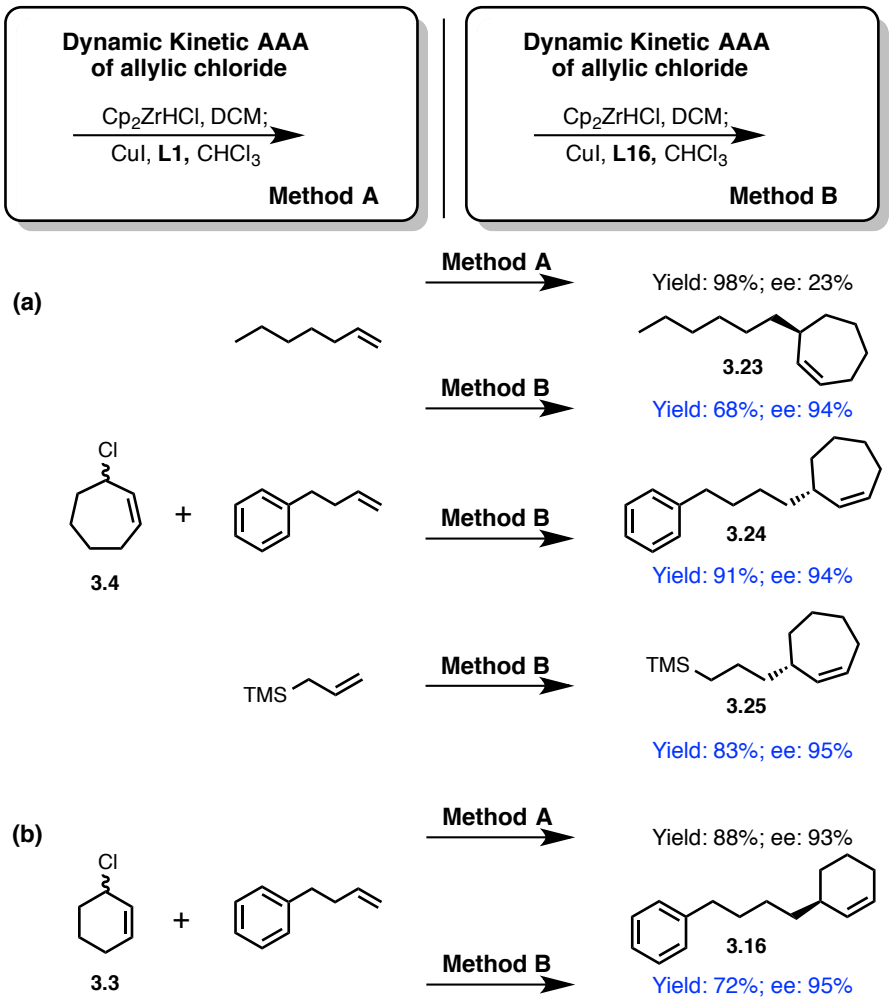


Figure 3.1 | Comparison between L1 and 16 using allyl chlorides.

Considering the closely reaction conditions used with both the allylic phosphate and allylic chloride systems, we suggest the ligand plays an important factor in inducing high enantioselectivity. Using Ligand **L16** (**Method B**) with 7-membered ring allyl chlorides was tested (Figure **3.1**, a) and we found that this is much more effective ligand than Ligand **L1** (**Method A**) to form **3.23** (23% vs 94% ee). Other alkenes were also explored to give substituted cycloheptenes products **3.24** and **3.25** with excellent levels of ee (94% and 95% respectively). In the case of 6-membered allyl chlorides, **L1** and **L16** gave comparable results in the formation of **3.16** (Figure **3.1**, b)

3.5 Mechanistic Considerations

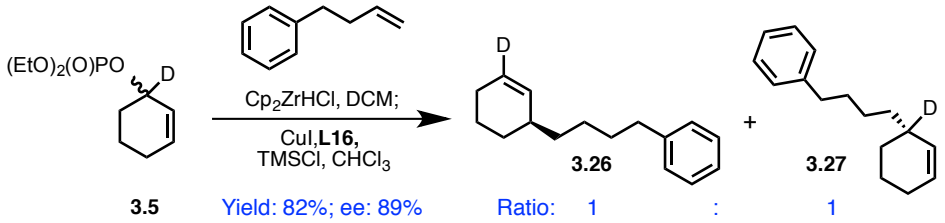


Figure 3.2 | Cu-catalyzed AAA with Deuterated cyclic phosphate.

To further extend the generality of this method and gain more insight into its mechanistic pathway, a range of more sophisticated reactions were explored. Due to its greater chemical stablity, the phosphate system may enable valuable control experiments. Notably, the selective deuteration of cyclic allylic phosphate substrate (**3.5**) proved to be a powerful tool to investigate the mechanistic proposal. Racemic deuterated cyclic allylic phosphate was subsequently prepared and implemented under the standard condition (Figure **3.2**). Interestingly, the reaction shows a γ/α ratio of 1:1 products in 82% total yield and 89% overall enantiomeric excess. This reaction outcome presented a completely unselective manner in terms of regioselectivity.

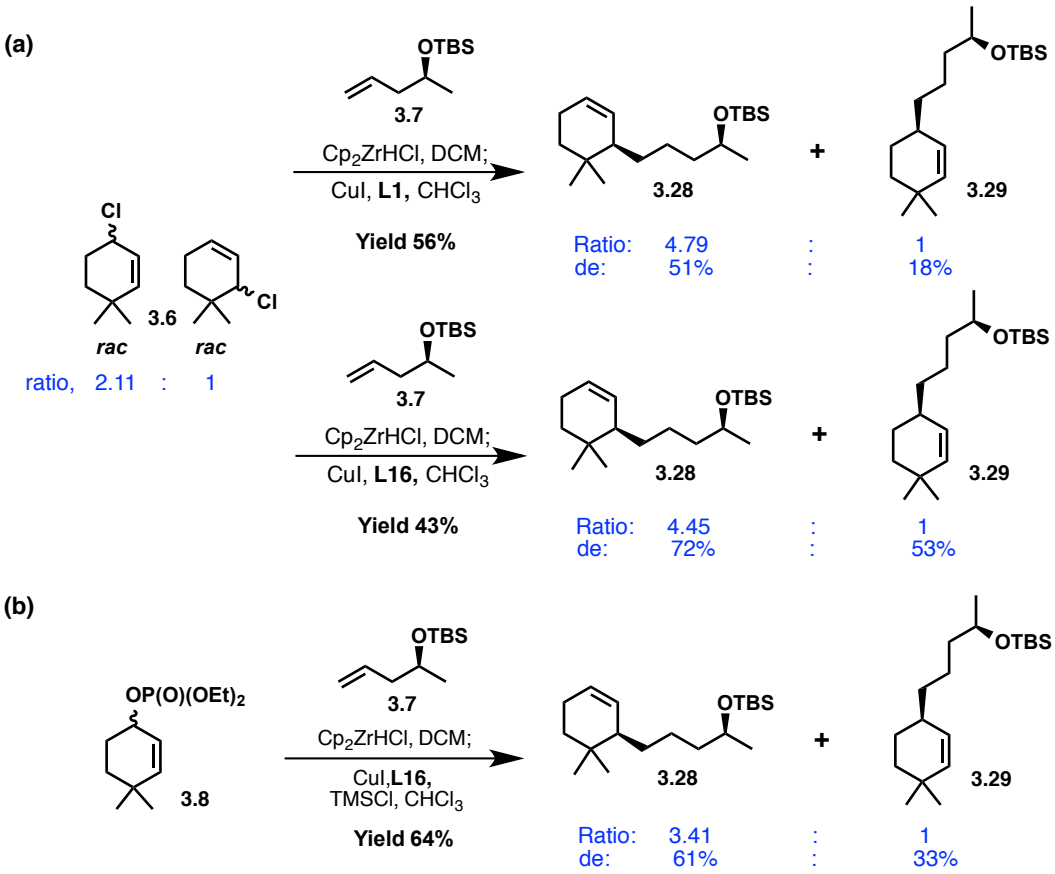


Figure 3.3 | Cu-catalyzed AAA with non-symmetrical substrates.

In order to learn more about the intrinsic regioselectivity of the system, non-symmetrical substrates were also studied. Due to the high reactivity, substituted allylic chloride **3.6** was prepared as a 2.11: 1 mixture of racemic compounds. Initially, the non-chiral alkene was used in the reaction until we found out we couldn't determine the enantioselectivity of the complex products. Here we use an enantiomerically pure chiral alkene so that the diastereo- and regio-selectivity could be determined by high resolution NMR spectroscopy. As show above, employing **L1** led to a major γ-preferred product with γ/α: 4.79/1 regioselectivity, where the products were obtained with 51% de and 18% de separately (Figure **3.3**, a). The reaction using **L16** shows a similar γ-preference with γ/α: 4.45/1 ratio, and high levels of diastereo selectivity: 72% de and 53% de (Figure **3.3**, a). In the case of allylic phosphate system an isolated, stable, 4,4-substituted substrate **3.8** was prepared. The product was obtained in γ/α: 3.41/1

regioselectivity and 61% de, 33% de was observed respectively (Figure **3.3**, b) suggesting that γ-substitution mechanism is preferred, but it is difficult to say anything concrete. Meanwhile, reactions using the other enantiomer of enantiomerically pure chiral alkene **3.7** were performed in both chloride and phosphate system, it's glad to see it didn't change the outcome of the reactions.

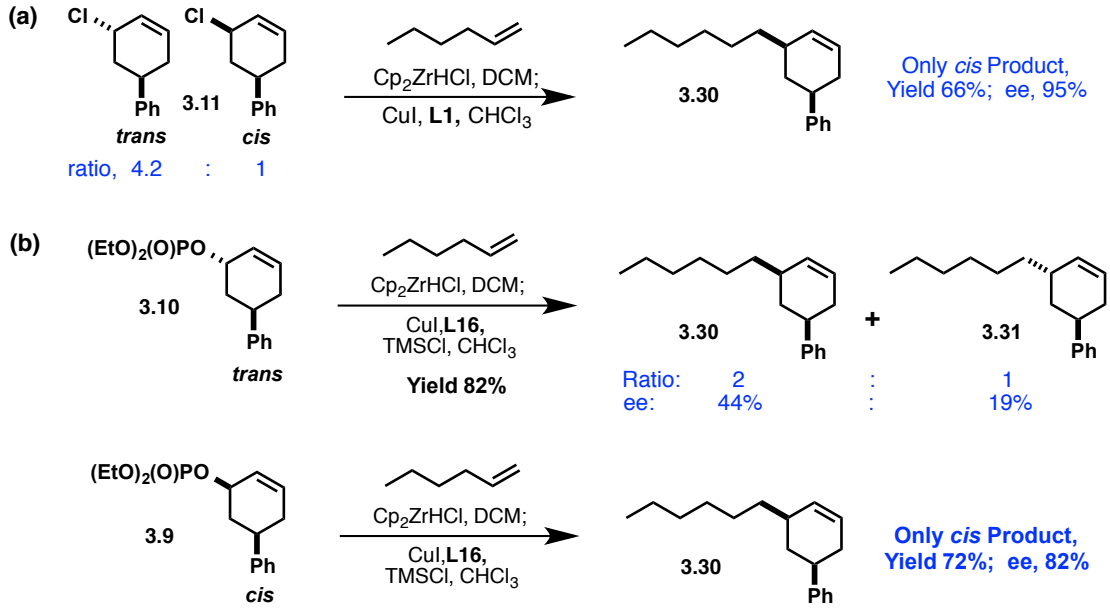


Figure 3.4 | Cu-catalyzed AAA with 5-phenyl substituted substrates

A phenyl group at C5 of the cyclic allylic substrates was introduced as a stereochemical probe. 5-substituted cyclic allyl chloride **3.11** was used as a racemic mixture in 4.2:1 *trans*/*cis* ratio. Remarkably, the CuI-**L1** combination gave only one observable product: *cis*-**3.30** with an excellent enantioselectivity (95% ee) in 62% yield (Figure **3.4**, a). Stable 5-substituted cyclic allylic phosphates enabled us to examine the *trans*/*cis* substrates separately (Figure **3.4**, b). Reactions with the racemic *trans* 5-substituted cyclic allylic phosphate **3.10** gave a 2: 1 *cis*/*trans* ratio of products, with 44% ee and 19% ee separately. In the case of *cis*-5-substituted cyclic allylic phosphate **3.9**, only one *cis* product was observed with a good enantioselectivity (82% ee) in 72% yield.

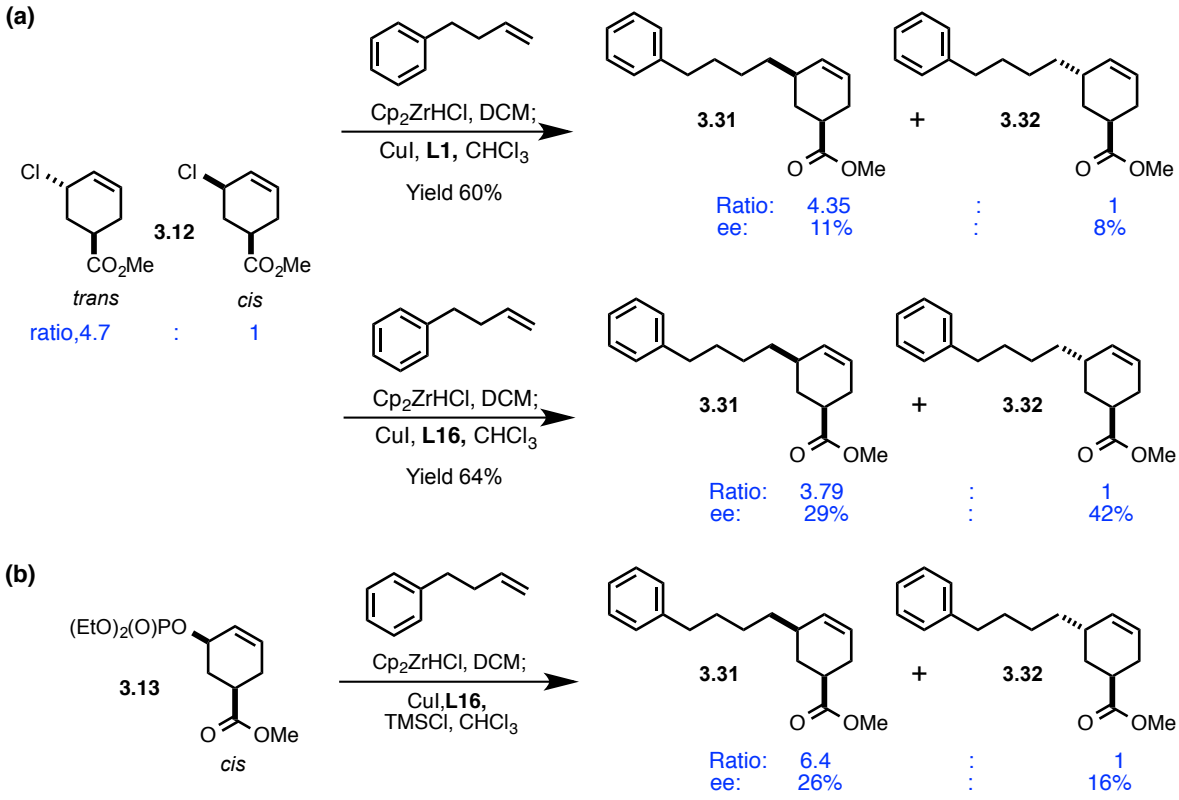


Figure 3.5 | Cu-catalyzed AAA with 5-carboxylate substituted substrates

In broadening the diversity of functional group tolerance, another carboxylate group was introduced at the same C5 of the cyclic allylic substrates. The chloride substrates **3.12** were prepared in 4.7:1 *trans*/*cis* ratio. Employing ligand **L1** led to major *cis*-preferred products in *cis*/*trans* 4.35:1 ratio combination, with 11% ee and 8% ee separately. Reaction using **L16** had a similar *cis*-preference, but with a bit lower 3.79:1 *cis*/*trans* ratio in products with 29% ee and 42% ee separately (Figure **3.5**, a). In the case of phosphate substrate, we are able to synthesis a pure *cis* starting material **3.13**, the products were obtained in 6.4:1 *cis*/*trans* ratio, with 26% ee and 16% ee (Figure **3.5**, b). Clearly, we saw a decreasing trend of enantioselectivities in products when compare to phenyl cases. We assumed the carboxylate group might involve into the ee determining step by coordination with the intermediates, which, had a negative effect on the enantioselectivities of the products.

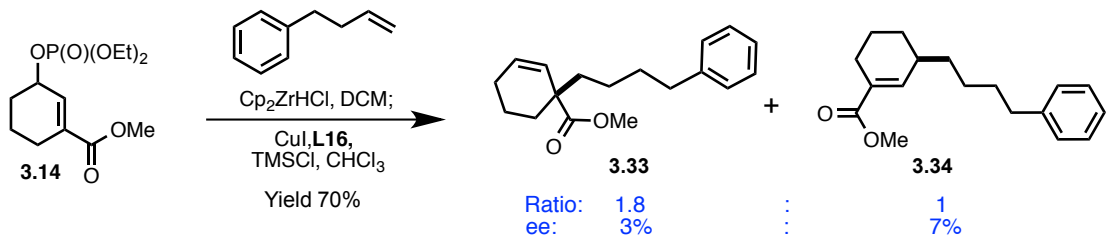


Figure 3.6 | Cu-catalyzed AAA with 3-carboxylate substituted substrates

Later on, we made our efforts in exploration of the Cu-catalyzed AAA reactions with 3-substituted substrates. These are valuable experiments as they offered possible routes for the asymmetric construction of quaternary centres in desired moleculars. Moreover, the S_N2 reaction product is a good candidate, which could afford 1, 4 addition for the further synthetic usage. However, attempts to synthesis the 3-methyl and 3- phenyl substituted allylic substrates are unsuccessful. After continuing efforts, we are only capable to synthesis the 3-carboxylate substituted allylic phosphate **3.14**. Reaction with this starting material under standard condition gave us 1.8:1 ratio of S_N2': S_N2 mixture products with 3% ee and 7% ee separately. We hypothesised the closer distance of carboxylate group to the double bond made it had a further negative impact on the enantioselectivity induction of the products (Figure **3.6**).

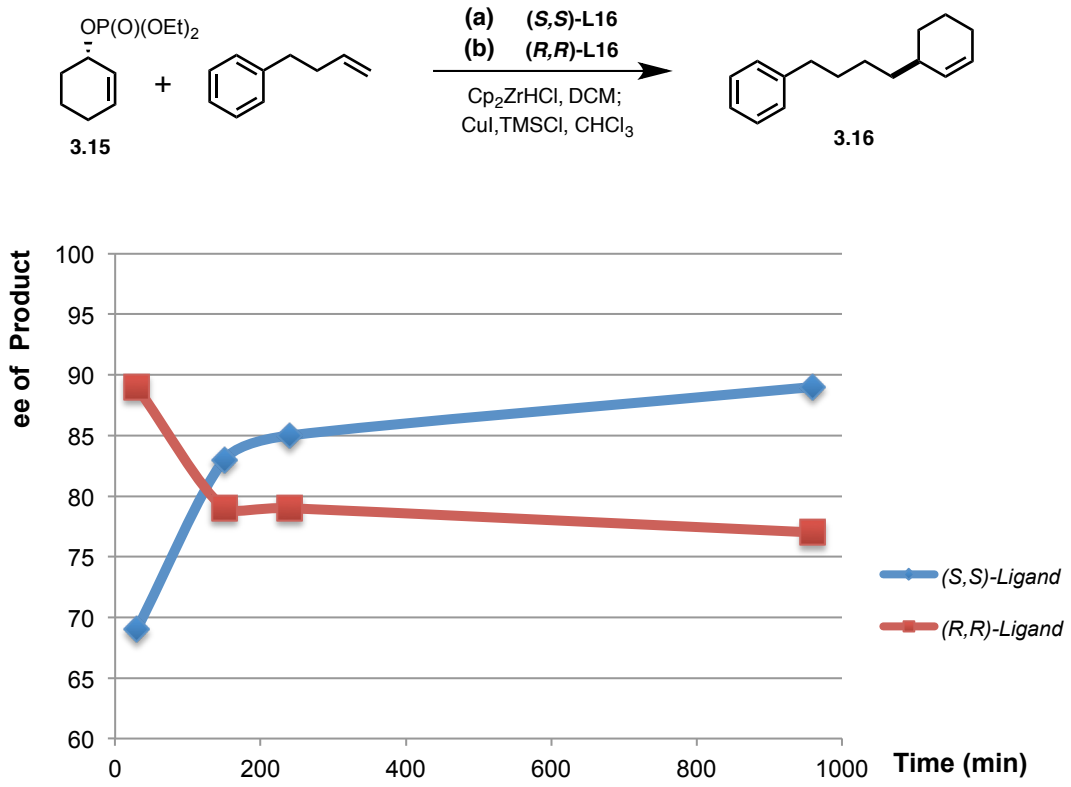


Figure 3.7 | Ligand effect on enantioselectivity: enantiopure phosphate

We then proceeded to use enantiopure cyclic allylic phosphate substrate **3.15** to explore the enantioselectivity of this process (Figure **3.7**). The experiments were designed to follow the enantioselectivity of products at different reaction time employing both enantiomers; (*S, S*)-**L16** and (*R, R*)-**L16**. We observed that the ee of the product increased over time when using (*S, S*)-**L16**, while in contrast, when the (*S*)-cyclic allylic phosphate reacted with the (*R, R*)-**L16** ligand the product ee is very high initially but had a dropping later before it induced the final ee.

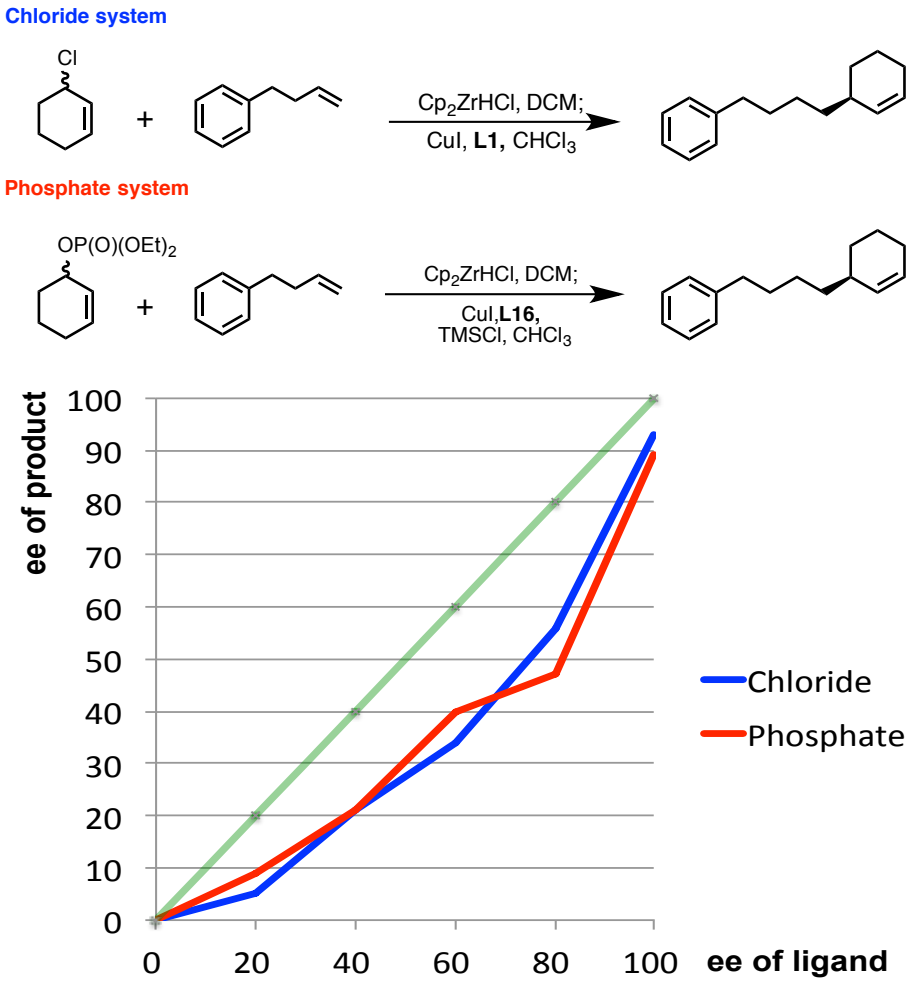


Figure 3.8 | Effect of Ligand on enantioselectivity of product

We also examined if there was a non-linear effect in these reactions [5] (Figure **3.8**). The chloride and phosphate reaction systems were performed with ligand of 20%, 40%, 60%, 80%, and 100% ee chiral ligands separately, and plotted against the corresponding enantioexcesses of products. Interestingly, we see a negative non-linear effect present in both of these two systems, indicating that the active catalytic species is not a monomer and that more complex metal-ligand systems are involved in the asymmetric reaction.

3.6 Future Work

Interesting future work may include further exploration to understand the intrinsic enantioselectivity induction mechanism as well as the further expansion of this chemistry. For

example, in case of the sterically more challenging substrates (5-substituted), there is a preference of the products formation into *cis* structure. It would be interesting if we look into certain ligands where could induce the *trans* products so that we can easily control the desired sterio selectivity we want in the synthesis. Also, the asymmetric quaternary centre induction through our Cu-catalyzed AAA reaction will be an attractive goal to fertilize this chemistry. Efforts toward more diverse substrates, such as linear substrates system or more functional group bearing substrates enabling multi modification of molecules; along with the application of this protocol in the synthesis of bioactive or natural products/ precursors are all meaningful.

3.7 Conclusions

To conclude, extension of the dynamic kinetic Cu-catalyzed AAA system was developed using allylic phosphates. The reaction provides delightful outcomes while employing readily available reaction partners in asymmetric carbon-carbon formation. The ligand **L16** shown to work best in this system also presents a meaningful and interesting improvement in some dynamic kinetic Cu-catalyzed AAA chloride reactions (See **Chapter 2**), enabling the synthesis of 7-membered-ring products from both allyl-chloride and -phosphate starting materials. Interesting reactions employing various substituted substrates: non-symmetrical 4,4-substituted, 5-carboxylate substituted, 3-carboxylate substituted etc. indicate that the reaction is complicated and not yet completely understood, however a strong negative non-linear effect was observed showing the active catalyst has more than one ligand incorporated into it. A case worthy to be noted is the5-phenol substituted cyclic allylic substrates, the reaction revealed ability to transform a mixture of 2-racemic diastereomers into one single isolated product with high ee in the case of allyl chlorides, although the reaction was far more complex with racemic diastreomerically pure allyl phosphates, further illustrating the complexity of these mechanistic pathways. We anticipate these dynamic kinetic Cu-catalyzed AAA studies will be useful in

synthetic organic chemistry and that they will provide insight into the mechanism of these reactions when it is eventually uncovered.

3.8 References

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Chapter 4

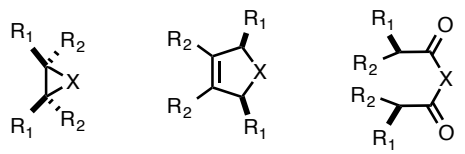
Cu-catalyzed Enantioselective desymmetrisation of *meso* compounds

4.1 Overview

This chapter describes the exploration of copper-catalyzed enantioselective desymmetrization of *meso* substrates using alkylzirconium reagents. More specifically, a study of copper-catalyzed enantioselective ring opening of oxabicyclic alkenes and a copper-catalyzed enantioselective desymmetrization of *meso*-cyclic allylic substrates. We anticipate the research will complement the well-established metal-catalyzed methods with stabilized nucleophiles and inspire future studies in new bond formation using non-stabilized nucleophiles.

4.2 Introduction

Enantioselective desymmetrization of *meso* compounds (Fig. **4.1**) has become one of the most versatile and powerful tools in organic synthesis, affording various enantioenriched compounds. The products of these reactions provide key intermediates for the synthesis of natural products and synthetic analogues with biological activitiy[1-7].



meso Compounds: X = O, NR_3 , CR_3R_4 ...

Figure 4.1 | General structures of *meso* substrates

In general, enantioselective desymmetrization involves the differentiation of two enantiotopic functional groups of *meso* molecules by a selective symmetry breaking operation. It can be achieved by the employment of a chiral reagent or catalyst. Compared to other catalytic methods, enantioselective desymmetrization shows the advantage with its ability to establish multiple stereogenic centres and highly functionalised intermediates in a single step [8].

Having established a copper-catalyzed asymmetric catalytic system employing alkylzirconium reagents in carbon-carbon bond formation as discussed in preceding chapters (See **Chapter 2,**

3) [9-11]. Here, we explored the application of this chemistry in enantioselective desymmetrization.

4.3 Asymmetric Ring-opening of Oxabicyclic Alkenes

Over the past decades, transition-metal-catalyzed asymmetric ring-opening reactions (ARO) of oxabicyclic alkenes haven been demonstrated to be a powerful strategy for the synthesis of chiral building blocks [4,12]. With its capability to establish multiple stereocentres rapidly and efficiently in one step, there has been increased attention and investigation has been received in this area. A variety of approaches have been reported using different metal catalysts such as Pd[13], Rh[14, 19, 21], Ni[15], Ru[16], Fe[17], Cu[18], Ir [19] etc., and a wide range of stabilized nucleophiles such as alcohols [20], phenols [19], amines [14]; non stabilized nucleophiles including organozinc reagents [13], Grignard reagents [17], organoboron reagents [21], organolithium reagents [18] etc. (Fig. **4.2**).

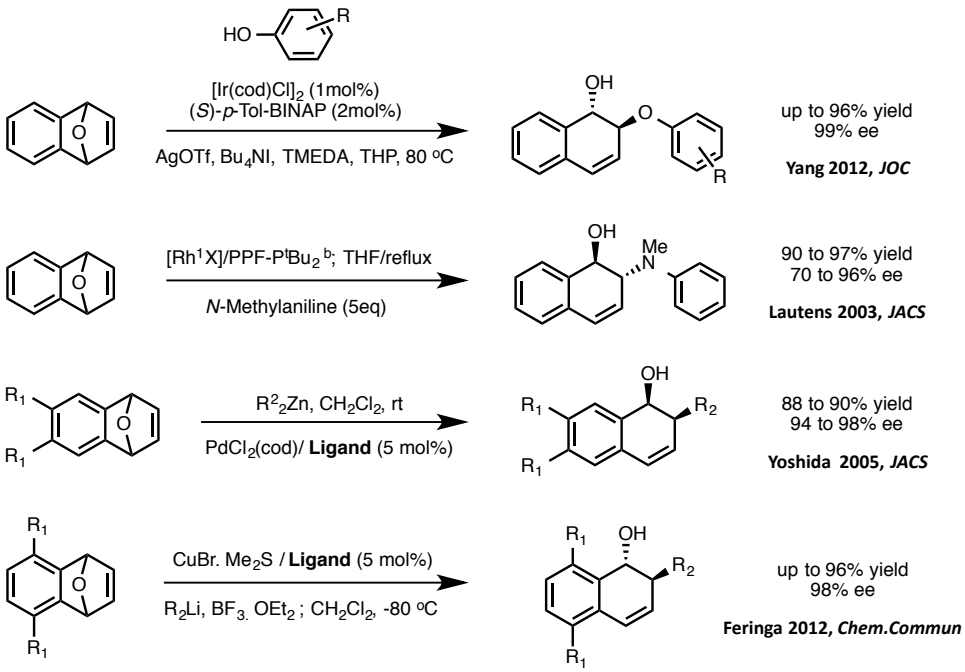
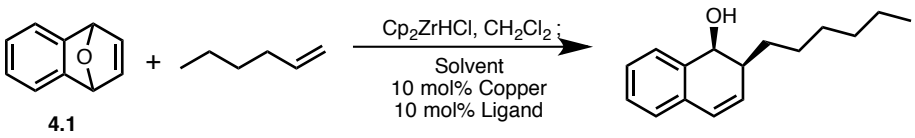


Figure 4.2 |Selected asymmetric ring-opening of oxabicyclic alkenes reaction

Table 4.1l Selected exploration experiments of ARO using alkylzirconium reagent [a]



Entry	Solvent	Copper source	Ligand	Temperature	Additive	Product[b]
1	CH_2Cl_2	$CuBr \cdot SMe_2$	_	25 °C	_	ND[c]
2	CH_2Cl_2	$CuBr \cdot SMe_2$	_	reflux	_	ND
3	CH_2Cl_2	$CuBr \cdot SMe_2$	_	25 °C	TMSCl	ND
4	THF	$CuBr \cdot SMe_2$	_	25 °C	TMSCl	ND
5	2-Methyl tetra hydrofuran	$CuBr \cdot SMe_2$	_	reflux	TMSCl	ND
6	Dichloroethane	$CuBr \cdot SMe_2$	_	reflux	TMSCl	ND
7	1,4-Dioxane	$CuBr \cdot SMe_2$	_	reflux	TMSCl	ND
8	Toluene	$CuBr \cdot SMe_2$	_	reflux	TMSCl	ND
9	CH_2Cl_2	$(CuOTf)_2 \cdot C_6H_6$	**L1**	25 °C	_	ND
10	CH_2Cl_2	$(CuOTf)_2 \cdot C_6H_6$	**L1**	25 °C	TMSCl	ND
11	THF	$(CuOTf)_2 \cdot C_6H_6$	**L1**	25 °C	_	ND
12	Toluene	$(CuOTf)_2 \cdot C_6H_6$	**L1**	reflux	_	ND

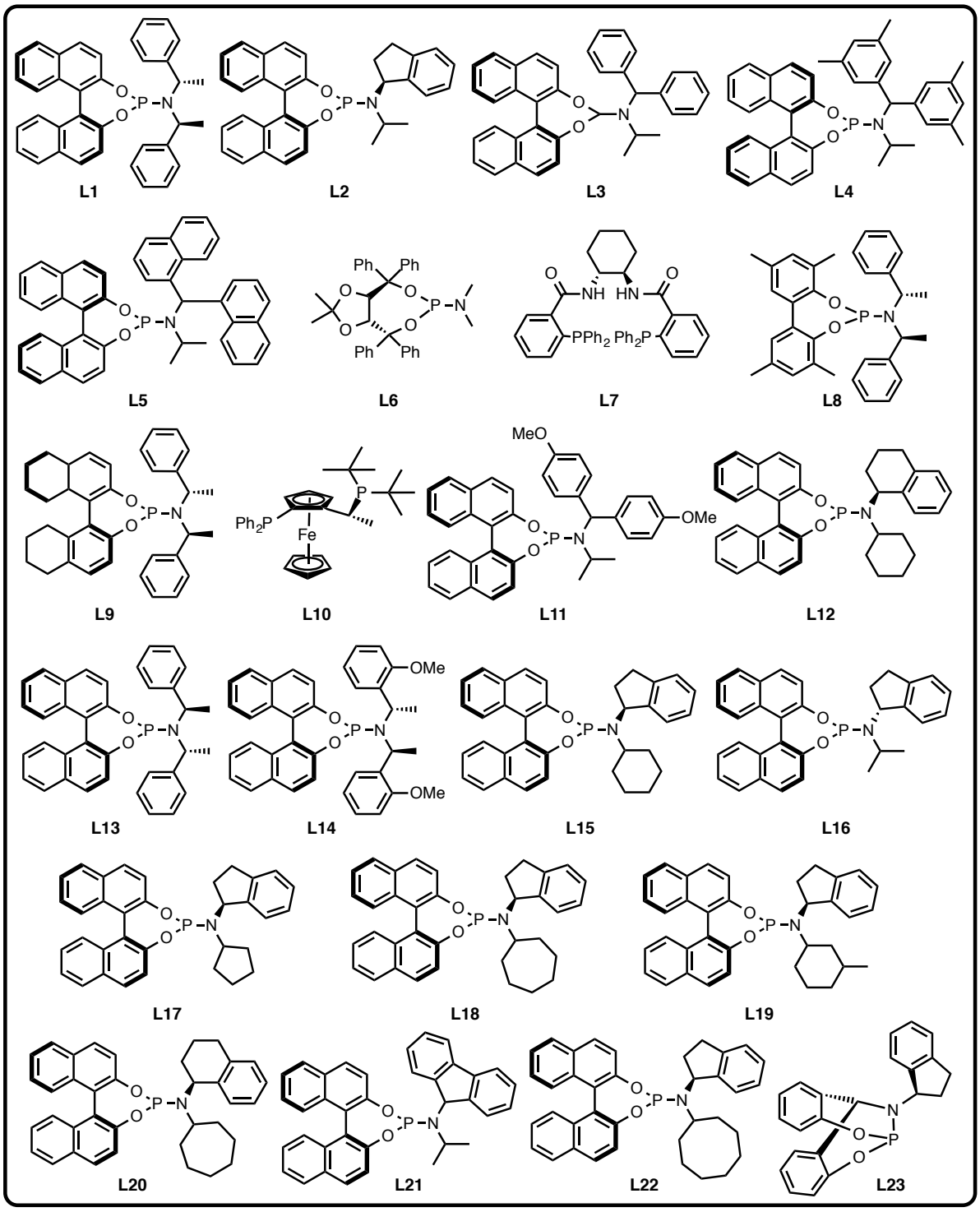
[a] Reaction screening: reactions were performed for the ARO of oxabicyclic under different conditions: Substrate **4.1** (1 equiv.), 1-hexene (2.5 equiv.), Cp_2ZrHCl (2 equi.), Copper source (10 mol%), Ligand (10 mol%).
[b] Products were determined by NMR analysis.
[c] ND refers to product was not detected.

We began our studies by exploring the ARO of 7-oxabenzonorbornadiene in a variety of conditions using 1-hexene as the alkene substrate (Table **4.1**). Under reaction conditions described earlier in the thesis, the oxabicyclic alkene remains unreacted after stirring overnight (Table **4.1**, entry 1) and so harsher conditions involving reflux condition, or addition of TMSCl, which was used as a Lewis acid to activate the oxabicyclic substrate, were used (Table **4.1**, entry 2 and 3). Unfortunately no desired product was detected. Further attempts to improve the reaction included the use of higher boiling solvents to achieve higher reaction temperatures, also gave no desired product.

With the expectation that phosphoramidite ligands [22] could stabilize the reaction intermediates and reduce the reaction energy barrier, a range of experiments using copper (I) triflate benzene complex combined with phosphoramidite ligand **L1** were tested (Table **4.1**, entries 9-12).

However, we still did not observe any desired products from the reaction. We decided to move on and direct our attention towards other projects.

Chapter 4: Ligand Pool



4.4 Desymmetrization of *meso*-cyclic allylic substrates via Cu-catalyzed AAA

Desymmetrization reactions of meso compounds via enantioselective catalysis provide a range of valuable building blocks for the synthesis of chiral molecules from simple starting materials [23, 24]. With the full conversion of *meso* substrates into designed stereoselective products, it has been an attractive approach and complementary strategy to dynamic kinetic resolution and DYKAT methods [11, 23], whereas traditional kinetic resolution reactions have a limited maximum theoretical yield of 50%.

In the case of *meso*, cyclic allylic substrates, the desymmetrization by allylic substitution is a powerful synthetic strategy for the construction of highly functionalized products. The resulting functionalized substitution motifs are present in various biologically active compounds and natural products [25, 26]. The allylic displacement may occur via an S_N2 or S_N2' reaction pathway, with overall retention or inversion in both cases (Fig. **4.3**). Specifically, in the case of S_N2 substitution, where new allylic derivatives were obtained, a second allylic substitution may take place, which will enhance the complexity of the products and makes the reaction more challenging in a controlled asymmetric fashion.

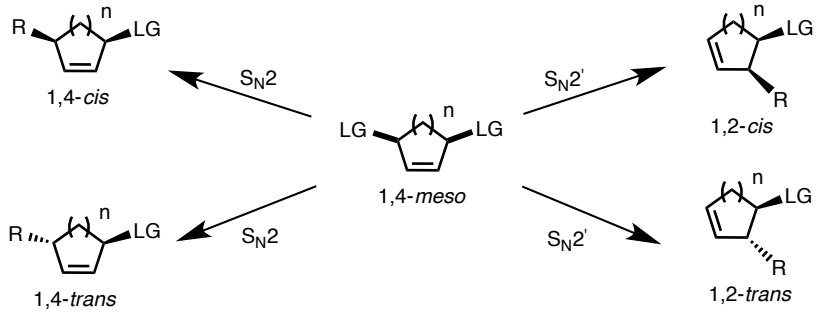


Figure 4.3 |Possible reaction pathways of a *meso*-cyclic allylic substrates

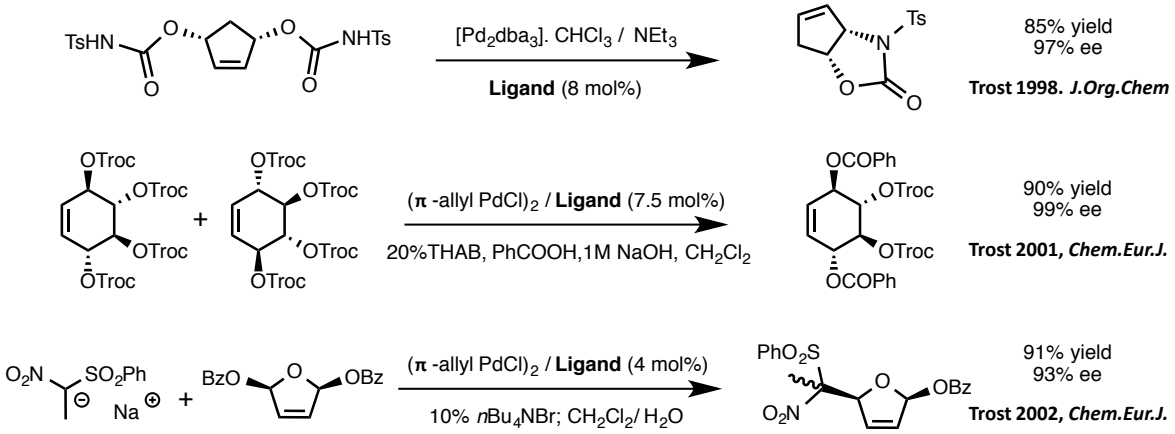


Figure 4.4 | Desymmetrization of *meso*-cyclic allylic substrates by stabilized nucleophiles

Among the well-known protocols, one highlighted process is the Pd-catalyzed desymmetrization chemistry. Pioneered by Trost and co-workers, the employment of stabilized nucleophiles such enolates, heteroatoms etc., presents an attractive and efficient tool in asymmetric catalysis [3, 23, 27-30] (Fig. **4.4**).

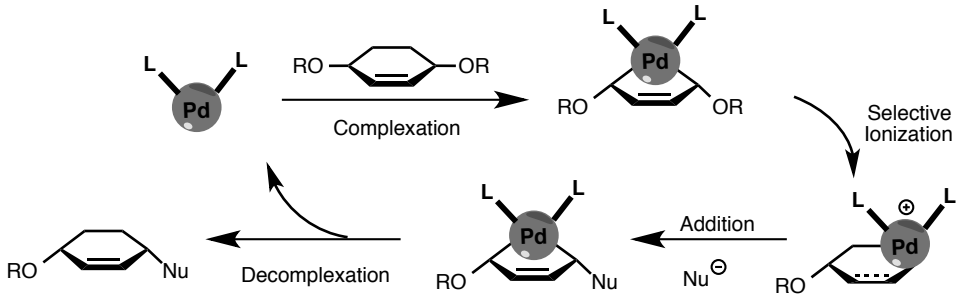


Figure 4.5 | A typical Pd-catalyzed desymmetrization pathway

This Pd-catalyzed desymmetrization chemistry usually involves the S_N2 substitution with an overall retention (Fig. 4.5) and has been demonstrated to be an efficient synthetic approach in various synthesis of natural products and bioactive precursors [3, 23, 27-30].

In contrast, non-stabilized nucleophiles proceed via a different reaction pathway, and current methods have reduced its functional group tolerance and selectivity compared to stabilized ones [11, 31]. However, elegant procedures have been achieved including the Cu-catalyzed highly

regio-, diastereo-, and enantioselective desymmetrization of *meso* cyclic allylic bis (diethyl phosphates) by organozinc reagents, pioneered by Piarulli, Feringa and co-workers [32, 33].

In addition Lautens and co-workers reported an Rh-catalyzed asymmetric allylic substitution using arylboronic acids and a *meso*-cyclic allylic dicarbonate [34]. Another use of *meso*-cyclic allylic dicarbonates in desymmetrization procedures is shown by the Cu-catalysed asymmetric borylation by Ito and co-workers (Fig. **4.6**) [5].

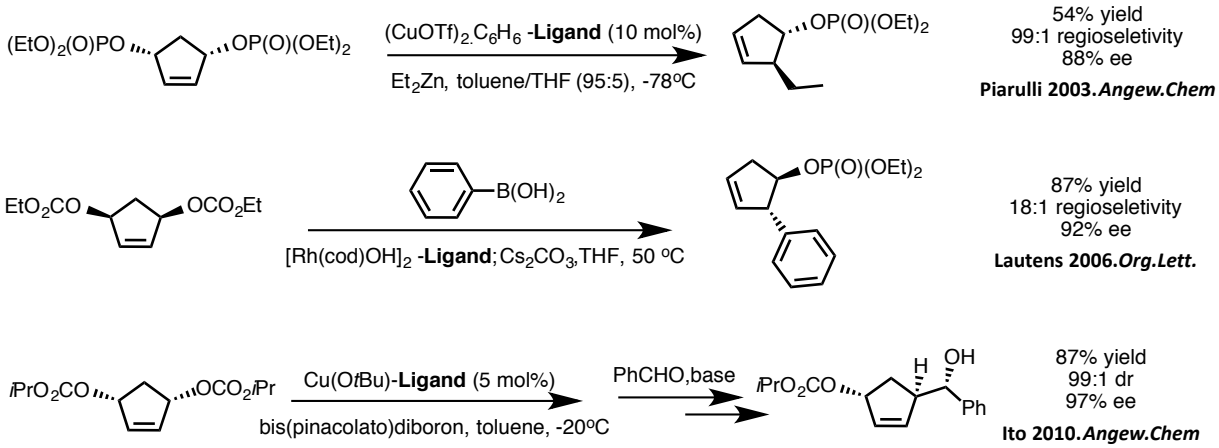
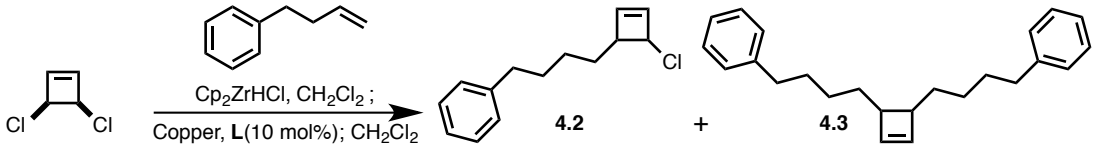


Figure 4.6 | Desymmetrization of *meso*-cyclic allylic substrates by non-stabilized nucleophiles

Based on our previous work employing organozirconium reagents in asymmetric catalysis [9, 10, 11], we present the study of a Cu-catalyzed desymmetrization of *meso*-cyclic allylic substrates using this system. The initial experiments were performed using the commercially available *cis*-3,4-dichlorocyclobutene and 4-phenyl-1-butene catalyzed by CuI and phosphoramidite ligands (Table **4.2**, entry 1 and 2) [11]. However, after stirring overnight at room temperature, there was only unreacted starting material observed by crude NMR. We then explored a set of different amine substituted phosphoramidite ligands, and no product was obtained (Table **4.2**, entry 3-5) [22]. Increasing the equivalents of organozirconium reagent used in reaction was also unsuccessful (Table **4.2**, entry 6), hence the strategy was changed and copper sources were investigated. A wide range of different copper sources were studied until we found CuTC and

$CuBr.SMe_2$ gave moderate yields of product **4.2**. Attempting to improve the yield, we further varied the reaction conditions by increasing the reaction time and temperature.

Table 4.2l Selected desymmetrization experiments of *cis*-3,4-dichlorocyclobutene [a]



Entry	Copper source	Ligand	4.2, yield(%)	4.2, *cis/trans*	4.2, ee(%)	4.3, yield(%)
1	CuI	**L1**	Trace	_	_	ND [e]
2	CuI	**L2**	Trace	_	_	ND
3	CuI	**L3**	Trace	_	_	ND
4	CuI	**L4**	Trace	_	_	ND
5	CuI	**L5**	Trace	_	_	ND
6 [b]	CuI	**L2**	Trace	_	_	ND
7	CuCl/ AgOTf	**L2**	Trace	_	_	ND
8	$(CuI)_4 \cdot 3SMe_2$	**L2**	Trace	_	_	ND
9	CuBr	**L2**	~20	99:1	0	ND
10	CuCl	**L2**	~30	99:1	0	ND
11	CuTC	**L2**	~30	99:1	0	ND
12 [b]	CuTC	**L2**	~50	99:1	0	ND
13 [b],[c]	CuTC	**L2**	~60	99:1	0	ND
14 [b],[d]	CuTC	**L2**	~40	99:1	0	ND
15	$CuBr.SMe_2$	**L2**	~50	99:1	0	ND
16	$CuBr.SMe_2$	**L6**	~40	99:1	9	ND
17	$CuBr.SMe_2$	**L7**	Trace	_	_	ND
18	$CuBr.SMe_2$	**L8**	~60	99:1	9	ND
19	$CuBr.SMe_2$	**L9**	Trace	_	_	ND
20	$CuBr.SMe_2$	**L10**	Trace	_	_	ND

[a] Reaction screening: reactions were performed for the desymmetrization of *cis*-3,4-dichlorocyclobutene under different conditions: *cis*-3,4-dichlorocyclobutene (1 equiv.), 4-phenyl-1-butene (2.5 equiv.), Cp_2ZrHCl (2 equiv.), Copper source (10 mol%), Ligand (10 mol%); Yields were estimated by NMR analysis; The enantiomeric excess (e.e.) was determined by HPLC.
[b] Reaction condition: 4-phenyl-1-butene (5 equiv.), Cp_2ZrHCl (4 equiv.), Copper (20 mol%), Ligand (20 mol%).
[c] Reaction condition: reaction was stirred for 48 hours.
[d] Reaction condition: reaction was refluxed overnight.
[e] ND refers to product was not detected.

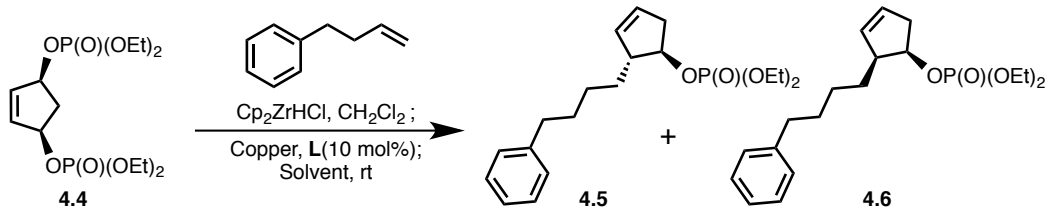
Despite the yield did improve, the enantiomeric excess of desired product keeps unobserved. This led us to question whether a different catalyst system is necessary to induce enantioselectivity in the reaction. Using $CuBr.SMe_2$ as a copper source, a variety of ligands bearing different backbones were tested (Table **4.2**, entry 16-20). Even though trace of enantioselectivity was observed when ligands **L6** and **L8** were used, in consideration of the difficulty and complexity of the synthesis of further modified derivatives, we instead decided

to look at other possible *meso*- cyclic allylic substrates. It is also interesting to note that among all these experiments no product **4.3** was observed, despite the presence of excess alkylzirconium reagent, and product **4.2** formed almost exclusively as the *cis* isomer.

We then considered 3,5-dichlorocyclopentene as a reaction substrate [11]. However, the preparation of 3,5-dichlorocyclopentene proved to be much more challenging than initially expected. After several attempts, we were unable to isolate the desired *meso*-cyclic allylic dichloride pure. We then turned our attention to the more stable *meso*-cyclic allylic bis (diethyl) phosphates.

We first used the best conditions previously found in the enantioselective AAA reactions with an allylic chloride (See **Chapter 2**) and allylic phosphate system (See **Chapter 3**); CuI with **L2** in CH_2Cl_2 and CuI with **L1** in $CHCl_3$ (Table **4.3**, entry 1,2). C*is* **4.6** was obtained as the major product (Table **4.3**, entry 1). Despite the low enantioselectivity, it was an interesting result as there is no enantioselective desymmetrization protocol to produce this *cis*-structure product [31]. The effect of the copper source was then examined. Interestingly, we did observe the copper (II) source again gave moderate yield and enantioselectivity of desired product in this system (Table **4.3**, entry 6). The initial exploration revealed that Cu(OTf) is the best copper source in terms of the enantioselectivity. We also observed that the nature of the solvent plays an important role in the reaction outcome, with CH_2Cl_2 giving the best results (Table **4.3**, entry 7-10). A set of phosphoramidite ligands was tested, and a strong match/mismatch effect was found between the absolute configuration of the BINOL moiety and the amine. (Table **4.3**, entry 7&15; entry 11&18). Ligand **L15** provided the highest enantioselectivity of 81% (Table **4.3**, entry 17).

Table 4.3l Selected desymmetrization experiments of *cis*-cyclic allylic bisdiethyl phosphate[a]



Entry	Solvent	Copper source	Ligand	Yield(%)	4.5 : 4.6	4.5, ee(%)	4.6, ee(%)
1[b]	CH_2Cl_2	CuI	**L2**	42	22:78	15	-3
2	$CHCl_3$	CuI	**L1**	46	95:5	5	_
3	CH_2Cl_2	Cu(OAc)	**L1**	<30	_	9	_
4	CH_2Cl_2	CuI	**L1**	>80	95:5	0	_
5	CH_2Cl_2	$CuBr.SMe_2$	**L1**	< 20	_	_	_
6	CH_2Cl_2	$Cu(OTf)_2$	**L1**	40	95:5	69	_
7	CH_2Cl_2	CuCl/ AgOTf	**L1**	60	97:3	70	_
8	Et_2O	CuCl/ AgOTf	**L1**	_	_	_	_
9	Toluene	CuCl/ AgOTf	**L1**	Trace	_	_	_
10	$CHCl_3$	CuCl/ AgOTf	**L1**	60	95:5	30	_
11	CH_2Cl_2	CuCl/ AgOTf	**L2**	60	97:3	72	_
12	CH_2Cl_2	CuCl/ AgOTf	**L3**	_	_	_	_
13	CH_2Cl_2	CuCl/ AgOTf	**L5**	70	97:3	67	_
14	CH_2Cl_2	CuCl/ AgOTf	**L12**	40	97:3	55	_
15	CH_2Cl_2	CuCl/ AgOTf	**L13**	< 20	_	57	_
16	CH_2Cl_2	CuCl/ AgOTf	**L14**	< 20	_	51	_
17	CH_2Cl_2	CuCl/ AgOTf	**L15**	30	95:5	81	_
18	CH_2Cl_2	CuCl/ AgOTf	**L16**	< 20	_	55	_
19	CH_2Cl_2	$Cu(NCCH_3)_4.\ CF_3SO_3$	**L15**	70	97:3	77	_
20	CH_2Cl_2	$(CF_3SO_3Cu)_2.\ C_6H_5CH_3$	**L15**	80	97:3	74	_
21	CH_2Cl_2	CuTC	**L15**	80	97:3	0	_
22	CH_2Cl_2	CuCl/ $AgNTf_2$	**L15**	80	97:3	81	_
23	CH_2Cl_2	CuCl/ AgOTs	**L15**	_	_	_	_
24	CH_2Cl_2	CuCl/ AgOMs	**L15**	< 20	_	21	_
25	CH_2Cl_2	$CuCl/AgClO_4$	**L15**	40	97:3	79	_
26	CH_2Cl_2	CuCl/ $AgBF_4$	**L15**	_	_	_	_
27	CH_2Cl_2	CuCl/ $AgCO_2CF_2CF_2CF_3$	**L15**	_	_	_	_
28	CH_2Cl_2	CuCl/ $AgNTf_2$	**L17**	60	97:3	75	_
29	CH_2Cl_2	CuCl/ $AgNTf_2$	**L18**	80	97:3	85	_
30	CH_2Cl_2	CuCl/ $AgNTf_2$	**L19**	70	97:3	81	_
31	CH_2Cl_2	CuCl/ $AgNTf_2$	**L20**	80	97:3	75	_
32	CH_2Cl_2	CuCl/ $AgNTf_2$	**L21**	60	97:3	64	_
33	$CHCl_3$	CuCl/ $AgNTf_2$	**L18**	80	97:3	65	_
34	Et_2O	CuCl/ $AgNTf_2$	**L18**	40	97:3	64	_

[a] Reaction screening: reactions were performed for the desymmetrization of *cis*-cyclic allylic bisdiethyl phosphate under different conditions: *cis*-cyclic allylic bisdiethyl phosphate (1 equiv.), 4-phenyl-1-butene (2.5 equiv.), Cp_2ZrHCl (2 equiv.), Copper source (10 mol%), Ligand (10 mol%); Yields were estimated by NMR analysis; The enantiomeric excess (e.e.) was determined by HPLC.
[b] Reaction condition: *cis*-cyclic allylic bisdiethyl phosphate (1 equiv.), 4-phenyl-1-butene (2.5 equiv.), Cp_2ZrHCl (2 equiv.), Copper source (10 mol%), Ligand (10 mol%), TMSCl (1 equiv.).

We then compared the performance of different copper sources with ligand **L15** (Table **4.3**, entry 19-27). Copper bis(trifluoromethanesulfonyl) imide gave the best yield and enantioselectivity of the desired product in 80% and 81% respectively (Table **4.3**, entry 22)[35].

We also explored analogs of ligand **L15**, which contained different modifications (Table **4.3**, entry 28-32). To our delight, the modified ligand **L18** gave an improved enantioselectivity of 85% with approximately 80% yield of desired product **4.5** in predominantly the *trans* form. The solvent screen of the optimal catalysis conditions indicated CH_2Cl_2 is still the best solvent for this desymmetrization system (Table **4.3**, entry 33-34).

Up to now, the conditions provide 85% enantiomeric excess and 97:3 *trans* selectivity of product **4.5** (Fig. **4.7**).

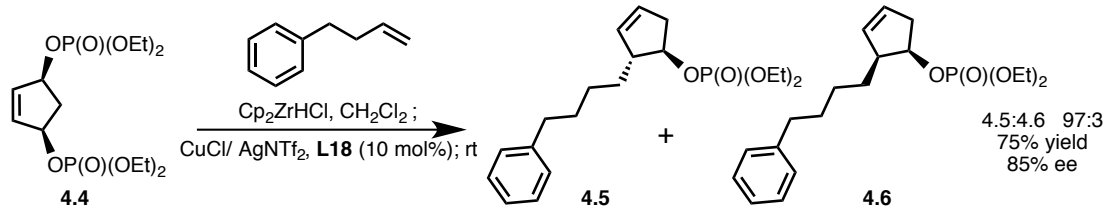


Figure 4.7 | Desymmetrization of *meso*-cyclic allylic substrates by non-stabilized nucleophiles via Cu-catalyzed AAA

4.5 Future Work

Developing a desymmetrization of *meso*-cyclic allylic substrates by non-stabilized nucleophiles via Cu-catalyzed AAA has proven to be an interesting challenge. The work carried out will complement the area of desymmetrization chemistry, but it will also provide more powerful and diverse methodologies for asymmetric bond formation in an efficient and practical synthetic manner. Future work will involve further study to develop a robust efficient protocol, with a focus on improving enantioselectivity further and expanding the alkene scope. Derivatives of the *meso*-cyclic allylic substrates could also be used in this chemistry, with potential applications in the synthesis of bioactive or natural products/ precursors.

4.6 Conclusions

In conclusion, here we described a thorough study of Cu-catalyzed enantioselective desymmetrization of *meso* compounds via organozirconium reagents. Even though the attempt of the asymmetric ring-opening of oxabicyclic alkenes turns out to be challenging with the alkylzirconium species, the insight might motivate further study involving other nucleophiles/ reagents/substrates in this area. Moreover, a new desymmetrization of *meso*-cyclic allylic substrates via Cu-catalyzed asymmetric allylic alkylation has been established, offering a major *trans* product with good yield and enantiomeric excess. This protocol is complementary to existing methods of the non-stabilized nucleophiles cases. Previous work using organozirconium reagents has often provided a wide functional group tolerance and scope, and with further work this could be achieved with the desymmetrization protocol. We are looking forward to further work in this area as well as its potential applications.

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35. The triflate anion owes its stability to resonance stabilization, which causes the negative charge to be spread over the three oxygen atoms and sulfur atoms, an additional stabilization is achieved by the trifluoromethyl group as a strong electron-withdrawing group.

Chapter 5

Experimental Section

5.1 General Information

Procedures using oxygen- and/or moisture-sensitive materials were performed with anhydrous solvents (vide infra) under an atmosphere of anhydrous argon in flame-dried flasks, using standard Schlenk techniques. Analytical thin-layer chromatography was performed on precoated glass-backed plates (Silica Gel 60 F254; Merck), and visualised using a combination of UV light (254 nm) and aqueous ceric ammonium molybdate (CAM), aqueous basic potassium permanganate stains or vanillin solution. Flash column chromatography was carried out using Apollo Scientific silica gel 60 (0.040 – 0.063 nm), Merck 60 Å silica gel, VWR (40-63 μm) silica gel and Sigma Aldrich silica gel. Pressure was applied at the column head via hand bellows or a flow of nitrogen with the solvent system used in parentheses.

Reactions at 0 °C were performed using an ice-water bath, covered with cotton and foil if overnight stirring is needed. Other temperatures were obtained using a Julabo FT902 immersion cooler or the heating plate of the stirrer.

Unless stated otherwise, solution NMR spectra were recorded at room temperature; ^{1}H and ^{13}C NMR experiments were carried out using Bruker DPX-200 (200/50 MHz), AVN-400 (400/100 MHz), DQX-400 (400/100 MHz) or AVC-500 (500/125 MHz) spectrometers. Chemical shifts are reported in ppm from the residual solvent peak. Chemical shifts (δ) are given in ppm and coupling constants (J) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Labels H and H' refer to diastereotopic protons attached to the same carbon and impart no stereochemical information. Assignments were made with the assistance of gCOSY, DEPT-135, gHSQC and gHMBC or gHMQC NMR spectra.

The distillation of certain products was performed at the related temperature by Buchi Glass Oven B-585 Kugelrohr (100V-230 V, 50/60 Hz).

Chiral HPLC separations were achieved using an Agilent 1230 Infinity series normal phase HPLC unit and HP Chemstation software. Chiralpak® columns (250 × 4.6 mm), fitted with matching Chiralpak® Guard Cartridges (10 × 4 mm), were used as specified in the text. Solvents used were of HPLC grade (Fisher Scientific, Sigma Alrich or Rathburn); all eluent systems were isocratic.

Chiral GC measurements were conducted on a HP6890 (H_2 as vector gas) or HP6850 (H_2 as vector gas) with the stated column in the characterization. Temperature programs are described as follows: initial temperature (°C) - initial time (min) - temperature gradient (°C/min) – [certain temperature – holding time - temperature gradient (°C/min)]- final temperature (°C) – holding time. Retention times (RT) are given in min.

Low-resolution mass spectra were recorded using a Walters LCT premier XE. High-resolution mass spectra (EI and ESI) were recorded using a Bruker MicroTOF spectrometer by the internal service at the University of Oxford.

Infrared measurements (neat, thin film) were carried out using a Bruker Tensor 27 FT-IR with internal calibration in the range 600-4000 cm^{-1}.

Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 25°C in a 10 cm cell in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} $deg.cm^2\,g^{-1}$ (concentration c given as g/100 mL).

5.2 Chemicals

Dry $CHCl_3$, THF, CH_2Cl_2, Et_2O, PhMe, benzene, hexane, pentane, DME, acetonitrile and 1,2-dichloroethane were collected fresh from an mBraun SPS-800 solvent purification system having been passed through anhydrous alumina columns. Dry *tert*-butyl methyl ether and 2-Me-THF were purchased from Acros with an AcroSeal® respectively. All other dry solvents

used were dried over 3 Å molecular sieves and stored under argon. All other solvents were used as purchased from Sigma Alrich, Rathburn or Fisher Scientific.

Unless stated otherwise, commercially available reagents were purchased from Sigma-Aldrich, Fisher Scientific, Apollo Scientific, Acros Organics, Strem Chemicals, Alfa Aesar or TCI UK and were used without purification. Petroleum ether refers to light petroleum boiling in the range 30-40 °C. Deuterated solvents were purchased from Sigma-Aldrich (CD_2Cl_2, $CDCl_3$).

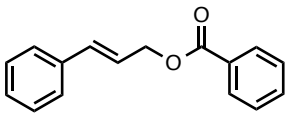
Schwartz reagent was prepared according to the literature procedure [1] from Cp_2ZrCl_2 provided by Alfa Aesar or Strem Chemicals.

5.3 Non-stabilized nucleophiles in Cu-catalyzed dynamic kinetic asymmetric allylic alkylation:

General synthesis of linear allylic substrates (2.3-2.12):

To a solution of cinnamyl alcohol (1 equiv.) in dichloromethane (15 ml) was added DMAP (1.2 equiv.) and triethyl amine (1.2 equiv.), followed by cautiously and slowly addition of the responding electrophile (1.2 equiv.). Under inert argon atmosphere, the reaction mixture was stirred (60 mins) at 0 °C followed by 2 hours at room temperature. A white precipitate was usually observed at this stage. H_2O (10 ml) was added and the reaction was washed with H_2O (20 ml), HCl (20 ml, 1 M), $NaHCO_3$ (sat. 20 ml), followed by brine (20 ml). The organic layer was isolated, dried ($MgSO_4$) and the solvent removed in vacuum. The resultant oil was purified by column chromatography using 10% ethyl acetate in petrol to provide the responding product.

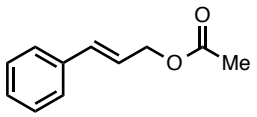
Cinnamyl benzoate (2.3)



^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.12 (dd, J = 8.2,1.2, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.48-7.26 (m, 7H), 6.77 (d, J = 15.8 Hz, 1H), 6.43 (dt, J = 15.8 Hz, 6.4, 1H), 5.01 (dd, J = 6.4, 1.3 Hz, 2H) [2];

^{13}C NMR (100 MHz, $CDCl_3$): δ =166.3, 136.1, 134.2, 132.9, 130.1, 129.6, 128.5, 128.3, 128.0, 126.6, 123.2, 56.4.

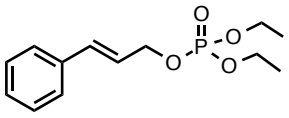
Cinnamyl acetate (2.4)



^{1}H NMR (400 MHz, $CDCl_3$): δ= 2.04 (s, 3H), 4.68 (d, J = 6.4 Hz, 2H), 6.19–6.29 (m, 1H), 6.58 (d, J = 16.2 Hz, 1H), 7.21–7.36 (m, 5H) [3];

^{13}C NMR (100 MHz, $CDCl_3$): δ =170.8, 136.2, 134.2, 128.6, 128.0, 126.6, 123.1, 65.0, 21.0;

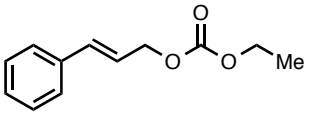
Cinnamyl diethyl phosphate (2.5)



^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.34 (t, J = 7.2 Hz, 3 H), 4.07-4.17 (m, 4 H), 4.70 (ddd, J = 8.4, 6.2, 1.2 Hz, 2 H), 6.30 (dt, J = 15.6, 6.2 Hz, 1 H), 6.68 (d, J = 15.6 Hz, 1 H), 7.23-7.28 (m, 1 H), 7.29-7.34 (m, 2 H), 7.37- 7.40 (m, 2 H) [4];

^{13}C NMR (100 MHz, $CDCl_3$): δ =16.2, 63.8, 67.9, 123.6, 126.7, 128.2, 128.6, 133.9, 136.0.

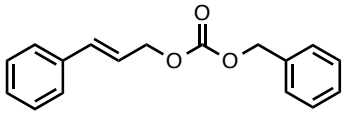
Cinnamyl ethyl carbonate (2.6)



^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.27 (t, *J* = 7.2 Hz, 3H), 4.17 (q, *J* = 7.2 Hz, 2H), 4.73 (dd, *J* = 6.5, 1.3 Hz, 2 H), 6.25–6.35 (m, 1H), 6.63 (d, *J* = 15.8 Hz, 1 H), 7.19–7.35 (m, 5H) [5];

^{13}C NMR (100 MHz, $CDCl_3$): δ =14.2, 64.4, 68.1, 122.4, 126.6, 128.1, 128.5, 134.6, 136.0, 155.0.

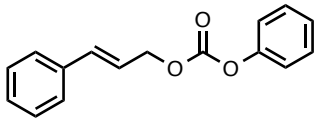
Cinnamyl benzyl carbonate (2.7)



^{1}H NMR (400 MHz, $CDCl_3$): δ= 4.78 (dd, *J* = 6.4, 1.2 Hz, 2H), 5.17 (s, 2 H), 6.26–6.30 (m, 1H), 6.67 (d, *J* = 16.0 Hz, 1H), 7.22–7.41 (m, 10 H) [6];

^{13}C NMR (100 MHz, $CDCl_3$): δ =68.5, 69.8, 122.4, 126.7, 128.2, 128.3, 128.5, 128.6, 134.7, 135.3, 135.9, 154.9.

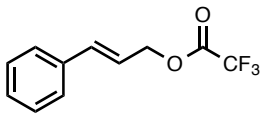
Cinnamyl phenyl carbonate (2.8)



^{1}H NMR (400 MHz, $CDCl_3$): δ= 4.89 (dd, *J* = 6.5, 1.0 Hz, 2H), 6.35 (dt, *J* = 16.0, 6.5 Hz, 1H), 6.75 (d, *J* = 16.0 Hz, 1H), 7.16-7.44 (m, 10H) [7];

^{13}C NMR (100 MHz, $CDCl_3$): δ =69.0, 120.9,121.8, 125.4, 126.7, 128.2, 128.6, 129.4, 135.3, 135.8, 151.1, 153.5.

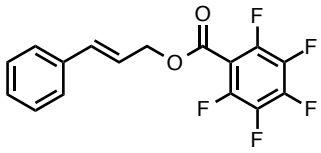
Cinnamyl 2,2,2-trifluoroacetate (2.9)



^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.45–7.43 (m, 2H), 7.39–7.31 (m, 3H), 6.78 (d, 1H), 6.31 (m, 1H), 5.00 (dd, 2H) [8];

^{13}C NMR (100 MHz, $CDCl_3$): δ =157.6, 137.33, 137.32, 135.6, 129.0, 127.1, 120.3, 114.7, 68.8.

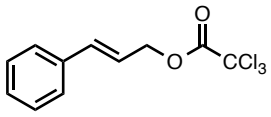
Cinnamyl 2,3,4,5,6-pentafluorobenzoate (2.10)



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42-7.45 (m, 2 H), 7.29 - 7.39 (m, 3 H), 6.78 (d, *J*=16.1 Hz, 1 H), 6.37 (dt, *J*=15.8, 6.5 Hz, 1 H), 5.05 (dd, *J*=6.5, 1.3 Hz, 2 H) [9];

^{13}C NMR (100 MHz, $CDCl_3$): 158.9, 145.4 (dm, *J*=258.23 Hz), 143.1 (dm, *J*=259.69 Hz), 137.8 (dm, *J*=253.09 Hz), 135.7, 135.5, 128.5 (2 C), 128.4, 126.7 (2 C), 121.5, 108.1 (td, *J*=15.77, 3.67 Hz), 67.2.

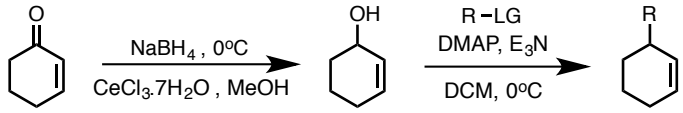
Cinnamyl 2,2,2-trichloroacetate (2.12)



^{1}H NMR (400 MHz, $CDCl_3$): δ= 4.99 (dd, *J* = 6.4, 1.0 Hz, 2H), 6.32 (dt, *J* = 16.1,6.4 Hz, 1H), 6.78 (d, *J* = 16.1 Hz, 1H), 7.28-7.43 (m, 5H) [10];

^{13}C NMR (100 MHz, $CDCl_3$): δ =157.6, 137.33, 137.32, 135.5, 129.0, 127.1, 120.3, 114.7, 68.7.

General synthesis of cyclic allylic substrates (2.13-2.18):



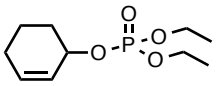
(a) In a 50 mL flame dried flask, 2-cyclohexenone (3.9 ml, 40 mmol, 1.0 eq) was added to a solution of $CeCl_3.7H_2O$ (15 g, 40 mmol, 1.0 eq) in MeOH (20 ml) under an argon atmosphere. After cooling to 0 ^oC in an ice-bath for around 15 min, $NaBH_4$ (1.52 g, 40 mmol, 1.0 eq) was added in portions over a period of 15 min. The ice-bath was left warm to room temperature and stirred for 3 h. The reaction was quenched with HCl (1 M, 20 ml), and the product was extracted with Et_2O (4×15 ml), washed with brine (20 ml), dried over $MgSO_4$, and evaporated under vacuum (300 mmbar, 50 ^oC) for 20 min to give pure product as a clear colorless oil (3.75 g, 38.4 mmol, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.60-2.11 (m, 6H), 5.22-5.28 (m, 1H), 5.65-5.70 (m, 1H), 5.94-5.96 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.8, 21.4, 28.3, 68.1, 125.7, 132.8.

(b) An appropriate electrophile (1.2 equiv.) was added to a solution of cyclohexen-1-ol (1 equiv.) combined with DMAP (1.2 equiv.) and triethyl amine (1.2 equiv.), in CH_2Cl_2 (10 ml) at 0 ºC under an argon atmosphere. And the mixture stirred for 1 h at 0 ºC, then overnight at room temperature. The mixture was diluted with ether (50 ml) and washed with hydrochloric acid (3 × 10 ml, 1 M), brine (1 × 10 ml) and saturated sodium bicarbonate (1 × 10 ml) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the product purified by flash chromatography using petrol and ethyl acetate as solvent.

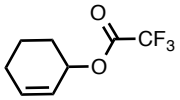
Cyclohex-2-enyl diethyl phosphate (2.13)



^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.28 (t, *J*=7.0 Hz, 6H), 1.53–1.60 (m, 1H), 1.71–1.75 (m, 1H), 1.80–2.06 (m, 4H), 4.03 (m, 2H), 4.07 (m, 2H), 4.82 (m, 1H), 5.74 (dd, *J*=10.0, 1.5 Hz, 1H), 5.88–5.92 (m, 1H) [11];

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0,18.3, 24.6, 29.8, 63.4, 72.1, 126.2, 132.6.

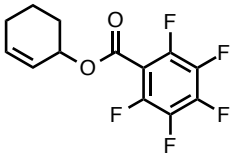
Cyclohex-2-enyl 2,2,2-trifluoroacetate (2.14)



^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.71-6.13 (2 H, m), 5.30-5.48 (1 H, m), 1.52-2.36 (6 H, m) [12];

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2, 24.8, 27.6, 73.8, 90.3, 123.2, 135.1, 161.5

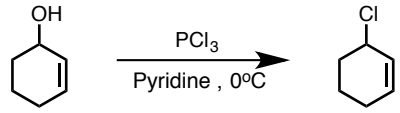
Cyclohex-2-enyl 2,3,4,5,6-pentafluorobenzoate (2.15)



^{1}H NMR (400 MHz, $CDCl_3$): δ= 6.13-5.98 (m, 1H), 5.83 (d, J = 9.9 Hz, 1H), 5.55 (s, 1H), 2.22-1.98 (m, 3H), 1.95-1.63 (m, 4H) [13];

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7, 146.5, 144.3, 143.9, 141.7, 138.9, 136.4, 134.2, 133.9, 124.2, 108.9, 71.1, 28.1, 24.8, 18.4

3-chlorocyclohexene (2.17)

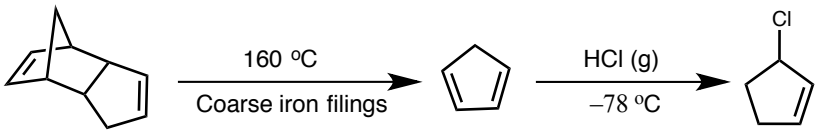


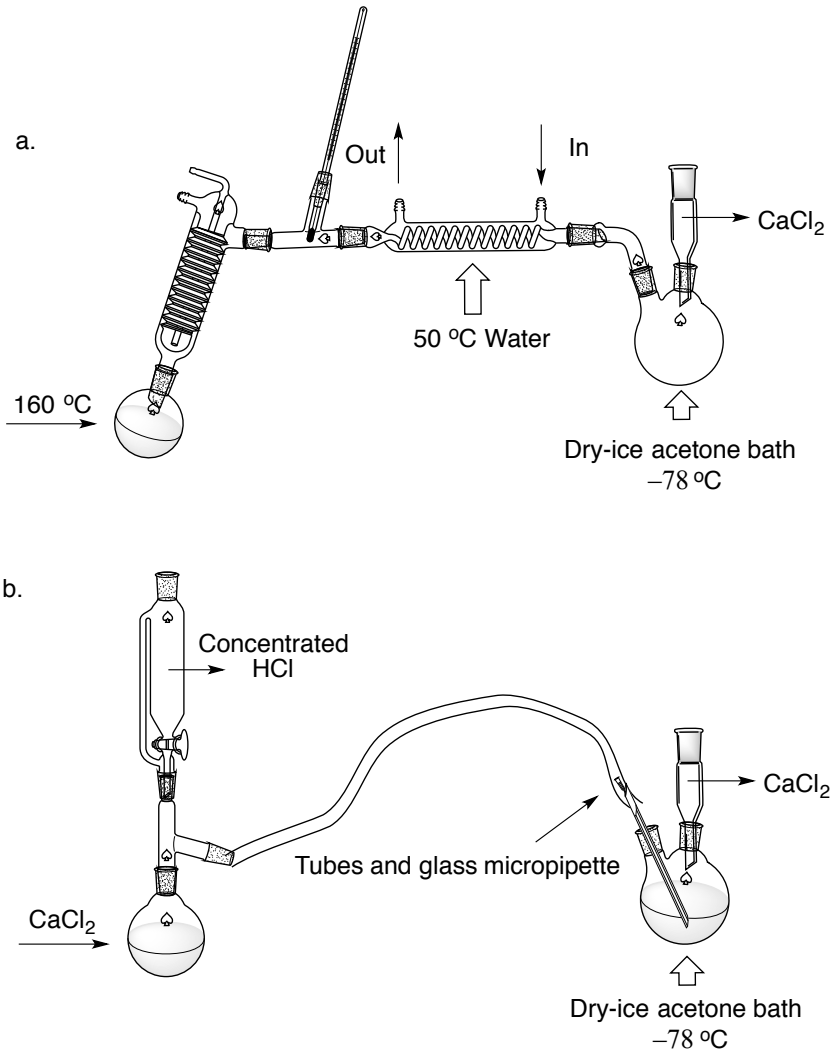
In a 10 mL flame dried flask, fresh distilled phosphorus trichloride (1.3 mL, 14.1 mmol, 0.37 eq) was added under an argon atmosphere. After cooling to 0 oC in an ice-bath for around 15 min, a mixture of cyclohex-2-enol (3.75 g, 38 mmol, 1 eq) and pyridine (0.31 mL, 3.8 mmol, 0.1 eq) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirring was continued overnight. Then the organic (top) layer was then removed by pipette and purified by Kugelrohr distillation (200 mmbar, 85 ^{o}C) for 15 min to remove pyridine. Further distillation (60 mmbar, 110 ^{o}C) for 1 h gave the pure product (3.51 g, 30.1 mmol, 79% yield) as colorless oil [14].

^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.84-5.90 (m, 1H), 5.80-5.86 (m, 1H), 4.60-4.62(m, 1H), 1.96-2.17(m, 4H), 1.84-1.95 (m, 1H), 1.59-1.71 (m, 1H).;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 24.7, 32.4, 55.6, 128.1, 131.3.

3-chlorocyclopentene (2.18)





(a) In a flame-dried distillation system (Scheme **a**), dicyclopentadiene (200 ml, 195 g) and coarse iron filings (2 g) were added to a 500mL flask. The outlet of the Friedrichs condenser is connected to a simple distilling head fitted with a thermometer and attached to an efficient water-cooled condenser. The collection flask was immersed into an acetone/dry ice bath and a $CaCl_2$ tube was connected to the top. The flask containing dicyclopentadiene was heated to 160 ºC. Cyclopentadiene distilled off at 42.5 ºC and dicyclopentadiene refluxes from the cold-finger (Friedrichs) condenser. After two-thirds of the dicyclopentadiene had been pyrolyzed, the residue is discarded according to the literature procedure.

(b) The flask containing cyclopentadiene was weighed and connected to the right hand side of the HCl gas-producing facility (Scheme **b**) and cooled to –78 ºC . Using a slow addition funnel, concentrated HCl was added dropwise to a flask containing half flask dry solid CaCl2. During this operation the cyclopentadiene-containing flask was swirled to ensure good mixing, and weighed quickly every 2 min in order to determine the amount of hydrogen chloride that has been added. The addition is stopped when the weight of the flask indicated that the reaction reached 86% theoretical yield based on weight. The crude was purified using a Kugelrohr (22 mmbar, 22 ^{o}C, about 15 min); further kugelrohr distillation (5 mmbar, 22 ^{o}C, for about 30 min) provided pure product as a colorless oil (8.7 g). The pure product should be stored in a –78 ^{o}C freezer [15].

^{1}H NMR (400 MHz, $CDCl_3$): δ= 6.02-6.07 (m, 1H), 5.85-5.93 (m, 1H), 5.02-5.06 (m, 1H), 2.52-2.74 (m, 1H), 2.12-2.47 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.0, 34.6, 65.6, 132.1, 136.1

General synthesis of products

Procedure used in the synthesis of racemic products

In a 5ml flame dried flask, Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkene (1.0 mmol, 2.5 eq) in CH_2Cl_2 (2.0 ml) under an argon atmosphere. After stirring for 20 to 40 min, CuBr·Me_2S (82 mg, 0.40 mmol 1.0 eq), was added to clear solution and the resulting black mixture was allowed to stir for an additional 10 min before a cyclic allylchloride (0.40 mmol, 1.0 eq) was added via microsyringe over about 1 min. Stirring at room temperature was continued arbitrarily overnight before the reaction was diluted and quenched by addition of petrol (ca 3 ml) and then NH_4Cl (1M aq., ca 1.5 ml). The mixture was partitioned between water and petrol and the aqueous phase extracted with petrol (3 × 10 ml). The combined organic phase was washed with $NaHCO_3$ (aq. sat. ca 10 ml), dried

($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Flash column chromatography of the residue (EtOAc/petrol; SiO_2) gave the desired cyclic allylic product. In most cases, Kugelrohr distillation was used to remove excess starting alkene.

Procedure used in the synthesis of asymmetric products

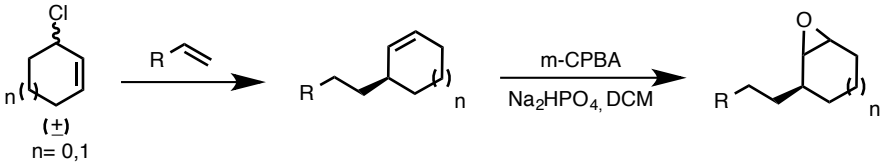
In a 5 mL flame dried flask, CuI (7.7 mg, 0.04 mmol, 0.1 eq) and the phosphoramidite ligand (21.2 mg, 0.04 mmol, 0.1 eq) were dissolved in $CHCl_3$ (0.8 ml) under an argon atmosphere and allowed to stir for 1 h at room temperature. In another flask, Cp_2ZrHCl (206.3 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of corresponding alkene (1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 ml) under an argon atmosphere. After stirring for 20 to 40 min, the resulting clear solution was transferred via syringe over about 1 min to the stirred solution containing the copper and ligand under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before the cyclic allylchloride (0.40 mmol, 1.0 eq) was added dropwise *via* microsyringe and the reaction was arbitrarity stirred overnight. Afterwards, the reaction mixture was diluted and quenched by addition of petrol (ca 3 ml) and then NH_4Cl (1 M aq., ca 1.5 ml). The mixture was partitioned between water and petrol and the aqueous phase extracted with petrol (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat. ca 10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Flash column chromatography of the residue (EtOAc/petrol; SiO_2) gave the desired cyclic allylic product. In most cases, Kugelrohr distillation was used to remove the excess of starting alkene.

Procedure used in selected optimization experiments

In a 5 mL flame dried flask, the copper reagent (0.02 mmol, 0.1 eq) and the phosphoramidite ligand (0.02 mmol, 0.1 eq) were dissolved in the selected solvent (0.4 ml) under an argon atmosphere and allowed to stir for 1 h at room temperature. In another flask, Cp_2ZrHCl (103

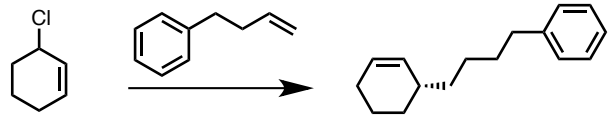
mg, 0.40 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 4-phenyl-1-butene (0.08 ml, 0.5 mmol, 2.5 eq) in CH_2Cl_2 (0.20 ml) under an argon atmosphere. After stirring for 20 min, the resulting clear yellow solution was transferred via syringe over about 1 min to the stirred solution containing the copper and ligand under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before 3-chlorocyclohexene (23.3 mg, 0.20 mmol, 1.00 eq) was added dropwise *via* a microsyringe. The reaction was stirred at room temperature arbitrarily for overnight before the reaction was diluted and quenched by addition of petrol (ca 3 ml) and then NH_4Cl (1 M aq., ca 1.5 ml). The mixture was partitioned between water and petrol and the aqueous phase extracted with petrol (3 × 10 ml). The combined organic phase was washed with $NaHCO_3$ (aq. sat. ca 10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. The enantiomeric excess was measured directly on the crude reaction products.

Derivatisation of products to the corresponding epoxides



In a 25 ml flame dried flask, the isolated product (1 eq) was dissolved in CH_2Cl_2 (6 ml, for 0.4 mmol scale reaction) under an argon atmosphere. m-CPBA (2 eq) and Na_2HPO_4 (3 eq) were added at room temperature and the reaction mixture was stirred arbitrarily for 2 h before being diluted and quenched by addition of Et_2O (10 ml) and an aqueous solution of saturated $Na_2S_2O_3$ (10 ml) . The organic layer was washed with NaOH (1 M aq., 3× 5ml), dried over Mg_2SO_4, filtered and concentrated under vacuum. The crude mixture of diastereoisomeric epoxides was directly analyzed by GC chromatography using a chiral non-racemic stationary phase [16].

(R)-(+)-4-(Cyclohex-2-en-1-yl)butyl)benzene (2.19)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)- **Ligand L1** (21.6 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 4-Phenyl-1-butene (0.15ml, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr (T = 110 °C and 55 mbar pressure) gave (R)-(–)-4-(cyclohex-2-en-1-yl) butyl) benzene (73.8 mg, 0.34 mmol) in 86% yield.

Enantiomeric excess of 93% was determined by HPLC [Chiralpak® IA; flow: 0.6 mL/min; hexane/i-PrOH: 99.9: 0.1; λ = 210 nm; major enantiomer t_R = 8.2 min; minor enantiomer t_R = 8.8 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.26 - 1.78 (m, 10 H), 1.99(m, 1 H), 2.07(m, 2 H), 2.62-2.67(m, 2 H), 5.58-5.62 (m, 1 H), 5.67-5.71 (m, 1 H), 7.20- 7.23 (m, 3 H), 7.28 - 7.31 (m, 2 H).

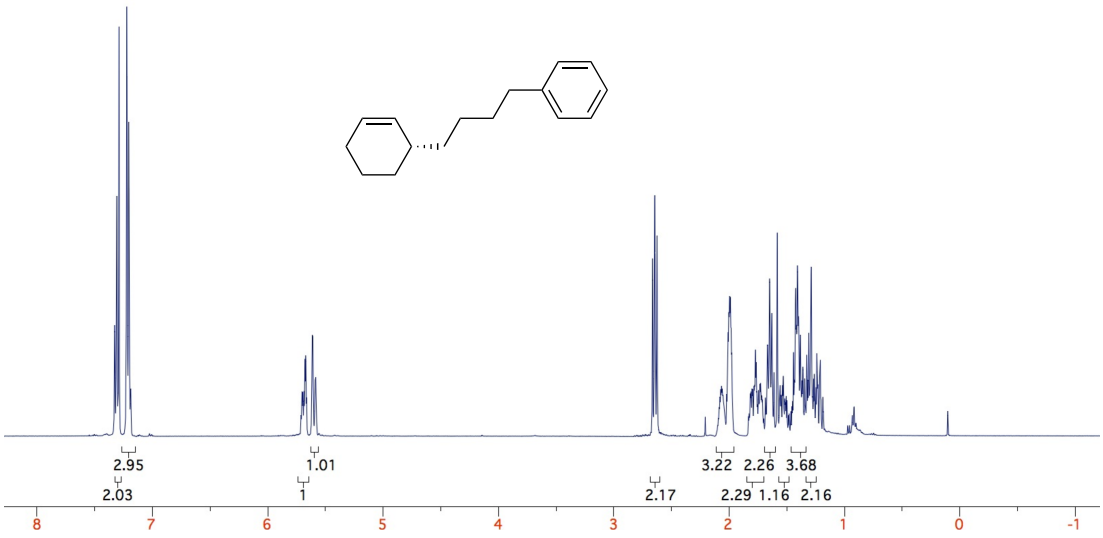
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 21.5, 25.4, 26.7, 29.1, 31.8, 35.1, 35.9, 36.2, 125.6, 126.7, 128.2, 128.4, 132.3, 142.9

HRMS (ESI) *m*/z calcd for $C_{16}H_{22}$ $[M]^+$: 214.1721, found: 214.1717.

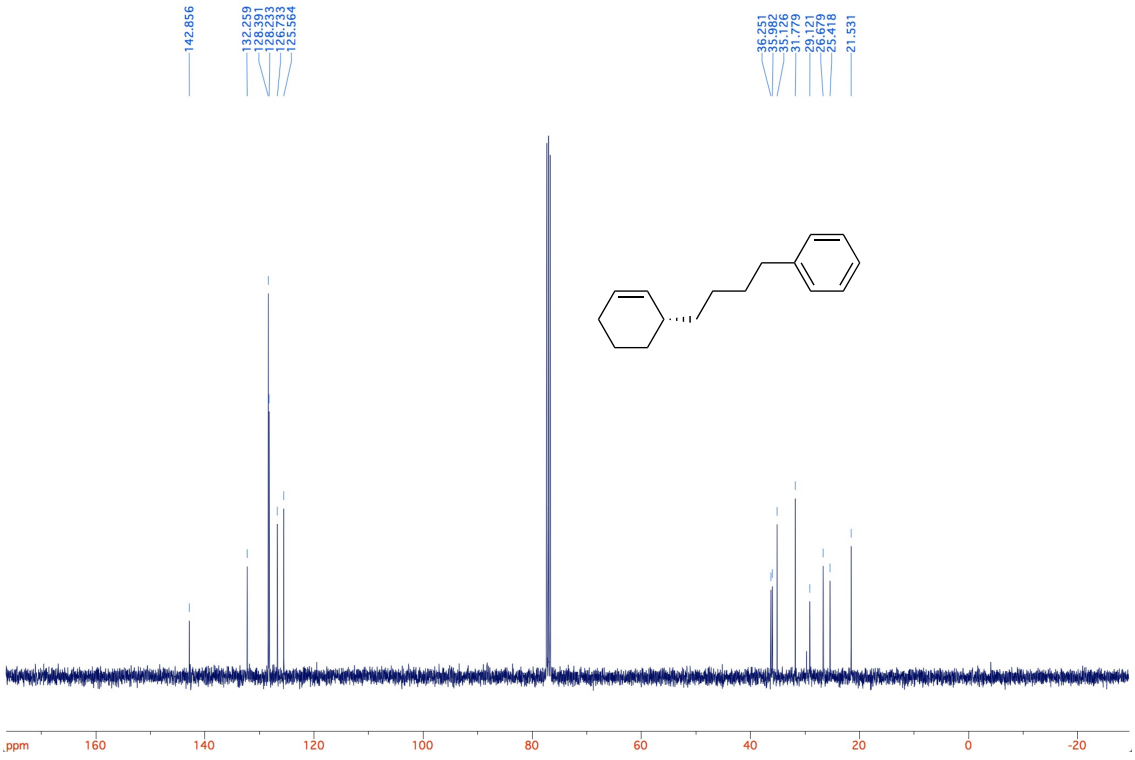
IR (ATR) ν (cm^{-1}, $CHCl_3$): 698, 1217, 1229, 1366,1454, 1739, 2855, 2926.

$[\alpha]^{20}_{589}$ = +11.8 (c=0.36 in $CHCl_3$, 93% ee).

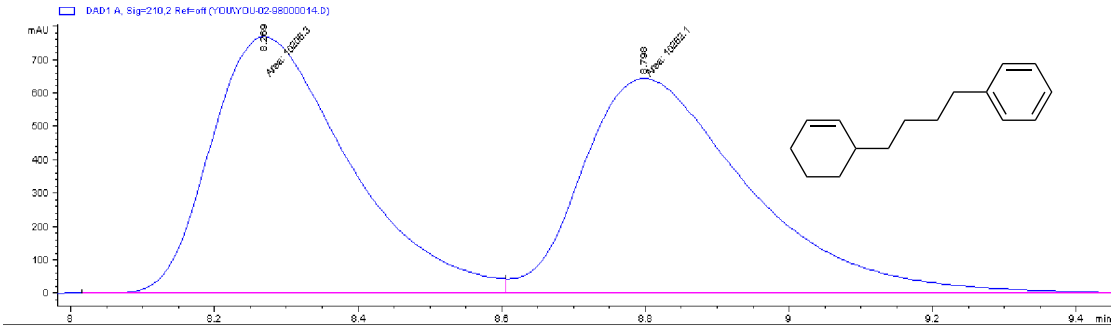
^{1}H NMR

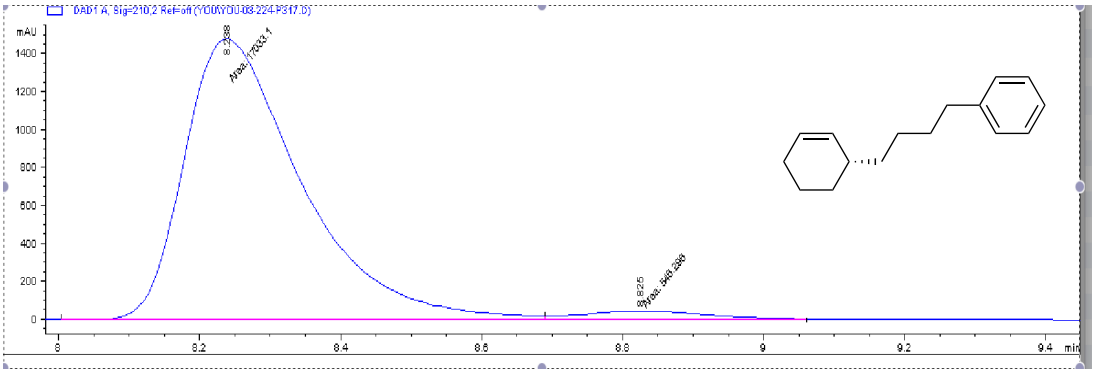


^{13}C NMR:

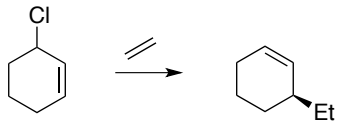

142.856
132.259
128.311
128.233
126.733
125.564
36.251
35.982
35.126
31.779
29.121
26.679
23.418
21.531
ppm
160
140
120
100
80
60
40
20
0
-20

HPLC trace:


DAD1 A, Sig=210,2 Ref=off (YOUYOU-02-98000014.D)
mAU
min


mAU
min

(S)-(–)-3-Ethylcyclohex-1-ene (2.20)



CuI (15.2 mg, 0.08 mmol, 0.10 eq), (*S*,*S*,*S*)-**Ligand L1** (43.2 mg, 0.08 mmol, 0.10 eq) and then $CHCl_3$ (1.6 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, Cp_2ZrHCl (412 mg, 1.60 mmol, 2.00 eq) and CH_2Cl_2 (0.8 mL) were added to another flame-dried flask, and smoothly stirred at room temperature. A balloon charged with ethylene is bubbled through the later solution for 3 min and the resulting mixture is then vigorously stirred at room temperature under the gaseous alkene atmosphere for 15 min; during this time a clear yellow solution developed, and the resulting organozirconium species is transferred to the copper-ligand solution using a syringe over about 1 minute. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully (the product is quite volatile) concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave (*S*)-(–)-3-ethylcyclohex-1-ene (58.9 mg, 0.54 mmol, 67% yield) as a clear colourless oil.

GC analysis of the crude mixture of epoxides derived from **2.20** indicated an enantiomeric excess of 94% (Hydrodex 6-TBDM, 60-100^{o}C at 5 ^{o}C/min, 110-170 ^{o}C at 20 ^{o}C/min, 10psi); major enantiomer t_R= 9.99, 11.82 min; minor enantiomer t_R = 10.14, 11.09 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 0.92 (t, *J*=7.46 Hz, 3 H), 1.13 - 1.43 (m, 3 H), 1.43 - 1.57 (m, 1 H) 1.65 - 1.84 (m, 2 H) 1.89 - 2.03 (m, 3 H) 5.56 - 5.64 (m, 1 H) 5.64 - 5.72 (m, 1 H).

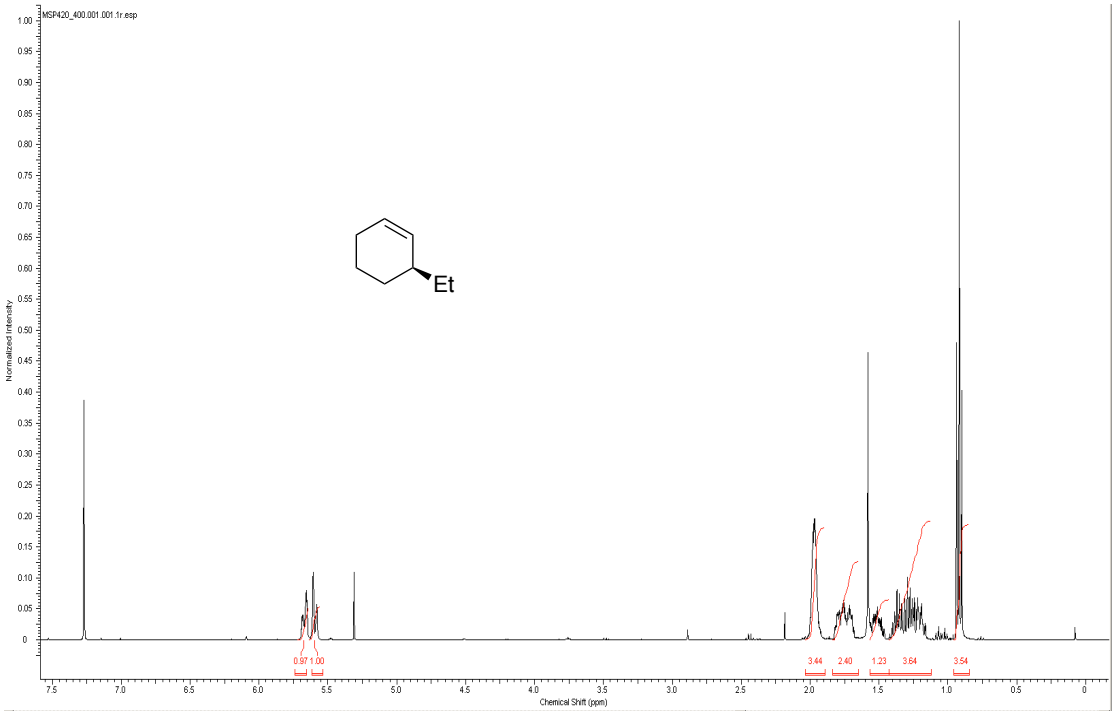
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 11.5, 21.6, 25.4, 28.6, 29.0, 36.8, 126.7, 132.1.

HRMS (ESI) *m*/*z* calcd for C_8H_{14} $[M]^+$: 110.1096, found: 110.0944.

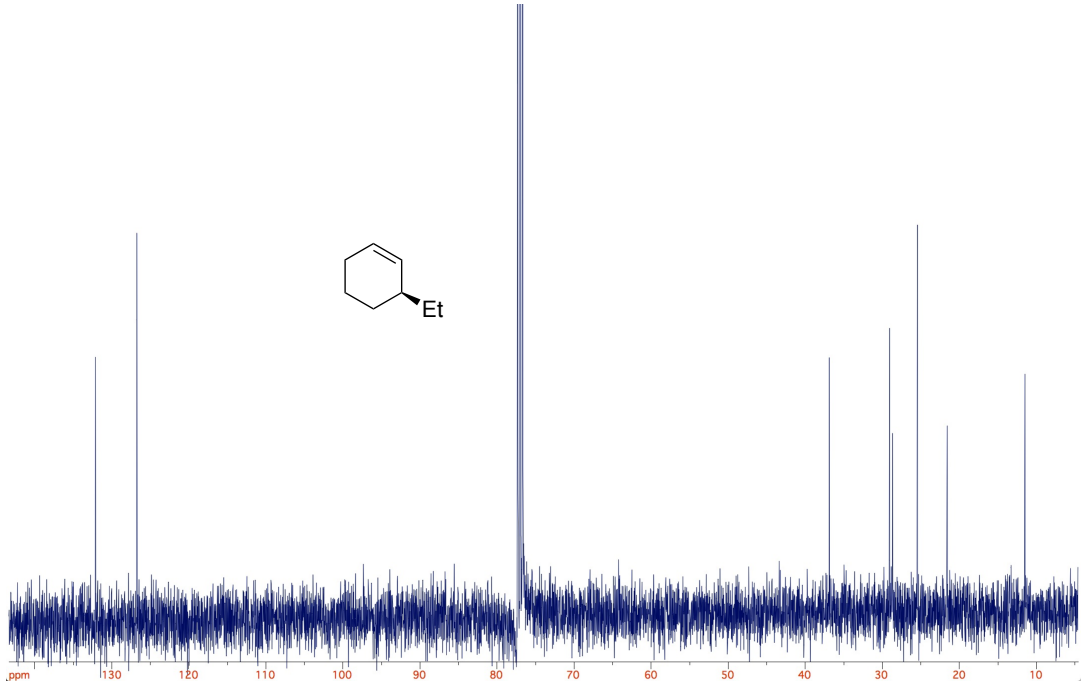
IR (ATR) ν (cm^{-1}): 2930, 2857, 1764, 1227.

$[\alpha]^{20}_{589}$ = –83.33 (*c* 0.04, $CHCl_3$) for 94% ee [lit. $[\alpha]^{20}_{589}$ = –83.34 (*c* 1.00, $CHCl_3$)].

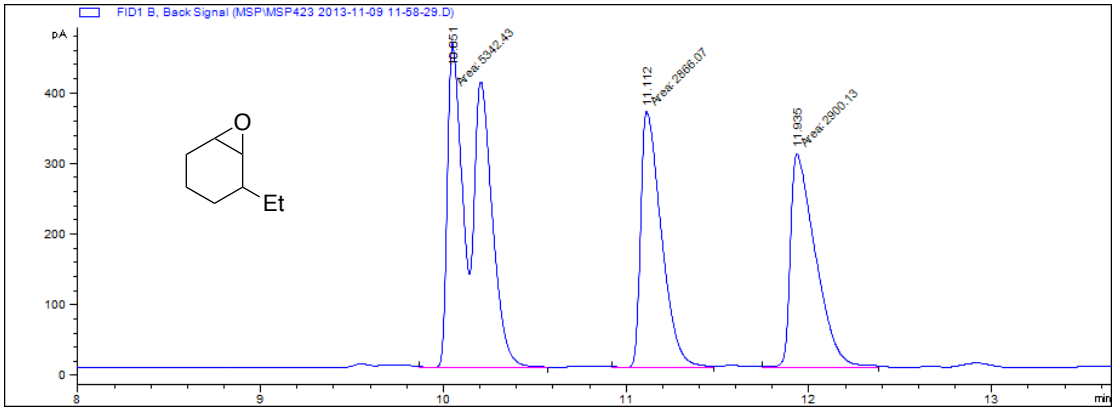
^{1}H NMR:

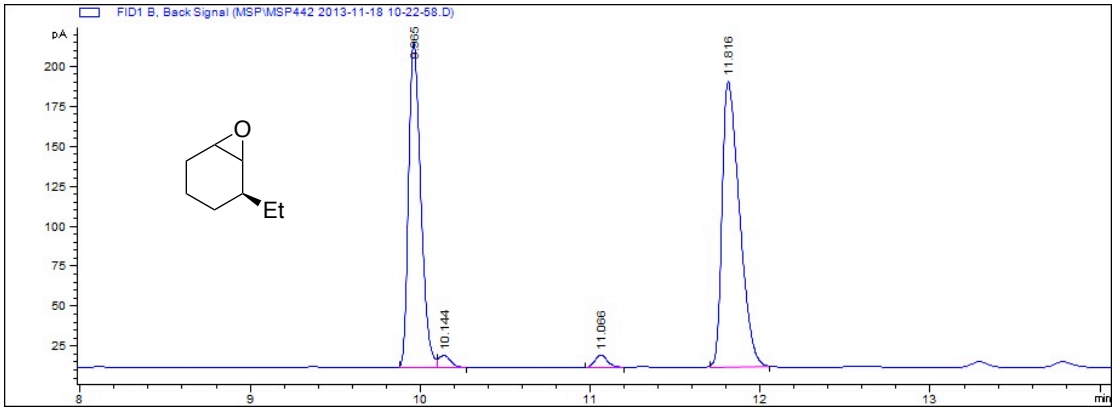


^{13}C NMR:

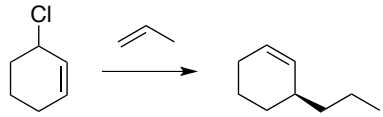

Et
ppm
130
120
110
100
90
80
70
60
50
40
30
20
10

GC traces:


FID1 B, Back Signal (MSP\MSP423 2013-11-09 11-58-29.D)
pA
O
Et
10.051
Area: 5342.43
11.112
Area: 2666.07
11.935
Area: 2900.13
min


FID1 B, Back Signal (MSP\MSP442 2013-11-18 10-22-58.D)
pA
O
Et
9.965
10.144
11.066
11.816
min

(S)-(–)-3-Propylcyclohex-1-ene (2.21)



CuI (15.2 mg, 0.08 mmol, 0.10 eq), (*S,S,S*)-**Ligand L1** (43.2 mg, 0.08 mmol, 0.10 eq) and then $CHCl_3$ (1.6 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, Cp_2ZrHCl (412 mg, 1.60 mmol, 2.00 eq) and CH_2Cl_2 (0.8 mL) were added to another flame-dried flask, and smoothly stirred at room temperature. A balloon charged with propylene is bubbled through the later solution for 3 min and the resulting mixture is then vigorously stirred at room temperature under the gaseous alkene atmosphere for 15 min; during this time a clear yellow solution developed, and the resulting organozirconium species is transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (93.3 mg, 0.80 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully (the product is quite volatile) concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave (*S*)-(–)-3-propylcyclohex-1-ene (78.0 mg, 0.71 mmol, 89% yield) as a colourless oil.

GC analysis of the crude mixture of epoxides derived from **2.21** indicated an enantiomeric excess of 92% (Hydrodex 6-TBDM, 60-100^{o}C at 5 ^{o}C/min, 110-170 ^{o}C at 20 ^{o}C/min, 10psi); major enantiomer t_R = 15.301 min; minor enantiomer t_R = 14.52 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 0.91 (t, *J*=7.0 Hz, 3 H), 1.15 - 1.44 (m, 5 H), 1.45 - 1.58 (m, 1 H), 1.65 - 1.86 (m, 2 H), 1.97 (br. s., 2 H), 2.06 (br. s., 1 H), 5.52 - 5.63 (m, 1 H), 5.63 - 5.70 (m, 1 H).

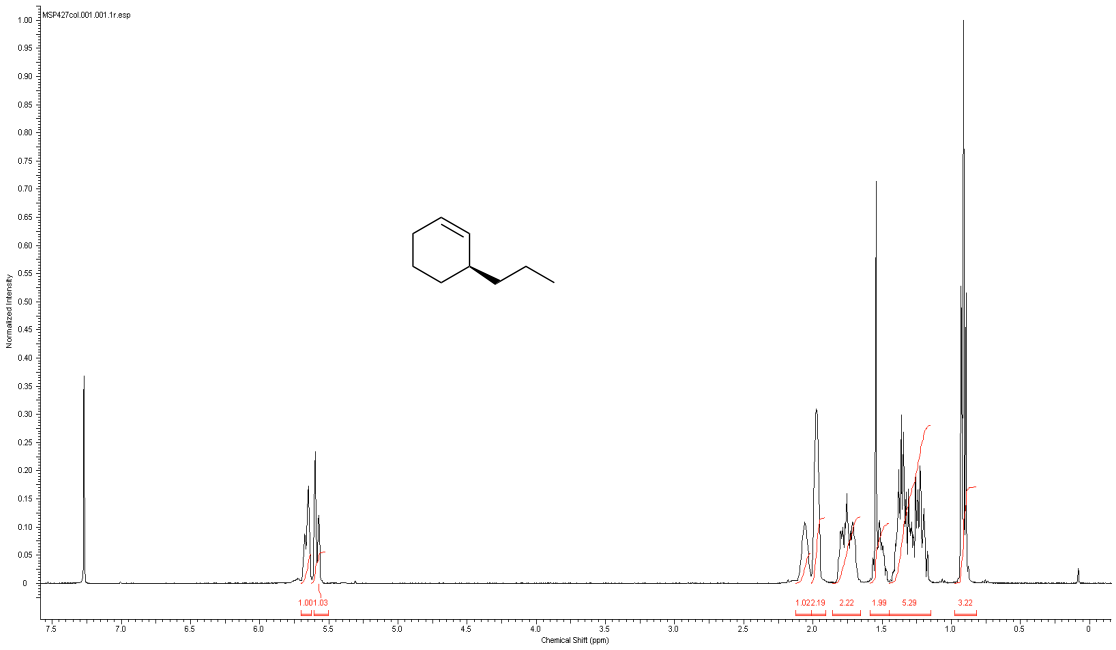
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 14.3, 20.0, 21.5, 25.4, 29.1, 34.9, 38.7, 126.6, 132.4.

HRMS (TOF) *m*/*z* calcd for C_9H_{16} $[M]^+$: 124.1252, found: 124.1250.

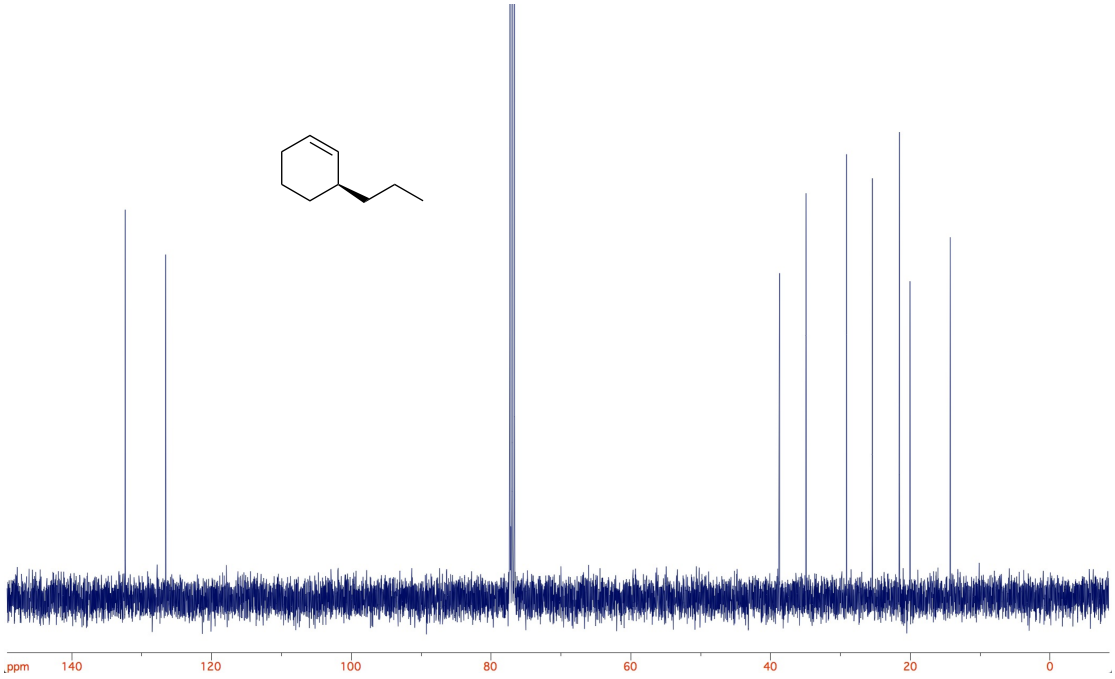
IR (ATR) ν (cm^{-1}): 2925.4, 2852.8, 1261.

$[\alpha]^{20}_{589}$ = –77.0 (*c* 0.27, $CHCl_3$) for 92% ee.

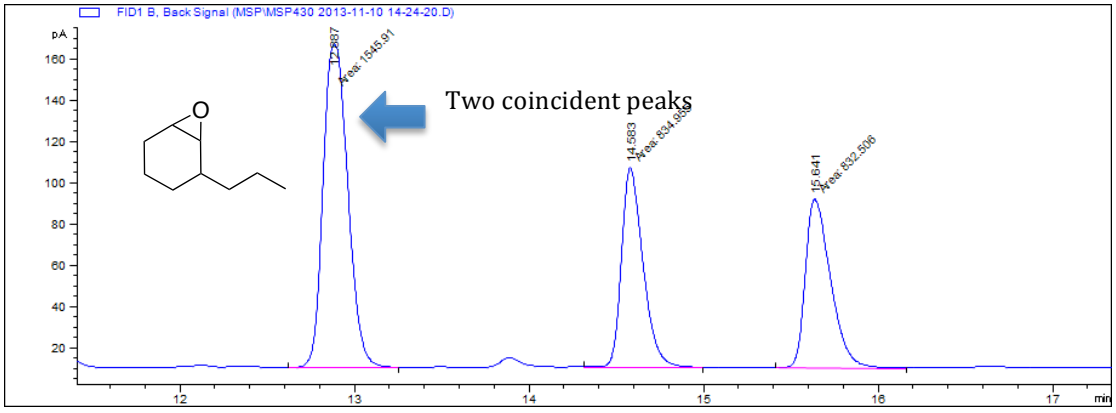
^{1}H NMR:

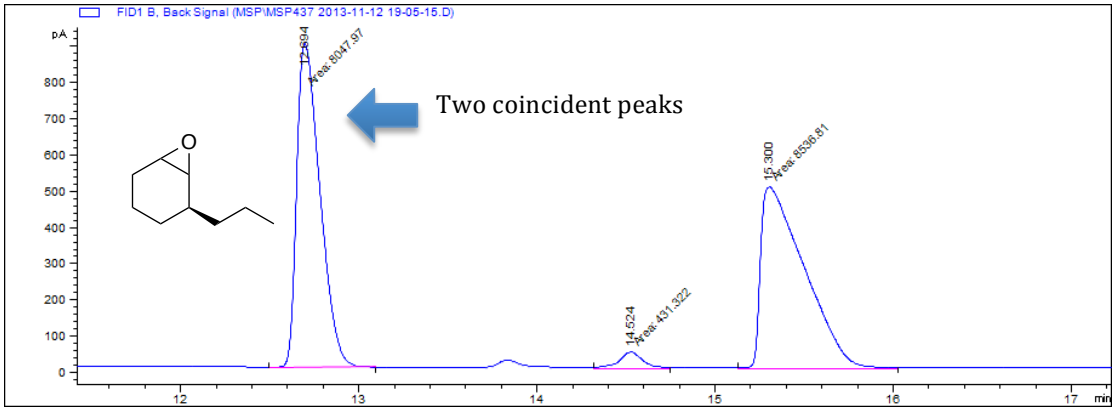


^{13}C NMR:

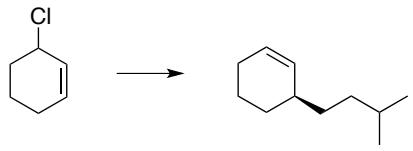

ppm
140
120
100
80
60
40
20
0

GC traces:


FID1 B, Back Signal (MSP\MSP430 2013-11-10 14-24-20.D)
pA
12.687
Area: 1545.91
Two coincident peaks
14.583
Area: 834.998
15.641
Area: 832.506
min


FID1 B, Back Signal (MSP\MSP437 2013-11-12 19-05-15.D)
pA
12.694
Area: 8047.97
Two coincident peaks
15.300
Area: 8536.81
14.524
Area: 431.322
min

(S)-(–)-3-Isopentylcyclohex-1-ene (2.22)



CuI (15.2 mg, 0.08 mmol, 0.10 eq), (*S*,*S*,*S*)-**Ligand L1** (43.2 mg, 0.08 mmol, 0.10 eq) and then $CHCl_3$ (1.6 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, Cp_2ZrHCl (412 mg, 1.60 mmol, 2.00 eq) and CH_2Cl_2 (0.8 mL) were added to another flame-dried flask, and smoothly stirred at room temperature. A balloon charged with 3-methyl-1-butene is bubbled through the later solution for 3 min and the resulting mixture is then vigorously stirred at room temperature under the gaseous alkene atmosphere for 15 min and the resulting organozirconium species is transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (93.3 mg, 0.80 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully (the product is quite volatile) concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave (*S*)-(–)-3-isopentylcyclohex-1-ene (112.0 mg, 0.74 mmol, 93% yield).

GC analysis of the crude mixture of epoxides derived from **2.22** indicated an enantiomeric excess of 91% (Hydrodex 6-TBDM, 60-100^{o}C at 5 ^{o}C/min, 110-170 ^{o}C at 20 ^{o}C/min, 10psi); major enantiomer t_R = 22.91 min; minor enantiomer t_R = 22.62 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 0.89 (d, *J*=6.6 Hz, 6 H), 1.13 - 1.41 (m, 5 H), 1.43 - 1.60 (m, 2 H), 1.64 - 1.86 (m, 2 H), 1.98 (br. s., 3 H), 5.59 (d, *J*=10.3 Hz, 1 H), 5.66 (d, *J*=10.5 Hz, 1 H).

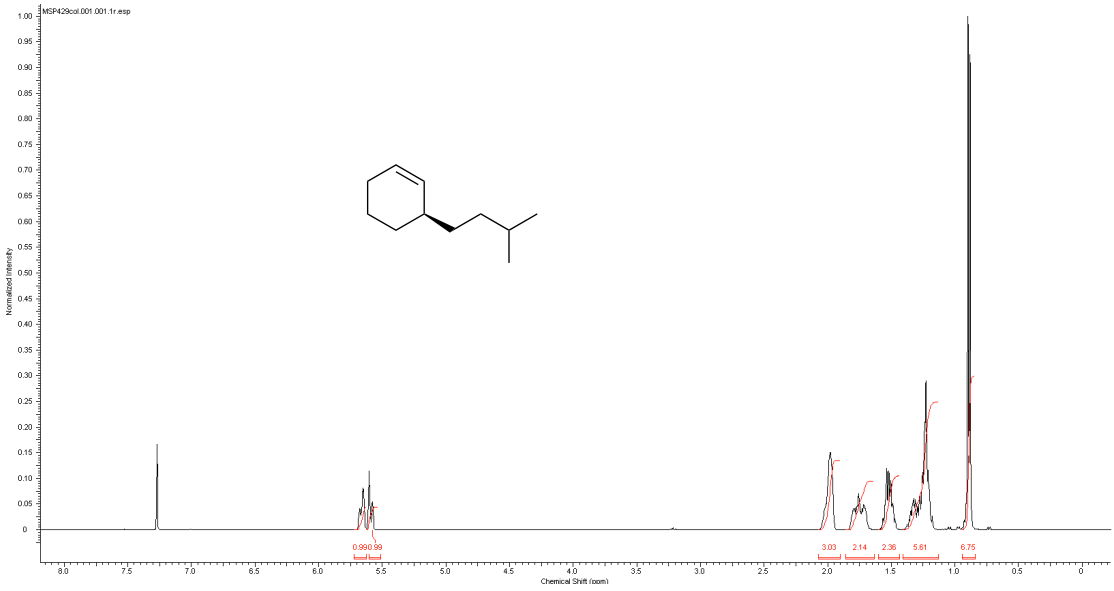
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 21.6, 22.6, 22.7, 25.4, 28.3, 29.2, 34.2, 35.5, 36.3, 126.6, 132.4.

HRMS (ESI) *m*/*z* calcd for $C_{11}H_{20}$ $[M]^+$: 152.1565, found: 152.1559.

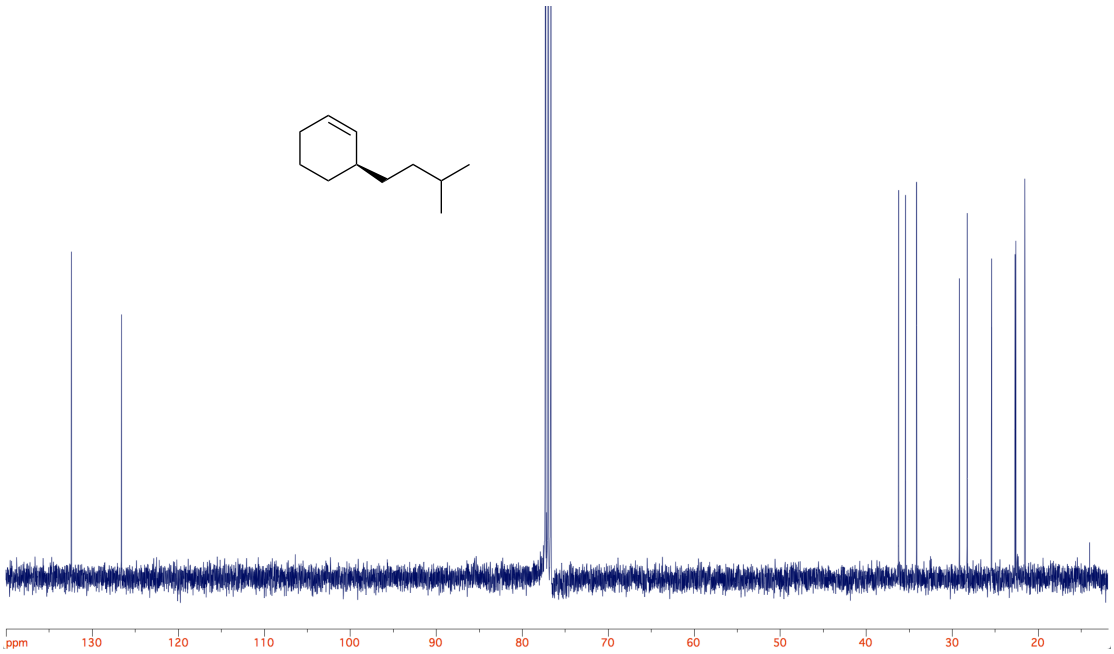
IR (ATR) ν (cm^{-1}): 2955.3, 2923.0, 2849.1, 1657.7, 1261.5.

$[\alpha]^{20}_{589}$ = – 60.7 (*c* 1.20, $CHCl_3$) for 91% ee.

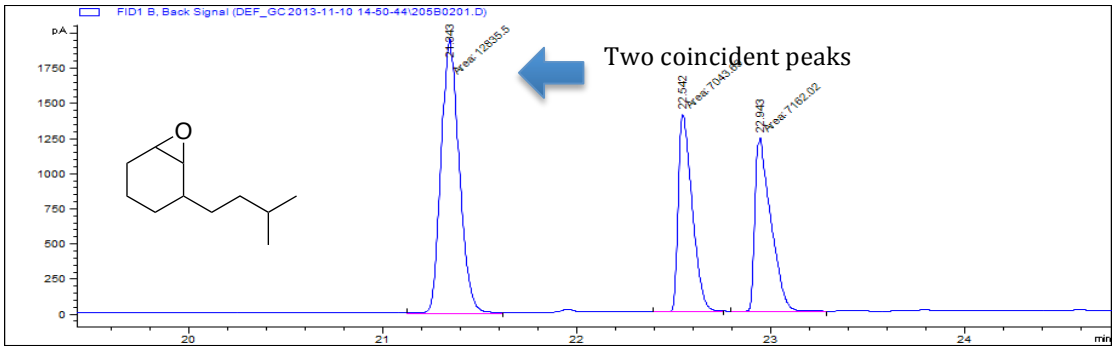
^{1}H NMR:

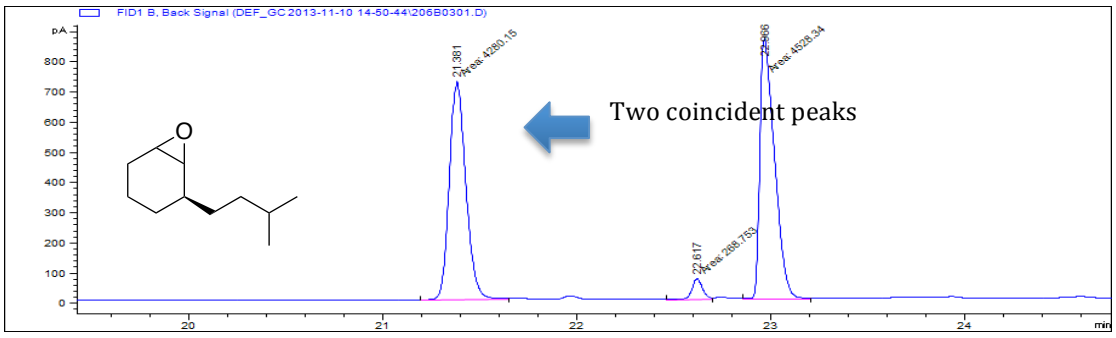


^{13}C NMR:

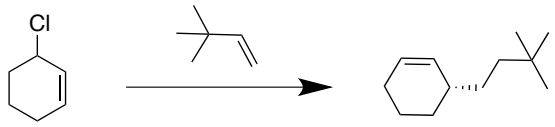


GC traces:





(R)-(+)-3-(3,3-Dimethylbutyl)cyclohex-1-ene (2.23)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)- **Ligand L1** (21.6 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 3,3-Dimethyl-1-butene (0.13 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.8 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask. The mixture is smoothly stirred at a reflux condition (T = 40 °C) under an argon atmosphere until it becomes a clear solution (approx. 30 min). The resulting organozirconium species is transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr (T = 28 °C and 200 mbar pressure) gave (R)-(+)-3-(3,3-dimethyl butyl) cyclohex-1-ene (36.6 mg, 0.22 mmol) in 56% yield.

GC analysis of the crude mixture of epoxides derived from **2.23** indicated an enantiomeric excess of 93% (Hydrodex 6-TBDM, 60-170^{o}C at 1 ^{o}C/min, 10psi); major enantiomer t_R = 50.3, 57.4 min; minor enantiomer t_R = 50.7, 61.8 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 0.88 (s, 9 H), 1.19-1.26 (m, 5 H), 1.48-1.56 (m, 1 H), 1.71-1.81 (m, 2 H), 1.96-1.98 (m, 3 H), 5.58-5.61 (m, 1 H), 5.65-5.66 (m, 1 H).

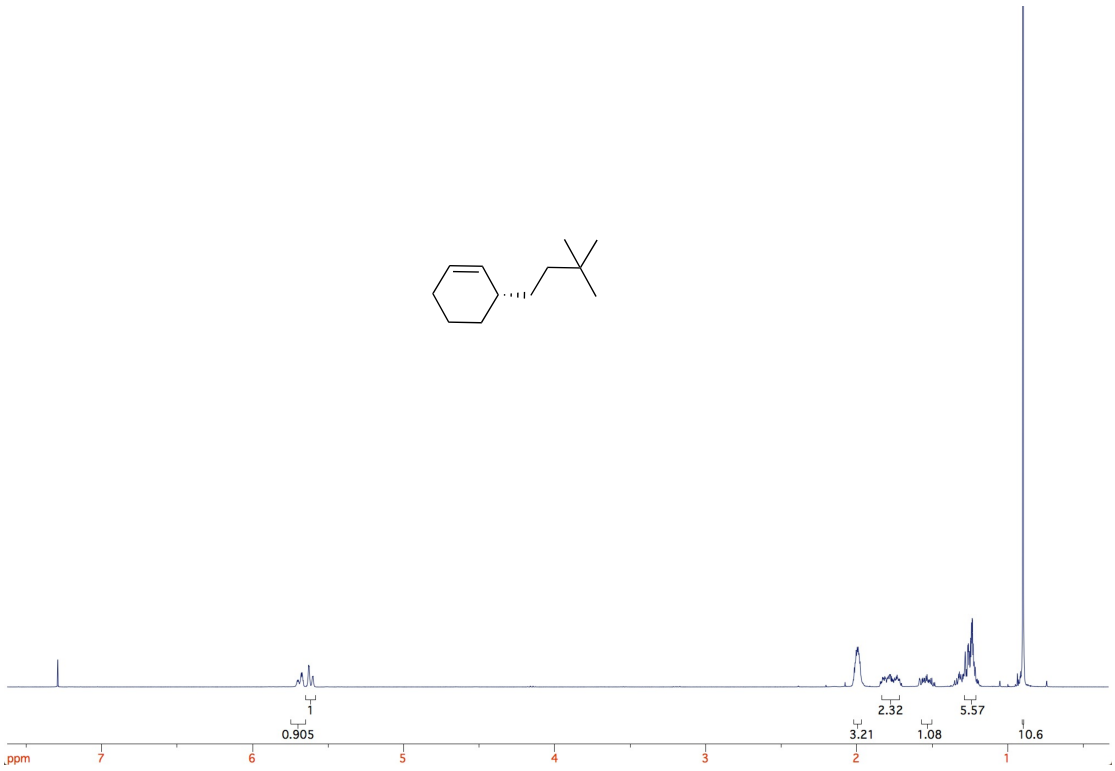
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 21.6, 25.4, 29.2, 29.4, 30.2, 31.2, 35.9, 41.3, 126.6, 132.5.

HRMS (ESI) *m*/z calcd for $C_{12}H_{22}$ $[M]^+$: 166.1722, found: 166.1723.

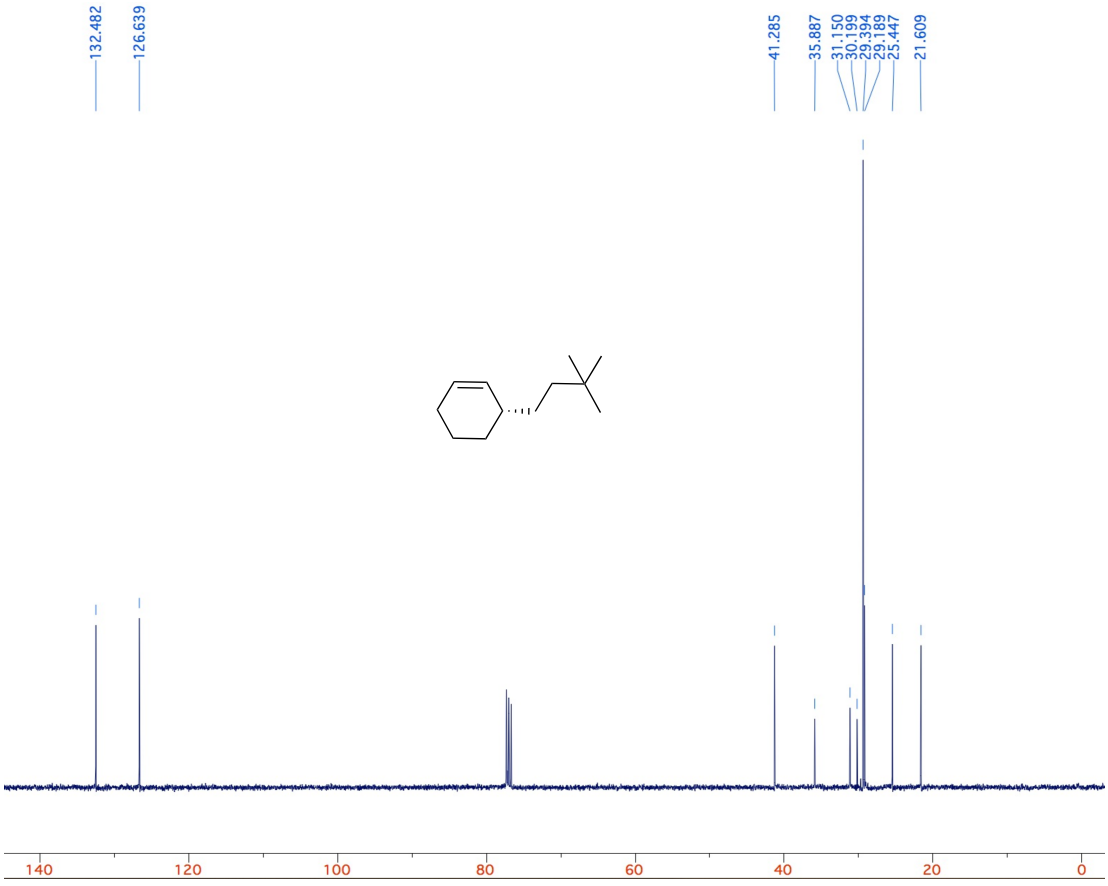
IR (ATR) ν (cm^{-1}, $CHCl_3$): 1262, 1468, 2925.

$[\alpha]^{20}_{589}$ =+ 29.2 (c= 1.75 in $CHCl_3$, 93% ee)

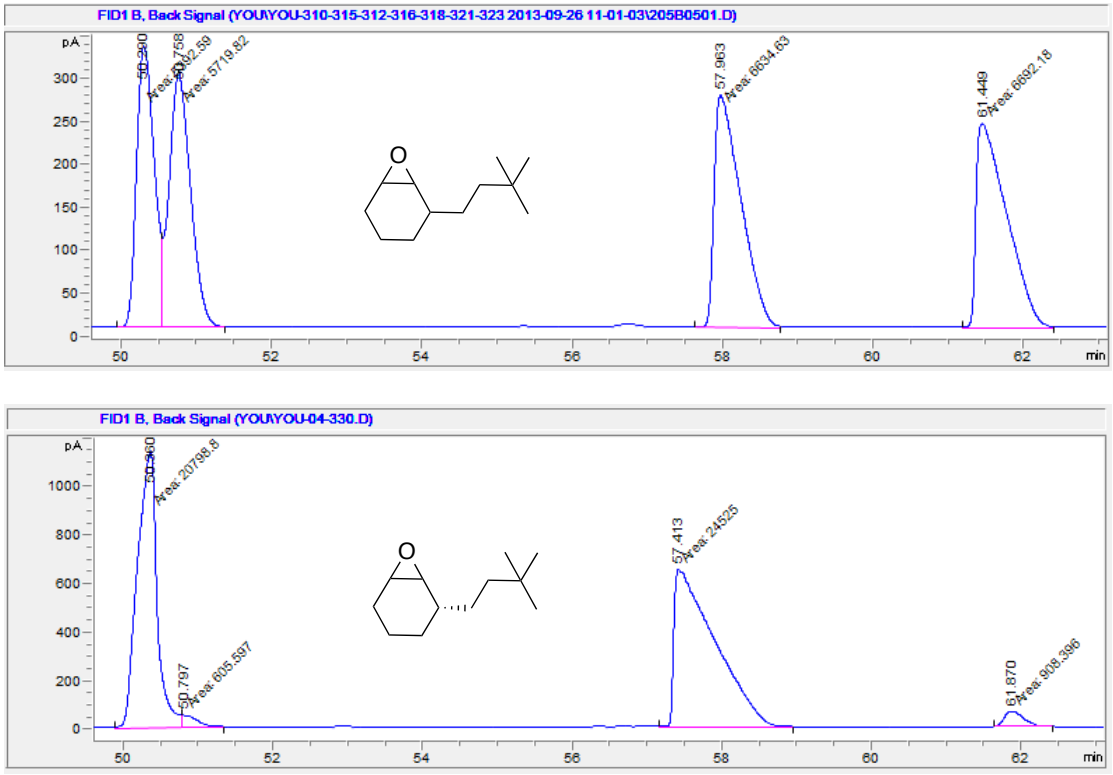
^{1}H NMR:



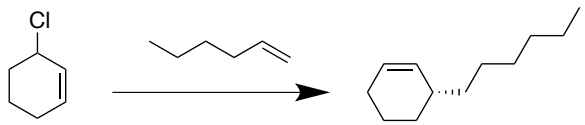
^{13}C NMR:


132.482
126.639
41.285
35.887
31.150
30.199
29.394
29.189
25.447
21.609
140
120
100
80
60
40
20
0

GC traces:


FID1 B, Back Signal (YOU\YOU-310-315-312-316-318-321-323 2013-09-26 11-01-03\205B0501.D)
pA
50.290
Area: 5719.82
57.963
Area: 6634.63
61.449
Area: 6692.18
min
FID1 B, Back Signal (YOU\YOU-04-330.D)
pA
50.460
Area: 20798.8
50.797
Area: 605.597
57.413
Area: 24525
61.870
Area: 909.396
min

(R)-(+)-3-Hexylcyclohex-1-ene (2.24)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)- **Ligand L1** (21.6 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 1-hexene (0.12 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx.15 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr (T = 30 °C and 100 mbar pressure) gave (R)-(+)-3-hexylcyclohex-1-ene (55.7 mg, 0.34 mmol) in 84% yield.

GC analysis of the crude mixture of epoxides derived from **2.24** indicated an enantiomeric excess of 95% (Hydrodex 6-TBDM, 60-170^{o}C at 1 ^{o}C/min, 10psi); major enantiomer t_R = 64.6, 68.1 min; minor enantiomer t_R = 65.3, 70.5 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 0.88-0.91 (t, 3 H, J =6.8 Hz), 1.25-1.31 (m, 11 H), 1.48-1.56(m, 1H), 1.69-1.81(m, 2 H), 1.95- 2.04 (m, 3 H), 5.57-5.60 (m, 1 H), 5.64-5.67 (m, 1 H).

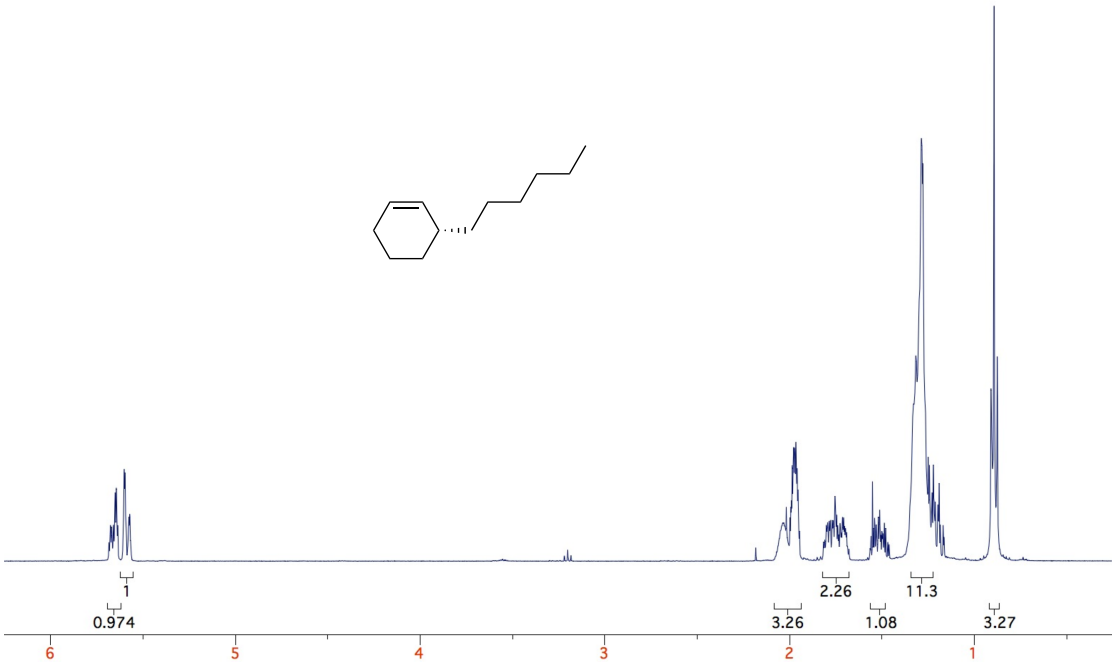
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 14.1, 21.6, 22.7, 25.4, 26.9, 29.2, 29.6，31.9，35.2，36.5，126.6, 132.4.

HRMS (ESI) *m*/z calcd for $C_{12}H_{22}$ $[M]^+$: 166.1722, found: 166.1725.

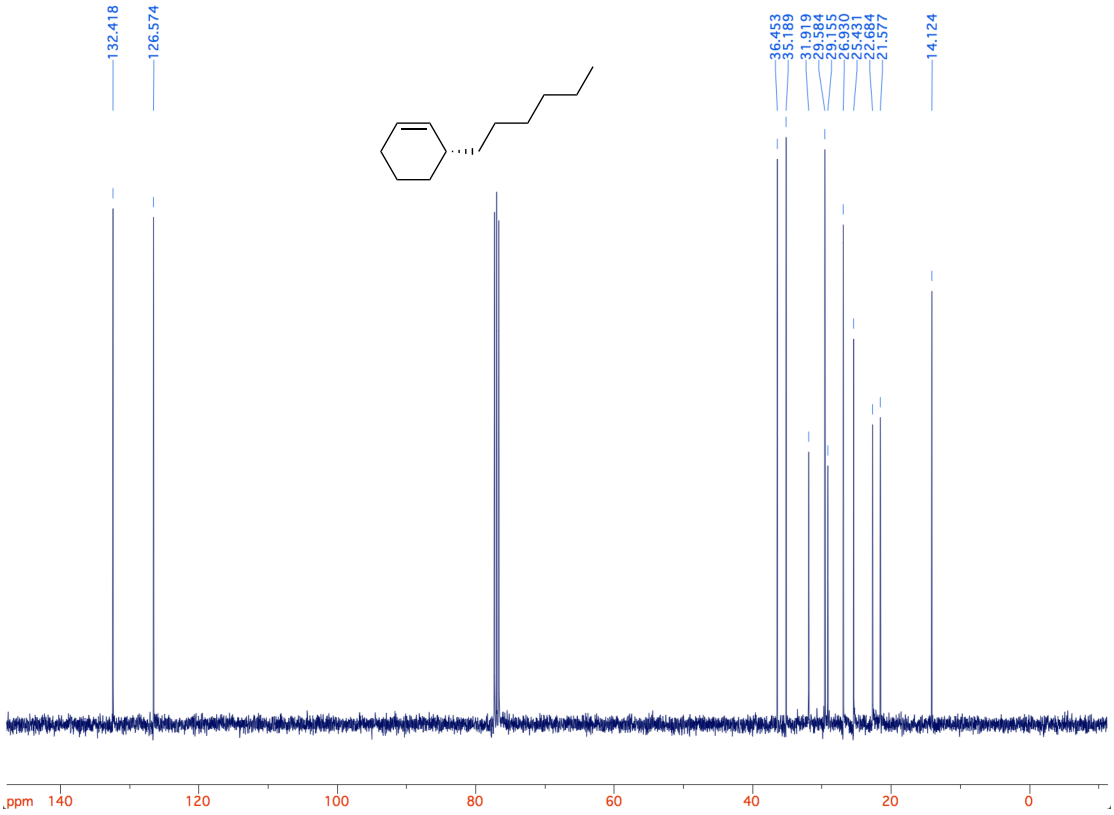
IR (ATR) ν (cm^{-1}, $CHCl_3$): 1216, 1229,1367, 1739, 2924.

$[\alpha]^{20}_{589}$ = + 4.7 (c=2.285 in $CHCl_3$, 95% ee).

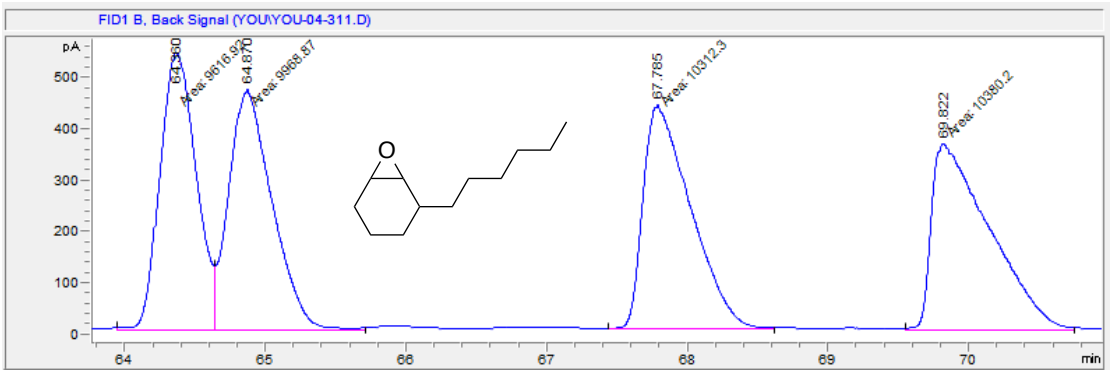
^{1}H NMR:

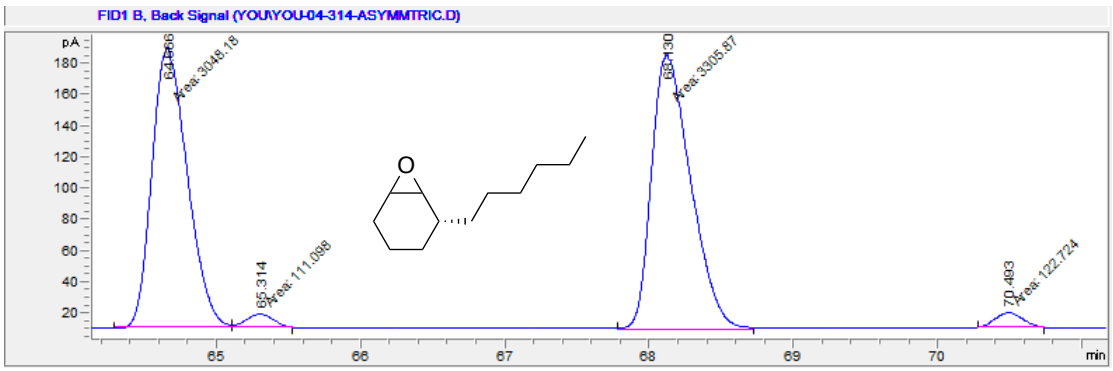


^{13}C NMR:

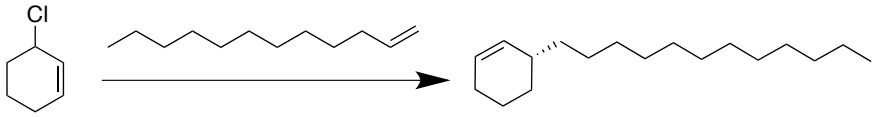

132.418
126.574
36.453
35.189
31.919
29.584
29.155
26.930
25.431
22.684
21.377
14.124
ppm 140
120
100
80
60
40
20
0

GC traces:


FID1 B, Back Signal (YOU\YOU-04-311.D)
pA
64.360
Area: 9616.99
64.870
Area: 9969.57
67.785
Area: 10312.3
69.822
Area: 10380.2
min


FID1 B, Back Signal (YOU\YOU-04-314-ASYMMTRIC.D)
pA
64.366
Area: 3048.18
65.314
Area: 111.098
68.430
Area: 3305.57
70.493
Area: 122.724
min

(R)-(+)-3-Dodecylcyclohex-1-ene (2.25)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)- **Ligand L1** (21.6 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 1-Dodecene (0.22 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr (T = 150 °C and 50 mbar pressure) gave (R)- (-)-3-dodecylcyclohex-1-ene (78.1 mg, 0.32 mmol) in 78% yield.

GC analysis of the crude mixture of epoxides derived from **2.25** indicated an enantiomeric excess of 95% (Hydrodex 6-TBDM, 60-170^{o}C at 1 ^{o}C/min, hold for 70 min, 10psi); major enantiomer t_R = 140.3 min; minor enantiomer t_R = 141.4 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 0.87-0.91 (t, 3 H, J =6.85 Hz), 1.22-1.32 (m, 23 H), 1.48-1.56 (m, 1 H), 1.71-1.81 (m, 2 H), 1.95-2.06 (m, 3 H), 5.57-5.60 (m, 1 H), 5.64-5.68 (m, 1 H).

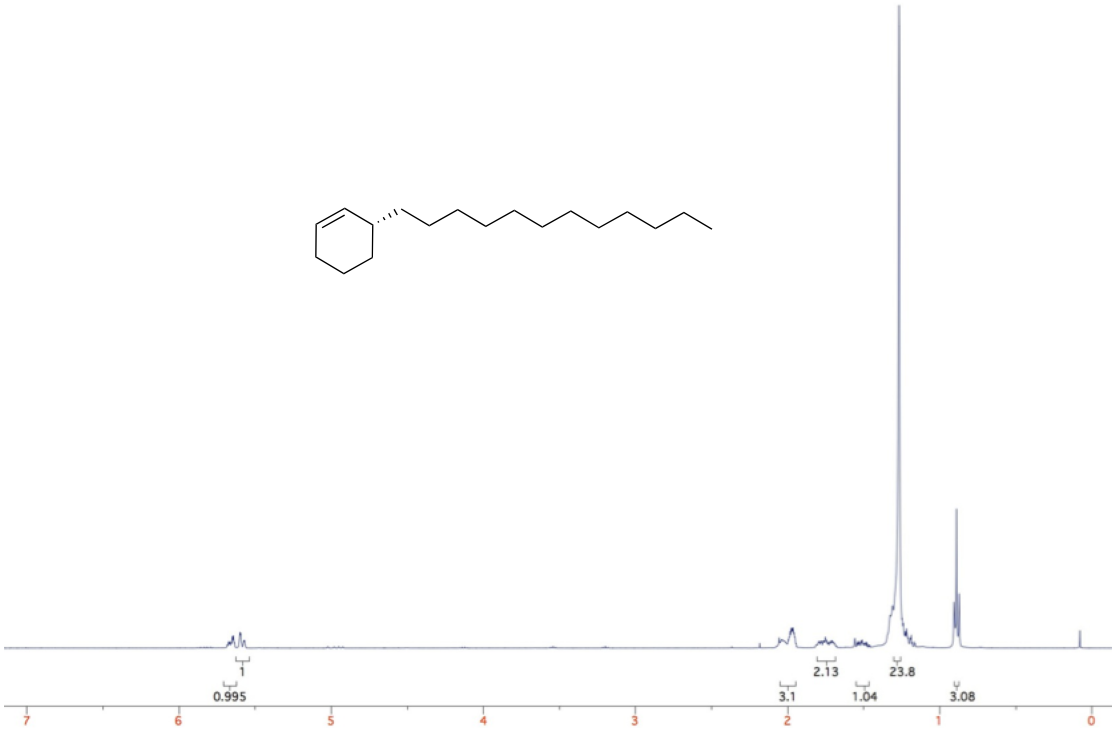
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 21.6, 22.7, 25.4, 27.0, 29.1, 29.3, 29.7 (br. m, 6C), 29.9, 31.9, 35.2, 36.5, 126.6, 132.4.

HRMS (ESI) *m*/z calcd for $C_{18}H_{34}$ $[M]^+$: 250.2661, found: 250.2664.

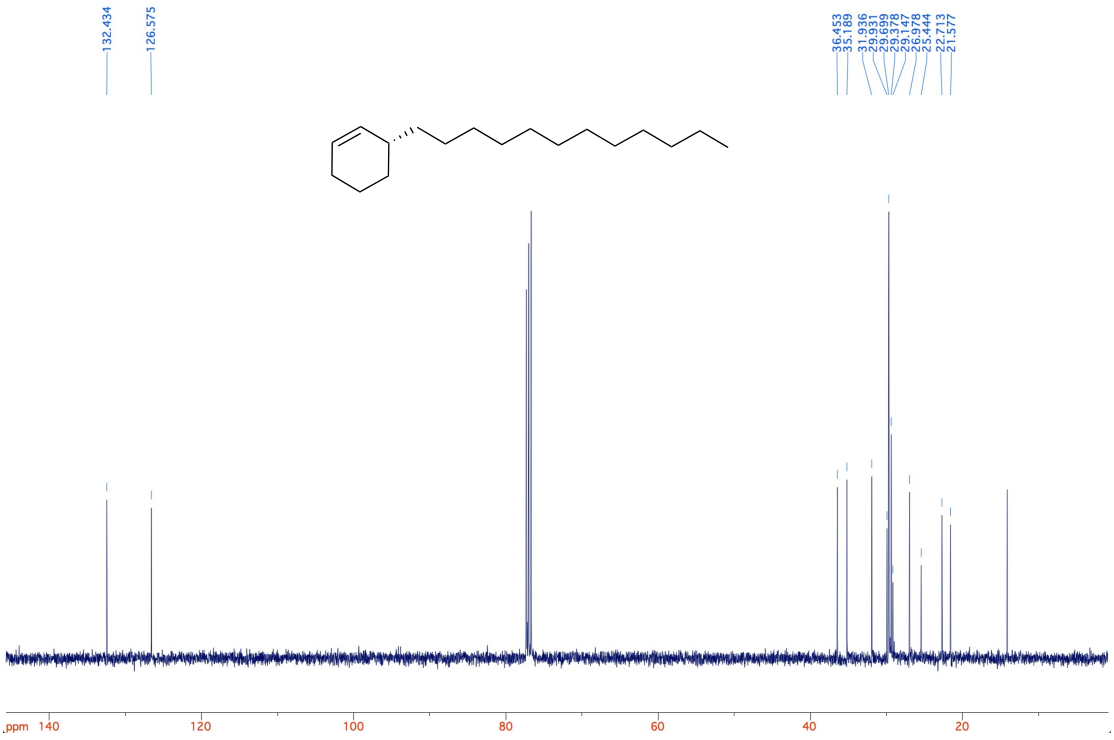
IR (ATR) ν (cm^{-1}, $CHCl_3$): 1733, 1739, 1742.

$[\alpha]^{20}_{589}$ = + 18.0 (c= 0.84 in $CHCl_3$, 95% ee)

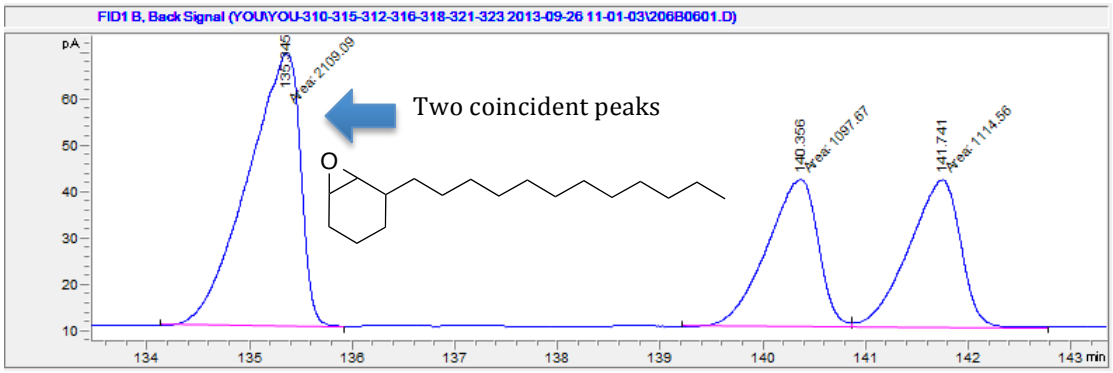
^{1}H NMR:

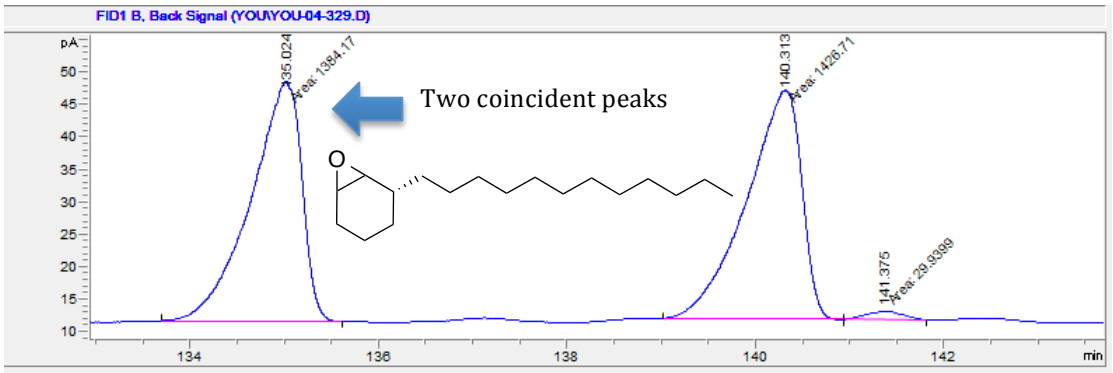


^{13}C NMR:

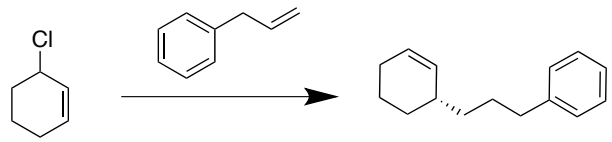

132.434
126.575
36.453
35.189
31.936
29.931
29.699
29.378
29.147
26.978
25.444
22.713
21.377
ppm 140
120
100
80
60
40
20

GC traces:


FID1 B, Back Signal (YOU\YOU-310-315-312-316-318-321-323 2013-09-26 11-01-03\206B0601.D)
pA
135.345
Area: 2109.09
Two coincident peaks
O
140.356
Area: 1097.67
141.741
Area: 1114.56
134
135
136
137
138
139
140
141
142
143 min


FID1 B, Back Signal (YOU\YOU-04-329.D)
pA
135.024
Area: 1384.17
Two coincident peaks
O
140.313
Area: 1426.71
141.375
Area: 29.9399
134
136
138
140
142
min

(R)-(+)-(3-(Cyclohex-2-en-1-yl)propyl)benzene (2.26)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)- **Ligand L1** (21.6 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, allylbenzene (0.13 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr (T = 100 °C and 50 mbar pressure) gave (R)-(-)-(3-(cyclohex-2-en-1-yl) propyl) benzene (60.9 mg, 0.31 mmol) in 76% yield.

GC analysis of the crude mixture of epoxides derived from **2.26** indicated an enantiomeric excess of 91% (Hydrodex 6-TBDM, 60-170^{o}C at 1 ^{o}C/min, hold for 70 min, 10psi); major enantiomer t_R = 114.9, 118.6 min; minor enantiomer t_R = 113.2, 118.8 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.22-1.43 (m, 3H), 1.50-1.56 (m, 1 H), 1.68-1.83 (m, 4 H), 1.97-2.01 (m, 2 H), 2.08-2.13 (m, 1 H), 2.62-2.66 (t, 2 H, J =7.77 Hz), 5.58-5.62 (m, 1 H), 5.67-5.71 (m, 1H), 7.21-7.23 (m, 3H), 7.29-7.33 (m, 2H).

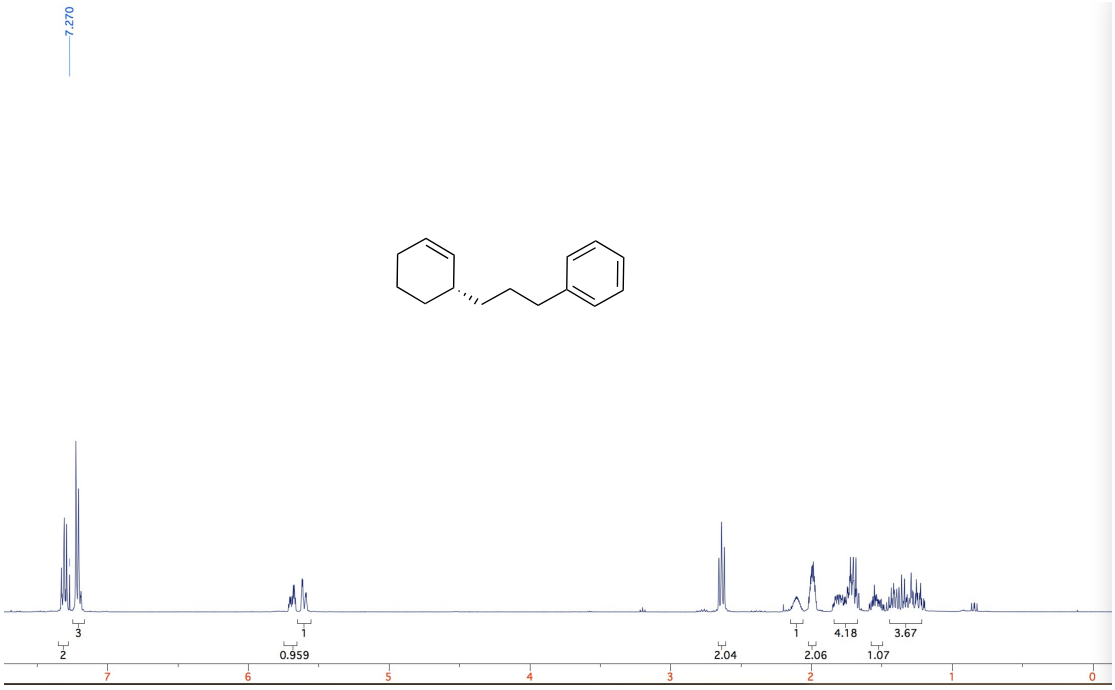
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 21.6, 25.4, 28.9, 29.1, 35.1, 36.1, 36.2, 125.6, 126.8, 128.3, 128.4, 132.1, 142.8.

HRMS (ESI) *m*/z calcd for $C_{15}H_{20}$ $[M]^+$: 200.1565, found: 200.1563.

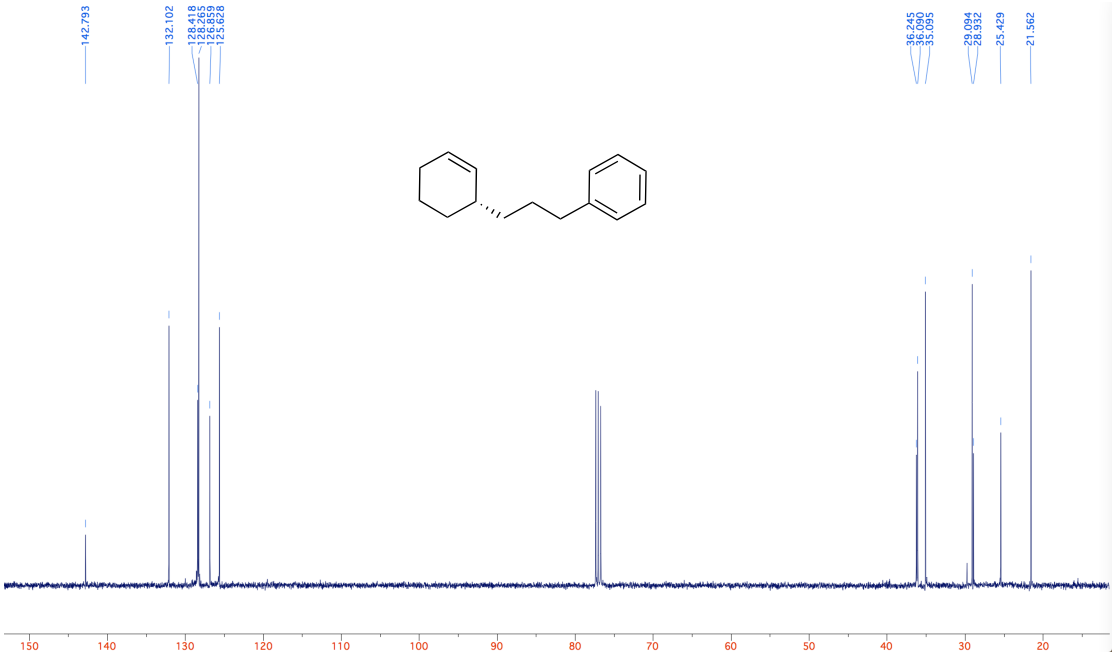
IR (ATR) ν (cm^{-1}, $CHCl_3$): 1736, 1743.

$[\alpha]^{20}_{589}$ = + 30.7 (c= 2.66 in $CHCl_3$, 95% ee)

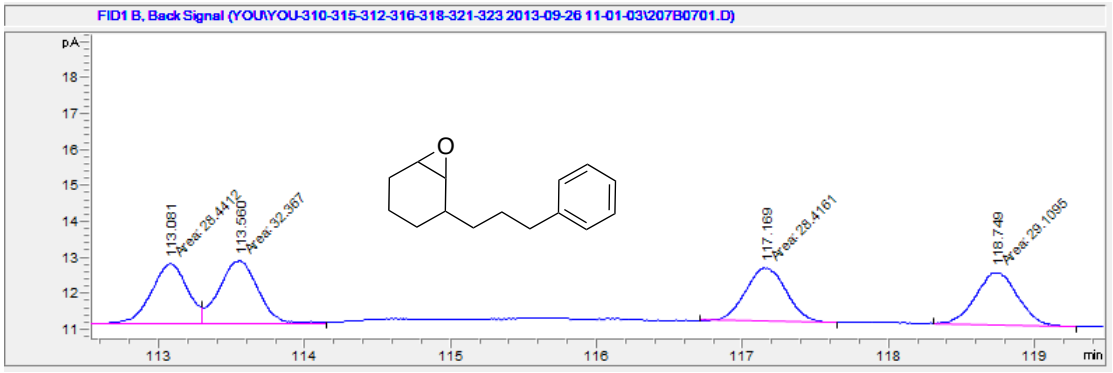
^{1}H NMR:

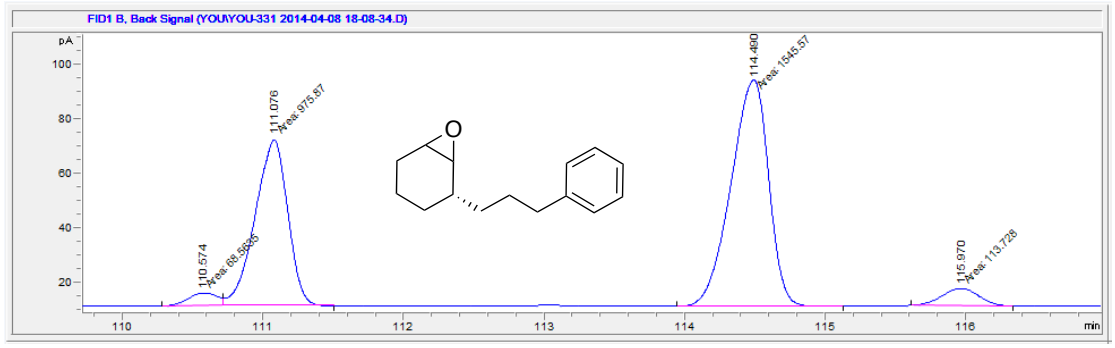


^{13}C NMR:

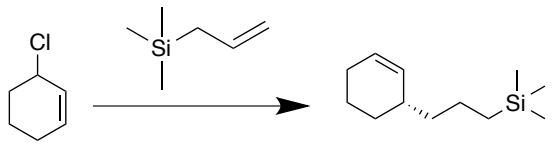

142.793
132.102
128.418
128.265
127.859
125.628
36.245
36.090
35.095
29.094
28.932
25.429
21.562
150
140
130
120
110
100
90
80
70
60
50
40
30
20

GC traces:


FID1 B, Back Signal (YOUYOU-310-315-312-316-318-321-323 2013-09-26 11-01-03\207B0701.D)
pA
18
17
16
15
14
13
12
11
O
113.081
Area: 28.4412
113.560
Area: 32.367
117.169
Area: 28.4161
118.749
Area: 29.1095
113
114
115
116
117
118
119
min


FID1 B, Back Signal (YOUAYOU-331 2014-04-08 18-08-34.D)
pA
100
80
60
40
20
O
110.574
Area: 68.5866
111.076
Area: 975.87
114.480
Area: 1545.57
115.970
Area: 113.728
110
111
112
113
114
115
116
min

(R)-(+)-(3-(Cyclohex-2-en-1-yl)propyl)trimethylsilane (2.27)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)- **Ligand L1** (21.6 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, Allyltrimethylsilane (0.16 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr (T = 40 °C and 40 mbar pressure) gave (R)-(-)-(3-(cyclohex-2-en-1-yl) propyl) trimethylsilane (40.8 mg, 0.21 mmol) in 52% yield.

GC analysis of the crude mixture of epoxides derived from **2.27** indicated an enantiomeric excess of 95% (Hydrodex 6-TBDM, 60-170^{o}C at 1 ^{o}C/min, 10psi); major enantiomer t_R = 65.8, 69.5 min; minor enantiomer t_R = 65.3, 71.5 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 0.005 (s, 9H), 0.49-0.53 (m, 2 H), 1.23-1.39 (m, 5 H), 1.50-1.57 (m, 1 H), 1.72-1.82 (m, 2 H), 1.98-2.01 (m, 2 H), 2.06-2.10 (m, 1 H), 5.58-5.62 (m, 1H), 5.66-5.70 (m, 1H).

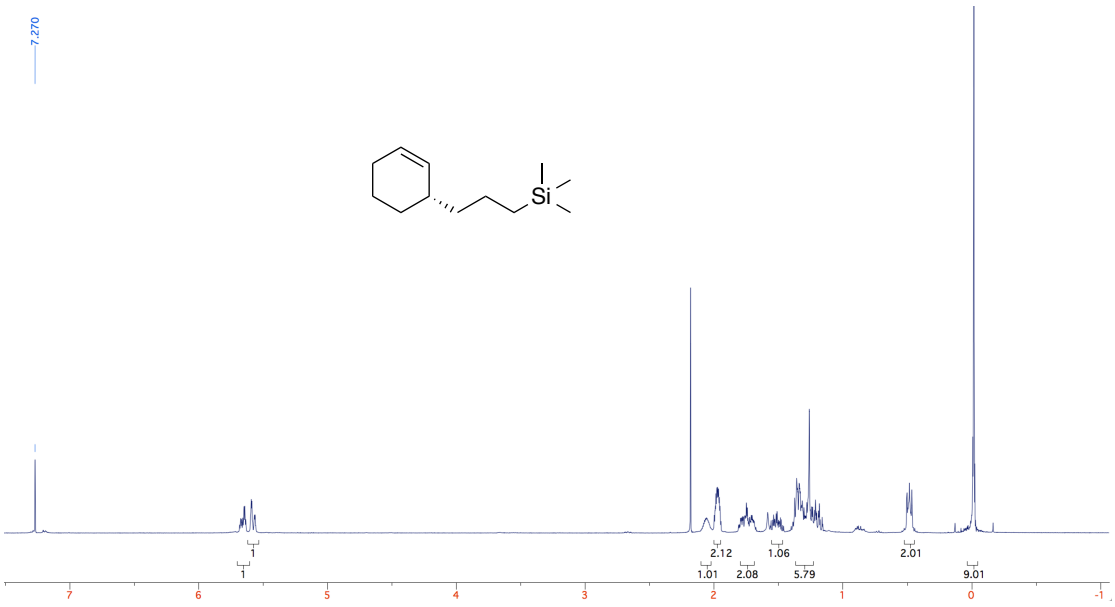
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm : -1.6, 16.8, 21.2, 21.5, 25.4, 29.1, 34.9, 40.4, 126.6, 132.4.

HRMS (ESI) *m*/z calcd for $C_{12}H_{24}Si$ $[M]^+$: 196.1647, found: 196.1641.

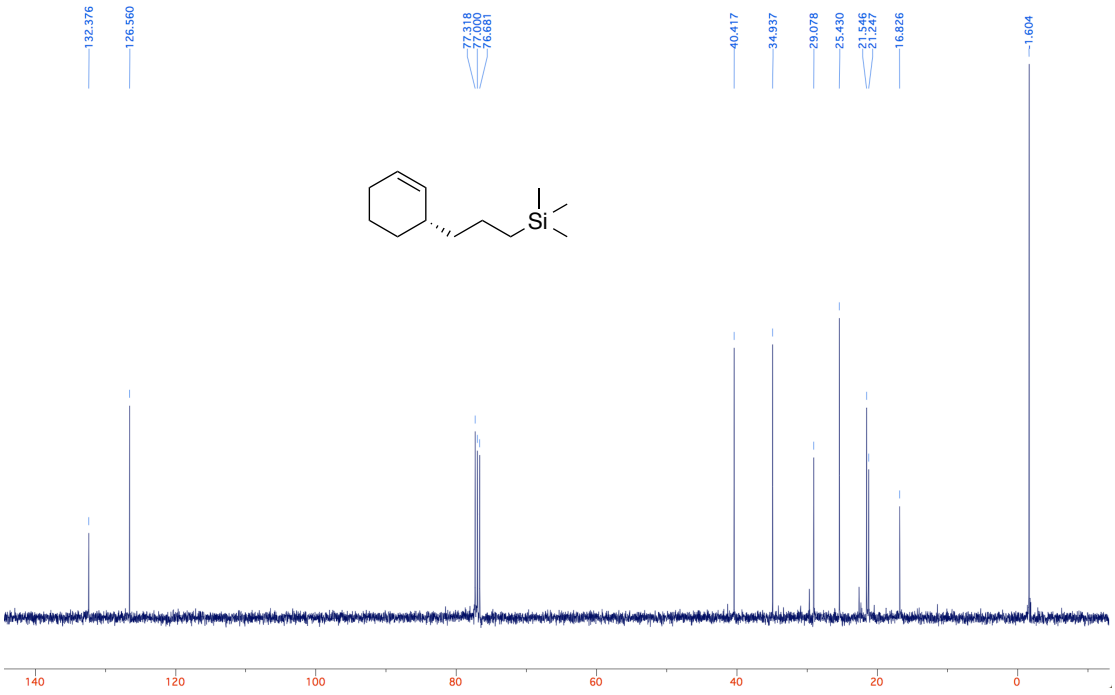
IR (ATR) ν (cm^{-1}, $CHCl_3$): 836.5, 860.8, 1247.7, 1457.3, 2853.9, 2923.1.

$[\alpha]^{20}_{589}$ = + 28 (c= 0.7 in $CHCl_3$, 93% ee)

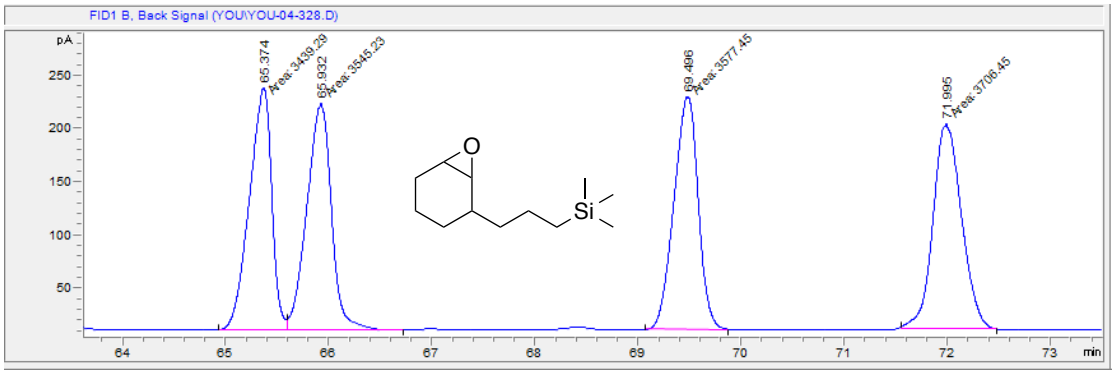
^{1}H NMR:

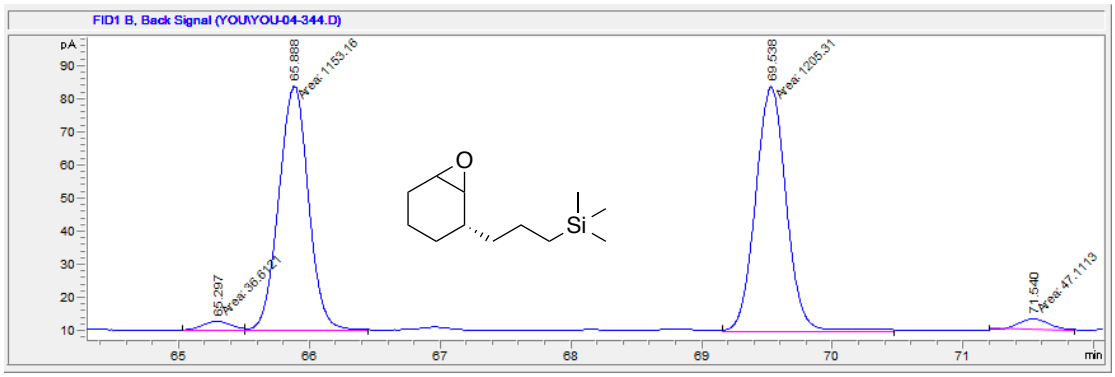


^{13}C NMR:

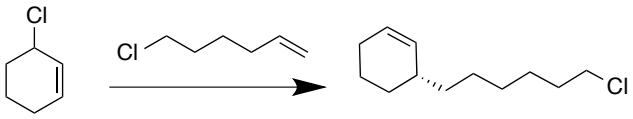

132.376
126.560
77.318
77.000
76.681
40.417
34.937
29.078
25.430
21.546
21.247
16.826
1.604
Si
140
120
100
80
60
40
20
0

GC traces:


FID1 B, Back Signal (YOU\YOU-04-328.D)
pA
250
200
150
100
50
65.374
Area:3439.29
65.932
Area:3545.23
69.486
Area:3577.45
71.995
Area:3706.45
O
Si
64
65
66
67
68
69
70
71
72
73
min


FID1 B, Back Signal (YOU\YOU-04-344.D)
pA
90
80
70
60
50
40
30
20
10
65.297
Area:36.6121
65.888
Area:1153.16
69.538
Area:1205.31
71.540
Area:47.1113
O
Si
65
66
67
68
69
70
71
min

(R)-(+)-3-(6-Chlorohexyl)cyclohex-1-ene (2.28)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)- **Ligand L1** (21.6 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 6-chlorohex-1-ene (106 µL, 1.0 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave (*R*)-(+)-3-(6-chlorohexyl)cyclohex-1-ene as a colourless oil (66.2 mg, 0.34 mmol, 84%).

GC analysis of the crude mixture of epoxides derived from **2.28** indicated an enantiomeric excess of 91% (Hydrodex 6-TBDM, 60-165^{o}C at 1 ^{o}C/min, hold for 30 min, 10psi); t_R = 1st diastereomer: 107.4 min, 2nd diastereomer: 113.8 min (major enantiomer), 116.2 min (minor enantiomer).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 5.72-5.62 (m, 1H), 5.61-5.53 (m, 1H), 3.54 (t, *J*=6.8 Hz, 2H), 2.09-2.00 (m, 1H), 2.00-1.91 (m, 2H), 1.83-1.74 (m, 3H), 1.73-1.66 (m, 1H), 1.55-1.48 (m, 1H), 1.48-1.39 (m, 2H), 1.38-1.28 (m, 5H), 1.28-1.15 (m, 2H);

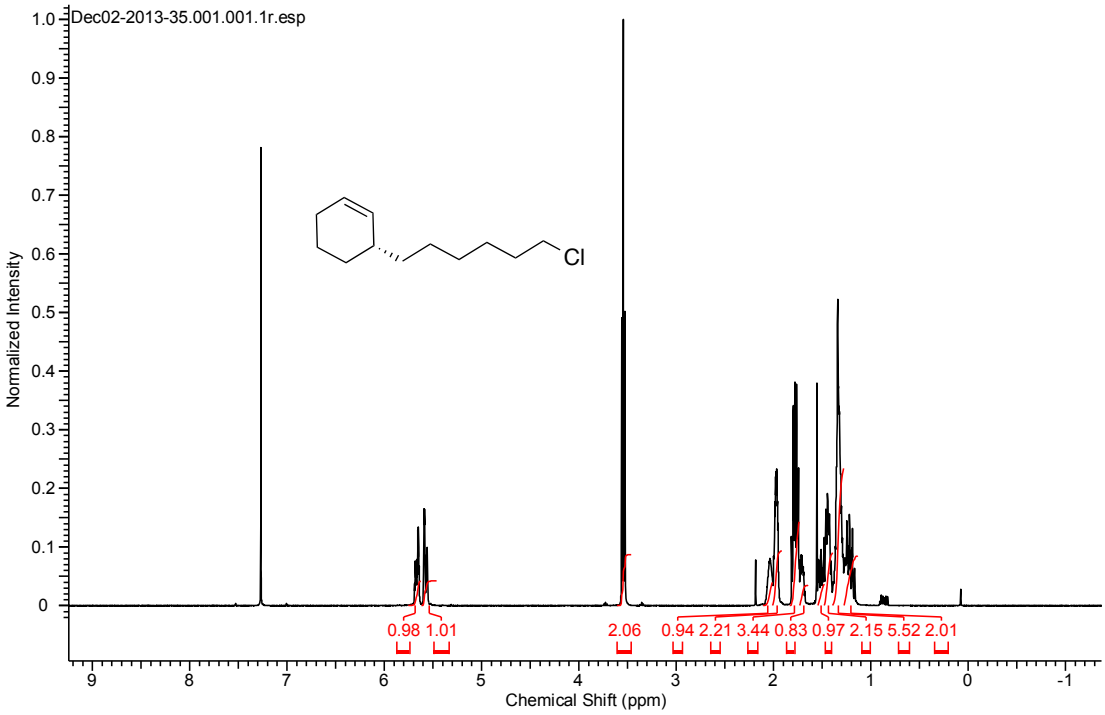
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 132.2, 126.8, 45.2, 36.3, 35.1, 32.6, 29.1, 29.1, 26.9, 26.8, 25.4, 21.5;

HRMS (EI/FI) *m/z* cald for $C_{12}H_{21}Cl$ $[M]^+$: 200.1335; found: 200.1332;

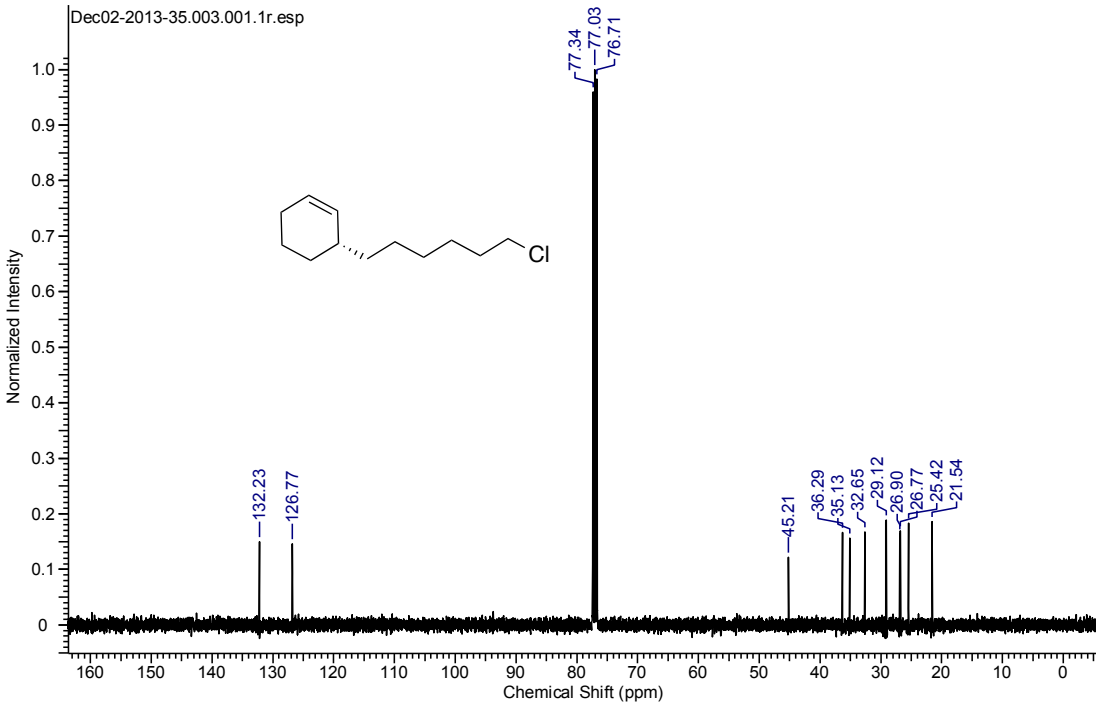
IR (ν_{max}/cm^{-1}) 2924, 2855, 1648, 1446, 1310, 885, 721, 698, 675, 653.

$[\alpha]^{20}_{589}$ = +14.89 (*c* 0.47, $CHCl_3$, 91% ee).

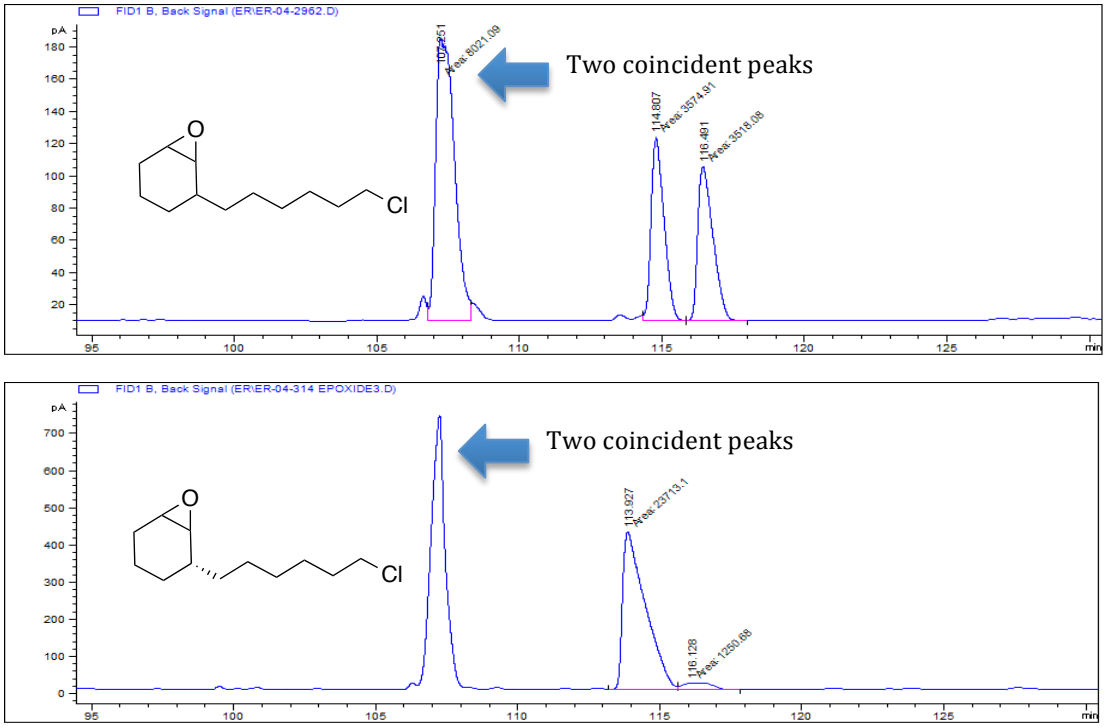
^{1}H NMR:



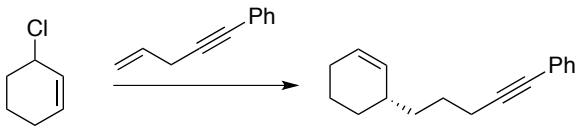
^{13}C NMR:



GC traces:



(*S*)-(+)-3-(5-Phenylpent-4-yn-1-yl)cyclohex-1-ene (2.29)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)- **Ligand L1** (21.6 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 1-phenyl-4-penten-1-yne (0.15 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave (+)-(*S*)-3-(5-phenylpent-4-yn-1-yl)cyclohex-1-ene (80.7 mg, 0.36 mmol) in 90% yield.

Enantiomeric excess of 81% was determined by HPLC [Chiralpak® IB; flow: 1.0 mL/min; 100% hexane; λ = 210 nm; major enantiomer t_R = 14.52 min; minor enantiomer t_R = 13.63 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.19 - 1.33 (m, 1 H), 1.35 - 1.60 (m, 3 H), 1.60 - 1.88 (m, 4 H), 1.93 - 2.04 (m, 2 H), 2.12 (br. s., 1 H), 2.42 (t, *J*=7.0 Hz, 2 H), 5.60 (d, *J*=10.1 Hz, 1 H), 5.69 (d, *J*=10.3 Hz, 1 H), 7.19 - 7.33 (m, 3 H), 7.40 (d, *J*=6.7 Hz, 2 H).

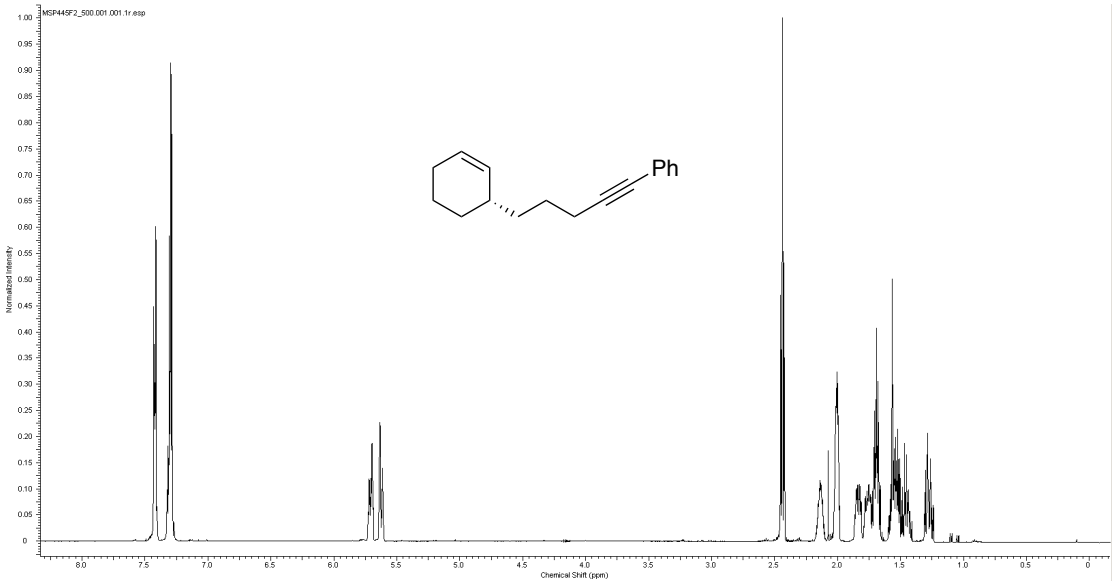
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 19.6, 21.4, 25.3, 26.1, 29.0, 34.8, 35.6, 80.6, 90.2, 124.0, 126.9, 127.4, 128.1 (2C), 131.5 (2C), 131.8.

HRMS (TOF+) *m/z* calcd for $C_{17}H_{20}$ $[M]^+$: 224.1565; found: 224.1574.

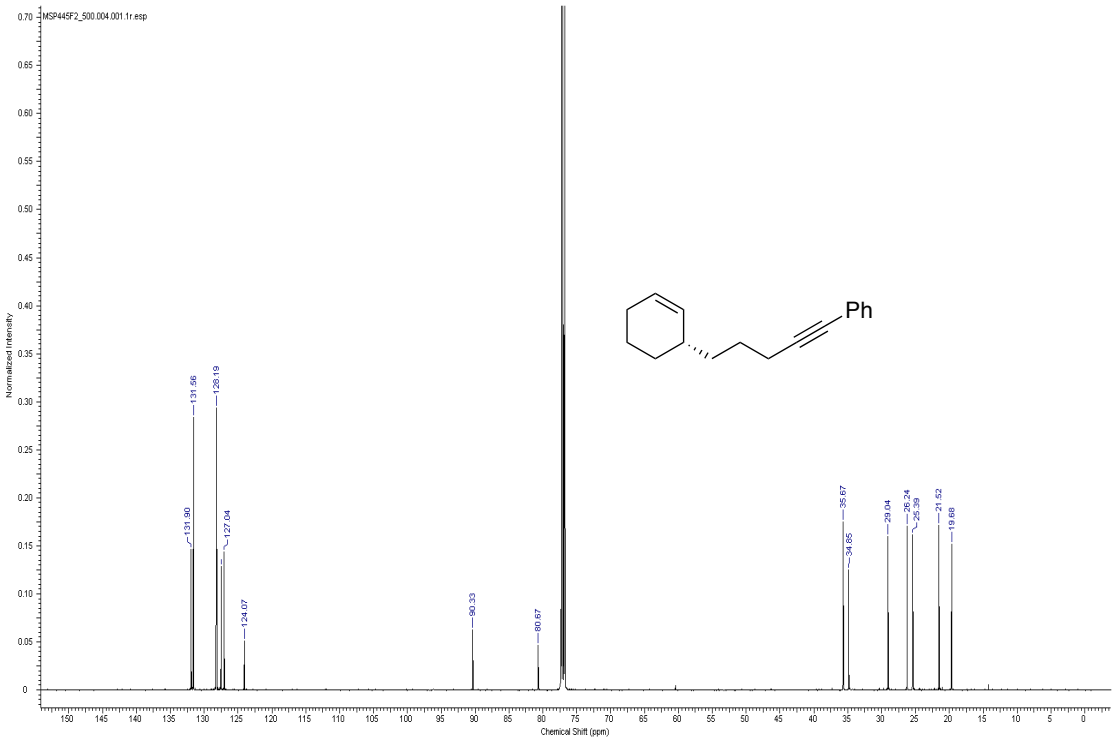
IR (ATR) ν (cm^{-1}): 3016.8, 2927.3, 2857.4, 1598.6, 1489.9.

$[\alpha]^{20}_{589}$ =+49.54 (*c* 0.72, $CHCl_3$).

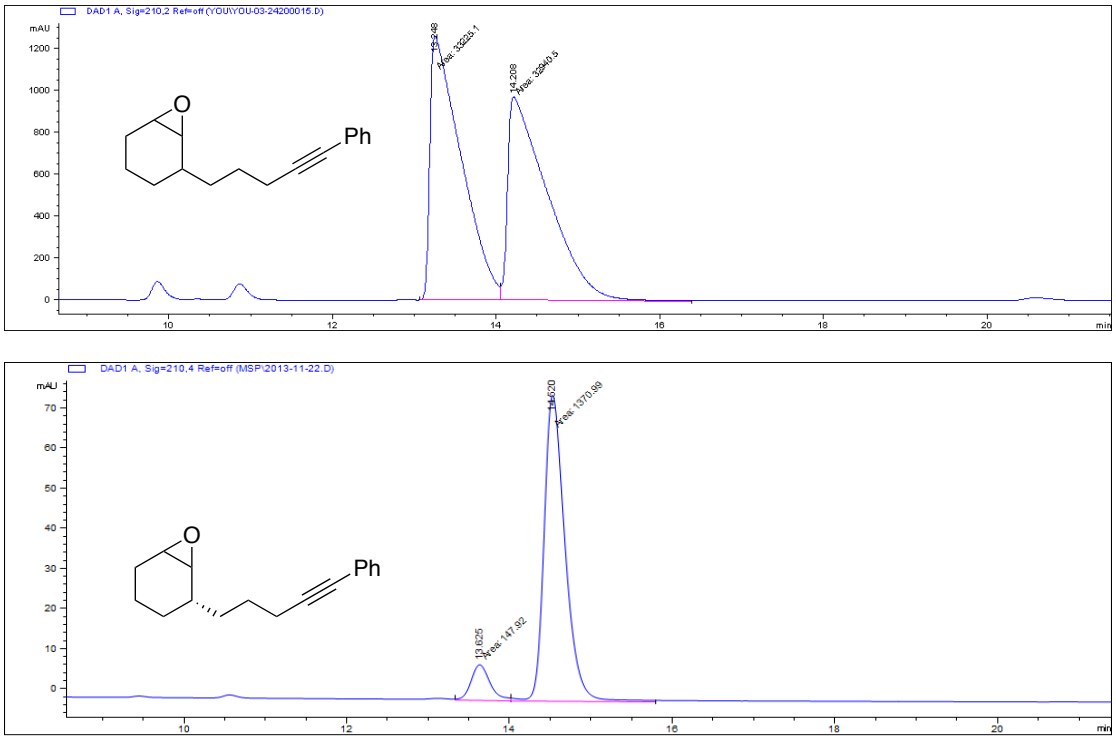
^{1}H NMR:



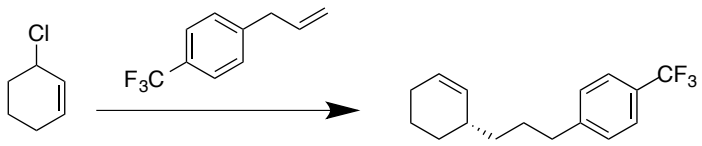
^{13}C NMR:



HPLC traces:



(S)-(+)-1-(3-(Cyclohex-2-en-1-yl)propyl)-4-(trifluoromethyl)benzene (2.30)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)- **Ligand L1** (21.6 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 1-allyl-4-(trifluoromethyl)benzene (0.17ml, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 25 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise.

The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr (T = 30 °C and 400 mbar pressure) gave (*S*)-1-(3-(cyclohex-2-en-1-yl)propyl)-4-(trifluoromethyl) benzene (100.6 mg, 0.37 mmol) in 93% yield.

GC analysis of the crude mixture of epoxides derived from **2.30** indicated an enantiomeric excess of 87% (Hydrodex 6-TBDM, 90-180^{o}C at 10 ^{o}C/min, hold for 10 min, 180-220^{o}C at 1 ^{o}C/min, 10psi); major enantiomer t_R = 28.4 min; minor enantiomer t_R = 28.8 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.20-1.43 (m, 3H), 1.50-1.56 (m, 1 H), 1.68-1.74 (m, 3 H), 1.76-1.83 (m, 1 H), 1.96-2.00 (m, 2 H), 2.06-2.13 (m, 1 H), 2.66-2.70 (t, 2 H, J= 7.74 Hz), 5.56-5.60 (m, 1H), 5.66-5.71 (m, 1H), 7.29-7.32 (m. 2 H), 7.53-7.55 (d, 2H, J= 7.87 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 21.5, 25.4, 28.6, 29.0, 35.0, 35.9, 36.0, 125.2 (2C), 127.1, 128.0 (q, J (C, F)=31.0 Hz), 128.7, 131.8, 146.8.

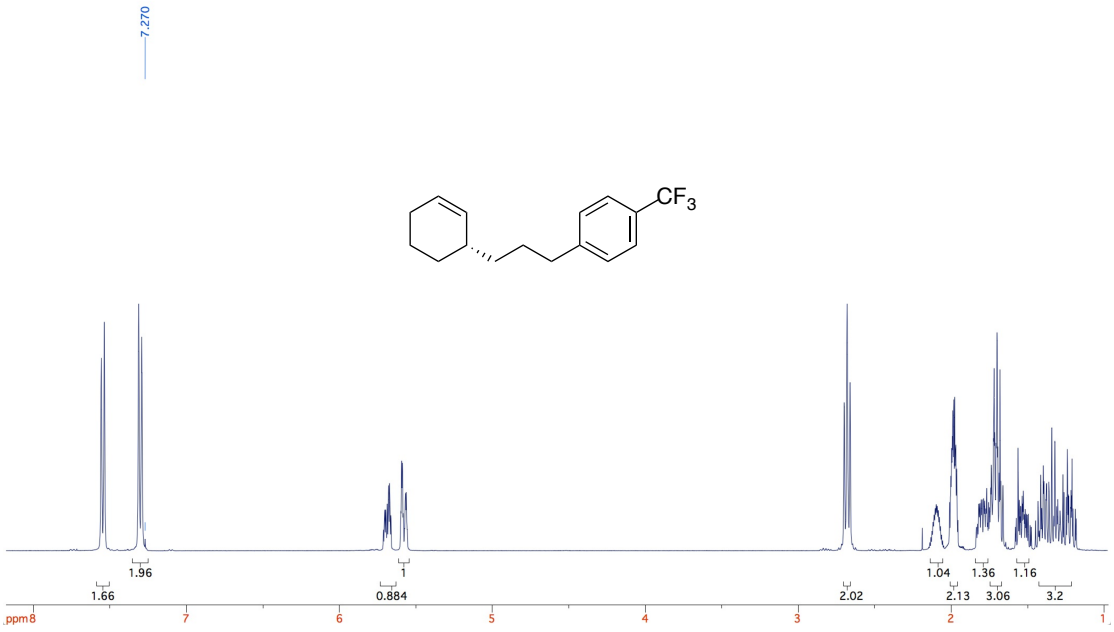
^{19}F NMR (380 MHz, $CDCl_3$) δ_F /ppm: -62.3.

HRMS (ESI) *m*/z calcd for $C_{16}H_{19}F_3$ $[M]^+$: 268.1439, found: 268.1437.

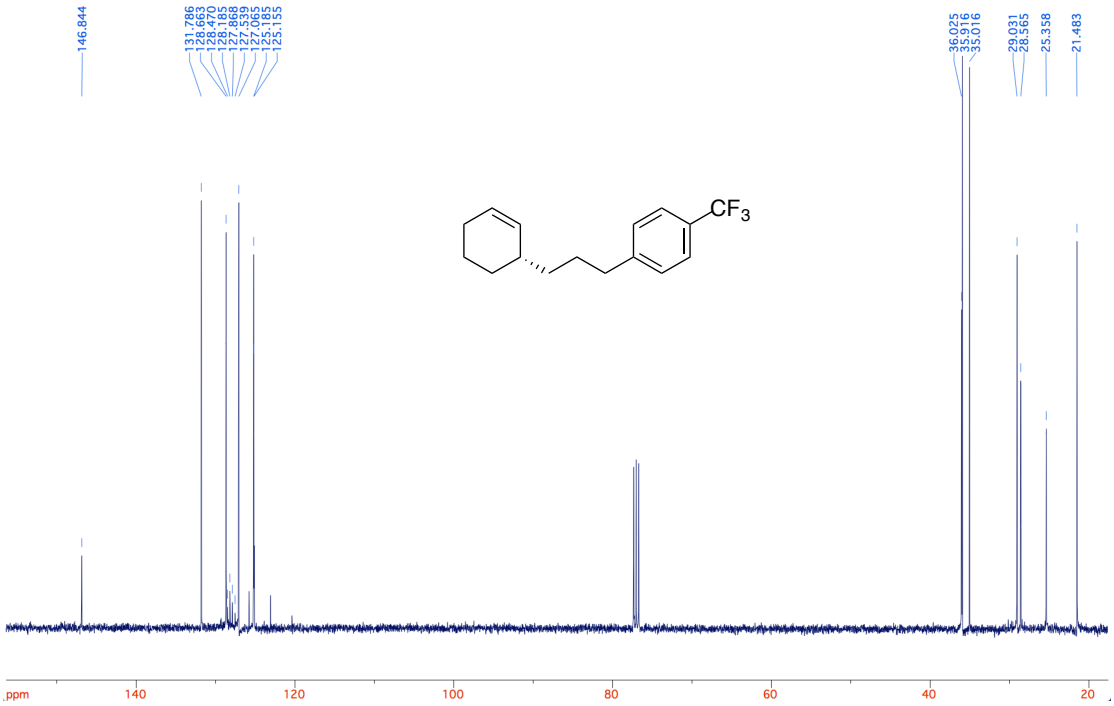
IR (ATR) ν (cm^{-1}, $CHCl_3$): 720, 843, 1018, 1067, 1122, 1162, 1323, 1618, 2928.

$[\alpha]^{20}_{589}$ = + 41.3 (c=2.62 in $CHCl_3$, 87% ee).

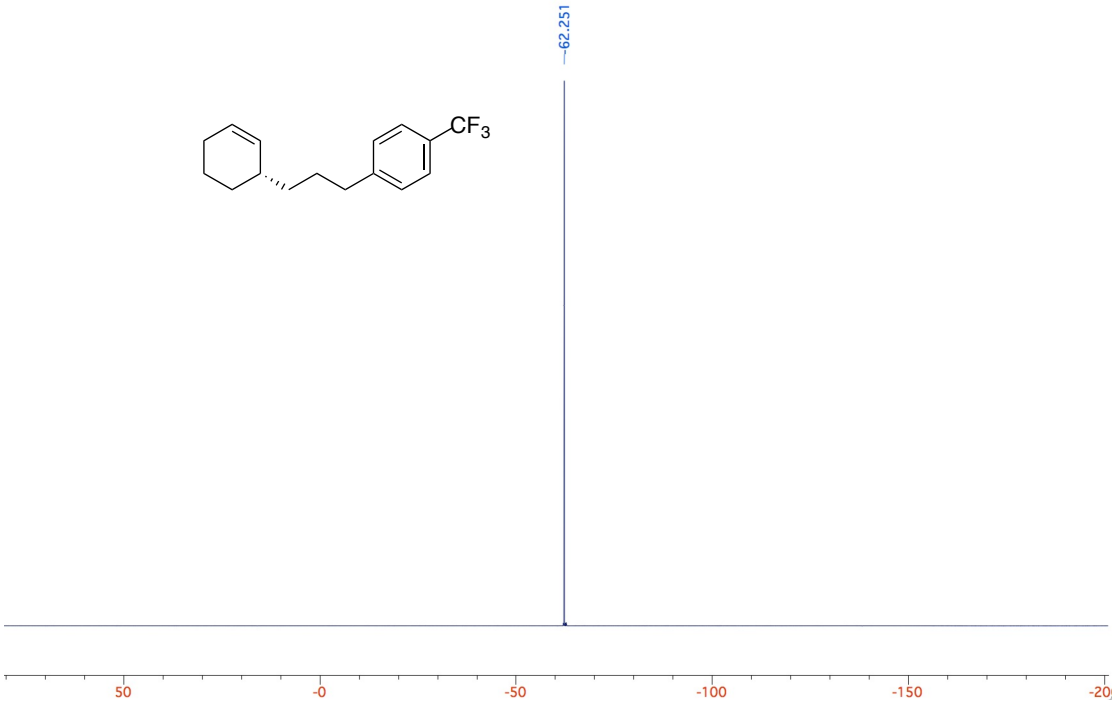
^{1}H NMR:



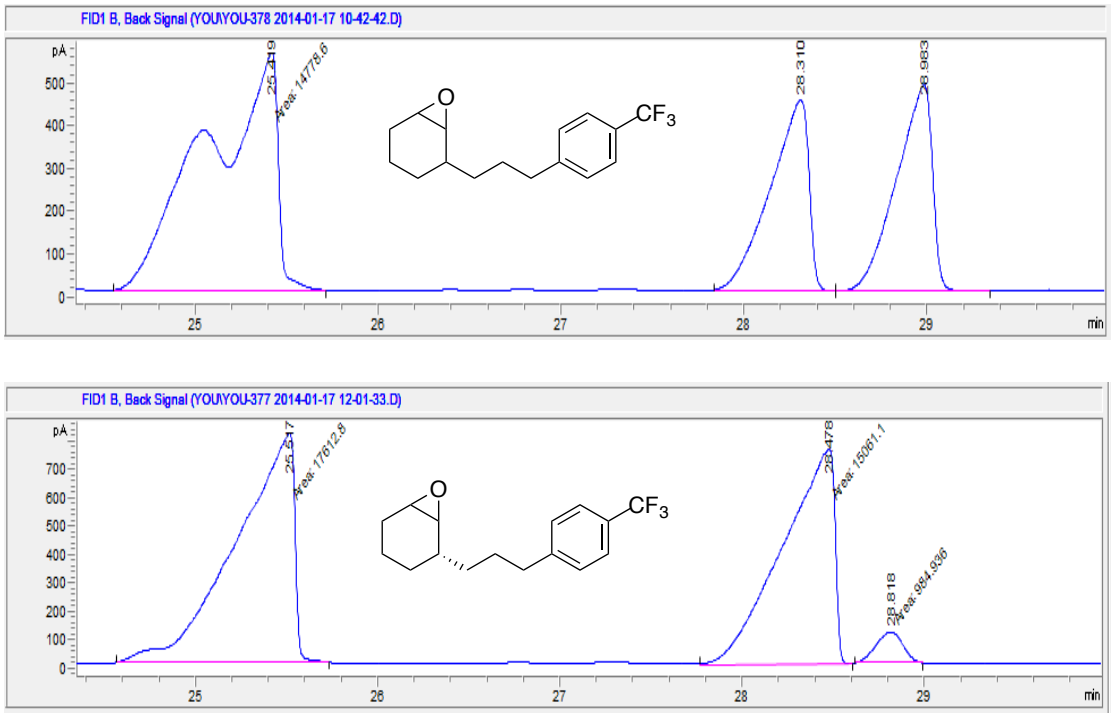
^{13}C NMR:



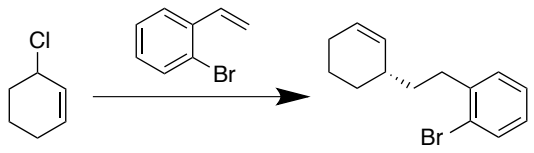
^{19}F NMR:


-62.251
CF3
50
-0
-50
-100
-150
-20

GC traces:


FID1 B, Back Signal (YOU\YOU-378 2014-01-17 10-42-42.D)
pA
25.419
Area: 14778.6
28.310
28.983
O
CF3
min
FID1 B, Back Signal (YOU\YOU-377 2014-01-17 12-01-33.D)
pA
25.417
Area: 17612.8
28.478
Area: 15061.1
28.818
Area: 984.936
O
CF3
min

(S)-(+)-1-Bromo-2-(2-(cyclohex-2-en-1-yl)ethyl)benzene (2.31)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)- **Ligand L1** (21.6 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 2-bromostyrene (0.13 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr (T = 60 °C and 10 mbar pressure) gave (S)-(-)-1-bromo-2-(2-(cyclohex-2-en-1-yl)ethyl)benzene (82.7 mg, 0.31 mmol) in 78% yield.

GC analysis of the crude mixture of epoxides derived from **2.31** indicated an enantiomeric excess of 87% (Hydrodex 6-TBDM, 90-200^{o}C at 1 ^{o}C/min, 10psi); major enantiomer t_R = 102.9 min; minor enantiomer t_R = 103.8 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.34-1.40 (m, 1H), 1.57-1.66 (m, 3 H), 1.76-1.81 (m, 1 H), 1.87-1.92 (m, 1 H), 2.01-2.04 (m, 2 H), 2.15-2.20 (m, 1 H), 2.75-2.85 (m, 2 H), 5.66-5.70 (m, 1H), 5.72-5.76 (m, 1H), 7.04-7.08 (m. 1 H), 7.24-7.25 (m, 2H), 7.53-7.55 (d, 1H, J= 7.89 Hz).

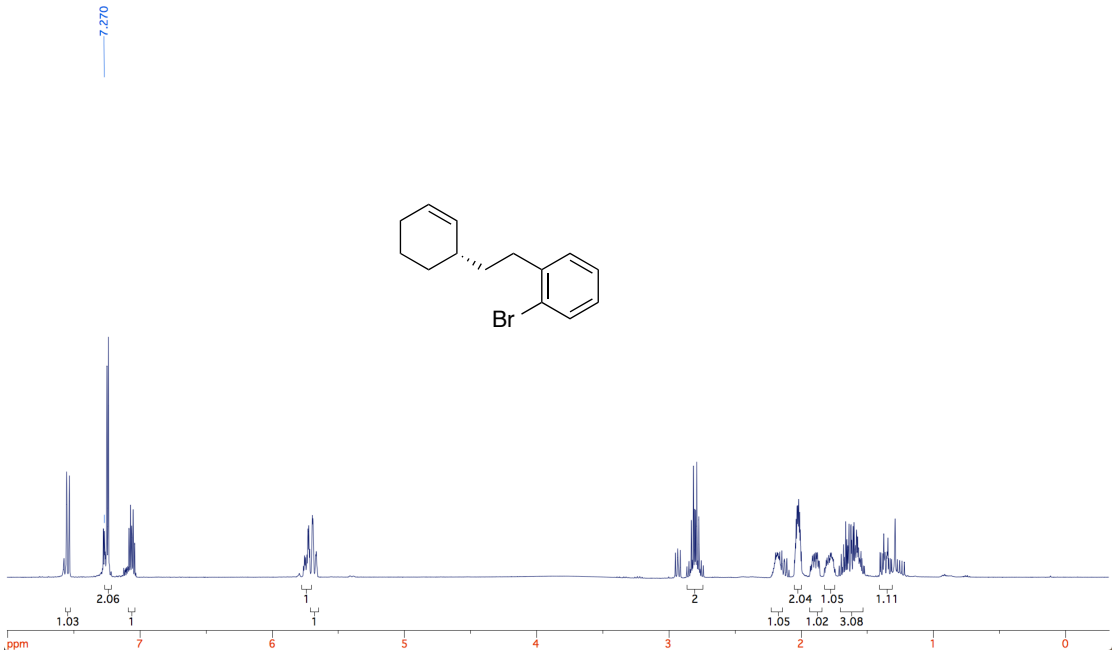
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm : 21.5, 25.4, 28.9, 33.7, 35.1, 36.6, 124.5, 127.3, 127.4, 127.5, 130.3, 131.6, 132.8, 142.2.

HRMS (ESI) *m*/z calcd for $C_{14}H_{17}Br$ $[M]^+$: 264.0514, found: 264.0515.

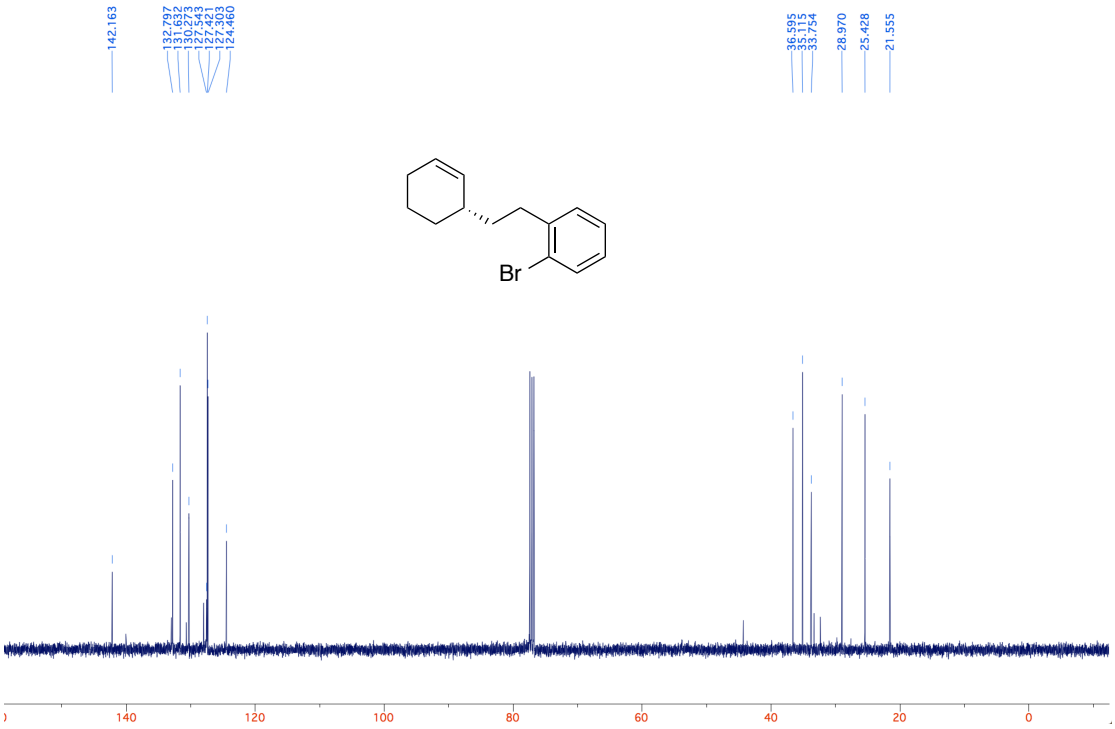
IR (ATR) ν (cm^{-1}, $CHCl_3$): 658.3, 721.1, 1023.2, 1438.9, 1470.6, 1567.2, 2855.3, 2924.6, 3015.7

$[\alpha]^{20}_{589}$ = + 37.2 (c= 2.85 in $CHCl_3$, 87% ee).

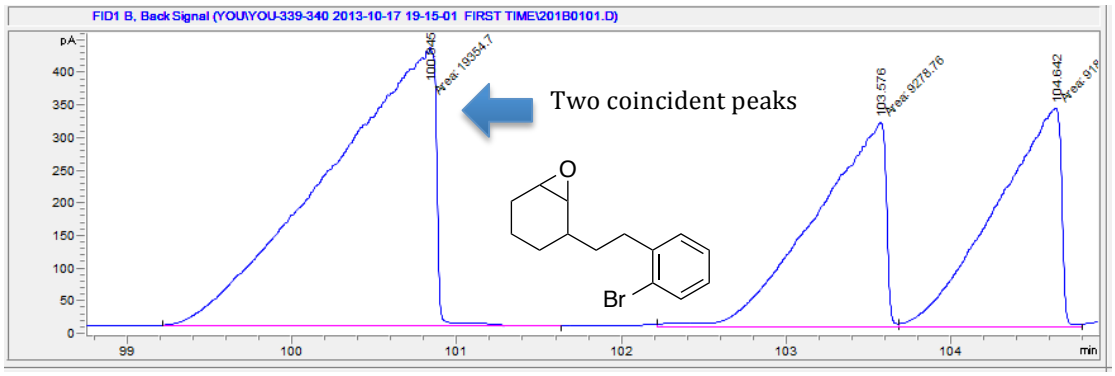
^{1}H NMR:

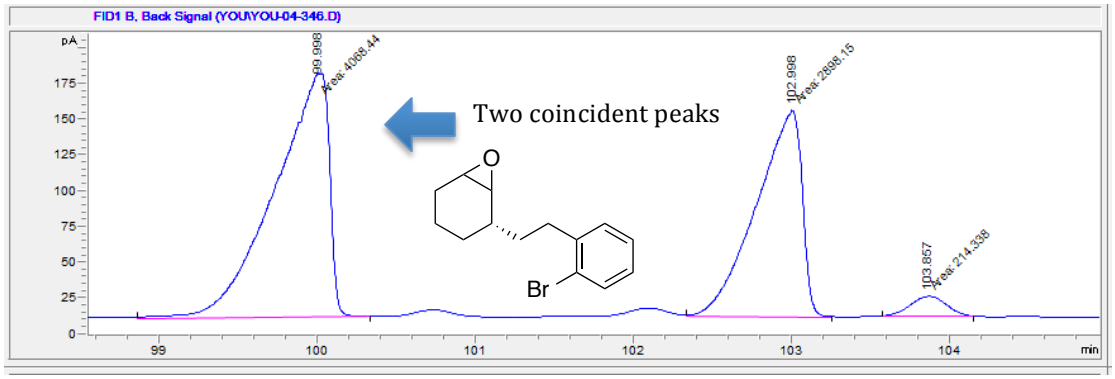


^{13}C NMR:

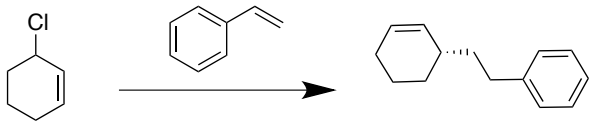

142.163
132.797
131.632
130.273
127.543
127.421
127.303
124.460
36.595
33.715
33.754
28.970
25.428
21.555
Br
140
120
100
80
60
40
20
0

GC traces:


FID1 B, Back Signal (YOU\YOU-339-340 2013-10-17 19-15-01 FIRST TIME\201B0101.D)
pA
Area: 19354.7
Two coincident peaks
Area: 9278.76
Area: 91
O
Br
99
100
101
102
103
104
min


FID1 B, Back Signal (YOU\YOU-04-346.D)
pA
Area: 4068.44
Two coincident peaks
Area: 2898.15
Area: 214.338
O
Br
99
100
101
102
103
104
min

(S)-(+)-(2-(Cyclohex-2-en-1-yl)ethyl)benzene (2.32)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)- **Ligand L1** (21.6 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, styrene (0.12 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr (T = 85 °C and 20 mbar pressure) gave (*S*)-(2-(cyclohex-2-en-1-yl)ethyl)benzene (49 mg, 0.26 mmol) in 66% yield.

GC analysis of the crude mixture of epoxides derived from **2.32** indicated an enantiomeric excess of 87% (Hydrodex 6-TBDM, 90-200^{o}C at 1 ^{o}C/min, 10psi); major enantiomer t_R = 78.0 min; minor enantiomer t_R = 79.9 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.25-1.33 (m, 1 H), 1.50-1.79 (m, 4H), 1.82-1.87 (m, 1 H), 1.98-2.02 (m, 2 H), 2.08-2.13 (m, 1 H), 2.64-2.69 (m, 2 H), 5.62-5.66 (m, 1H), 5.69-5.74 (m, 1H), 7.16-7.23 (m, 3H), 7.28-7.32 (m, 2H).

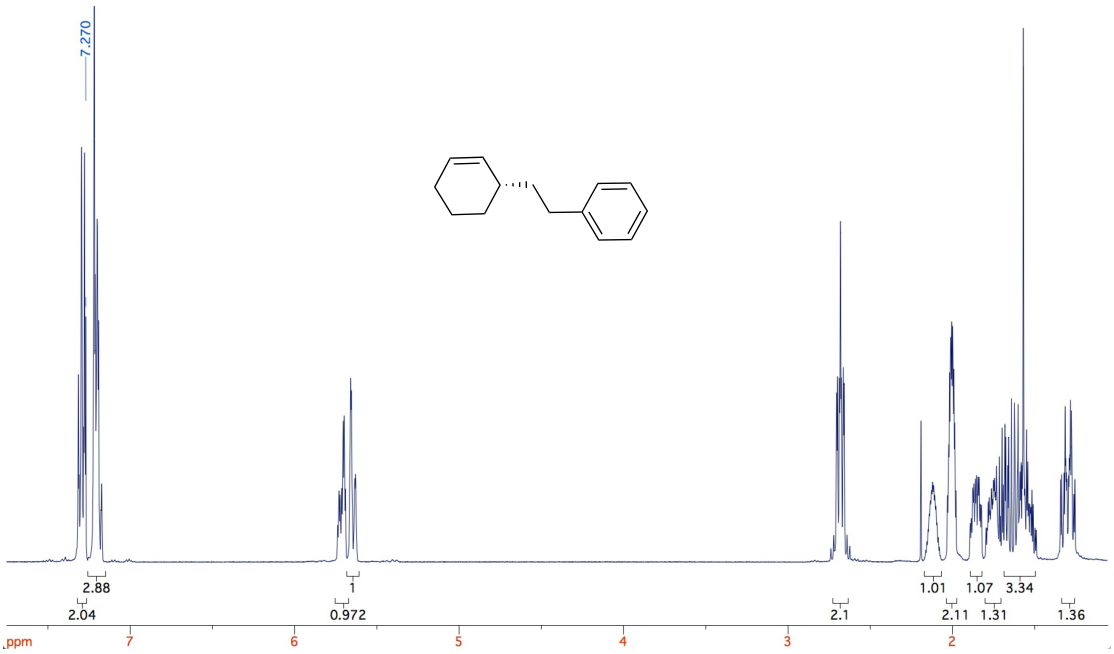
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm : 21.4, 25.4, 29.0, 33.3, 34.7, 38.2, 125.6, 127.1, 128.3, 128.4, 131.7, 142.8.

HRMS (ESI) *m*/z calcd for $C_{14}H_{18}$ $[M]^+$: 186.1409, found: 186.1407.

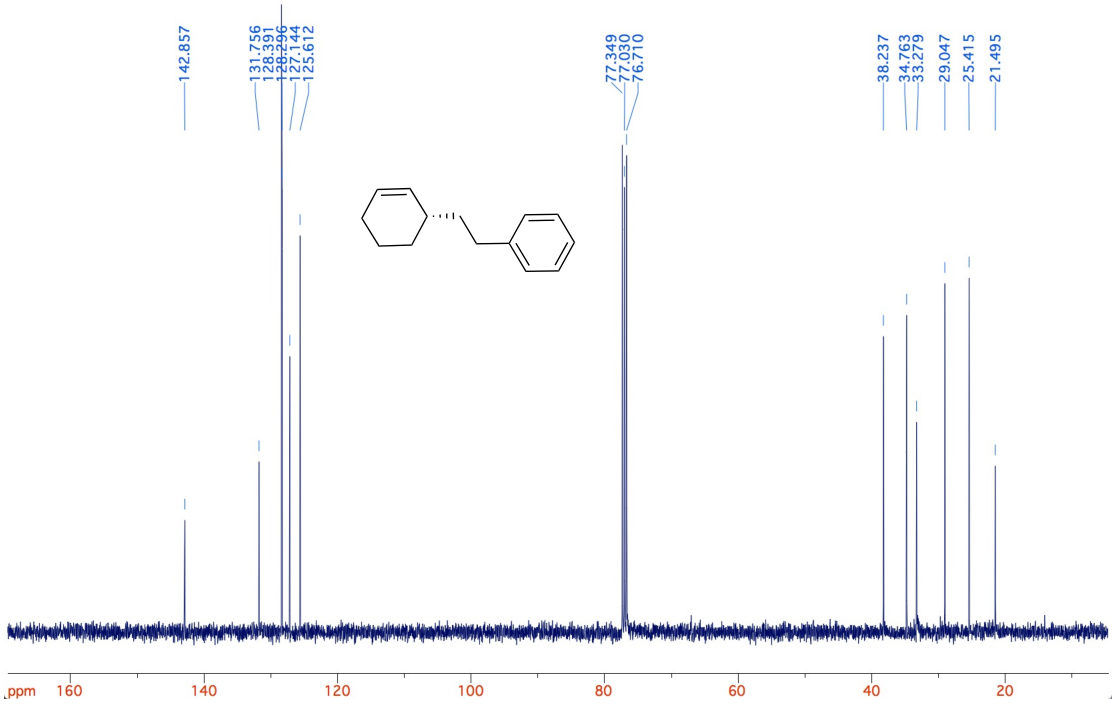
IR (ATR) ν (cm^{-1}, $CHCl_3$): 772.7, 1219.7, 2922.0.

$[\alpha]^{20}_{589}$ = + 14.4 (c= 0.25 in $CHCl_3$, 83% ee)

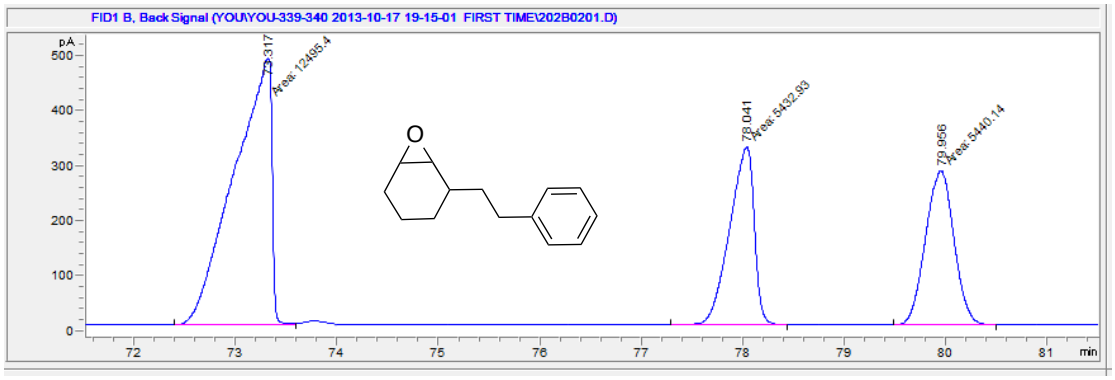
^{1}H NMR:

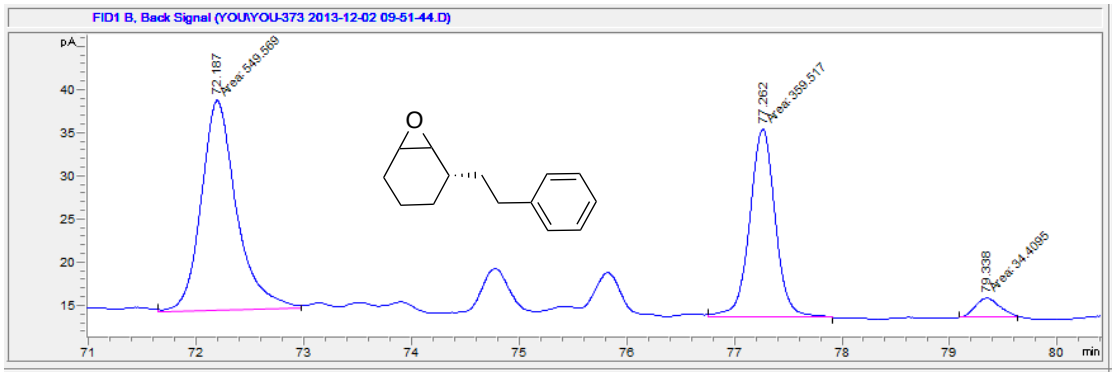


^{13}C NMR:

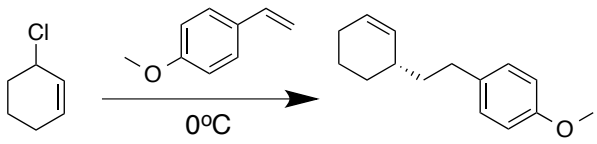

142.857
131.756
128.391
128.246
127.244
125.612
77.349
77.030
76.710
38.237
34.763
33.279
29.047
25.415
21.495
ppm
160
140
120
100
80
60
40
20

GC traces:


FID1 B, Back Signal (YOU\YOU-339-340 2013-10-17 19-15-01 FIRST TIME\202B0201.D)
pA
500
400
300
200
100
0
79.317
Area: 12495.4
78.041
Area: 5432.93
79.956
Area: 5440.14
72
73
74
75
76
77
78
79
80
81
min


FID1 B, Back Signal (YOU\YOU-373 2013-12-02 09-51-44.D)
pA
40
35
30
25
20
15
72.187
Area: 549.569
77.262
Area: 359.517
79.338
Area: 34.4095
71
72
73
74
75
76
77
78
79
80
min

(S)-(+)-1-(2-(Cyclohex-2-en-1-yl)ethyl)-4-methoxybenzene (2.33)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)- **Ligand L1** (21.6 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature before cooled with ice bath for 10 min. Meanwhile, 4-Vinylanisole (0.13 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min), then cooled with ice bath for 10 min. The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring in the ice bath for 10 additional minutes 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight at 0°C before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr (T = 120 °C and 25 mbar pressure) gave (*S*)-1-(2-(cyclohex-2-en-1-yl) ethyl)-4-methoxybenzene (54.6 mg, 0.26 mmol) in 63% yield.

GC analysis of the crude mixture of epoxides derived from **2.33** indicated an enantiomeric excess of 95% (Hydrodex 6-TBDM, 60-200°C at 1 °C/min, 10psi); major enantiomer t_R = 136.5 min; minor enantiomer t_R = 137.2 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.53-1.66 (m, 2H), 1.74-1.77 (m, 1 H), 1.84-1.86 (m, 1 H), 1.98-2.03 (m, 2 H), 2.07-2.13 (m, 1 H), 2.60-2.65 (m, 2 H), 3.81 (s, 3 H), 5.63-5.66 (m, 1H), 5.70-5.74 (m, 1H), 6.84-6.86 (m, 2H), 7.12-7.14 (m, 2H).

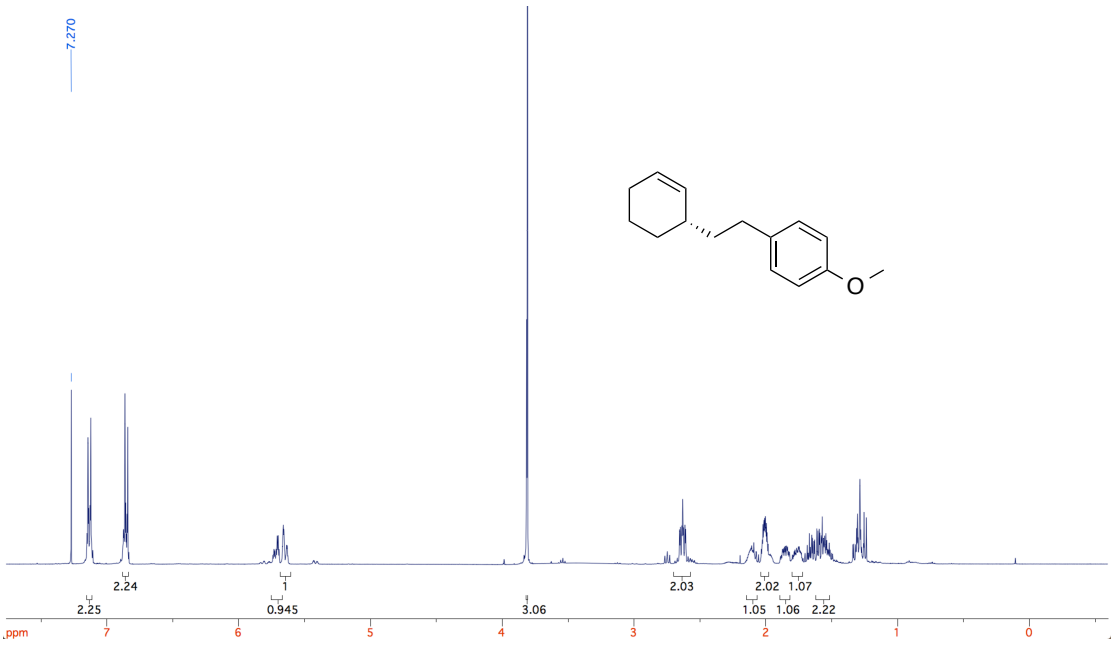
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm : 21.5, 25.4, 29.1, 32.3, 34.7, 38.5, 55.3, 113.7, 127.1, 129.2, 131.8, 134.9, 157.6.

HRMS (ESI) *m*/z calcd for $C_{15}H_{20}O$ $[M]^+$: 216.1514, found: 216.1520.

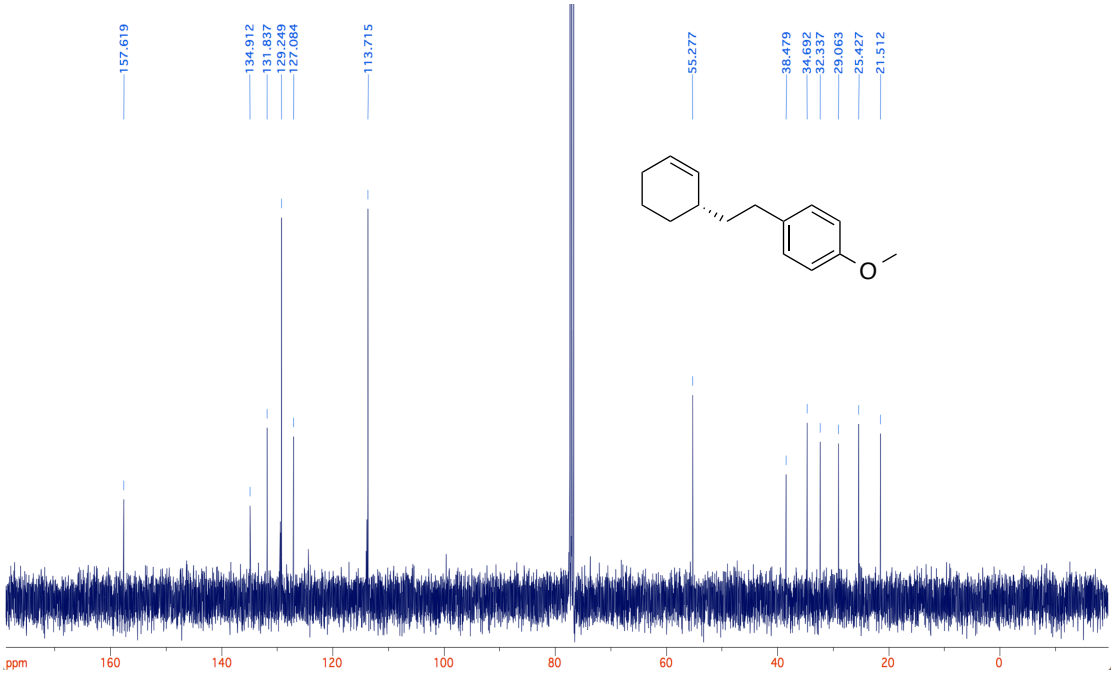
IR (ATR) ν (cm^{-1}, $CHCl_3$): 822.1, 1038.9, 1177.1, 1246.0, 1463.6, 1511.9, 1612.6, 2925.5.

$[\alpha]^{20}_{589}$ =+ 45.7 (c= 0.505 in $CHCl_3$, 95% ee).

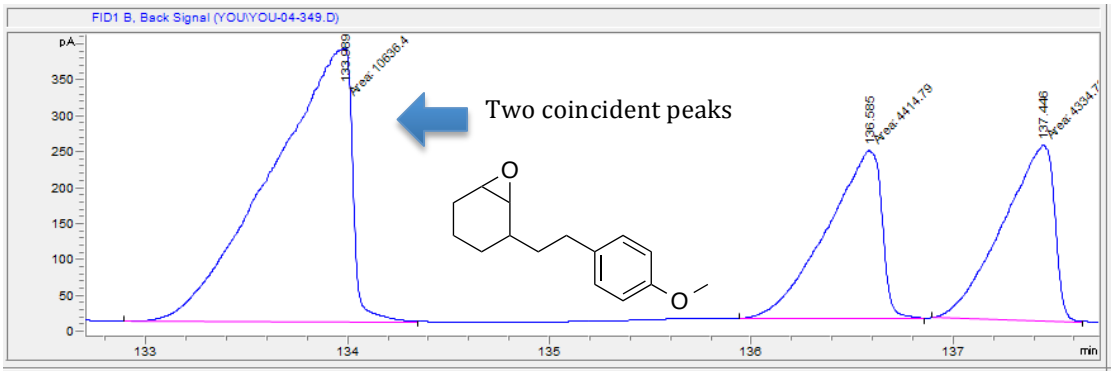
^{1}H NMR:

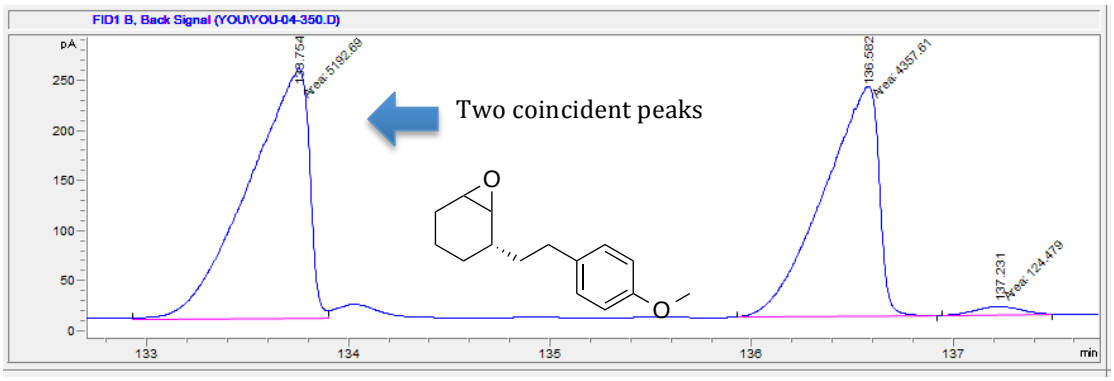


^{13}C NMR:

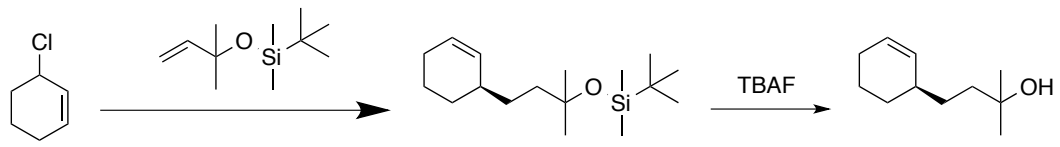

157.619
134.912
131.837
129.249
127.084
113.715
55.277
38.479
34.692
32.337
29.063
25.427
21.512
O
ppm
160
140
120
100
80
60
40
20
0

GC traces:


FID1 B, Back Signal (YOU\YOU-04-349.D)
pA
133.089
Area: 10636.4
Two coincident peaks
136.585
Area: 4414.79
137.446
Area: 4334.7
O
O
133
134
135
136
137
min


FID1 B, Back Signal (YOU\YOU-04-350.D)
pA
133.754
Area: 5192.69
Two coincident peaks
136.582
Area: 4357.61
137.231
Area: 124.479
O
O
133
134
135
136
137
min

(R)-(−)-(Cyclohex-2-en-1-yl)-2-methylbutan-2-ol (2.34)



In a 5ml flame dried flask, tert-butyldimethyl((2-methylbut-3-en-2-yl)oxy)silane (200 mg, 1.00 mmol, 2.50 eq) is dissolved in CH_2Cl_2 (0.40 mL) and then Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) is added in one portion. The mixture is smoothly stirred at room temperature under an argon atmosphere until it becomes a clear solution (overnight). In another 5ml flame-dried flask CuI (7.6 mg, 0.04 mmol, 0.10 eq) and (*S,S,S*)- **Ligand L1** (21.6 mg, 0.04 mmol, 0.10 eq) are dissolved in $CHCl_3$ (0.8 mL) under an argon atmosphere. The mixture is stirred for 1 h at room temperature. The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave crude product. Then treated it with tetrebutylammonium fluoride solution (1M in THF, 6.4 ml, 6.4 mmol, 16 eq) in THF (5 mL) under an argon atmosphere in a reflux condition (T = 45 °C), affording aromatic smelling (R)-4-(cyclohex-2-en-1-yl)-2-methylbutan-2-ol. A second column to obtain the pure alcohol is necessary with 20% ethyl acetate in petrol. 45% yield was achieved based on the calculation of the corresponding alcohol (30 mg, 0.18 mmol).

GC analysis of the crude mixture of epoxides derived from the alcohol indicated an enantiomeric excess of 94% (Hydrodex 6-TBDM, 60-150°C at 1 °C/min, 10psi); major enantiomer t_R = 63.7, 83.9 min; minor enantiomer t_R = 64.4, 85.0 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.22 (s, 6 H), 1.25-1.26 (m, 1 H), 1.31-1.45 (m, 2 H), 1.48-1.56 (m, 3 H), 1.70-1.81 (m, 2 H), 1.95-2.05 (m, 3 H), 5.57-5.60 (m, 1H), 5.67-5.70 (m, 1H).

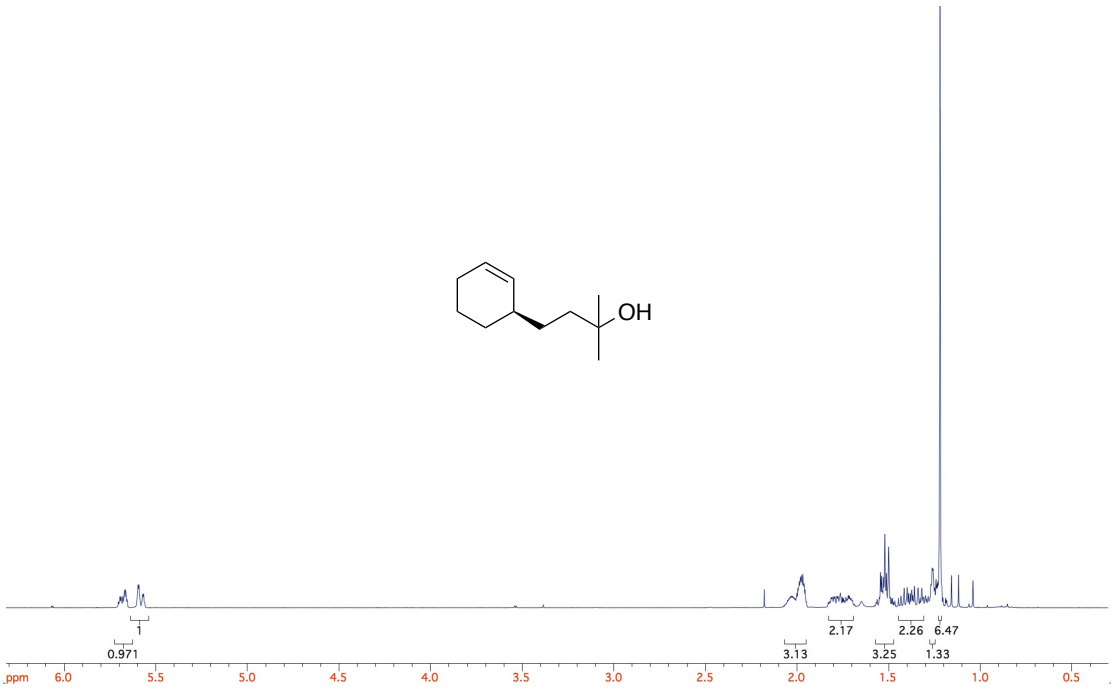
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 21.5, 25.4, 29.1, 29.20, 29.25, 30.8, 35.5, 41.1, 71.1, 127.1, 131.9.

HRMS (ESI) *m*/z calcd for $C_{11}H_{20}O$ $[M]^+$: 168.1514, found: 168.1511

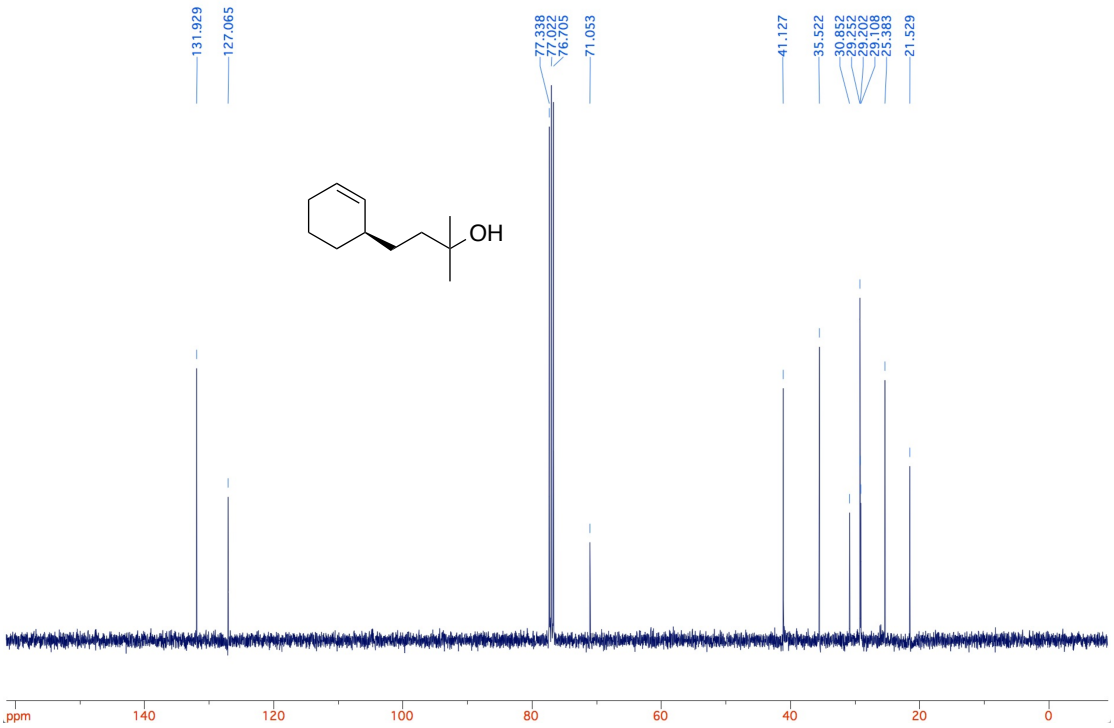
IR (ATR) ν (cm^{-1}, $CHCl_3$): 676.8, 719.4, 932.7, 1149.3, 1377.3, 1454.2, 2858.3, 2927.9, 2967.9, 3016.7,3362.4.

$[\alpha]^{20}_{589}$ = –31.3 (c= 0.75 in $CHCl_3$, 94% ee).

^{1}H NMR:



^{13}C NMR:



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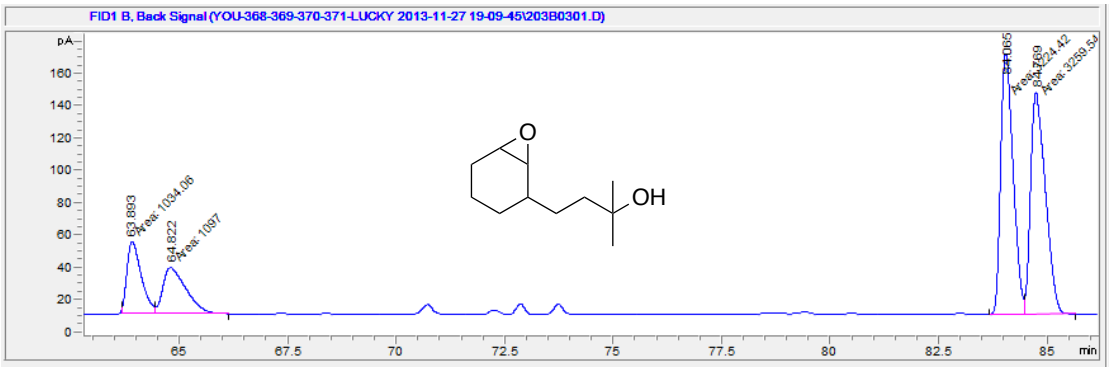
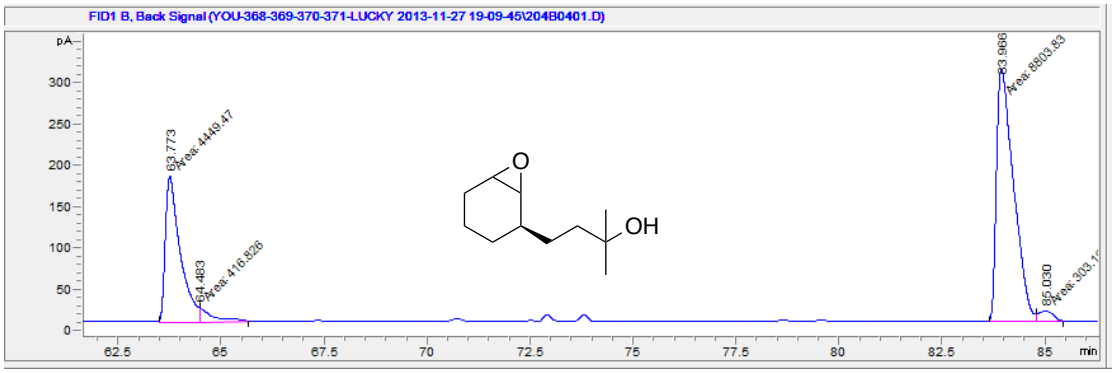
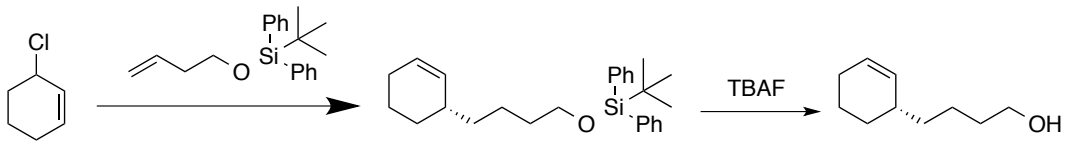




(S)-(+)-4-(Cyclohex-2-en-1-yl) butan-1-ol (2.35)



Cp_2ZrHCl (206 mg, 0.8 mmol, 2.0 eq.) was added in one portion to a stirred solution of (but-3-en-1-yloxy)(tert-butyl)diphenylsilane (310 mg, 1.0 mmol, 2.5 eq.) in CH_2Cl_2 (0.4 mL) and stirred until a clear yellow solution was obtained (20 min). Simultaneously, in a different round-bottom flask, CuI (7.7 mg, 0.04 mmol, 0.1 eq.) and (*R,R,R*)-**Ligand L1** (21.6 mg, 0.04 mmol, 0.1 eq.) were dissolved in $CHCl_3$ (0.8 mL) and stirred for 1 h. The resulting catalyst complex mixture was then added to the freshly prepared alkenylzirconium species. After 10 min, 3-chlorocyclohex-1-ene (48 µL, 0.4 mmol, 1 eq.) was added to the resulting black solution and stirred for 12 h. The reaction mixture was diluted with Et_2O (2 mL) and NH_4Cl (aq., 1M) was added. The mixture was partitioned, then the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with $NaHCO_3$ (aq., sat.), dried over $MgSO_4$, filtered and concentrated under reduced pressure. After flash column chromatography (SiO_2, 0-2% Et_2O in pentane), a mixture of (S)-tert-butyl(4-(cyclohex-2-en-1-yl) butoxy)diphenylsilane and (but-3-en-1-yloxy)(tert-butyl)diphenylsilane was obtained as a pale yellow oil. TBAF in THF (0.8 mL, 1M, 0.8 mmol, 2.0 eq.) was added dropwise the yellow oil dissolved in THF (3 mL) and stirred for 3h30. The reaction mixture was diluted with Et_2O (1 mL) and NaCl (aq., sat.) was added. The mixture was partitioned, then the aqueous phase was extracted with Et_2O (3 x 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. After flash column chromatography (SiO_2, 30% Et_2O in hexane), (*S*)-4-(cyclohex-2-en-1-yl)butan-1-ol was obtained as a colourless oil (34 mg, 0.22 mmol, 55%).

The enantiomeric excess 89%, was determined by GC on a chiral stationary phase after derivatisation into the corresponding epoxides (Hydrodex 6TBDM column, Method: 60-0-1-150-30, 10 psi, major enantiomer t_R = 95.5, 104.6 min; minor enantiomer t_R = 94.8, 107.5 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 5.71-5.64 (m, 1H), 5.58 (dd, ^3J=9.8, 2.1 Hz, 1H), 3.66 (t, ^3J=6.6 Hz, 2H), 2.11-2.01 (m, 1H), 2.01-1.94 (m, 2H), 1.84-1.67 (m, 2H), 1.64-1.55 (m, 2H), 1.55-1.45 (m, 1H), 1.45-1.37 (m, 2H), 1.37-1.28 (m, 1H), 1.28-1.16 (m, 2H);

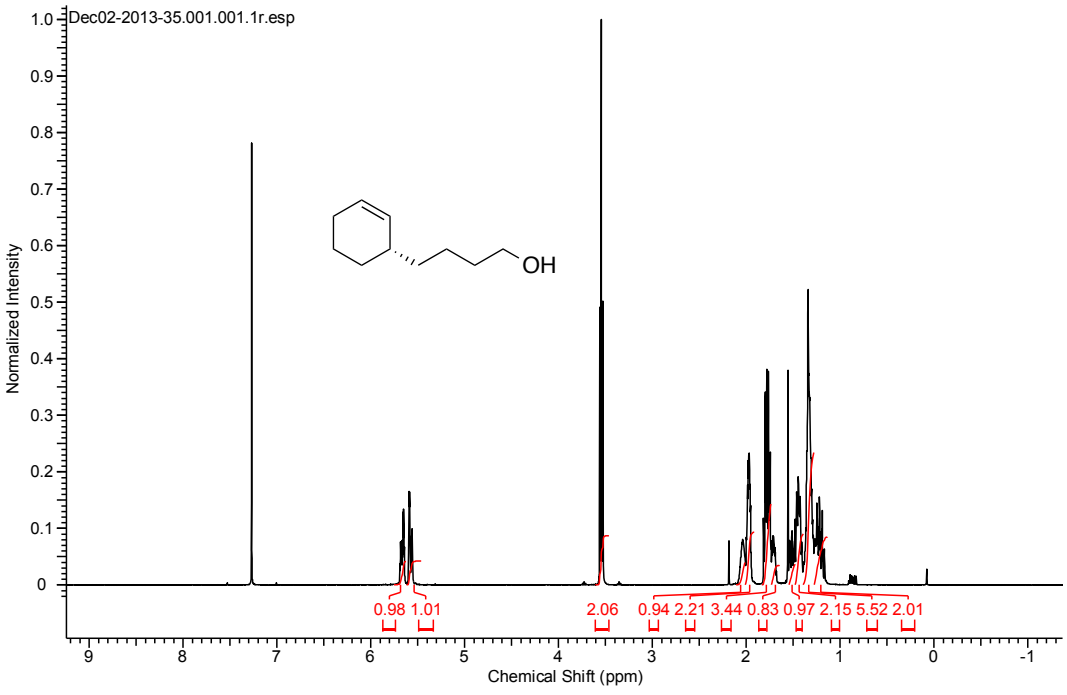
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 132.0, 126.9, 63.0, 36.1, 35.1, 33.0, 29.1, 25.4, 23.1, 21.5;

HRMS (EI/FI) *m/z* cald for $C_{10}H_{18}O$ $[M]^+$: 154.1358; found: 154.1354;

IR (ATR) ν (cm^{-1}): 3327, 3016, 2928, 2858, 1447, 1059, 720, 675.

$[\alpha]^{20}_{589}$ = +26.64 (*c* 1.02, $CHCl_3$, 89% ee).

^{1}H NMR:



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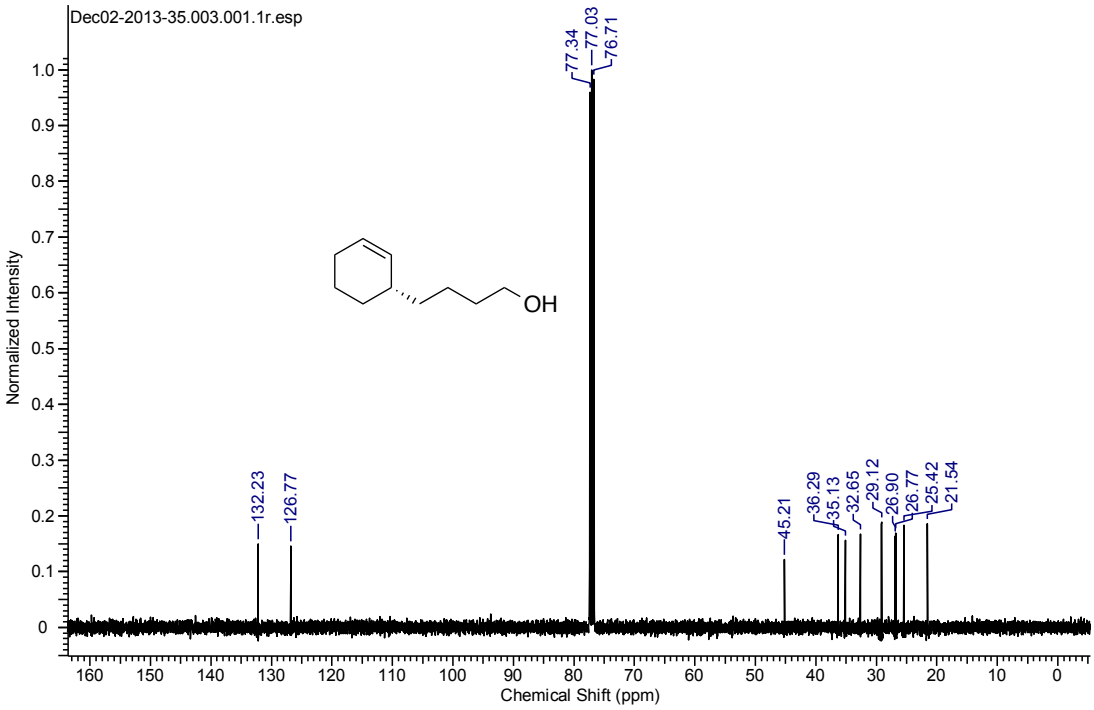
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76.71
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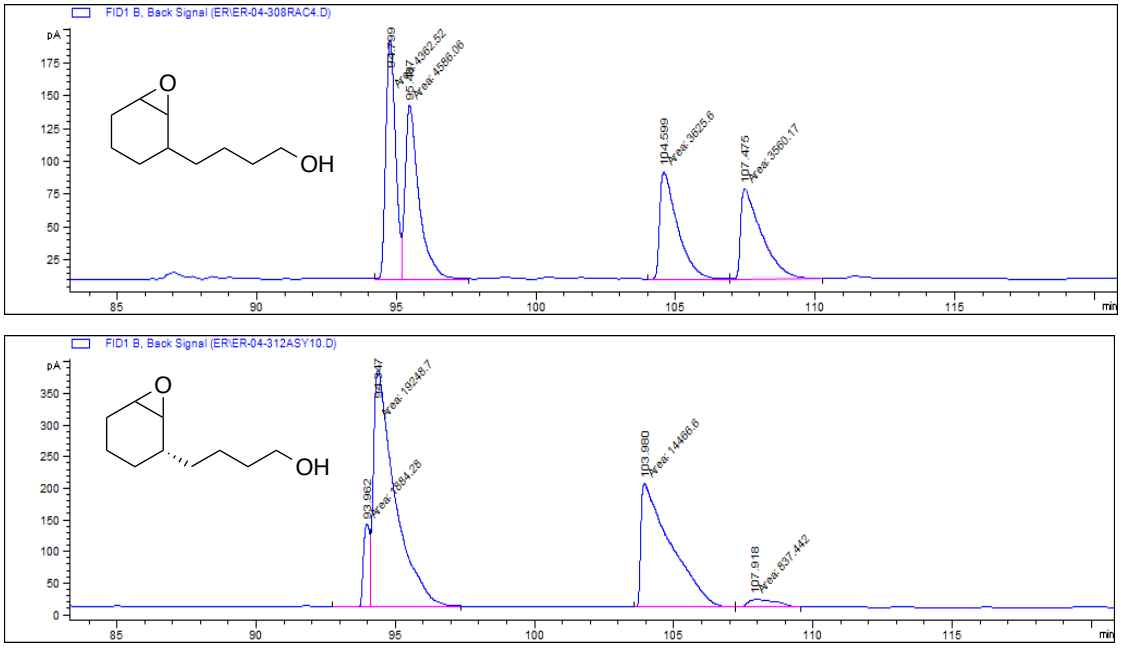
OH

GC traces: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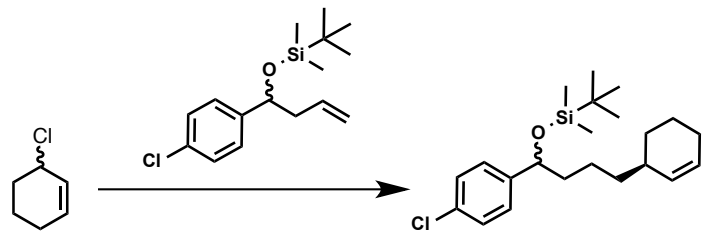
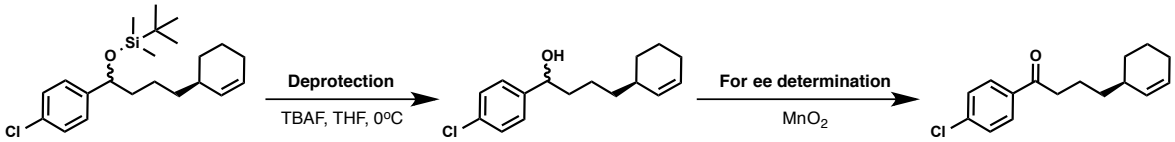
(S)-(–)-tert-Butyl(1-(4-chlorophenyl)-4-(cyclohex-2-en-1-yl)butoxy)dimethylsilane (2.36)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S,S*)- **Ligand L1** (21.6 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, tert-butyl ((1-(4-chlorophenyl) but-3-en-1-yl) oxy) dimethylsilane (297 mg, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave (*S*)-(-)-tert-butyl(1-(4-chlorophenyl) -4-(cyclohex-2-en-1-yl)butoxy)- -dimethylsilane (137.9 mg, 0.36 mmol) in 91% yield.



For ee determination, the product was treated with tetrebutylammonium fluoride solution (1M in THF, 1.6 ml, 1.6 mmol, 4 eq) in THF (5 mL) under an argon atmosphere at 0°C for 4h. The reaction mixture was diluted with Et_2O (1 mL) and NaCl (aq., sat.) was added. The mixture was partitioned, and then the aqueous phase was extracted with Et_2O (3 x 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was directed added to a flame-dried flask, and then Et_2O (6 mL) and 1g MnO_2 (12 mmol, 30 eq.) were added and left stirring overnight. Worked up the reaction by filtering it through the cotton, removed the solvent and the crude product was directly used for the enantiomeric excess determination.

Enantiomeric excess of 91% was determined by HPLC of the associated ketone [Chiralpak® IA; flow: 1.0 mL/min; hexane/i-PrOH: 100: 0; λ = 210 nm; major enantiomer t_R = 57.5 min; minor enantiomer t_R = 72.1 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: -0.12 (s, 3H), 0.05 (s, 3 H), 0.9 (s, 9 H), 1.17-1.36 (m, 4 H), 1.39-1.46 (m, 1 H), 1.49-1.60 (m, 2 H), 1.65-1.78 (m, 3 H), 1.95-2.03 (m, 3H), 4.61-4.64 (m, 1H), 5.54-5.56 (d, 1H, J=10.13 Hz), 5.64-5.68 (m, 1H), 7.22-7.30 (m, 4H).

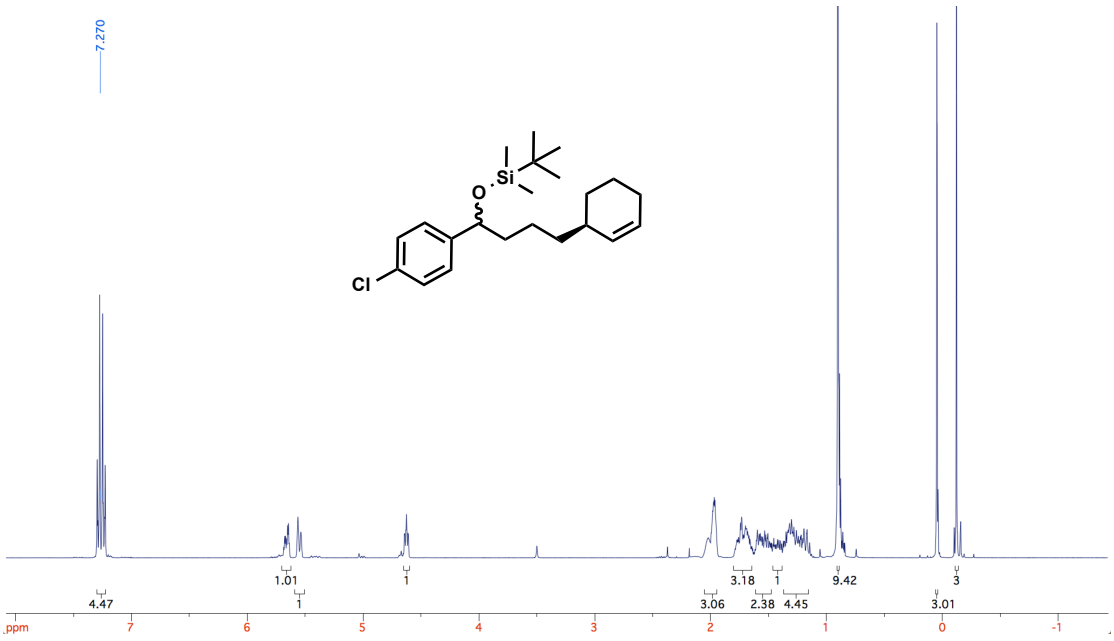
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: -4.9, -4.5, 18.2, 21.5, 22.9, 25.4, 25.8, 29.1, 35.1, 36.3, 41.2, 74.4, 126.8, 127.2, 128.2, 132.1, 132.3, 144.5.

HRMS (ESI) *m*/z calcd for $C_{22}H_{35}ClOSi$ $[M]^+$: 378.2146, found: 378.2180.

IR (ATR) ν (cm^{-1}, $CHCl_3$): 675.8, 718.4, 775.3, 835.3, 1014.1, 1084.9, 1251.9, 1360.9, 1471.5, 1489.2, 2856.4, 2928.3.

$[\alpha]^{20}_{589}$ = –30.9 (c= 3.5 in $CHCl_3$, 91% ee).

^{1}H NMR:



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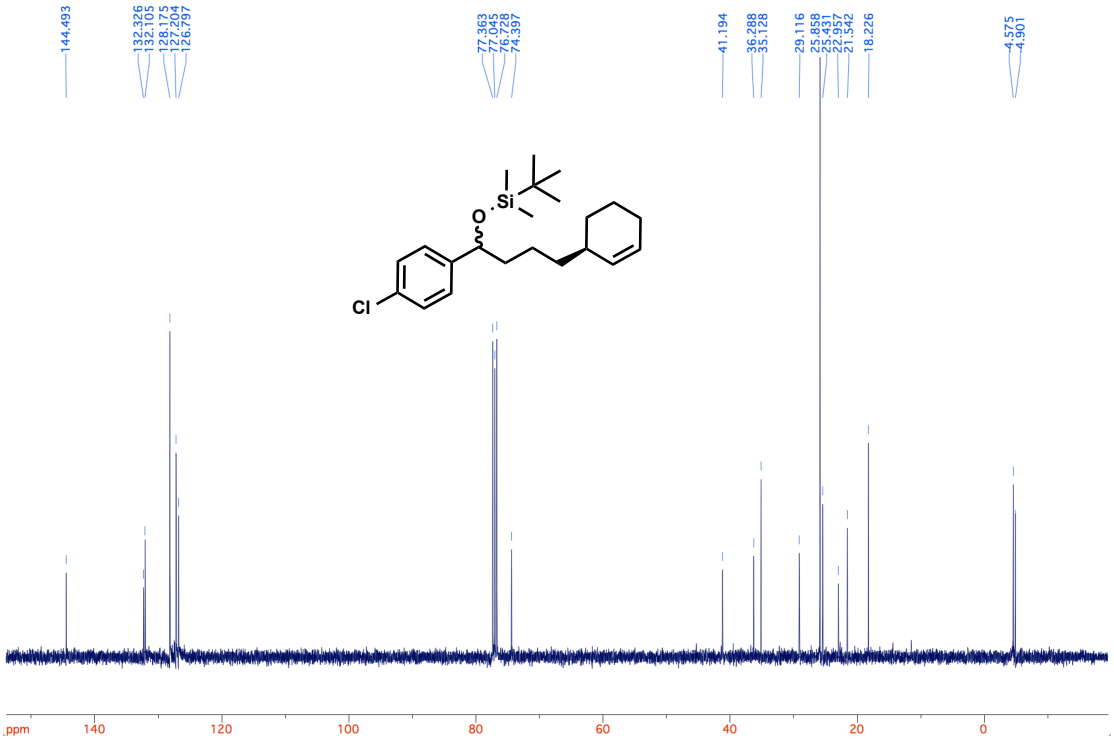

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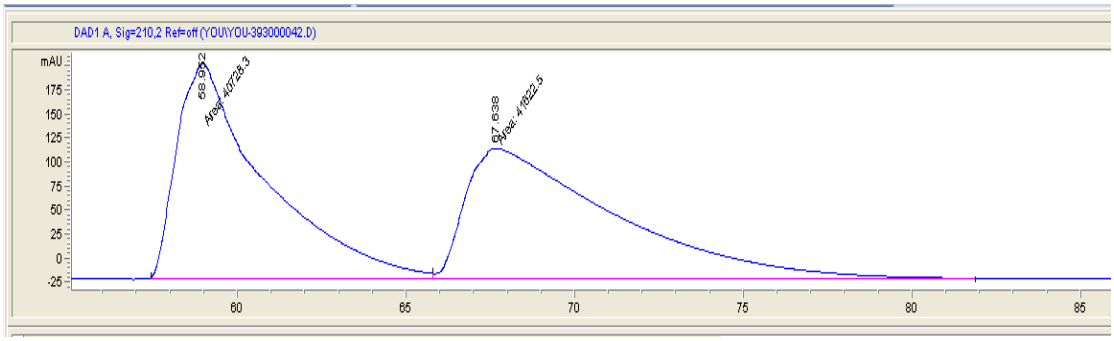
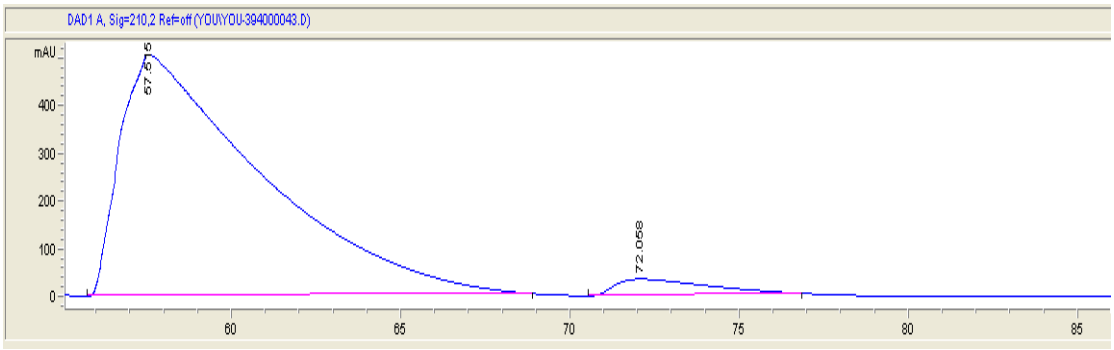
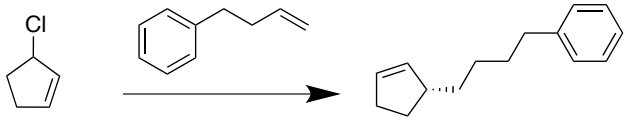




(R)-(+)-(4-(Cyclopent-2-en-1-yl)butyl)benzene (2.37)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R,R*)- **Ligand L1** (21.6 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 4-Phenyl-1-butene (0.15ml, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclopent-1-ene (41.0 mg, 0.40 mmol, 1.00 eq)was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0

mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr (T = 110 °C and 55 mbar pressure) gave (*R*)-(-)-(4-(cyclopent-2-en-1-yl)butyl)benzene (45.7 mg, 0.23 mmol) in 57% yield.

GC analysis of the crude mixture of epoxides derived from **2.37** indicated an enantiomeric excess of 92% (Hydrodex 6-TBDM, 60-110^{o}C at 5 ^{o}C/min, 110-140^{o}C at 10 ^{o}C/min, hold for 10 min, 140-170^{o}C at 5 ^{o}C/min, hold for 10 min, 170-210^{o}C at 5 ^{o}C/min, 10psi); major enantiomer t_R = 39.5 min, 41.3 min; minor enantiomer t_R = 39.2 min, 41.7 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.33-1.49 (m, 5 H), 1.66-1.68 (m, 2 H), 2.05-2.09(m, 1H), 2.32-2.37(m, 2 H), 2.65- 2.69 (t, 3 H, J =7.8 Hz), 5.71-5.73 (m, 1 H), 5.74-5.77 (m, 1 H), 7.22- 7.24 (m, 3 H), 7.28 - 7.33 (m, 2 H).

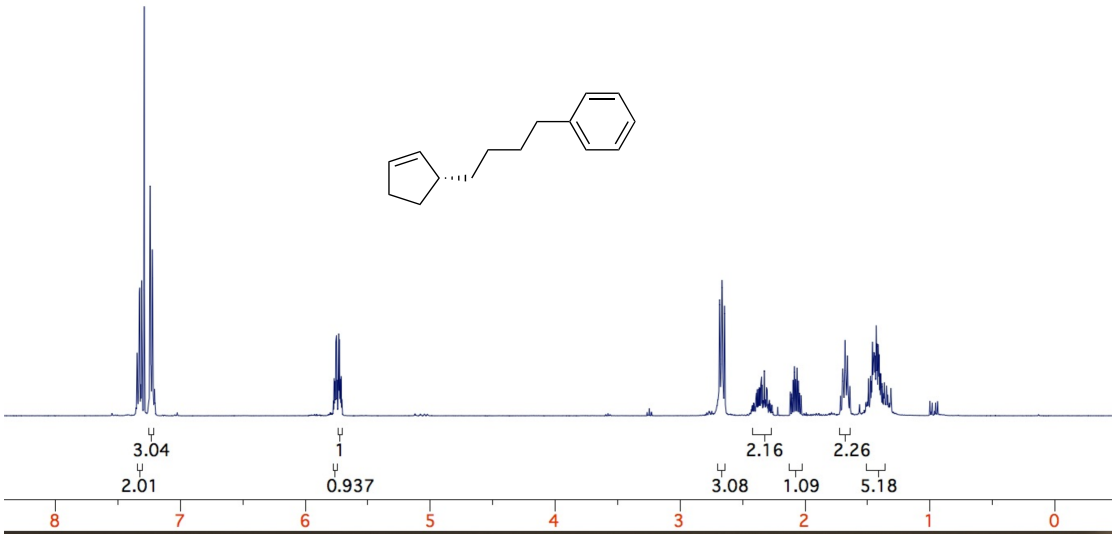
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm : 27.7, 29.9, 31.8, 32.0, 36.0, 45.6, 125.6, 128.2, 128.4, 130.1, 135.3, 142.9.

HRMS (ESI) *m*/z calcd for $C_{15}H_{20}$ $[M]^+$: 200.1564, found: 200.1565.

IR (ATR) ν (cm^{-1}, $CHCl_3$): 698, 718,1454, 1496, 1604, 2853, 2926,3027.

$[\alpha]^{20}_{589}$ = + 59.2 (c= 1.759 in $CHCl_3$, 92% ee).

^{1}H NMR:



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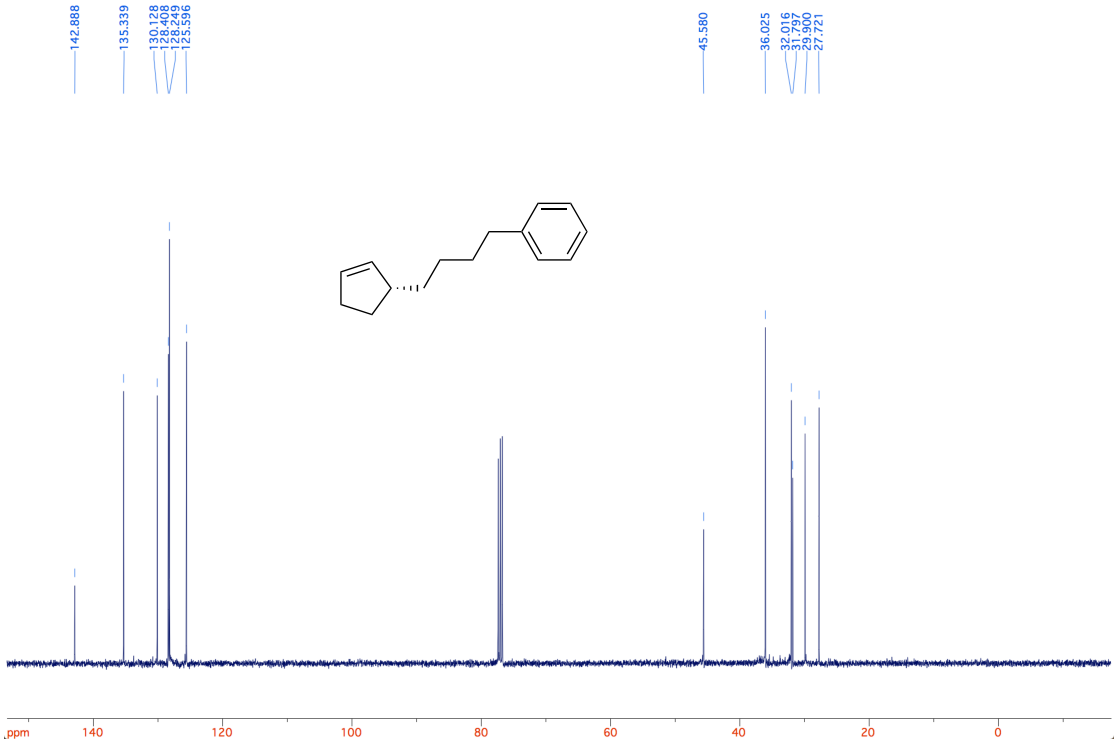
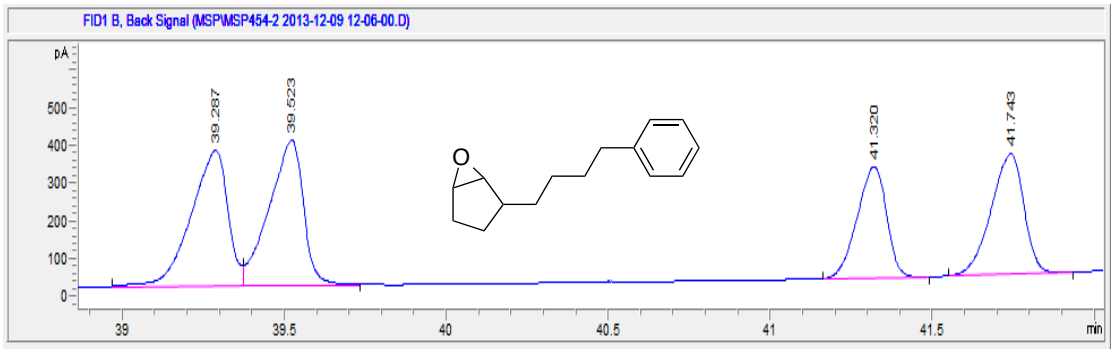
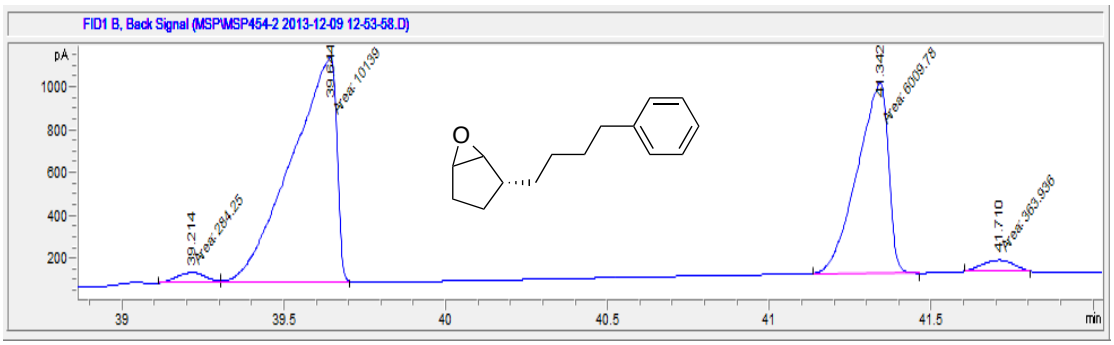
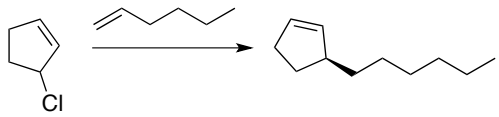


GC traces:





(S)-(–)-3-Hexylcyclopent-1-ene (2.38)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S,S*)- **Ligand L1** (21.6 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 1-hexene (84 µL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclopent-1-ene (41.0 mg, 0.40 mmol, 1.00 eq)was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic

phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave (*S*)-(–)-3-hexylcyclopent-1-ene (46.4 mg, 0.31 mmol) in 77% yield.

GC analysis of the crude mixture of epoxides derived from **2.38** indicated an enantiomeric excess of 90% (Hydrodex 6-TBDM, 60-110°C at 5 °C/min, 110-170°C at 20°C/min, hold for 20 min, 10psi); major enantiomer t_R = 22.79, 24.58 min; minor enantiomer t_R = 23.04, 24.24 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 0.89 (t, *J*=6.0 Hz, 3 H), 1.29 (br. s., 9 H), 1.33 - 1.46 (m, 2 H), 2.05 (m, 1 H), 2.30 (m, 2 H), 2.63 (m, 1 H), 5.70 (m, 2 H).

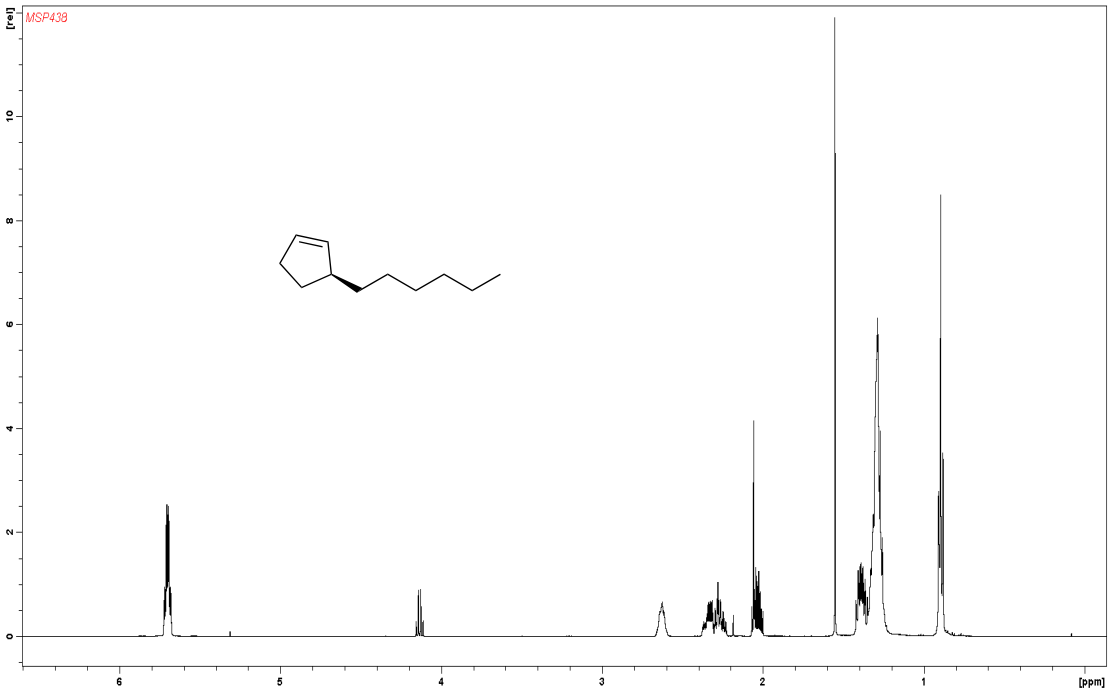
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 14.1, 22.7, 27.9, 29.6, 29.9, 31.9, 32.0, 36.2, 45.6, 130.0, 135.5.

HRMS (ESI) *m*/*z* calcd for $C_{11}H_{20}$ $[M]^+$: 152.1565, found: 152.1559.

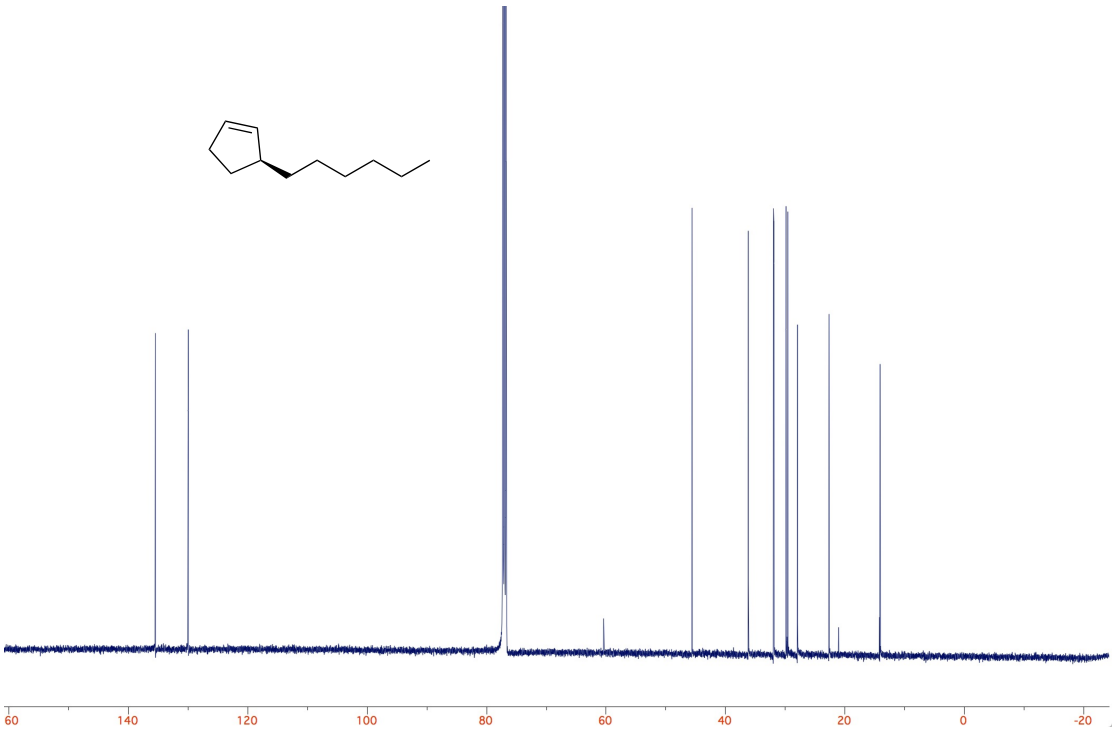
IR (ATR) ν (cm^{-1}): 2323.8, 2854.9, 1462.9.

$[\alpha]^{20}_{589}$ = –105.1 (*c* 0.92, $CHCl_3$) for 90% ee.

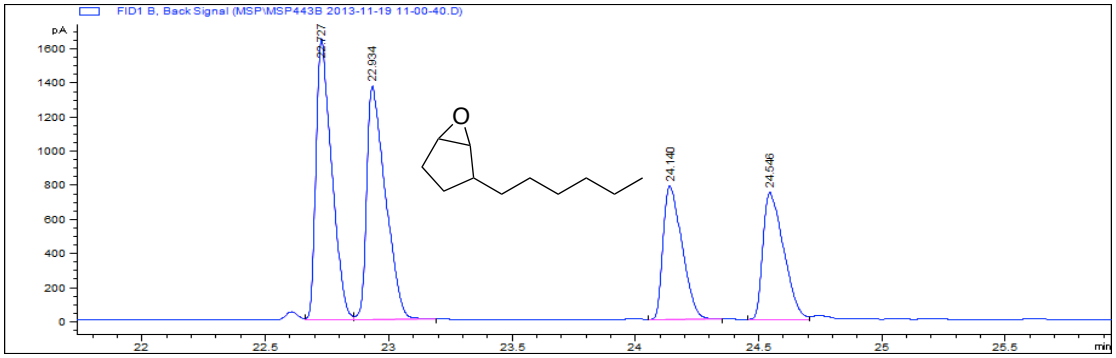
^{1}H NMR:

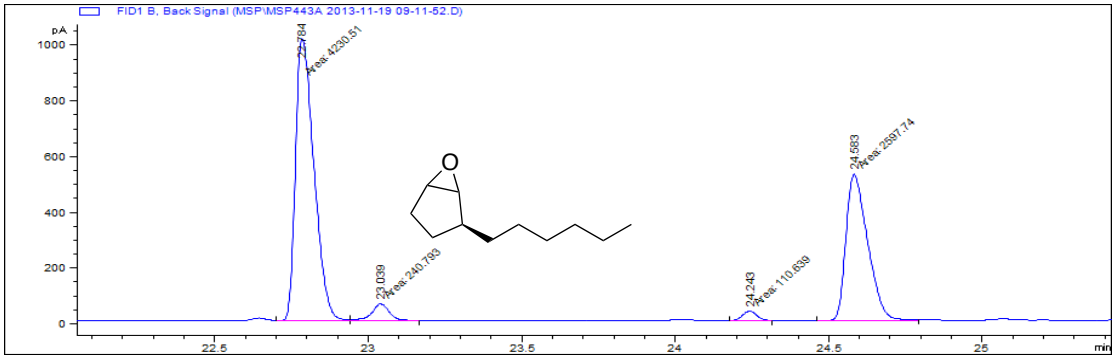


^{13}C NMR:

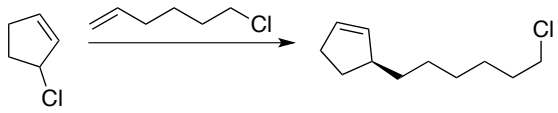


GC traces:





(*S*)-(−)-3-Propylcyclohex-1-ene (2.39)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S,S*)- **Ligand L1** (21.6 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 6-chloro-1-hexene (0.13 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes 3-chlorocyclopent-1-ene (41.0 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0

mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL) dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave (*S*)-(–)-3-(6-chlorohexyl) cyclopent-1-ene (54.3 mg, 0.29 mmol) in 72% yield.

GC analysis of the crude mixture of epoxides derived from **2.39** indicated an enantiomeric excess of 90% (Hydrodex 6-TBDM, 60-110^{o}C at 5 ^{o}C/min, 110-170^{o}C at 1 ^{o}C/min, hold for 20 min, 10psi); major enantiomer t_R = 33.47, 38.45 min; minor enantiomer t_R = 33.78, 37.82 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.25 - 1.48 (m, 9 H), 1.74 - 1.83 (m, 2 H), 1.99 - 2.08 (m, 1 H), 2.28 (m, 1 H), 2.31 - 2.40 (m, 1 H), 2.56 - 2.69 (m, 1 H), 3.54 (t, *J*=6.8 Hz, 2 H), 5.65 - 5.70 (m, 1 H), 5.71 (dt, *J*=5.8, 2.0 Hz, 1 H).

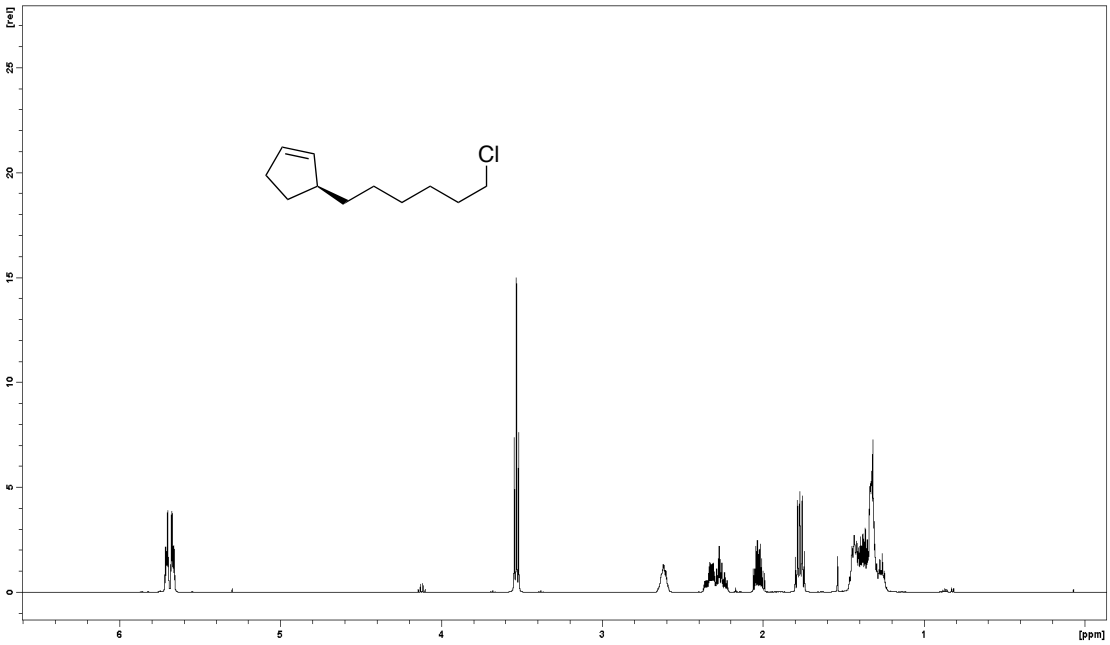
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 26.9, 27.8, 29.1, 29.8, 32.0, 32.6, 36.0, 45.2, 45.5, 130.1, 135.3.

HRMS (ESI) *m*/*z* calcd for $C_{11}H_{19}Cl$ $[M]^+$: 186.1175, found: 186.1168.

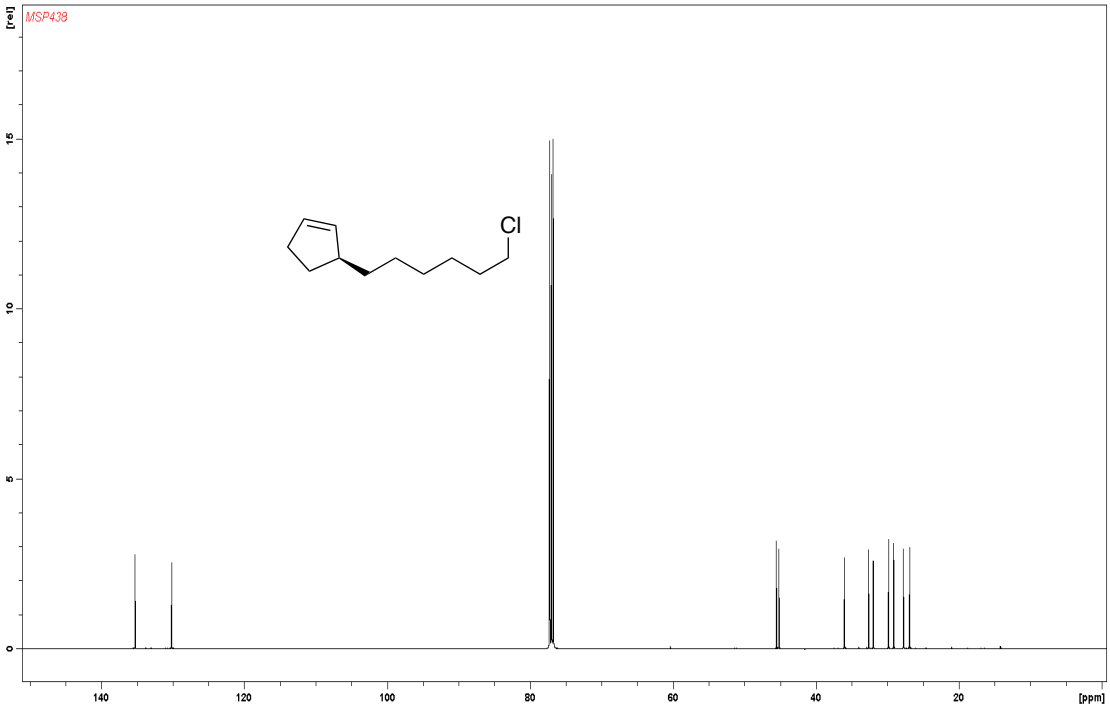
IR (ATR) ν (cm^{-1}): 3050.9, 2925.8, 2853.2, 1461.5, 719.8.

$[\alpha]^{20}_{589}$ = –85.7 (*c* 1.12, $CHCl_3$) for 90% ee.

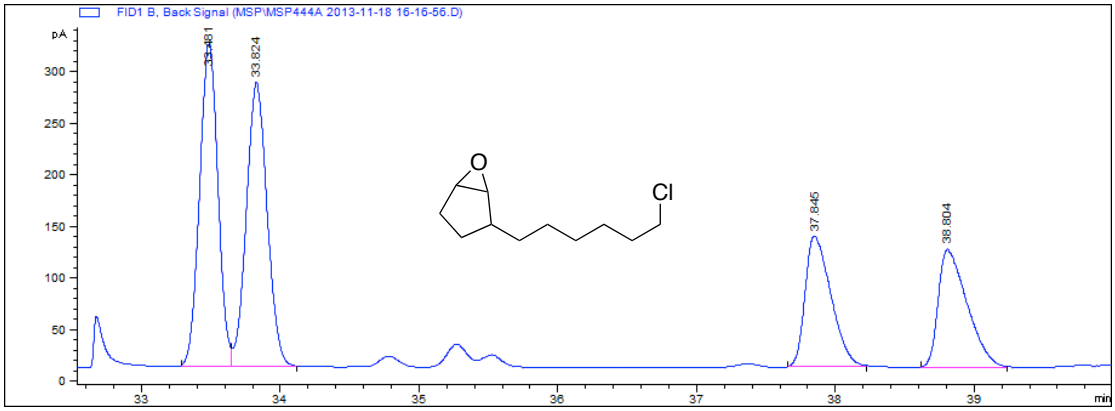
^{1}H NMR:

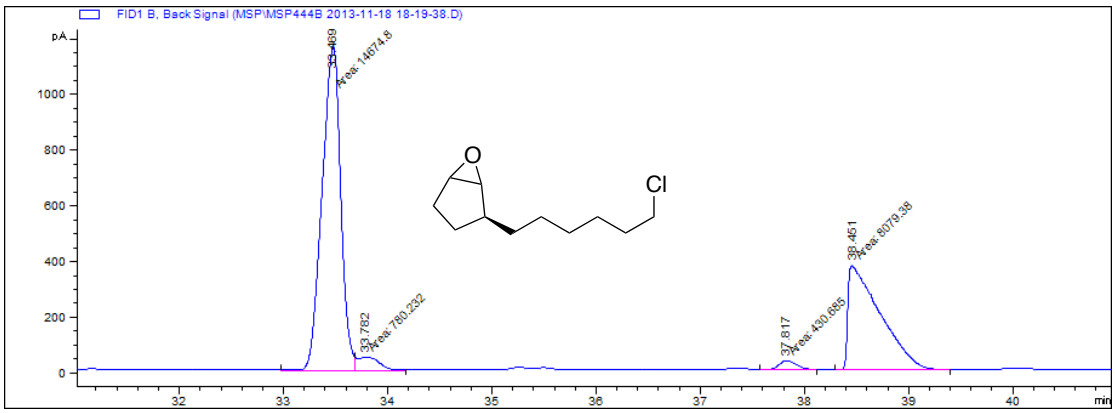


^{13}C NMR:



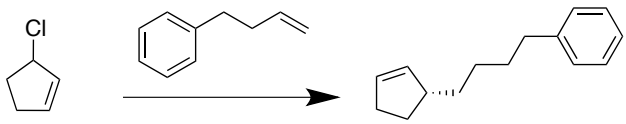
GC traces:





Gram-scale

Synthesis of (R)-(+)-(4-(cyclopent-2-en-1-yl)butyl)benzene (2.37)

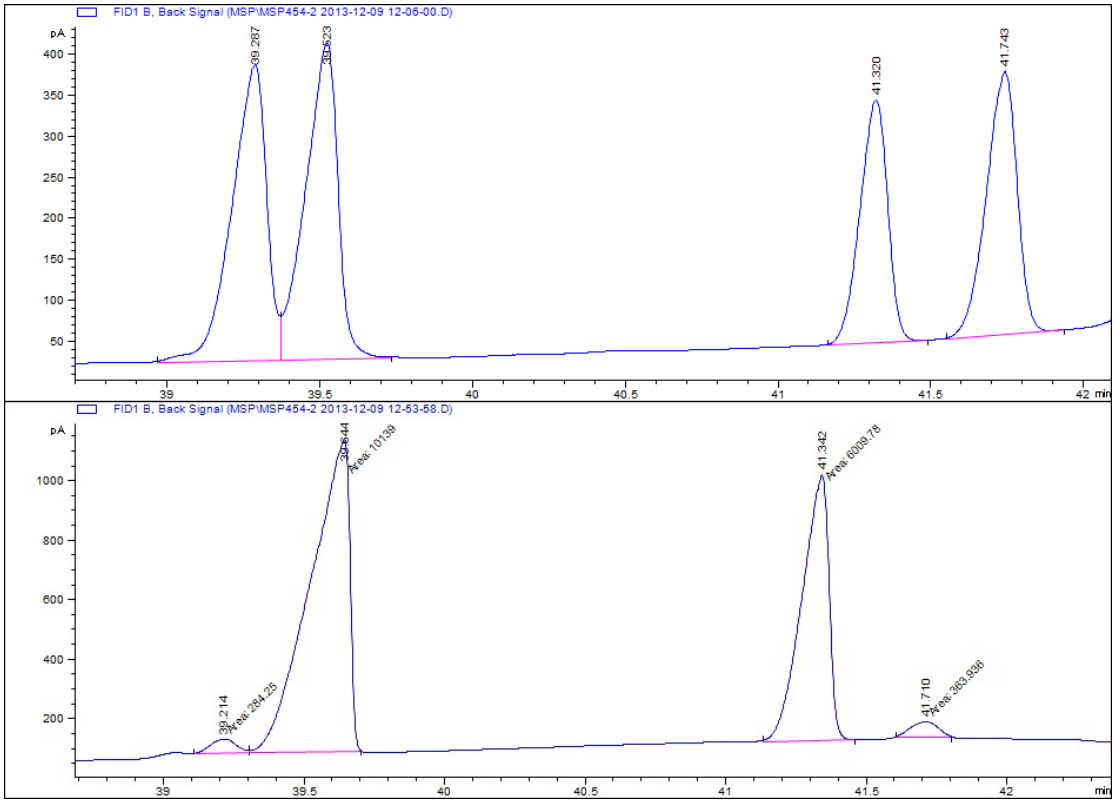


In a 50 mL flame dried flask, CuI ((291.4 mg, 1.53 mmol, 0.10 eq) and (*R,R,R*)- **Ligand** C (825.7 mg, 1.53 mmol, 0.10 eq) are dissolved in $CHCl_3$ (30 mL) and the mixture is stirred at room temperature for 1 h. Meanwhile, in another 50 mL flame-dried flask, 4-Phenyl-1-butene (5.75 mL, 38.25 mmol, 2.50 eq) is dissolved in CH_2Cl_2 (15 mL) and then Cp_2ZrHCl (7.89 g, 30.60 mmol, 2.00 eq) is added in one portion at room temperature. The mixture is rapidly stirred until it becomes a clear yellow solution (approx. 20 min). The resulting organozirconium reagent is transferred to the copper-ligand solution using a syringe. After 5

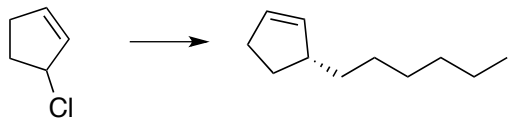
min of additional stirring 3-chlorocyclopent-1-ene (1.49 mL, 15.30 mmol, 1.00 eq) is added dropwise. Stirring was continued arbitrarily overnight and the reaction quenched by addition of NH_4Cl 1M (35.0 mL) and then dilution with with CH_2Cl_2 (40.0 mL). The organic phase was washed with $NaHCO_3$ (aq. sat. *ca.,* 40.0 mL), and then water (40.0 mL), and then dried ($MgSO_4$), filtered and then the solvent was carefully removed by evaporated rotavapor (T = 30 °C and 400 mbar pressure). Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr (T = 110 °C and 55 mbar pressure) gave (*R*)-(–)-3-isopentylcyclohex-1-ene (1.77 g, 22.2 mmol) in 58% yield.

GC analysis of the crude mixture of epoxides derived from **2.37** indicated an enantiomeric excess of 94% (Hydrodex 6-TBDM, 60-110°C at 5 °C/min, 110-140°C at 10 °C/min, hold for 10 min, 140-170°C at 5 °C/min, hold for 10 min, 170-210°C at 5 °C/min, 10psi); major enantiomer t_R = 39.5 min, 41.3 min; minor enantiomer t_R = 39.2 min, 41.7 min.

GC traces:



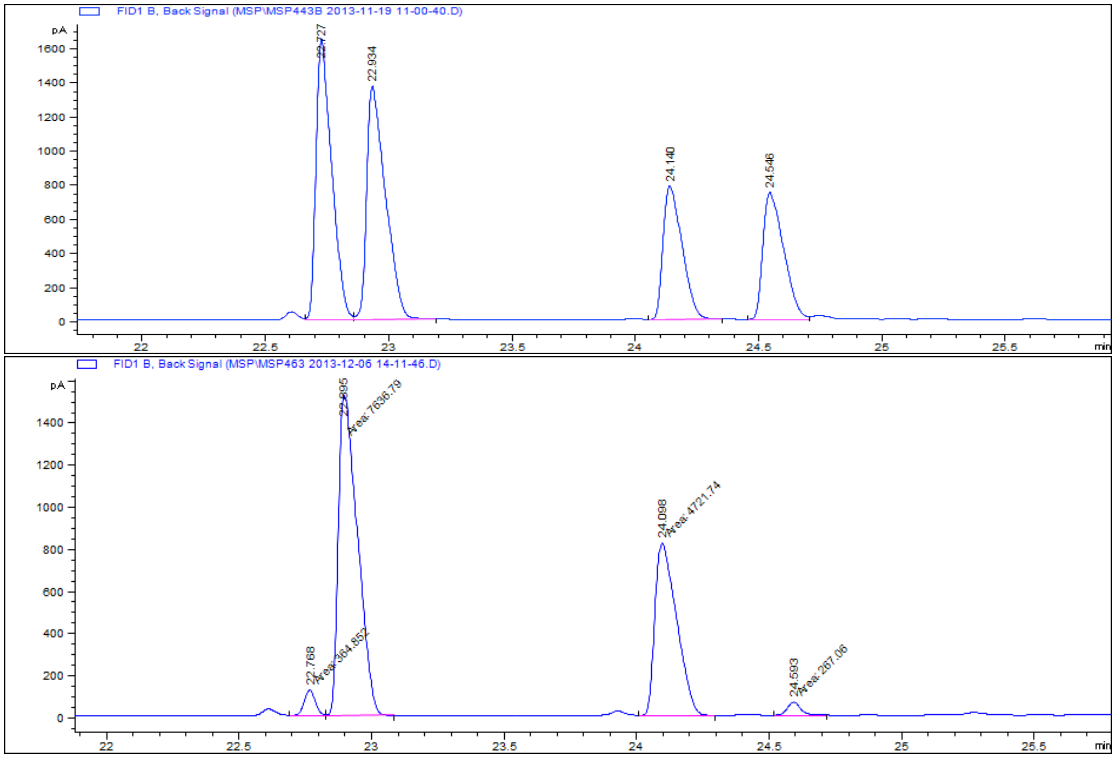
Synthesis of (R)-(+)-3-Hexylcyclopent-1-ene (2.38)



In a 50 mL flame dried flask, CuI (190.5 mg, 1.10 mmol, 0.10 eq) and *(R,R,R)*-**Ligand L1** (593.6 mg, 1.10 mmol, 0.10 eq) are dissolved in $CHCl_3$ (22 mL) and the mixture is stirred at room temperature for 1 h. Meanwhile, in another 25 mL flame-dried flask, 1-hexene (2.32 mL, 84.16 mmol, 1.70 eq) is dissolved in CH_2Cl_2 (11 mL) and then Cp_2ZrHCl (4.25 g, 16.5 mmol, 1.50 eq) is added in one portion at room temperature. The mixture is rapidly stirred until it becomes a clear yellow solution (approx. 20 min). The resulting organozirconium reagent is transferred to the copper-ligand solution using a syringe. After 5 min of additional stirring 3-chlorocyclopent-1-ene (0.90 mL, 11.0 mmol, 1.00 eq) is added dropwise. Stirring was continued arbitrarily overnight and the reaction quenched by addition of NH_4Cl 1M (15 mL) and then dilution with with CH_2Cl_2 (15 mL). The organic phase was washed with $NaHCO_3$ (aq. sat. *ca.,* 30.0 mL), and then water (30.0 mL), and then dried ($MgSO_4$), filtered and then the solvent was carefully removed by evaporated rotavapor (T = 30 °C and 350 mbar pressure). Flash column chromatography of the residue (pentane; SiO_2) gave (*R*)-(+)-3-hexylcyclopent-1-ene (1.20 g, 9.46 mmol) in 86% yield.

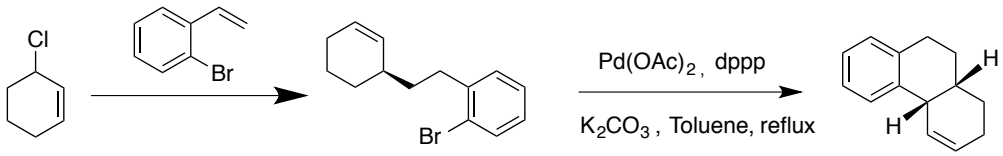
GC analysis of the crude mixture of epoxides derived from **2.38** indicated an enantiomeric excess of 91% (Hydrodex 6-TBDM, 60-110^{o}C at 5 ^{o}C/min, 110-170^{o}C at 20^{o}C/min, hold for 20 min, 10psi); major enantiomer t_R = 22.90, 24.08 min; minor enantiomer t_R = 22.77, 24.59 min.

GC traces:



Application of the method

AAA-Intramolecular Heck reaction (2.40)



(a) CuI (61.6 mg, 0.32 mmol, 0.10 eq), (*S,S,S*)- **Ligand L1** (172.8 mg, 0.32 mmol, 0.10 eq) and then $CHCl_3$ (6.4 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 2-Bromostyrene (1.1 mL, 8.00 mmol, 2.50 eq), CH_2Cl_2 (3.2 mL) and Cp_2ZrHCl (1.648 g, 6.40 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 25 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for

10 additional minutes 3-chlorocyclohex-1-ene (0.373 g, 3.20 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~10.0 mL) and diluted by addition of CH_2Cl_2 (10.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 10.0 mL), water (10.0 mL) dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr (T = 60 °C and 10 mbar pressure) gave (*R*)-1-bromo-2-(2-(cyclohex-2-en-1-yl)ethyl)benzene (750.3 mg, 2.81 mmol) in 88% yield.

GC analysis of the crude mixture of epoxides derived from (*R*)-1-bromo-2-(2-(cyclohex-2-en- 1-yl)ethyl) benzene indicated an enantiomeric excess of 87% (Hydrodex 6-TBDM, 90-200^{o}C at 1 ^{o}C/min, 10psi); major enantiomer t_R = 101.1 min; minor enantiomer t_R = 99.4 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.34-1.40 (m, 1H), 1.57-1.66 (m, 3 H), 1.76-1.81 (m, 1 H), 1.87-1.92 (m, 1 H), 2.01-2.04 (m, 2 H), 2.15-2.20 (m, 1 H), 2.75-2.85 (m, 2 H), 5.66-5.70 (m, 1H), 5.72-5.76 (m, 1H), 7.04-7.08 (m. 1 H), 7.24-7.25 (m, 2H), 7.53-7.55 (d, 1H, J= 7.89 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 21.5, 25.4, 28.9, 33.7, 35.1, 36.6, 124.5, 127.3, 127.4, 127.5, 130.3, 131.6, 132.8, 142.2.

(b) In a flame-dried 25 ml round-bottom flask, a solution of (R)-1-bromo-2-(2-(cyclohex -2-en-1-yl)ethyl) benzene (250 mg, 0.943 mmol, 1.00 eq), $Pd(OAc)_2$ (32.5 mg, 0.141 mmol, 0.15 eq), 1,3-Bis(diphenylphosphino)propane (dppp) (118.8 mg, 0.283 mmol, 0.3 eq) and K_2CO_3 (533 mg, 3.772 mmol, 4.00 eq) in anhydrous Toluene (10.0 mL) was heated in a reflux condition under argon for 28 h. The reaction mixture was cooled to room temperature, filtered through Celite and rinsed with EtOAc. A sat. solution of NaCl was added (10 mL) and it was extracted with EtOAc (3 x 10 mL). The combined organic

extracts were dried over Mg_2SO_4 and the solvent was evaporated. Flash column chromatography of the residue (pentane; SiO_2) gave (4a*R*, 10a*S*)-1,2,4a,9,10,10a–hexahydro phenanthrene (152.7 mg, 0.829 mmol) in 88% yield.

Enantiomeric excess of 87% was determined by HPLC [Chiralpak® IB; flow: 0.5 mL/min; hexane/i-PrOH: 100: 0; λ = 210 nm; major enantiomer t_R = 10.7 min; minor enantiomer t_R = 11.7 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.73-1.81 (m, 2H), 1.82-1.91 (m, 2 H), 2.09-2.15 (m, 2 H), 2.21-2.26 (m, 1 H), 2.85-2.89 (m, 2 H), 3.53-3.55 (m, 1 H), 5.72-5.76 (m, 1H), 5.80-5.83 (m, 1H), 7.13-7.19 (m, 2 H), 7.21-7.25 (m, 1H), 7.28-7.30 (m, 1 H).

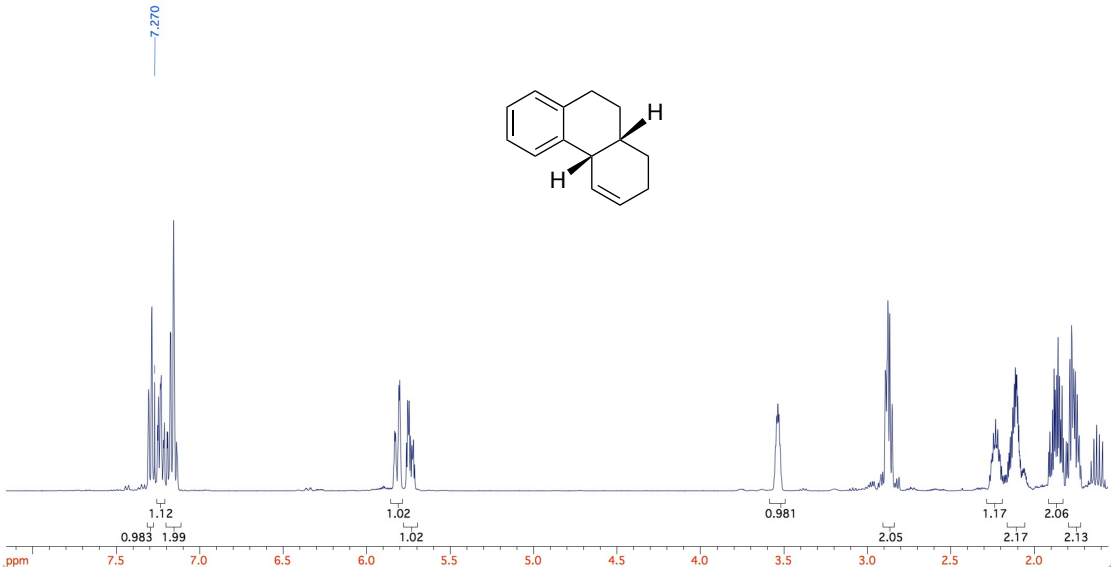
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 21.9, 24.6, 27.1, 29.1, 32.2, 39.2, 125.6, 125.8, 125.9, 128.8, 128.9, 131.2, 136.8, 140.3.

HRMS (ESI) *m*/z calcd for $C_{14}H_{16}$ $[M]^+$: 184.1252, found: 184.1249.

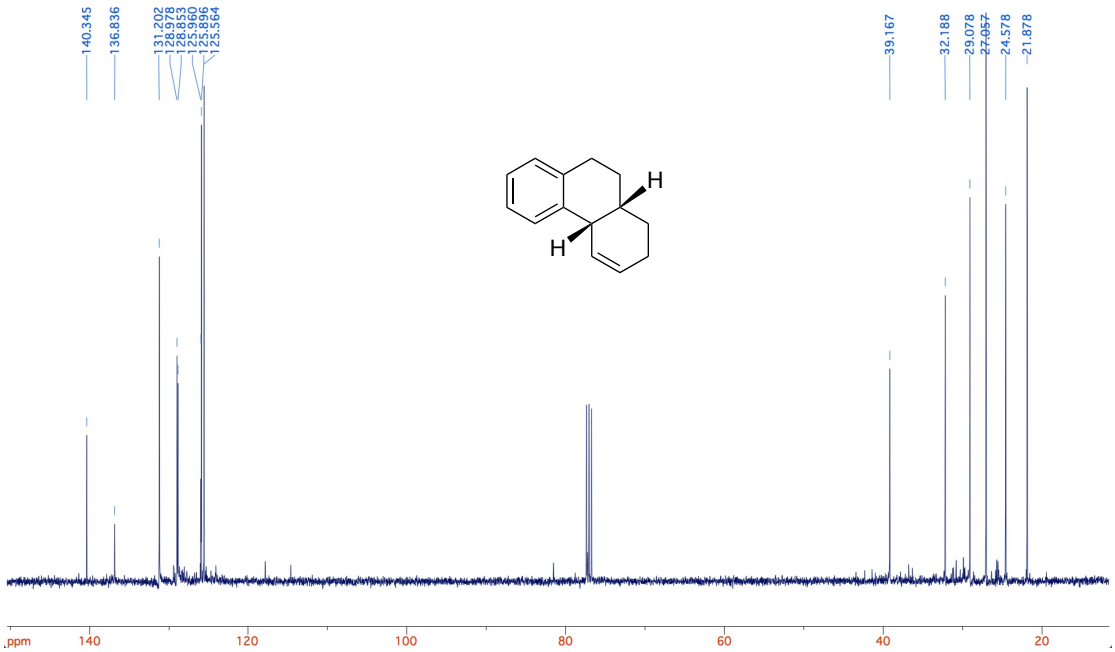
IR (ATR) ν (cm^{-1}, $CHCl_3$): 630.4, 666.5, 739.4, 1257.5, 1449.7, 1487.5, 2919.5

$[\alpha]^{20}_{589}$ = –101 (c= 0.702 in $CHCl_3$, 87% ee).

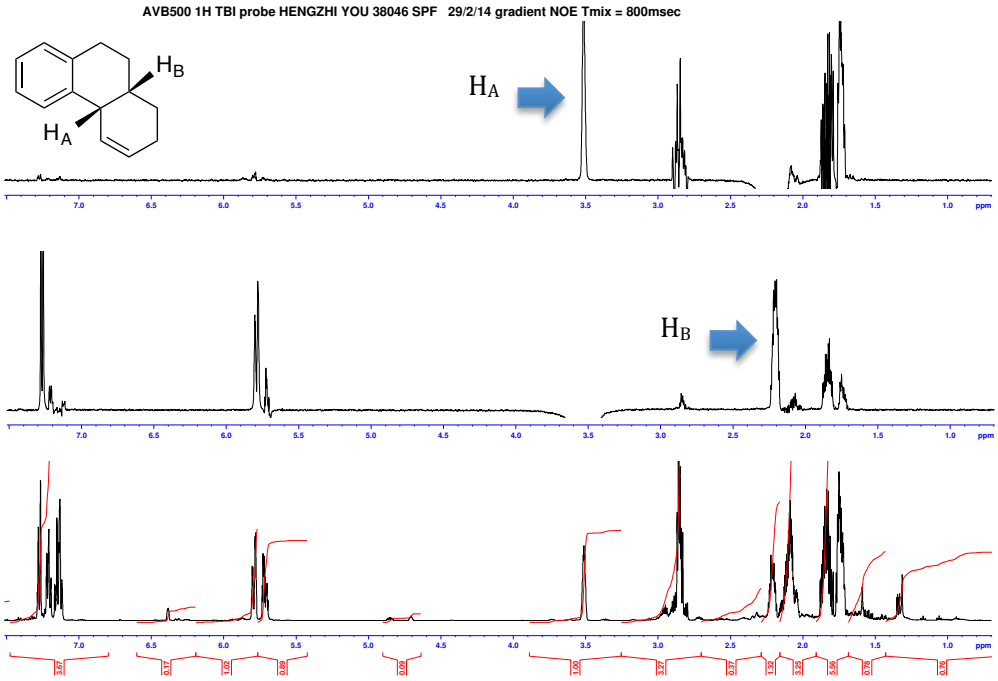
^{1}H NMR:



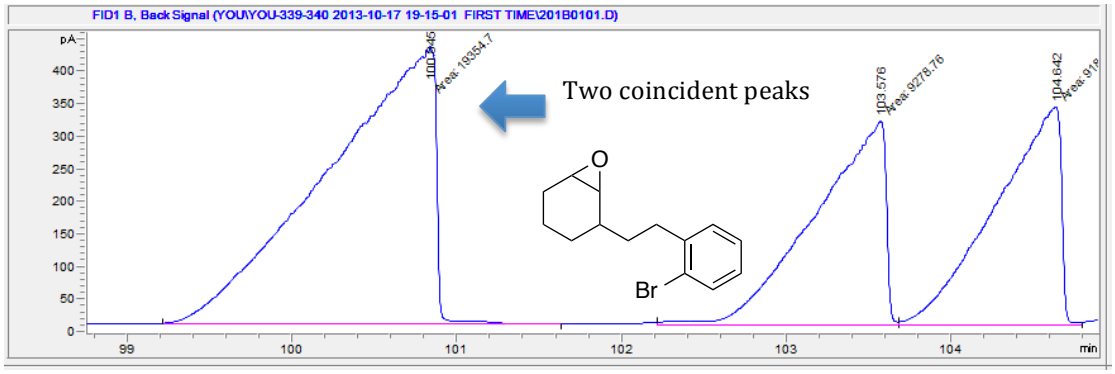
^{13}C NMR:



NOESY NMR:



GC traces: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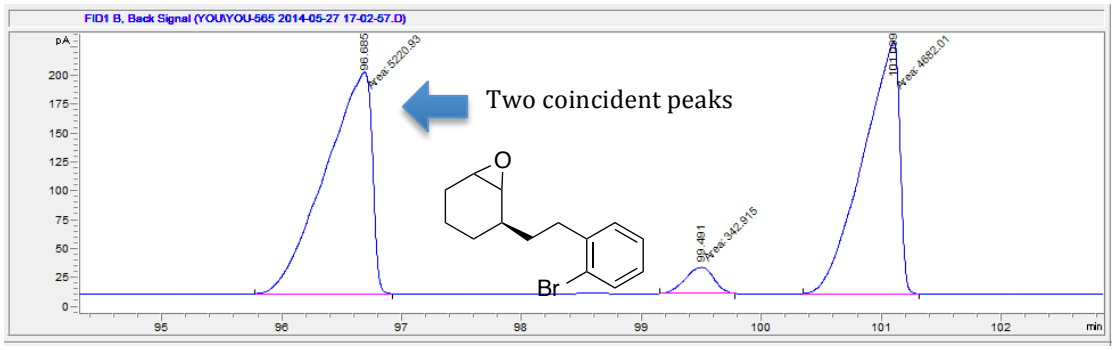
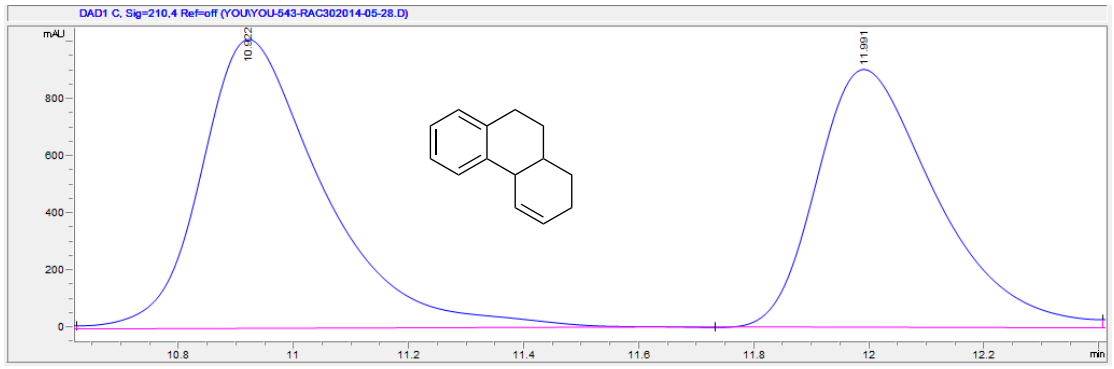
pA
Two coincident peaks
O
Br
min


FID1 B, Back Signal (YOU\YOU-565 2014-05-27 17-02-57.D)
pA
Two coincident peaks
O
Br
min

HPLC traces: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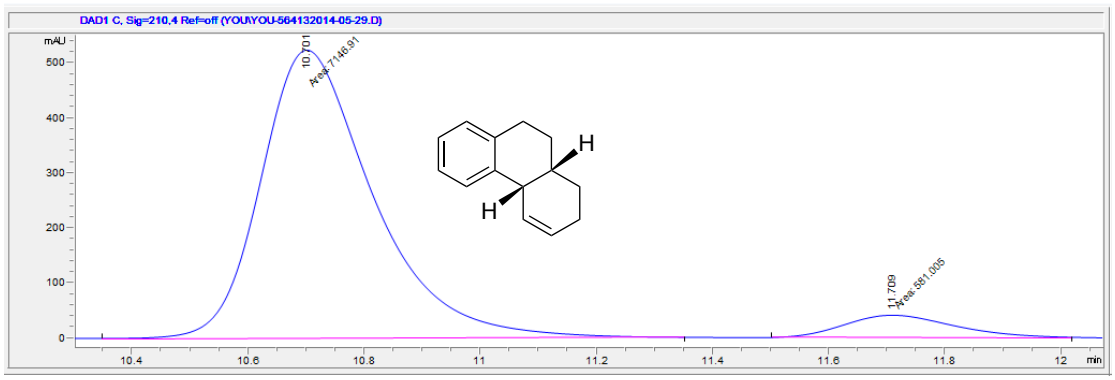
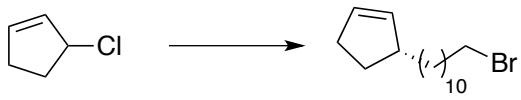
mAU
min


DAD1 C, Sig=210,4 Ref=off (YOU\YOU-564132014-05-29.D)
mAU
H
H
min

Natural products: synthesis of Hydnocarpic Acid (2.41-2.42)

(+)-(S)-3-(Bromoundecenyl)cyclopent-1-ene (2.41)



In a flame-dried flask, CuI 98% (23.4 mg, 0.12 mmol, 0.10 eq) and (*R*,*R*,*R*)-Ligand **L1** (65.0 mg, 0.12 mmol, 0.10 eq) were stirred in $CHCl_3$ (4.8 mL) at room temperature for 1 h. In another flask Cp_2ZrHCl (618.9 mg, 2.40 mmol, 2.00 eq) was added to a solution of 11-bromoundec-1-ene (0.65 mL, 3.00 mmol, 2.50 eq) in CH_2Cl_2 (2.4 mL) at room temperature and it was then stirred until it became a clear yellow solution (15-20 min). The freshly prepared organozirconium reagent was then transferred to the copper-ligand solution using a 5 mL syringe dropwise over 3 min. The orange solution was stirred for 10 minutes before adding 3-chlorocyclopent-1-ene (0.12 mL, 1.20 mmol, 1.00 eq). The resulting mixture was arbitrarily stirred 12 h and then quenched by the addition of Et_2O (7 mL) and NH_4Cl 1 M solution (5 mL). The aqueous phase was extracted with Et_2O (2x3 mL) and the combined organic phase was washed with saturated solution of $NaHCO_3$ (5 mL), water (5 mL) and brine (5 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was then removed under reduced pressure. Purification by flash column chromatography using 100% pentane yielded the desired product contaminated with 11-bromoundec-1-ene in a 1:1.1 ratio. To remove the alkene the oil was subjected to kugelrohr distillation at 125 °C under high vacuum. The desired product, which constituted the residue of the distillation, was obtained in 42% yield (153.0 mg, 0.51 mmol).

GC analysis of the crude mixture of epoxides derived from **2.41** indicated an enantiomeric excess of 92% (Hydrodex 6-TBDM in the following conditions: 60-190 °C at 5 °C/min, held for 50 min and 1 °C/min to 210 °C and held 10 min); major enantiomer t_R = 69.5 min, minor enantiomer t_R = 67.7 min.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H /ppmδ_H /ppm: 1.28 (br. s., 14 H), 1.32 - 1.48 (m, 5 H), 1.86 (quin, *J*=7.2 Hz, 2 H), 1.97 - 2.11 (m, 1 H), 2.19 - 2.42 (m, 2 H), 2.62 (br. s., 1 H), 3.42 (t, *J*=6.8 Hz, 2 H), 5.59 - 5.81 (m, 2 H)

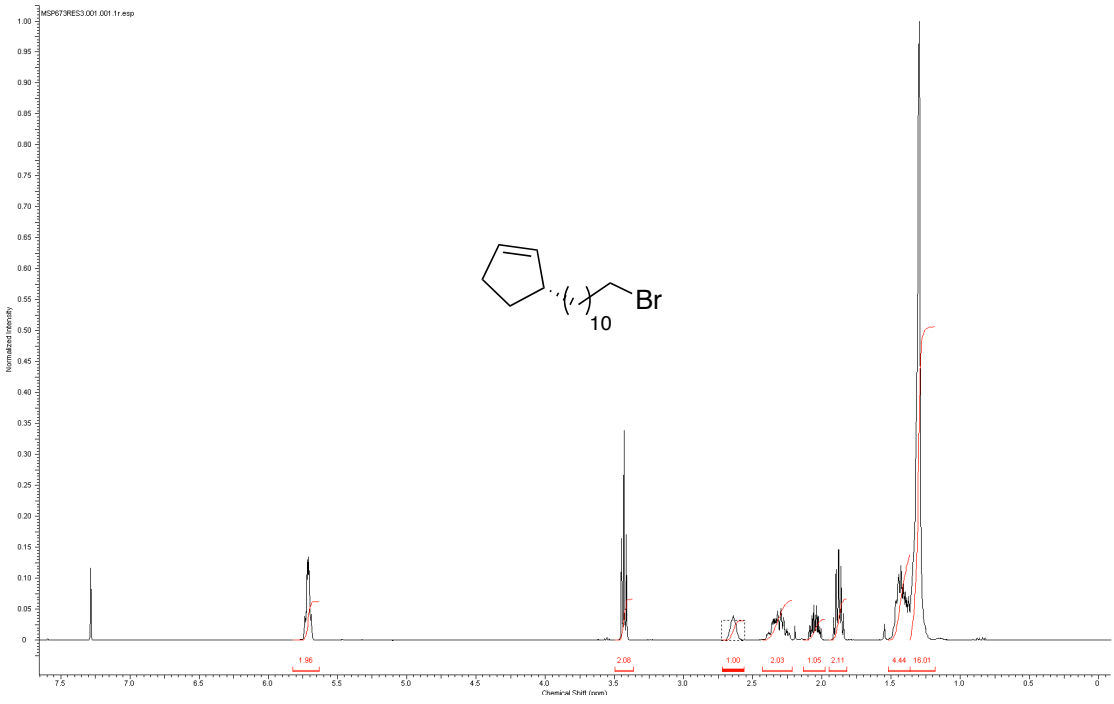
^{13}C NMR (126 MHz, $CDCl_3$) δ_C /ppm 28.0, 28.2, 28.8, 29.4, 29.5, 29.6, 29.6, 29.9 (2C), 32.0, 32.9, 34.0, 36.2, 45.6, 130.0, 135.5.

HRMS (ESI) *m*/*z* calcd for $C_{16}H_{29}Br$ $[M]^+$: 300.1453, found: 300.1456.

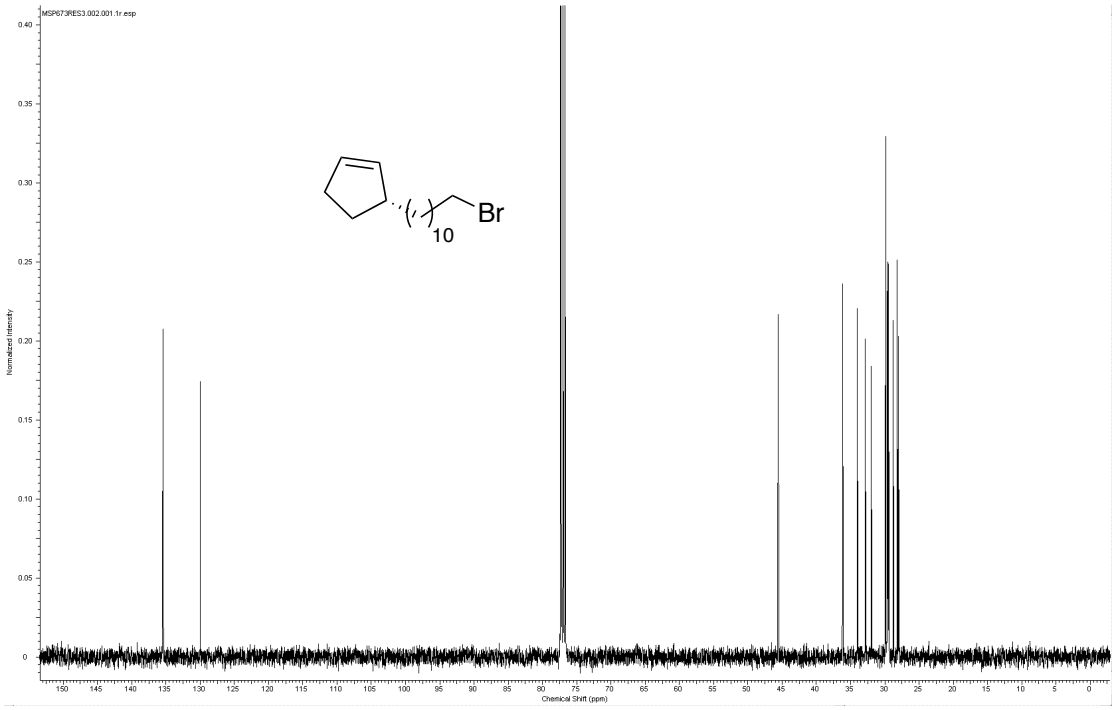
IR (ATR) ν (cm^{-1}): 2923, 2852, 1463.

$[\alpha]^{20}_{589}$ = +50.33 (*c* 1.01, $CHCl_3$) for 92% ee.

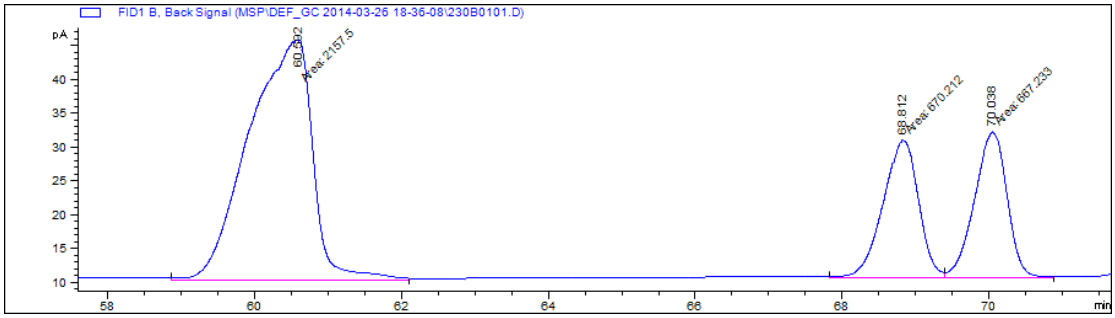
^{1}H NMR:

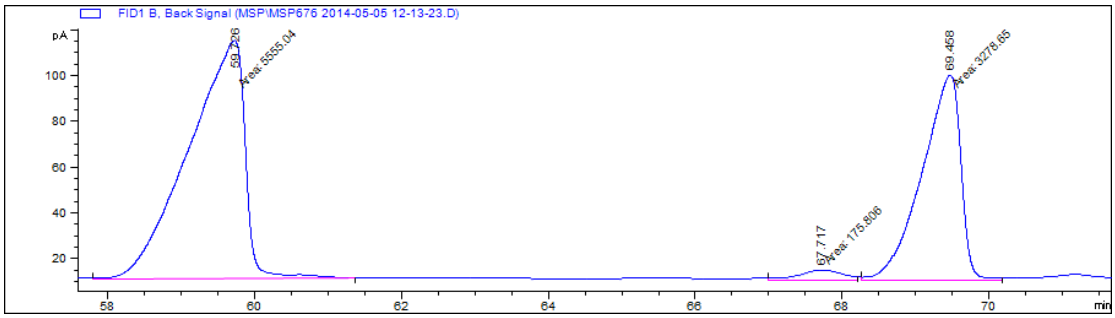


^{13}C NMR:

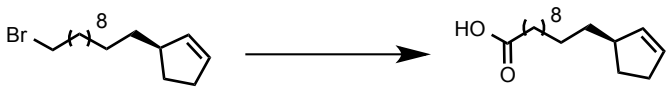

MSP673RES3.002.001.1r.esp
Br
10
Normalized Intensity
Chemical Shift (ppm)

GC traces:


FID1 B, Back Signal (MSP\DEF_GC 2014-03-26 18-36-08\230B0101.D)
pA
60.092
Area: 2157.5
68.812
Area: 670.212
70.038
Area: 667.233
min


FID1 B, Back Signal (MSP\MSP676 2014-05-05 12-13-23.D)
pA
59.206
Area: 5555.04
67.717
Area: 175.806
69.458
Area: 3278.65
min

(+)-(R)-11-(Cyclopent-2-enyl)-undecanoic acid (2.42)



(a) $NaHCO_3$ (44.6 mg, 0.53 mmol, 3.11 eq) was added to a stirred solution of the bromide **2.41** (50.0 mg, 0.17 mmol, 1.00 eq) in a mixture of DMSO (0.85 mL) and water (0.22 mL). The resulting suspension was stirred 22 h at 95 °C. It was quenched by addition of water (2 mL). The aqueous phase was extracted with Et_2O (3x1 mL) and the combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product that was used in the next step without further purification.

(b) Dess-Martin periodinane (148.4 mg, 0.35 mmol, 2.00eq) was added to a stirred solution of the crude alcohol (0.17 mmol) in 8.5 mL of CH_2Cl_2. The suspension was stirred for 30 min at room temperature before 5 mL mixture of $NaHCO_3$:$Na_2S_2O_3$ (1:5) was added in one portion and diluted with 5 mL of CH_2Cl_2. The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3x2 mL). The crude aldehyde was used in the next step without further purification.

(c) The crude aldehyde (0.17 mmol, 1.00 eq) was dissolved in 2.8 mL of *t*BuOH before a freshly prepared solution of $NaClO_2$ (153.7 mg, 1.70 mmol, 10.00 eq) in 20% aqueous NaH_2PO_4 (0.94 mL) were added and the mixture was vigorously stirred at room temperature 1 h. It was then poured onto EtOAc and the phases separated. The aqueous phase was extracted with EtOAc (4x2 mL). The crude oil was purified by flash column chromatography eluting with hexane:EtOAc (8:2) producing the desired product in 79% yield after the three steps (33.0 mg, 0.13 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.16 - 1.46 (m, 18 H), 1.57 - 1.71 (m, 2 H), 2.03 (m, 1 H), 2.22 - 2.34 (m, 2 H), 2.36 (t, *J*=7.7 Hz, 2 H), 2.62 (br. s., 1 H), 5.62 - 5.79 (m, 2 H).

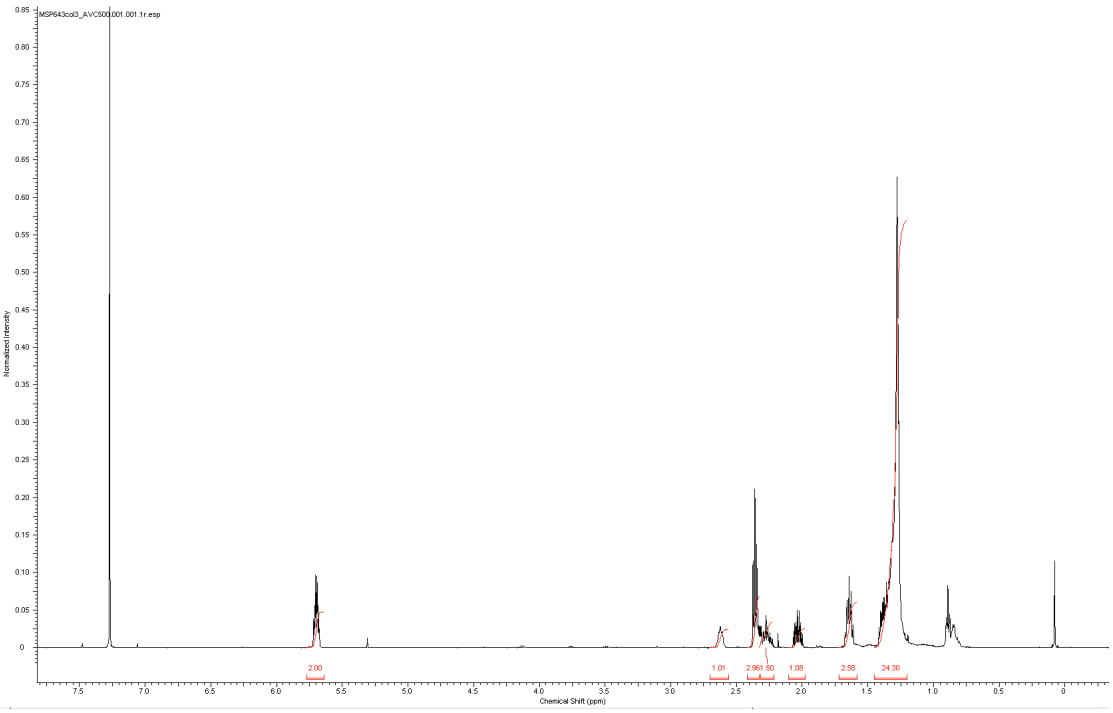
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 24.7, 28.0, 29.0, 29.2, 29.4, 29.6, 29.6, 29.9 (2C), 32.0, 33.8, 36.2, 45.6, 130.0, 135.5, 178.8.

HRMS (ESI) *m*/*z* calcd for $C_{16}H_{28}O_2$ $[M]^+$: 252.2089, found: 252.2078.

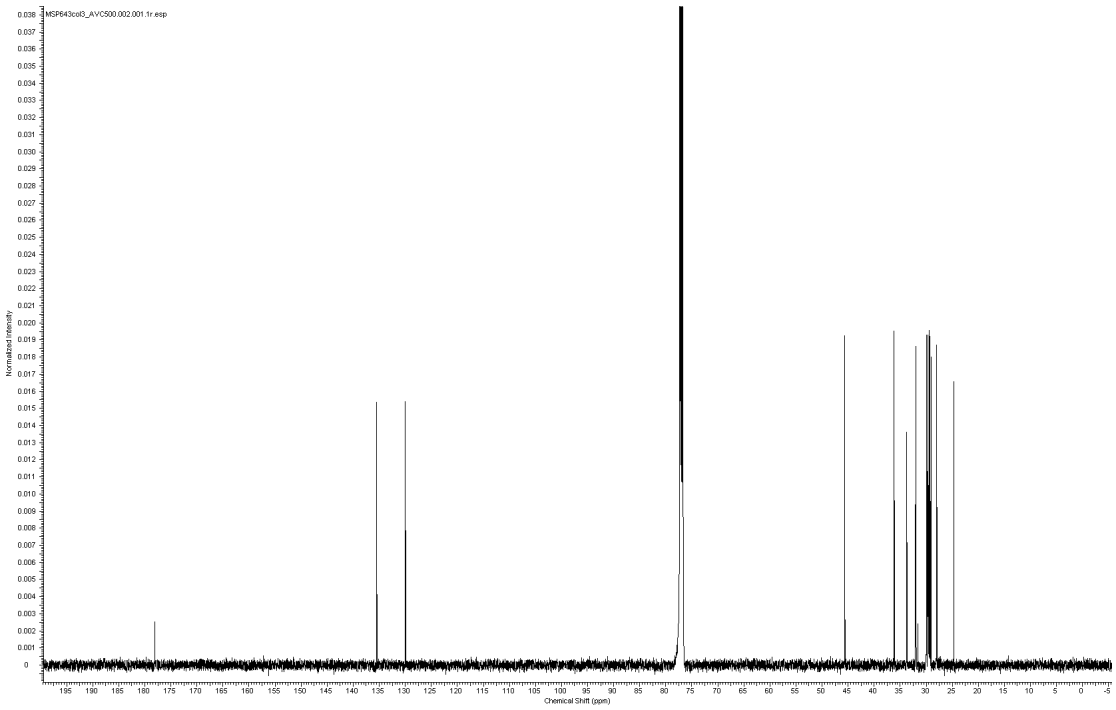
IR (ATR) ν (cm^{-1}): 3015.2, 2918.9, 2851.7, 1700.9.

$[\alpha]^{20}_{589}$ = +48.51 (*c* 0.67, $CHCl_3$); [lit. +69.2, *c* 10.00] [17].

^{1}H NMR:



^{13}C NMR:



Natural products: synthesis of Chaulmoogric Acid (2.43-2.44)

13-Cyclopent-2-en-1-yltridecan-1-ol (2.43)

In a flame dried flask equipped with a condenser, Mg (48.2 mg, 1.98 mmol, 2.50 eq) and an I_2 crystal were flamed under Ar until I_2 sublimes. It was allowed to cool down before adding a minimum amount of THF (0.10 mL). The mixture was then stirred before a solution of bromide **2.41** (239.2 mg, 0.79 mmol, 1.00 eq) in THF (1.0 mL) was added at an adequate rate to keep constant reflux. If necessary, the reaction can be heated up to reflux to initiate it. Once the addition was finished the mixture was refluxed for 1 h and cooled down to room temperature. The Grignard reagent was then transferred via syringe over 20 min to another flask containing ethylene oxide 2.5 M solution in THF (1.07 mL, 2.69 mmol, 3.40 eq) and CuI

(15.0 mg, 0.08 mmol, 0.10 eq) at 0 °C at which point the reaction mixture was dark grey. It was stirred for 75 min at 0 °C before adding in one portion a saturated solution of NH_4Cl (4 mL). The aqueous phase was extracted with Et_2O (3x2 mL). The organic extract was washed with water (3 mL) and brine (3 mL), it was then dried over $MgSO_4$, filtered and concentrated. The crude oil was purified by flash column chromatography using hexane:EtOAc (8:2) which afforded the desired product as a white solid in 76% yield (160.2 mg, 0.60 mmol).

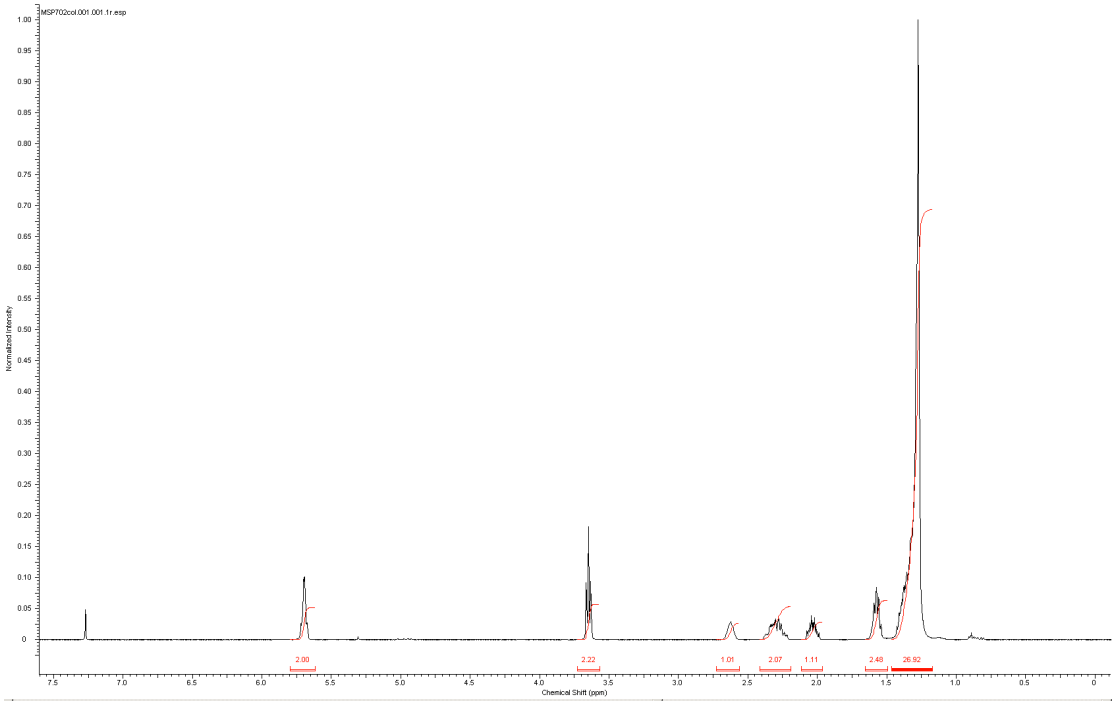
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.17 - 1.46 (m, 24 H), 1.51 - 1.66 (m, 2 H), 1.95 - 2.11 (m, 1 H), 2.18 - 2.42 (m, 2 H), 2.62 (m, 1 H), 3.65 (t, *J*=6.6 Hz, 2 H), 5.62 - 5.77 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 25.7, 28.0, 29.4, 29.6, 29.6, 29.7 (4C), 29.9, 29.9, 32.0, 32.8, 36.2, 45.6, 63.1, 129.9, 135.5.

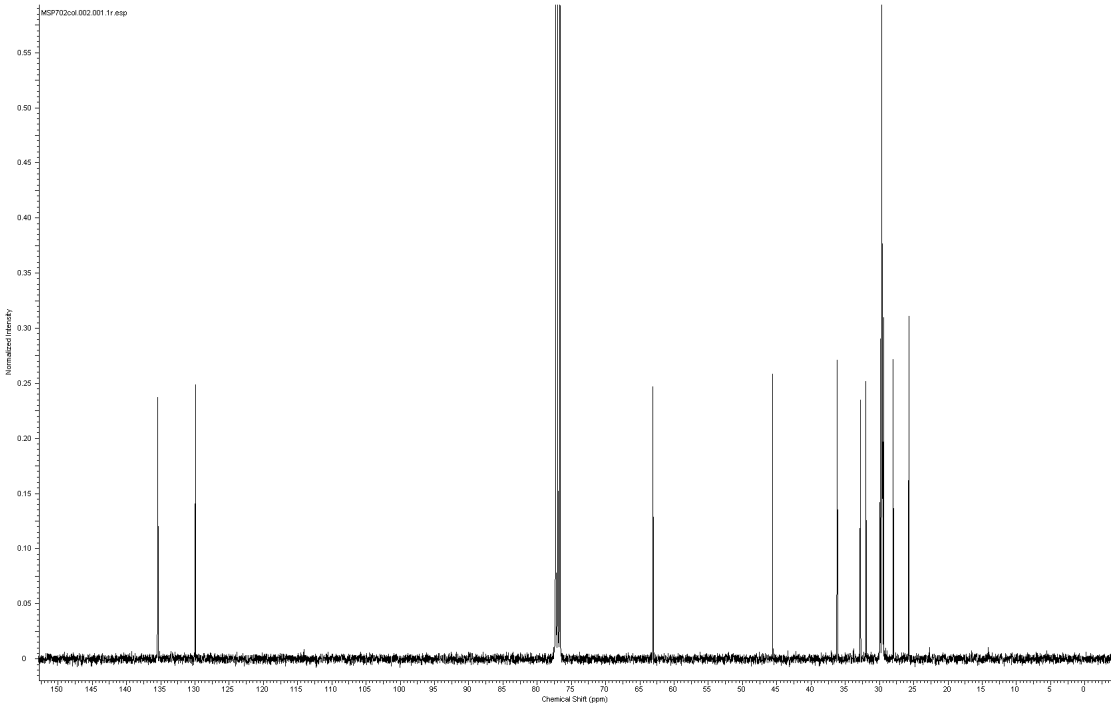
HRMS (ESI) *m/z* calcd for $C_{18}H_{34}O$ $[M]^+$: 266.2610, found: 266.2611.

IR (ATR) ν (cm^{-1}): 3451.3, 2922.1, 2851.9, 1538.9.

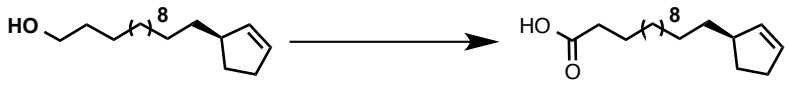
^{1}H NMR:



^{13}C NMR:



(+)-(R)-13-(cyclopent-2-en-1-yl)tridecanoic acid (2.44)



(a) Dess-Martin periodinane (415.7 mg, 0.98 mmol, 2.00eq) was added to a stirred solution of the crude alcohol **2.43** (0.49 mmol, 1.00 eq) in 4.9 mL of CH_2Cl_2. The suspension was stirred for 30 min at room temperature before 5 mL mixture of $NaHCO_3$:$Na_2S_2O_3$ (1:5) was added in one portion and diluted with 5 mL of CH_2Cl_2. The phases were separated and the aqueous phase extracted with CH_2Cl_2 (3x2 mL). The crude aldehyde was used in the next step without further purification.

(b) The crude aldehyde (0.49 mmol, 1.00 eq) was dissolved in 8.2 mL of *t*BuOH before a freshly prepared solution of $NaClO_2$ (443.0 mg, 4.90 mmol, 10.00 eq) in 20% aqueous NaH_2PO_4 (2.72 mL) was added and the mixture was vigorously stirred at room temperature 1 h. It was then poured onto EtOAc and the phases separated. The aqueous

phase was extracted with EtOAc (4x4 mL). The crude oil was purified by flash column chromatography eluting with hexane:EtOAc (8:2) producing the desired product as a white solid in 90% yield after the two steps (124.7 mg, 0.44 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.16 - 1.36 (m, 21 H), 1.56 (quin, *J*=7.4 Hz, 2 H), 1.95 (m, 1 H), 2.10 - 2.26 (m, 3 H), 2.28 (t, *J*=7.5 Hz, 2 H), 2.48 - 2.60 (m, 1 H), 5.55 - 5.69 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 24.7, 28.0, 29.1, 29.3, 29.4, 29.6, 29.6, 29.7, 29.7, 29.9, 29.9, 32.0, 34.0, 36.2, 45.6, 130.0, 135.5, 179.9.

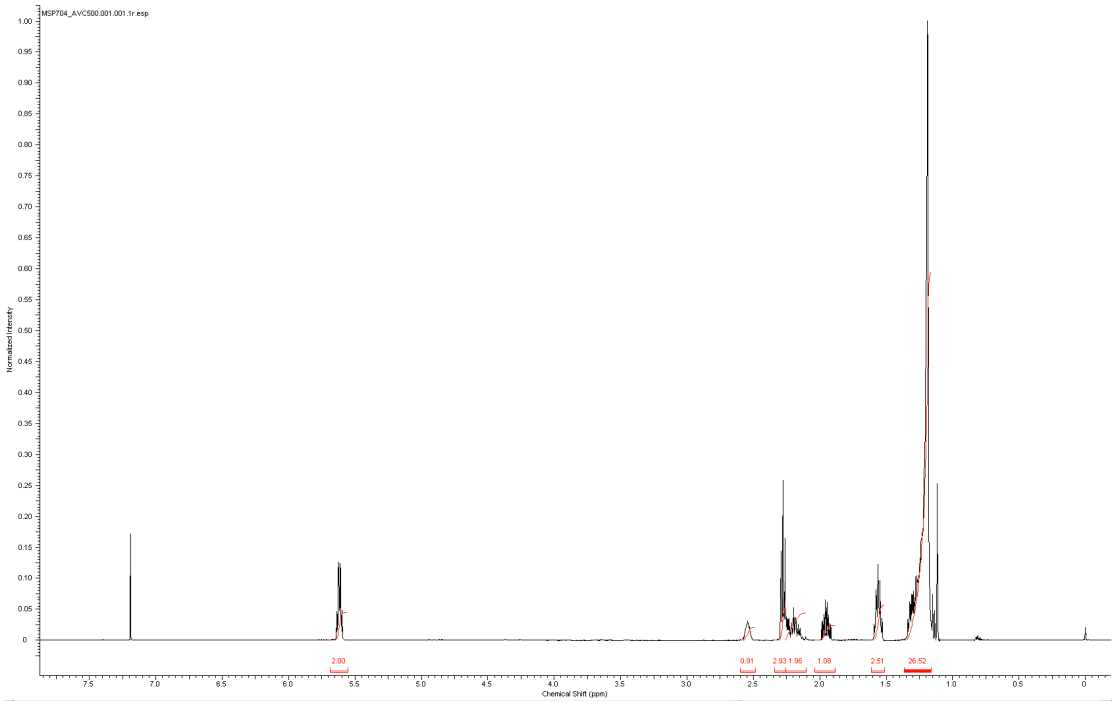
HRMS (ESI) *m*/*z* calcd for $C_{18}H_{32}O_2$ $[M]^+$: 280.2402, found: 280.2397.

IR (ATR) ν (cm^{-1}): 3120.1, 2918.9, 2850.9, 1699.7.

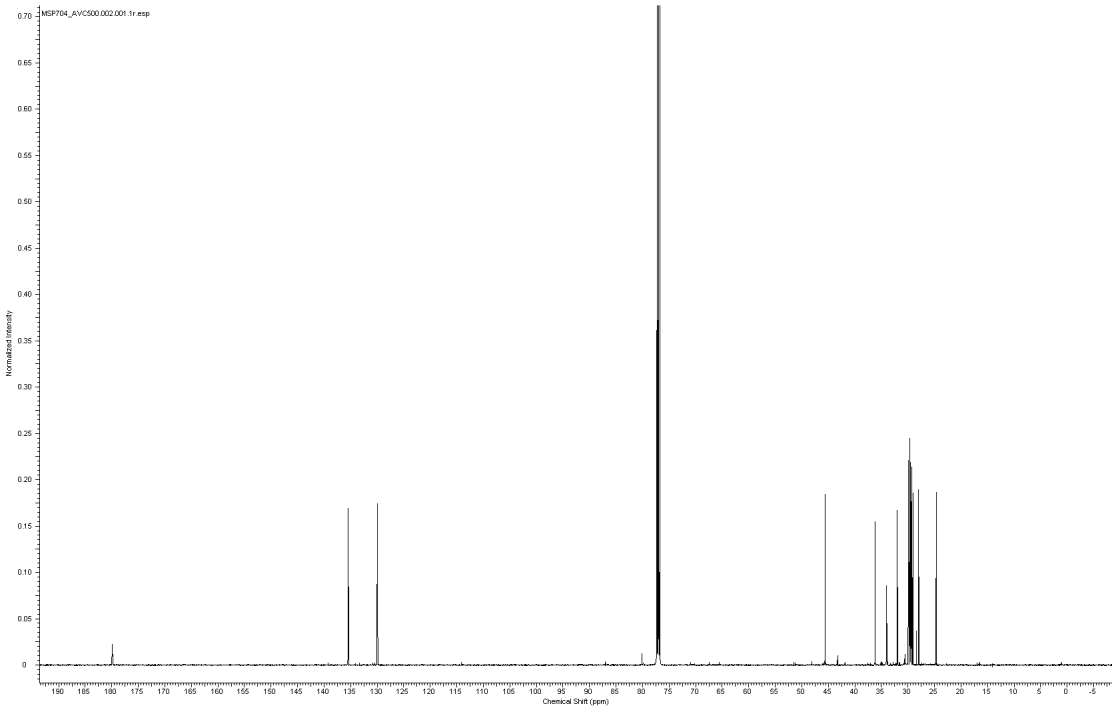
$[\alpha]^{20}_{589}$ = +61.57 (*c* 0.38, $CHCl_3$) [lit. +61.7, *c* 4.82 $CHCl_3$] [18].

m.p. = 67.0–68.5 °C [lit. 67.5 - 68.5 °C] [19].

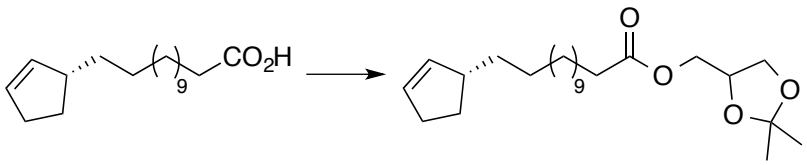
^{1}H NMR:



^{13}C NMR:



Natural products: synthesis of Anthelminthicin C (2.45)



(a) DCC (17.7 mg, 0.09 mmol, 1.00 eq) and DMAP (1.05 mg, 0.009, 0.10) were added to a stirred solution of the acid **7** (24.0 mg, 0.09 mmol, 1.00 eq) in CH_2Cl_2 at 0 °C. The mixture was stirred at 0 °C for 30 min and then a solution of solketal (11.1 μL, 0.09 mmol, 1.01 eq) in CH_2Cl_2 (0.1 mL) was added over 5 min. The resulting suspension was stirred for 2 h at room temperature. After that time EtOAc (2 mL) was added and stirred for 10 min before filtering the formed DCU. The filtrate was concentrated and diluted with EtOAc (3 mL) and water (3 mL). The organic extracts were washed with a saturated solution of $NaHCO_3$ (2.0 mL) and brine (2.0 mL), dried ove $MgSO_4$, filtered and the solvent was then removed

under vacuum. The crude oil was purified by flash column chromatography eluting with hexane:EtOAc (9:1) affording the product as a colourless oil in 94% yield (33.5 mg, 0.084 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 1.22 - 1.31 (m, 17 H), 1.36 - 1.41 (m, 2 H), 1.38 (s, 3 H), 1.47 (s, 3 H), 1.63 (m, 2 H), 1.95 - 2.09 (m, 1 H), 2.20 - 2.32 (m, 3 H), 2.35 (t, *J*=7.6 Hz, 2 H), 2.62 (m, 1 H), 3.74 (dd, *J*=8.4, 6.3 Hz, 1 H), 4.06 - 4.12 (m, 2 H), 4.17 (dd, *J*=11.2, 4.6 Hz, 1 H), 4.32 (quin, *J*=5.8 Hz, 2 H), 5.61 - 5.78 (m, 2 H).

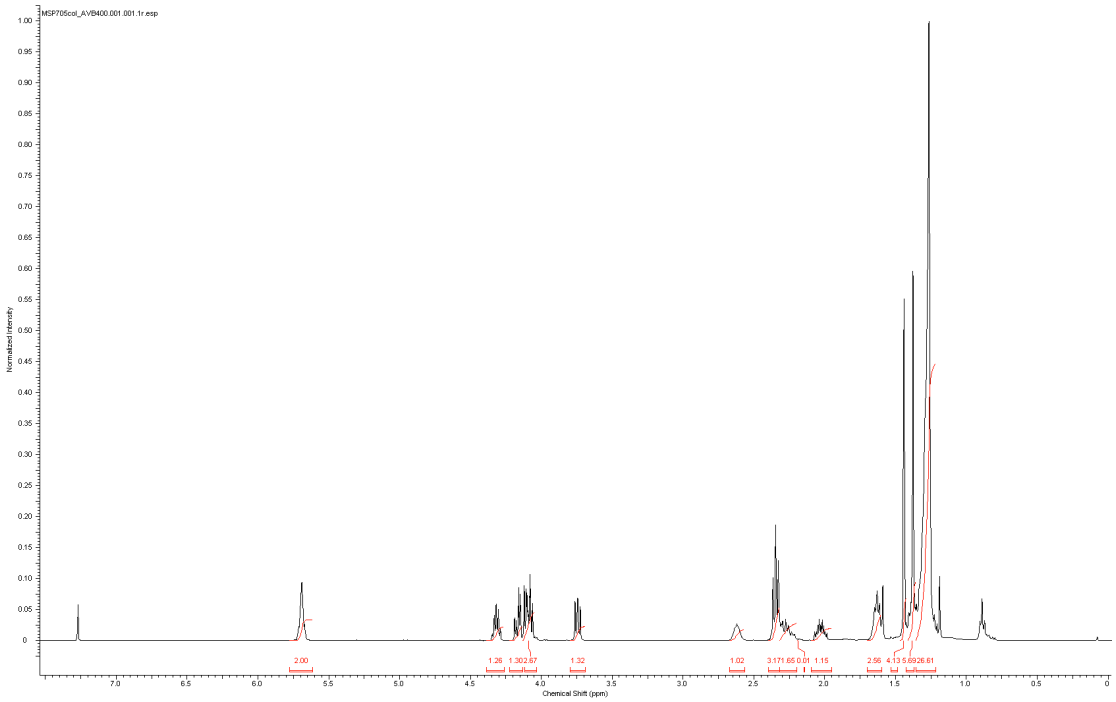
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 24.9, 25.4, 26.7, 28.0, 29.1, 29.2, 29.4, 29.6, 29.6, 29.6, 29.7, 29.9, 29.9, 32.0, 34.1, 36.2, 45.6, 64.5, 66.4, 73.7, 109.8, 130.0, 135.5, 173.6.

HRMS (ESI) *m*/*z* calcd for $C_{24}H_{42}O_4$ $[M]^+$: 394.3083, found: 394.3094.

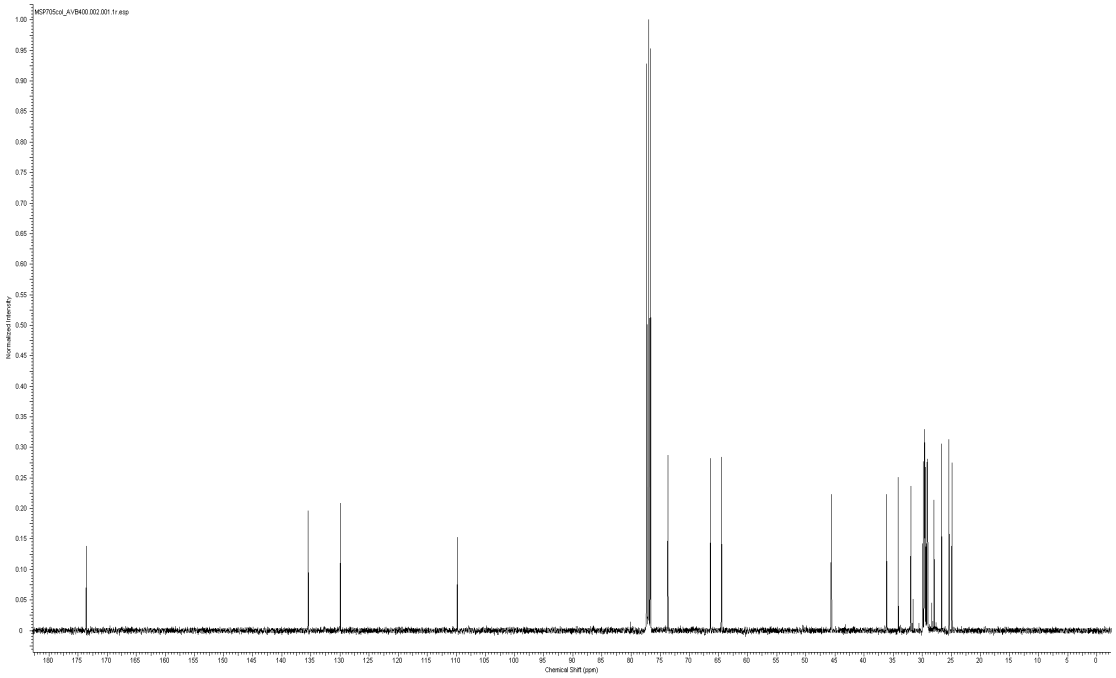
IR (ATR) ν (cm^{-1}): 2924.1, 2853.3, 1742.1.

$[\alpha]^{20}_{589}$ = +43.51 (*c* 0.41, $CHCl_3$).

^{1}H NMR:



^{13}C NMR:



(b) Amberlyst 15 (1.0 mg) was added to a stirred solution of the ester **X** (11.5 mg, 0.029 mmol) in dry MeOH (0.6 mL). The resulting solution was stirred for 20 h at room temperature. The resine was then filtered off and he filtrate was concentrated. The crude was purified by flash column chromatography eluting with CH_2Cl_2:MeOH (95:5) to afford the pure product as a colorless oil in 97% yield impurified with 3% of the 1,2-*O*-acyl migration product which could not be separated (11.1 mg, 0.028 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.24 - 1.32 (m, 18 H), 1.35 - 1.45 (m, 2 H), 1.61 - 1.68 (m, 2 H), 1.99-2.06 (m, 1 H), 2.13 (m, 1 H), 2.22 - 2.29 (m, 1 H), 2.31 - 2.37 (m, 1 H), 2.36 (t, *J*=8.0, 2 H), 2.62 (m, 1 H), 3.62 (m, 1 H), 3.70 (m, 1 H), 3.94 (m, 1 H), 4.15 (dd, *J*=11.7, 6.1 Hz, 1 H), 4.21 (dd, *J*=11.7, 4.6 Hz, 1 H), 5.64 - 5.76 (m, 2 H).

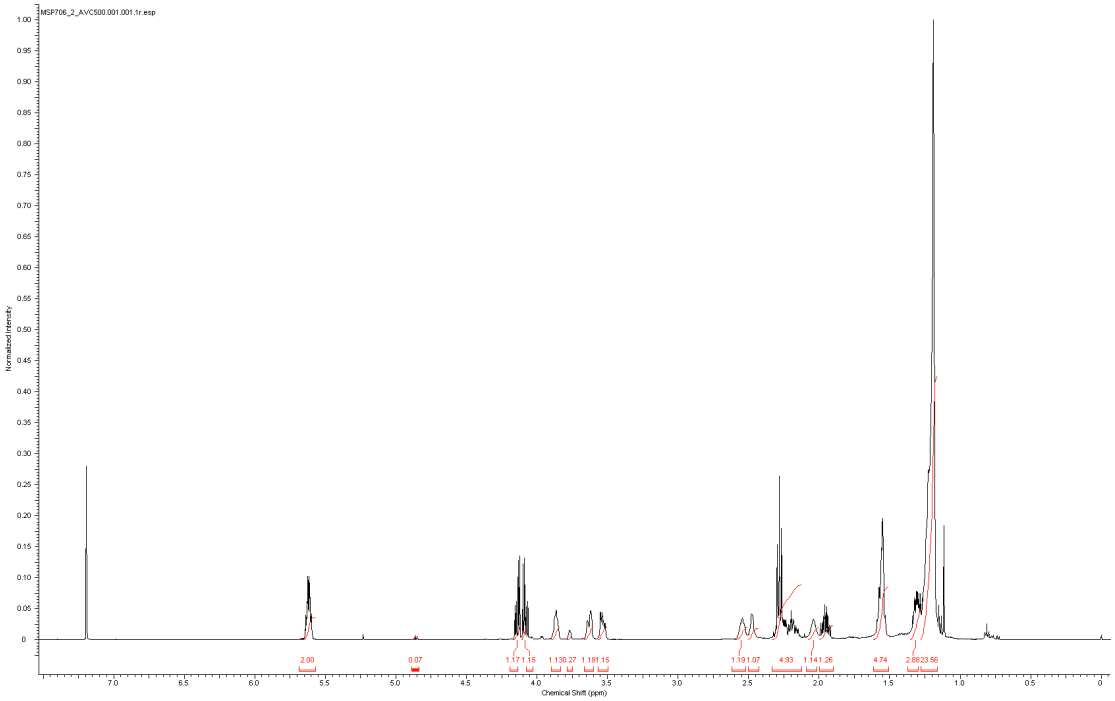
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 24.9, 28.0, 29.1, 29.3, 29.5, 29.6, 29.6, 29.7, 29.7, 29.9, 29.9, 32.0, 34.2, 36.2, 45.6, 63.3, 65.2, 70.3, 130.0, 135.5, 174.4.

HRMS (ESI) *m*/*z* calcd for $C_{21}H_{38}O_4$ $[M]^+$: 354.2770, found: 354.2778.

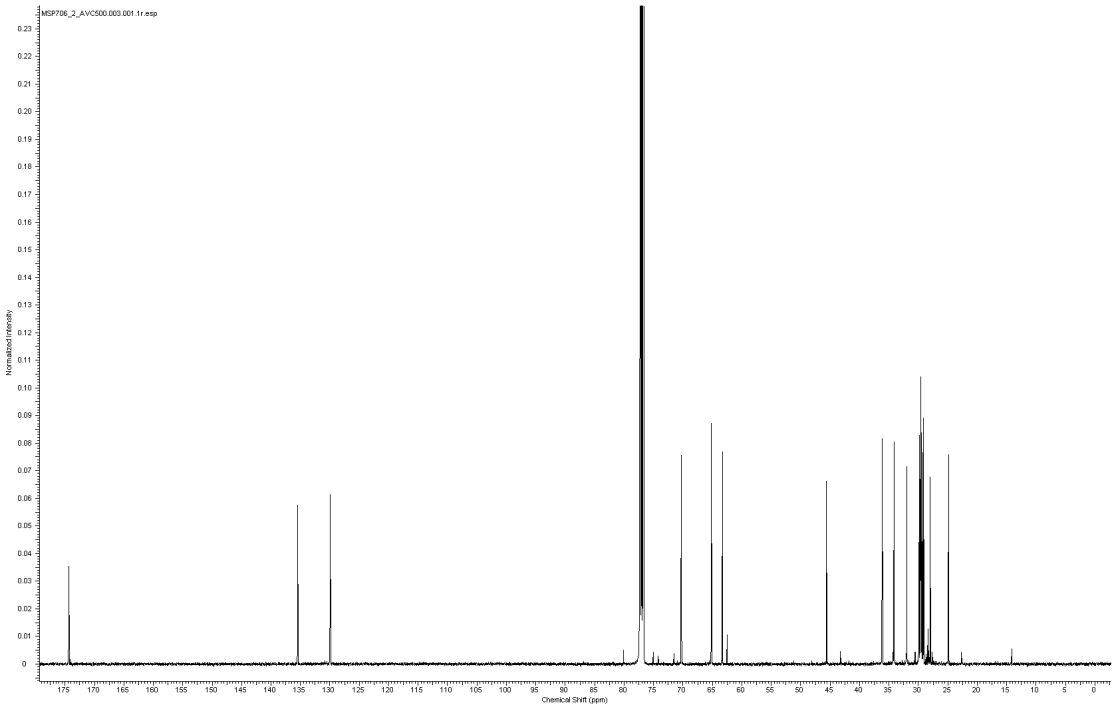
IR (ATR) ν (cm^{-1}): 3393.5, 2918.5, 2850.0, 1735.8.

$[\alpha]^{20}_{589}$ = +50.00 (*c* 0.01, $CHCl_3$) [lit. +32.55, *c* 1.37 $CHCl_3$] [20].

^{1}H NMR:



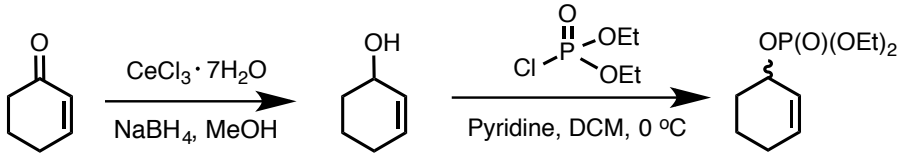
^{13}C NMR:



5.4 Cu-catalyzed Dynamic Kinetic Asymmetric Allylic Alkylation of Racemic Phosphates Using Organozirconium species

Synthesis of starting materials (3.1-3.15)

2-cyclohexenyl-diethyl phosphate (3.1)



(a) In a 50 mL flame dried flask, 2-cyclohexenone (3.9 mL, 40 mmol, 1.0 eq) was added to a solution of $CeCl_3.7H_2O$ (15 g, 40 mmol, 1.0 eq) in MeOH (20 mL) under an argon atmosphere. After cooling to 0 ^oC in an ice-bath for around 15 min, $NaBH_4$ (1.52 g, 40 mmol, 1.0 eq) was added in portions over a period of 15 min. The ice-bath was left warm to room temperature and stirred for 3 h. The reaction was quenched with HCl (1 M, 20 mL),

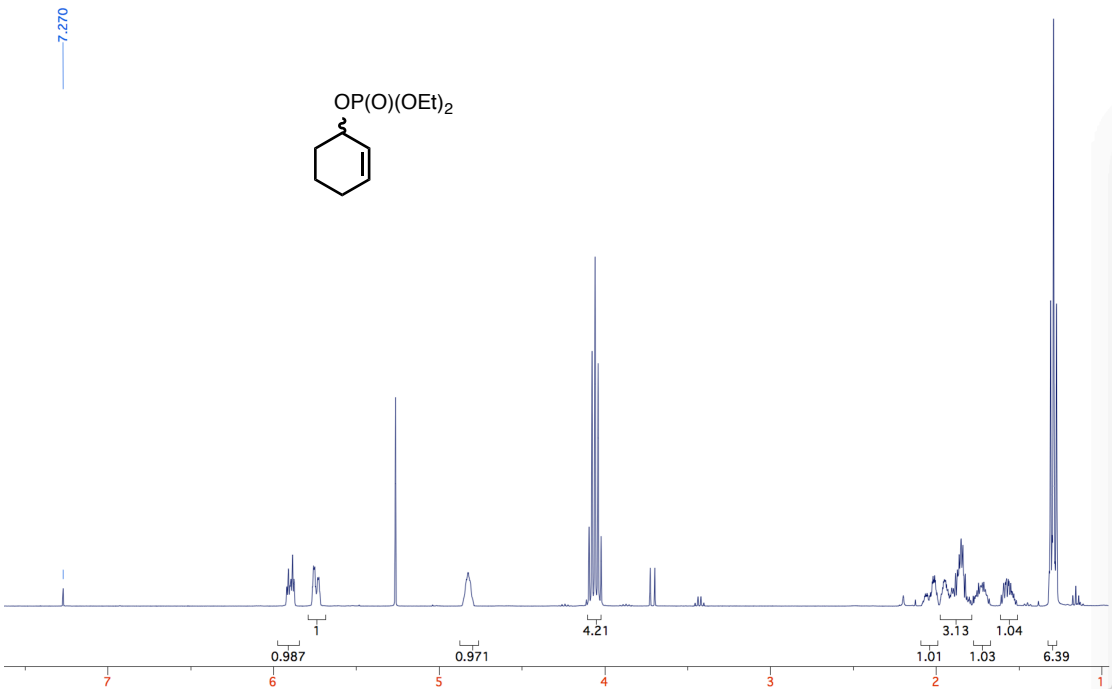
and the aqueous phase was extracted with Et_2O (4×15 mL), resulting organic phase was washed with brine (20 mL), dried over $MgSO_4$, and evaporated under vacuum (300 mmbar, 50 ^oC) for 20 min to give pure product as colorless oil (3.75 g, 38.4 mmol, 96%).

(b) In a 100 mL flame dried flask, Pyridine (8.2 mL, 100 mmol, 5 eq) was added to a solution of 2-cyclohexenol (2 mL, 20 mmol, 1.0 eq) in CH_2Cl_2 (50 mL) under an argon atmosphere. After cooling to 0 ^oC in an ice-bath for around 10 min, diethyl chlorophosphate (3.2 mL, 22 mmol, 1.1 eq) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirring was continued overnight. Then the reaction mixture was diluted with CH_2Cl_2 (100 mL) and quenched with H_2O (100 mL). The phases were partitioned and the organic phase was washed with sat. $CuSO_4$ (50 mL×2) and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified carefully through flash column chromatography (Et_2O: Et_3N, 99:1; SiO_2) to provide the product in 68% yield (3.19 g, 13.6 mmol) as colorless oil.

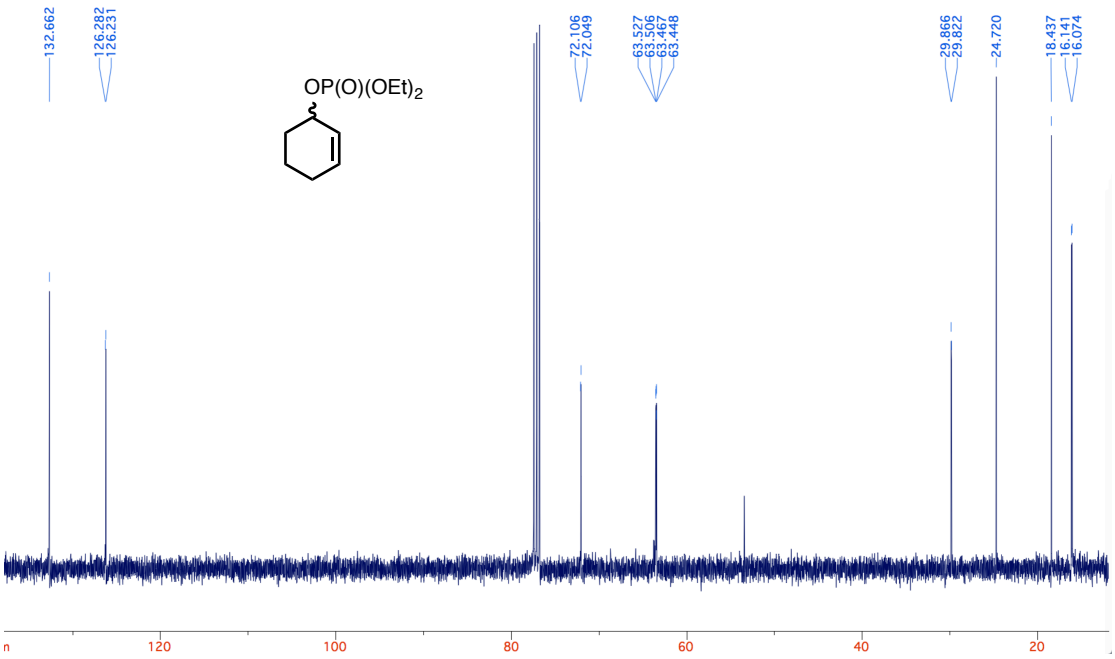
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.29 (t, *J*=7.09 Hz, 6 H), 1.53 - 1.61 (m, 1 H), 1.65 - 1.77 (m, 1 H), 1.82 - 1.97 (m, 3 H), 2.00 - 2.07 (m, 1 H), 4.06 (quint, *J*=7.26 Hz, 4 H), 4.83(brs, 1 H), 5.74 (m, 1 H), 5.90 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 16.1, 16.1, 18.4, 24.7, 29.8, 63.4, 63.5, 72.1, 126.3, 132.7.

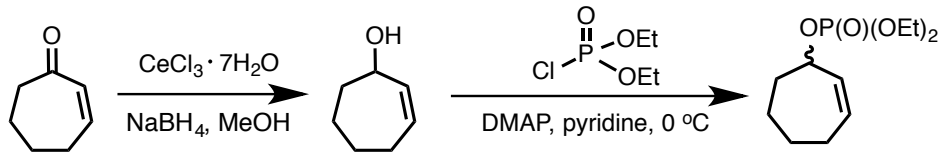
^{1}H NMR:


7.270
OP(O)(OEt)2
1
0.987
0.971
4.21
3.13
1.04
1.01
1.03
6.39
7
6
5
4
3
2
1

^{13}C NMR:


132.662
126.282
126.231
OP(O)(OEt)2
72.106
72.049
63.527
63.506
63.467
63.448
29.866
29.822
24.720
18.437
16.141
16.074
120
100
80
60
40
20

2-cycloheptenyl-diethyl phosphate (3.2)



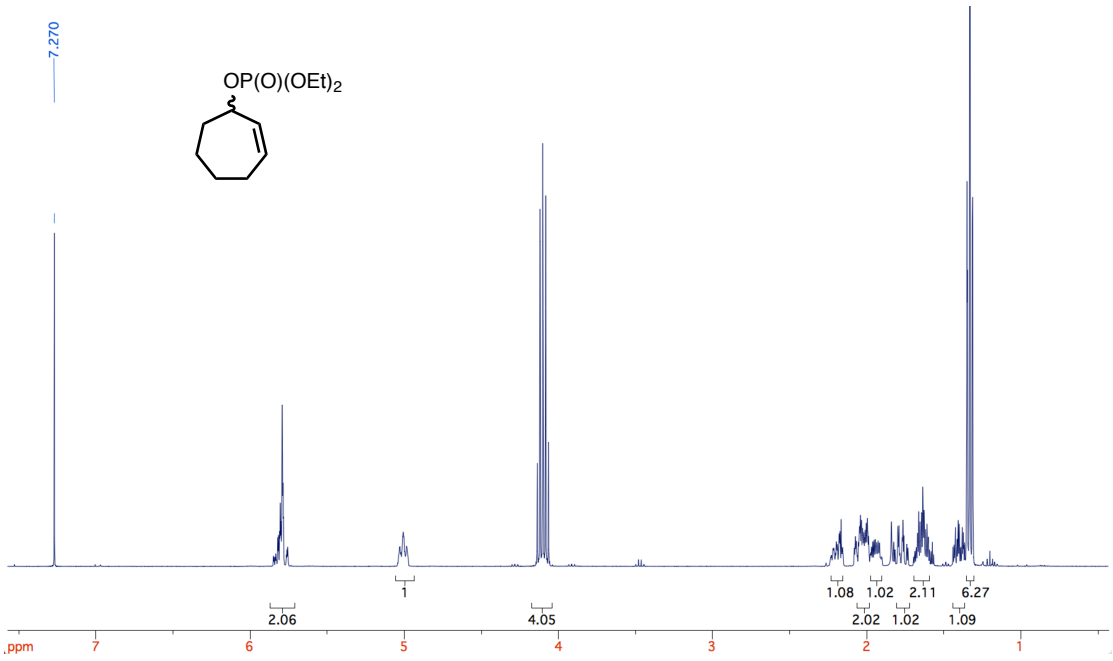
(a) In a 25 mL flame dried flask, 2-cyclohexenone (1 mL, 9.1 mmol, 1.0 eq) was added to a solution of $CeCl_3.7H_2O$ (3.4 g, 9.1 mmol, 1.0 eq) in MeOH (10 mL) under an argon atmosphere. After cooling to 0 ^oC in an ice-bath for around 15 min, $NaBH_4$ (0.35 g, 9.1 mmol, 1.0 eq) was added in portions over a period of 15 min. The ice-bath was left warm to room temperature and stirred for 3 h. The reaction was quenched with HCl (1 M, 10 mL), and the aqueous phase was extracted with Et_2O (4×10 mL), resulting organic phase was washed with brine (20 mL), dried over $MgSO_4$, and evaporated under vacuum (300 mmbar, 50 ^oC) for 20 min to give pure product as colorless oil (990 mg, 8.8 mmol, 97%).

(b) In a 10 mL flame dried flask, DMAP (0.13 g, 1.1 mmol, 0.1 eq) was added to the solution of responding alcohol (1.2 g, 10.8 mmol, 1.0 eq) in Pyridine (4.5 mL, 54 mmol, 5 eq) under an argon atmosphere. After cooling to 0 ^oC in an ice-bath for around 10 min, diethyl chlorophosphate (1.87 mL, 13 mmol, 1.2 eq) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirring was continued overnight. Then the reaction mixture was diluted with CH_2Cl_2 (50 mL) and quenched with H_2O (50 mL). The phases were partitioned and the organic phase was washed with sat. $CuSO_4$ (50 mL×2) and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified carefully through flash column chromatography (Et_2O: Et_3N, 99:1; SiO_2) to provide the product in 88% yield (2.36 g, 9.5 mmol) as colorless oil.

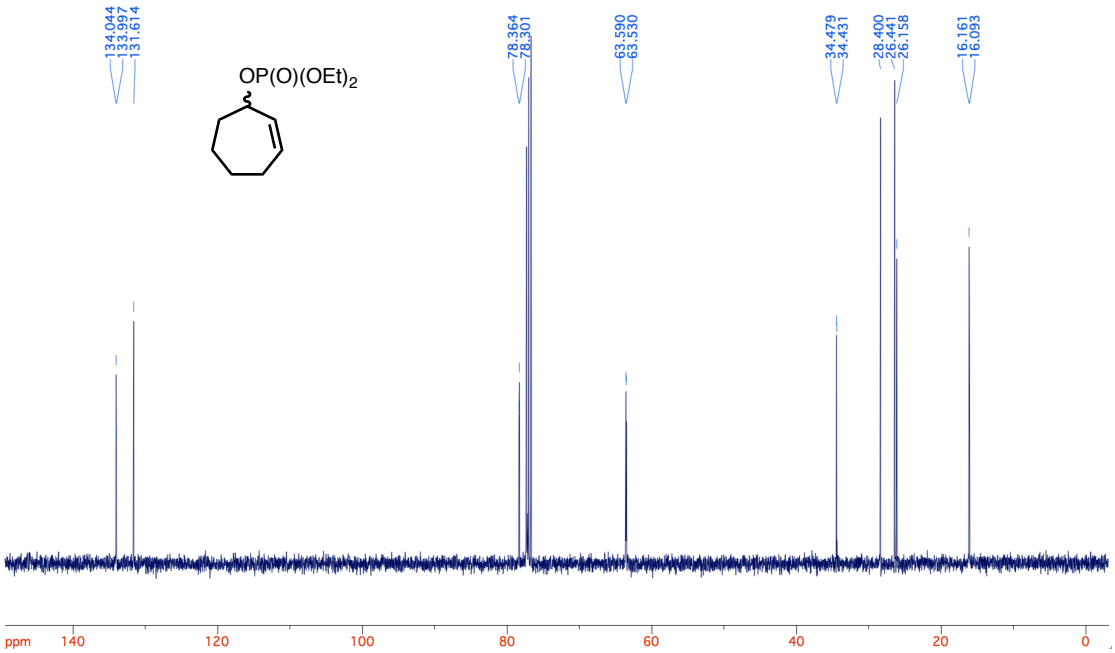
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.31-1.35 (m, 6 H), 1.36-1.44 (m, 1 H), 1.59-1.69 (m, 2 H), 1.73-1.80 (m, 1 H), 1.92-1.96 (m, 1 H), 1.99-2.07 (m, 2 H), 2.16-2.23 (m, 1 H), 4.06-4.14 (m, 4 H), 4.98-5.04 (m, 1 H), 5.75-5.85 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 16.1, 16.2, 26.2, 26.4, 28.4, 34.5, 63.5, 63.6, 78.3, 131.6, 134.0.

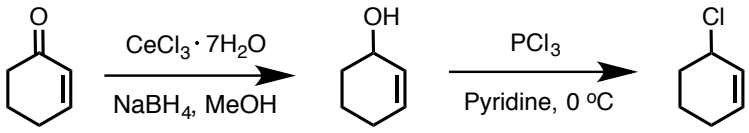
^{1}H NMR:



^{13}C NMR:



3-chlorocyclohexene (3.3)



(a) In a 50 mL flame dried flask, 2-cyclohexenone (3.9 mL, 40 mmol, 1.0 eq) was added to a solution of $CeCl_3.7H_2O$ (15 g, 40 mmol, 1.0 eq) in MeOH (20 mL) under an argon atmosphere. After cooling to 0 °C in an ice-bath for around 15 min, $NaBH_4$ (1.52 g, 40 mmol, 1.0 eq) was added in portions over a period of 15 min. The ice-bath was left warm to room temperature and stirred for 3 h. The reaction was quenched with HCl (1 M, 20 mL), and the product was extracted with Et_2O (4×15 mL), washed with brine (20 mL), dried over $MgSO_4$, and evaporated under vacuum (300 mmbar, 50 °C) for 20 min to give pure product as a clear colorless oil (3.75 g, 38.4 mmol, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.60-2.11 (m, 6H), 5.22-5.28 (m, 1H), 5.65-5.70 (m, 1H), 5.94-5.96 (m, 1H).

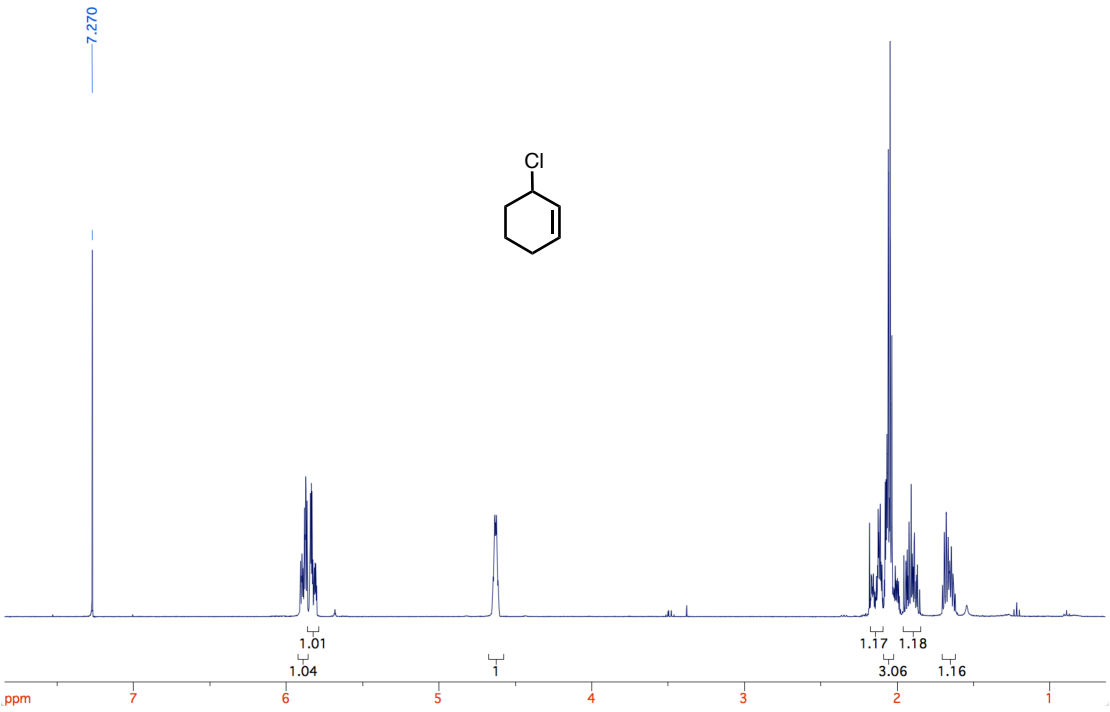
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 18.8, 21.4, 28.3, 68.1, 125.7, 132.8.

(b) In a 10 mL flame dried flask, fresh distilled phosphorus trichloride (1.3 mL, 14.1 mmol, 0.37 eq) was added under an argon atmosphere. After cooling to 0 °C in an ice-bath for around 15 min, a mixture of cyclohex-2-enol (3.75 g, 38 mmol, 1 eq) and pyridine (0.31 mL, 3.8 mmol, 0.1 eq) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirring was continued overnight. Then the organic (top) layer was then removed by pipette and purified by Kugelrohr distillation (200 mmbar, 85 °C) for 15 min to remove pyridine. Further distillation (60 mmbar, 110 °C) for 1 h gave the pure product (3.51 g, 30.1 mmol, 79% yield) as colorless oil.

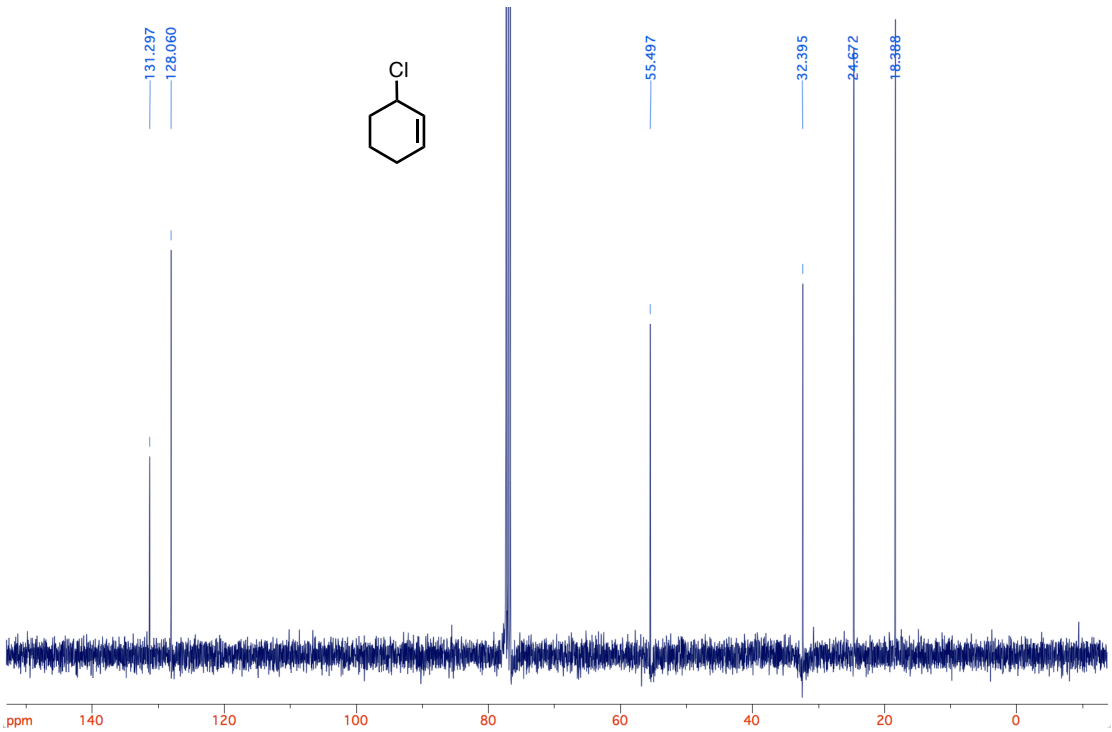
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 5.84-5.90 (m, 1H), 5.80-5.86 (m, 1H), 4.60-4.62(m, 1H), 1.96-2.17(m, 4H), 1.84-1.95 (m, 1H), 1.59-1.71 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 18.4, 24.7, 32.4, 55.6, 128.1, 131.3.

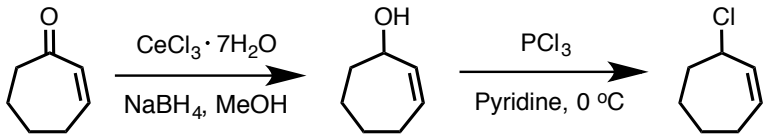
^{1}H NMR:



^{13}C NMR:



3-chlorocycloheptene (3.4)



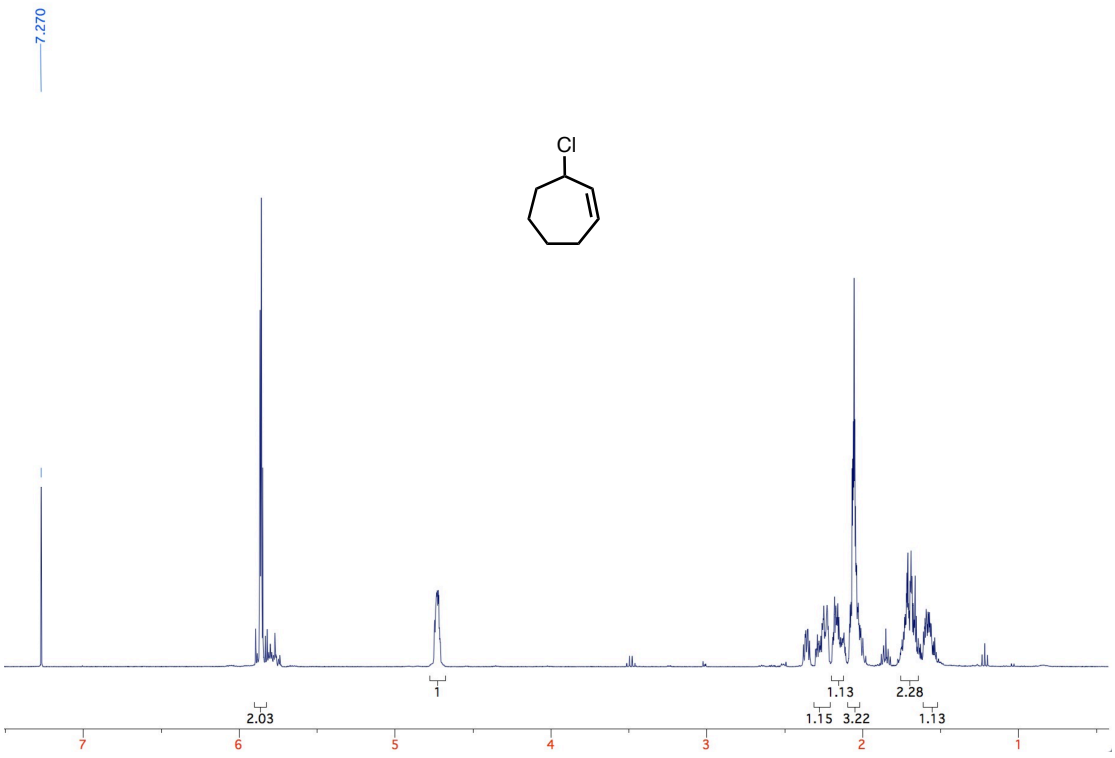
(a) In a 50 mL flame dried flask, 2-cycloheptenone (2 mL, 18.2 mmol, 1.0 eq) was added to a solution of $CeCl_3.7H_2O$ (6.8 g, 18.2 mmol, 1.0 eq) in MeOH (20 mL) under an argon atmosphere. After cooling to 0 °C in an ice-bath for around 15 min, $NaBH_4$ (0.7 g, 18.2 mmol, 1.0 eq) was added in portions over a period of 15 min. The ice-bath was left warm to room temperature and stirred for 4 h. The reaction was quenched with HCl (1 M, 20 mL), and the aqueous phase was extracted with Et_2O (4×15 mL), resulting organic phase was washed with brine (30 mL), dried over $MgSO_4$, and evaporated under vacuum (300 mmbar, 50 °C) for 20 min to give pure product as colorless oil (1.98 g, 17.6 mmol, 97%).

(b) In a 10 mL flame dried flask, fresh distilled phosphorus trichloride (0.4 mL, 4.3 mmol, 0.37 eq) was added under an argon atmosphere. After cooling to 0 °C in an ice-bath for around 15 min, a mixture of cyclohept-2-enol (1.31 g, 11.7 mmol, 1 eq) and pyridine (0.09 mL, 1.2 mmol, 0.1 eq) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirring was continued overnight. Then the organic (top) layer was then removed by pipette and purified by Kugelrohr distillation (200 mmbar, 85 °C) for 15 min to remove pyridine. Further distillation (60 mmbar, 130 °C) for 1 h gave the product contamined with varying amounts of cycloheptadiene (10-15%) (1.0 g, 7.8 mmol, 67% yield) as colorless oil.

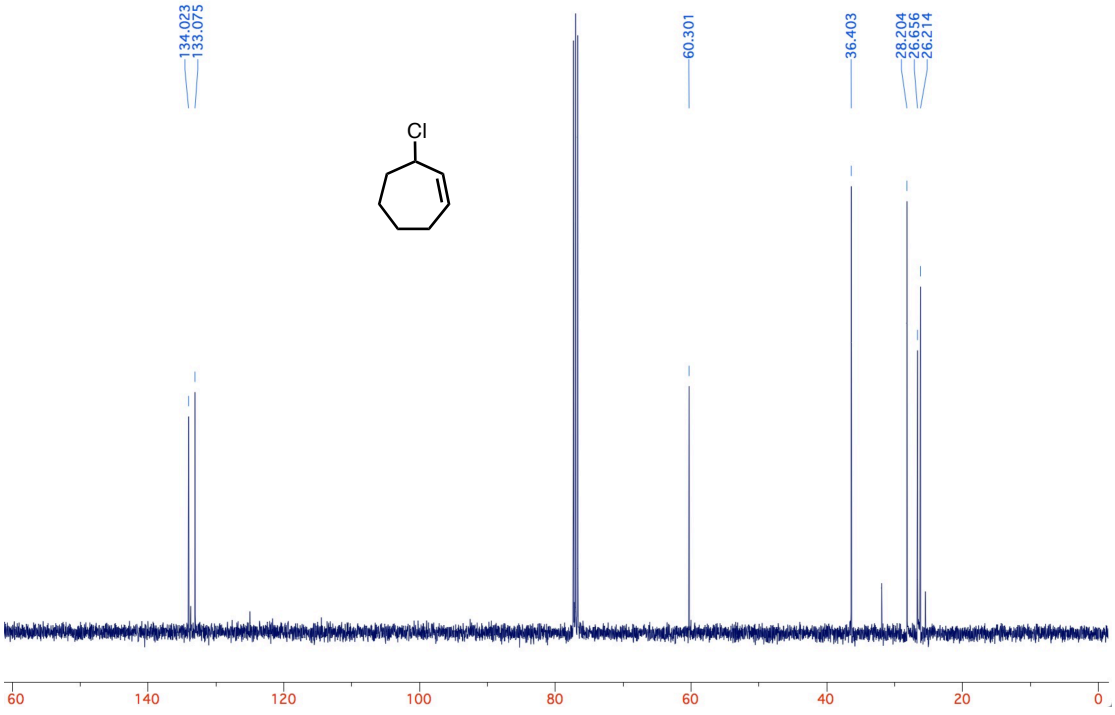
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 5.83-5.89 (m, 2H), 4.71-4.75 (m, 1H), 2.22-2.30 (m, 1H), 2.12-2.19 (m, 1H), 2.02-2.08 (m, 3H), 1.64-1.75 (m, 2H)， 1.53-1.61 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 26.2, 26.7, 28.2, 36.4, 60.3, 133.1, 134.0.

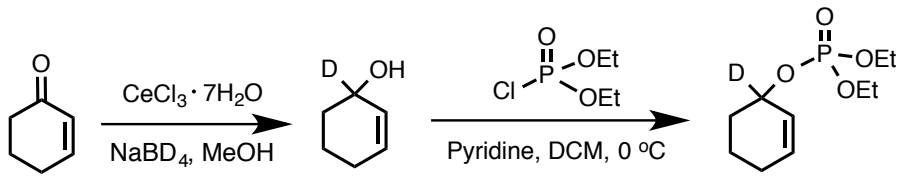
^{1}H NMR:


7.270
Cl
2.03
1
1.13
1.15
3.22
2.28
1.13
7
6
5
4
3
2
1

^{13}C NMR:


134.023
133.075
60.301
36.403
28.204
26.656
26.214
Cl
60
140
120
100
80
60
40
20
0

Cyclohex-2-en-1-yl-1-d diethyl phosphate (3.5)



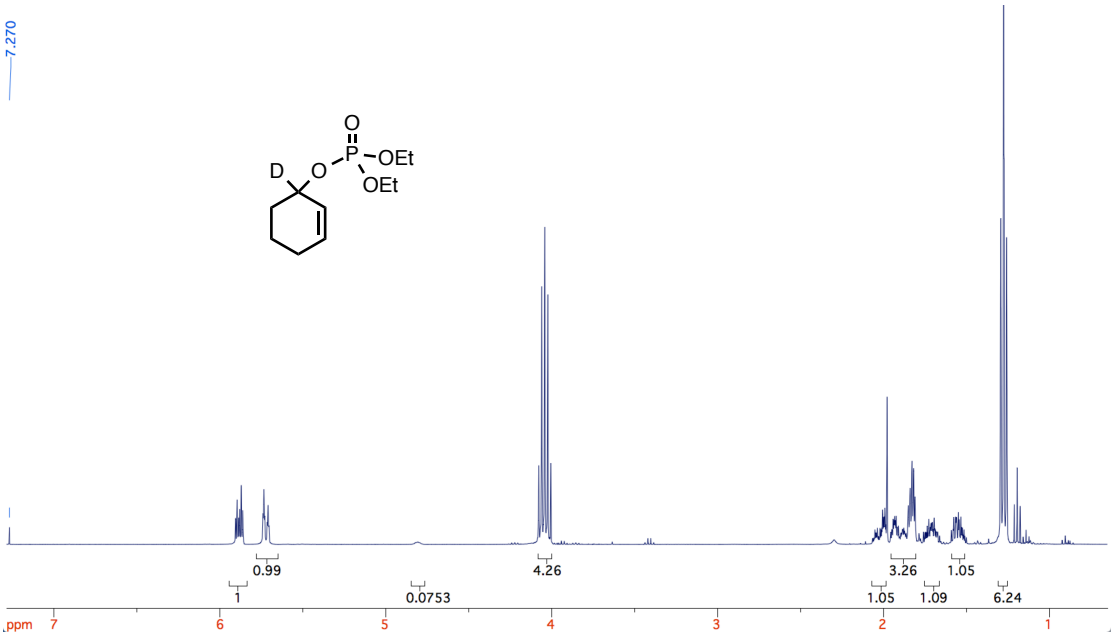
Same procedure refers to the preparation of **2-cyclohexenyl-diethyl phosphate (3.1)**

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.26-1.29 (m, 6 H), 1.51 - 1.58 (m, 1 H), 1.67 - 1.75 (m, 1 H) 1.81 - 1.96 (m, 3 H), 1.98 - 2.05 (m, 1 H), 4.01-4.08 (m, 4 H), 5.72 (dt, *J*=10.08, 2.10 Hz, 1 H), 5.88(dt, *J*=10.07, 3.70 Hz, 1 H).

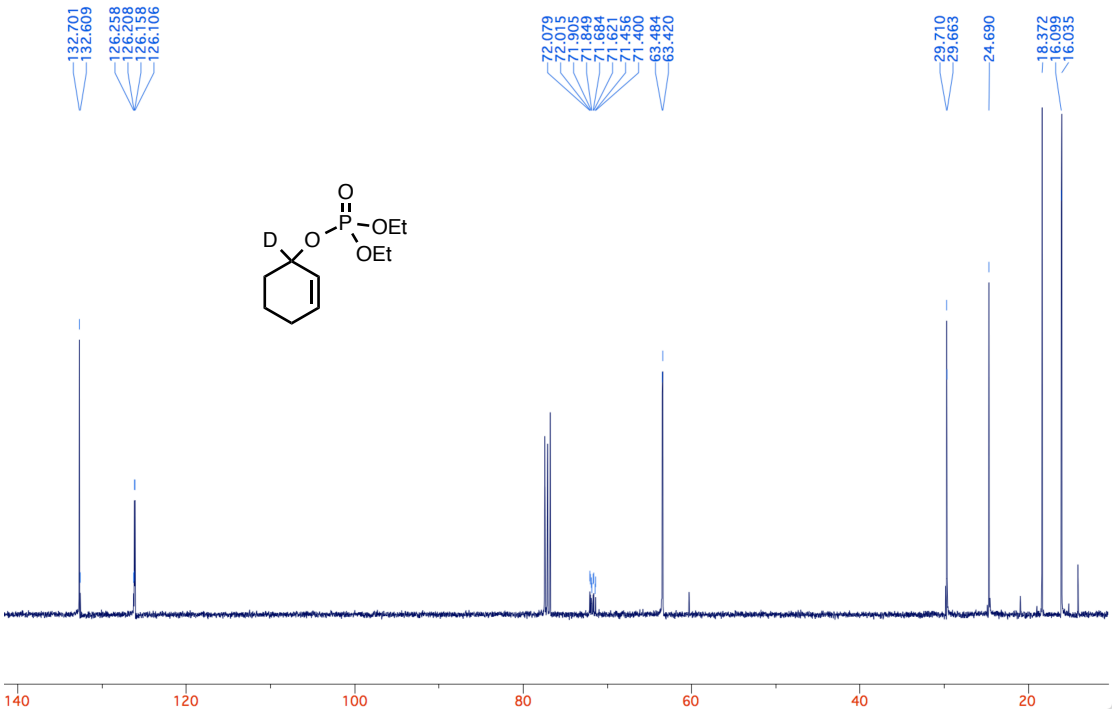
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 16.0, 16.1, 18.4, 24.7, 29.7, 63.4, 63.5, 71.8, 126.2, 132.7.

^{31}P NMR: –1.33.

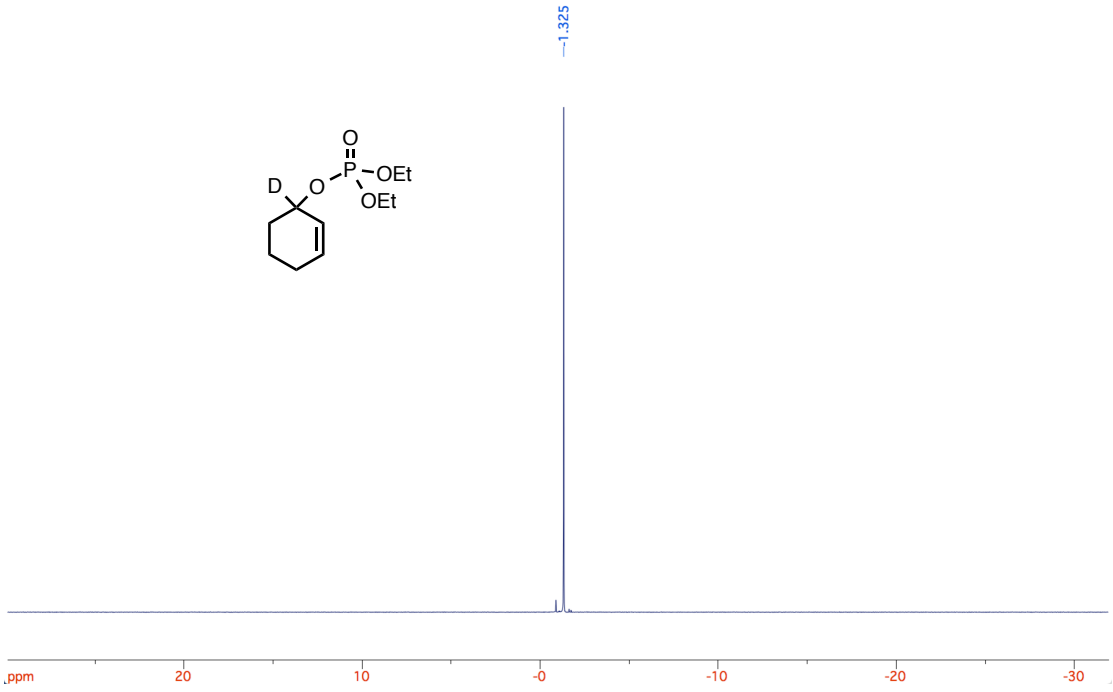
^{1}H NMR:



^{13}C NMR:

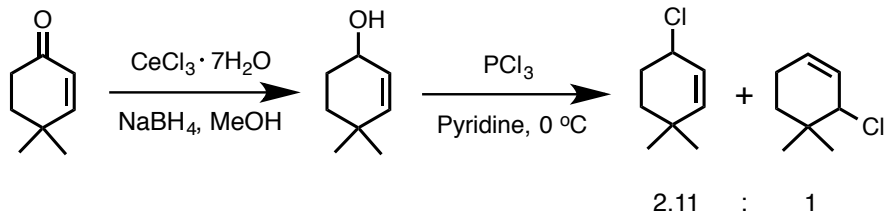


^{31}P NMR:



6-chloro-3,3-dimethylcyclohex-1-ene;

3-chloro-4,4-dimethylcyclohex-1-ene (3.6)

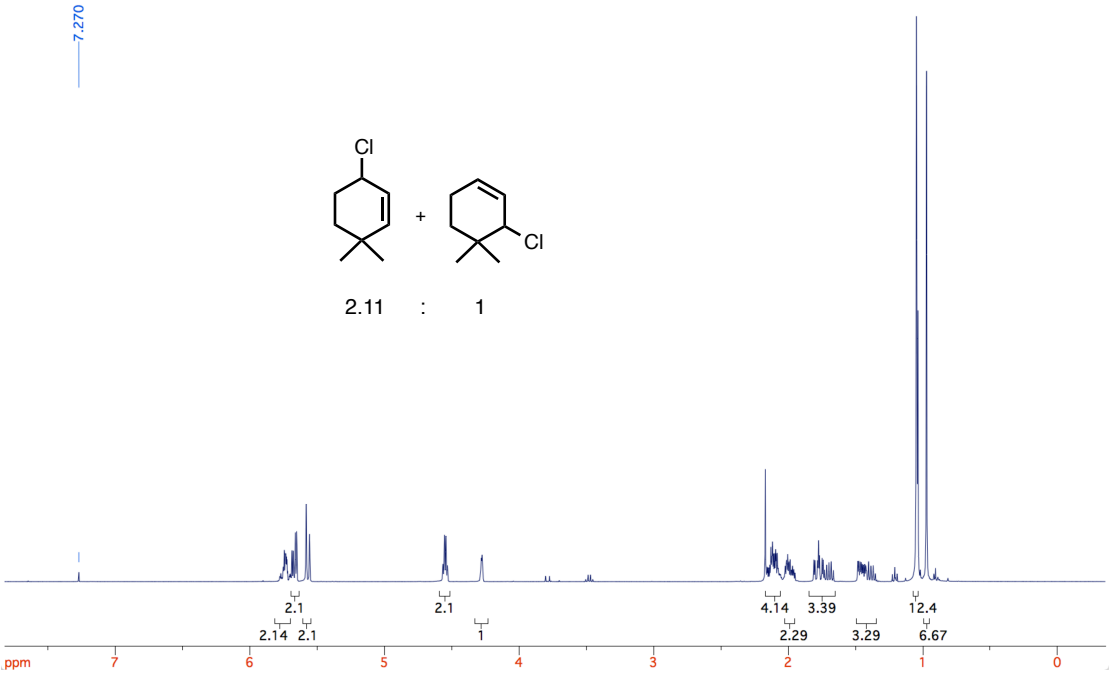


Same procedure refers to the preparation of **3-chlorocyclohexene (3.3)**

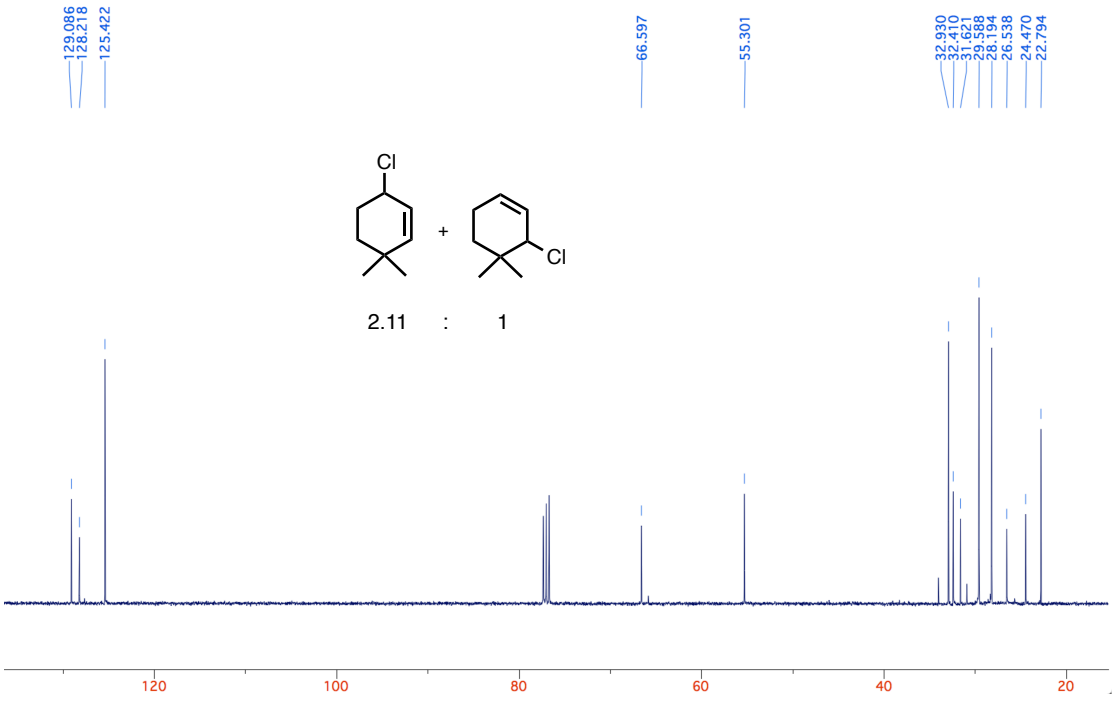
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 0.97 (s, 6H), 1.04 (m, 12H), 1.40-1.48 (m, 3H), 1.68-1.81 (m, 3H), 1.94-2.03 (m, 2H), 2.08-2.17 (m, 4H), 4.28 (d, *J*=2.32 Hz, 1H), 4.55 (m, 2H), 5.57 (m, 2H), 5.64-5.69 (m, 2H), 5.70-5.78 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 22.8, 24.5, 26.5, 28.2 (2C), 29.6 (2C), 31.6, 32.4, 32.9, 55.3, 66.6, 125.4, 128.2, 129.1, 141.2

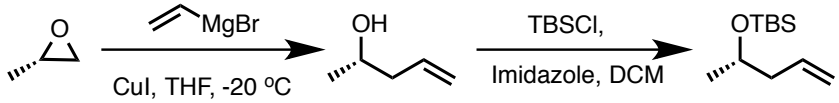
^{1}H NMR:



^{13}C NMR:



(S)-tert-butyldimethyl(pent-4-en-2-yloxy)silane (3.7)



(a) In a 500 mL flame dried flask, CuI (1.64 g, 8.6 mmol, 1.0 eq) was added in THF (20 mL) under an argon atmosphere at –20 °C by a cooling machine. The vinylmagnesium bromide (1 m in THF, 172 mL, 172.4 mmol) was injected into the mixture. And then a solution of propylene oxide (5 g, 86.1 mmol) in THF (10 mL) was added slowly to the above reagent, and the mixture was stirred at –20 °C for overnight. The reaction was quenched with saturated aqueous solution of NH_4Cl, resulting organic phase was washed with brine, dried over Na_2SO_4, vacuum to concentrate. Further purification was done by Kugelrohr apparatus (T = 95 °C, 200 mbar) to give the pure product (6.0g) as a colorless liquid in 80% yield.

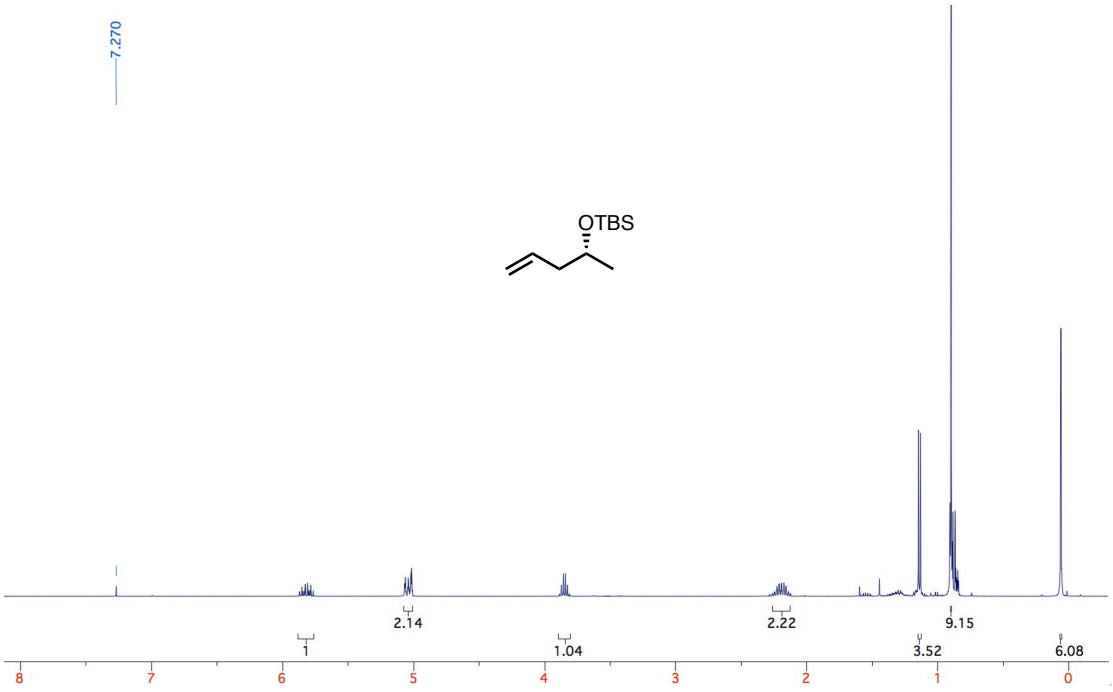
(b) In a 250 mL flame dried flask, imidazole (6.62 g, 96.9 mmol, 2.5 eq) was added to a stirred solution of responding alcohol (3.31 g, 38.8 mmol, 1.0 eq) in CH_2Cl_2 (85 mL). *tert*-Butyl

dimethyl- chlorosilane (12.32 g, 77.6 mmol, 2.0 eq) was then added to this solution at 0 ^{o}C, and reaction was stirred at room temperature overnight. Resulting reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3×50 mL). The organic phase were washed with brine, dried over Na_2SO_4, and then concentrated. Silica-gel column chromatography of the crude (Petroleum ether/EtOAc 50:1) provided the pure product (5.71 g) as a colorless liquid in 73% yield [21].

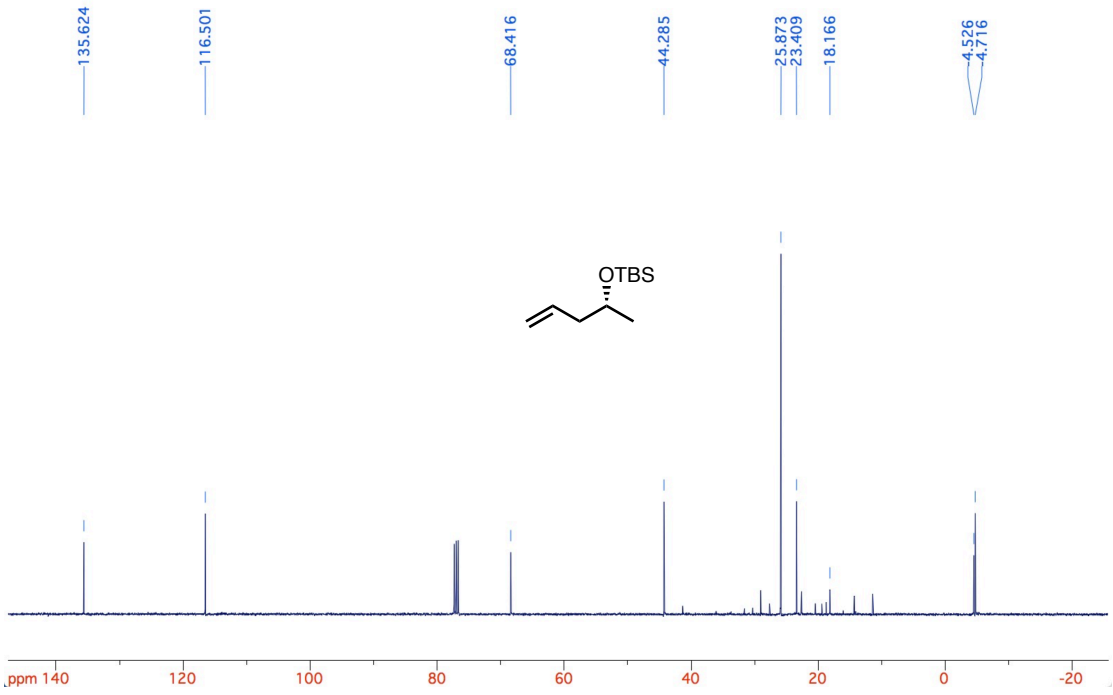
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 5.81 (m, 1H), 5.01- 5.07 (m, 2 H), 3.85 (q, *J*=6.08 Hz, 1 H), 2.16-2.21 (m, 2 H), 1.14 (d, *J*=6.09 Hz, 3 H), 0.90 (s, 9H), 0.61 (d, *J*=0.81 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 135.6, 116.5, 68.4, 44.3, 25.9, 23.4, 18.2, -4.5, -4.7

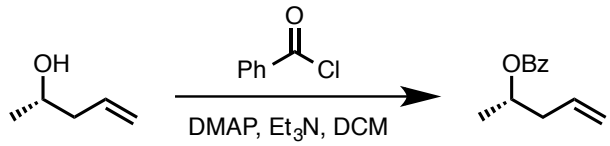
^{1}H NMR:



^{13}C NMR:

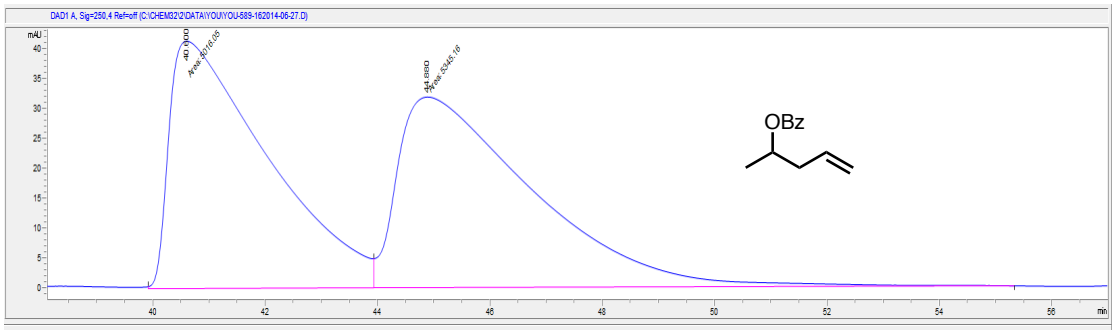


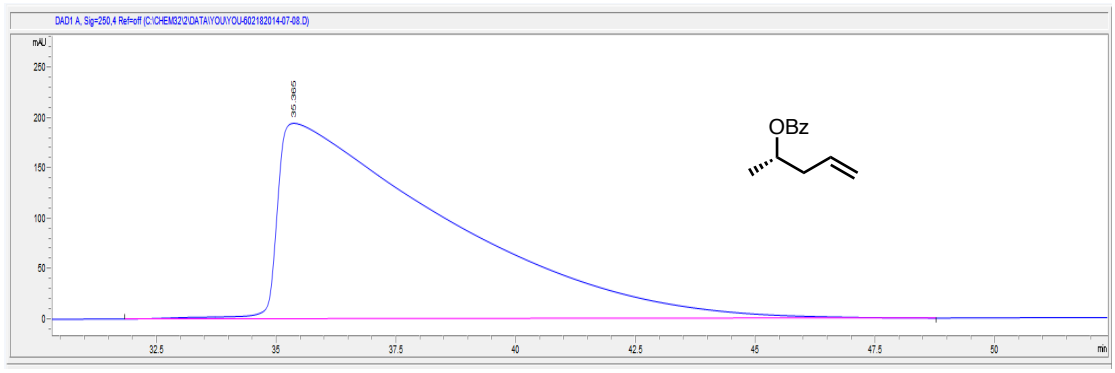
ee determination:



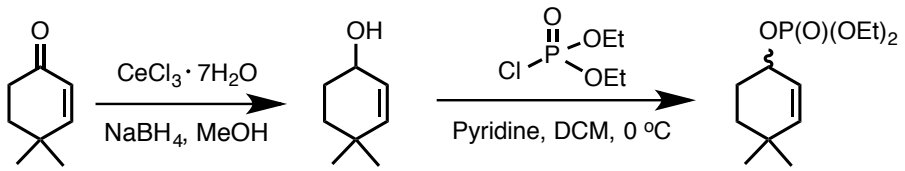
In a 10 mL flame dried flask, a solution of corresponding alcohol (86 mg, 1 mmol, 1 equiv.) in dichloromethane (5 ml) was added DMAP (61.1 mg, 0.5 mmol, 0.5 equiv.) and triethyl amine (0.25 mL, 1.8 mmol, 1.8 equiv.), followed (cautiously) by addition of benzoyl chloride (0.16 mL, 1.4 mmol, 1.4 equiv.) to the flask. Under inert argon atmosphere, the reaction mixture was stirred (60 mins) at 0 °C followed by 2 hours at room temperature. Then the reaction was quenched by addition of water (5 ml), The phases were partitioned and the organic phase was washed with hydrochoric acid (10 ml, 1M), NaHCO3 (sat. 10 ml), followed by brine (10 ml). The organic layer was isolated, dried (MgSO4), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue gave the product (161.7 mg, 0.85 mmol) in 85% yield.

HPLC traces:





4,4-dimethylcyclohexenyl-diethyl phosphate (3.8)

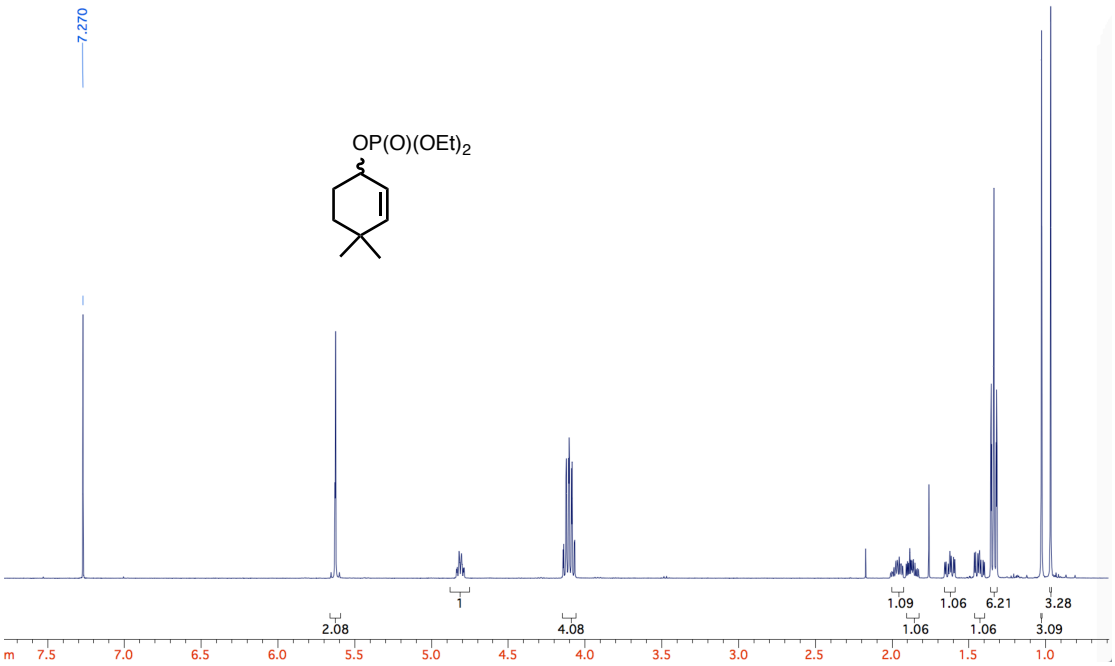


Same procedure refers to the preparation of **2-cyclohexenyl-diethyl phosphate (3.1)**

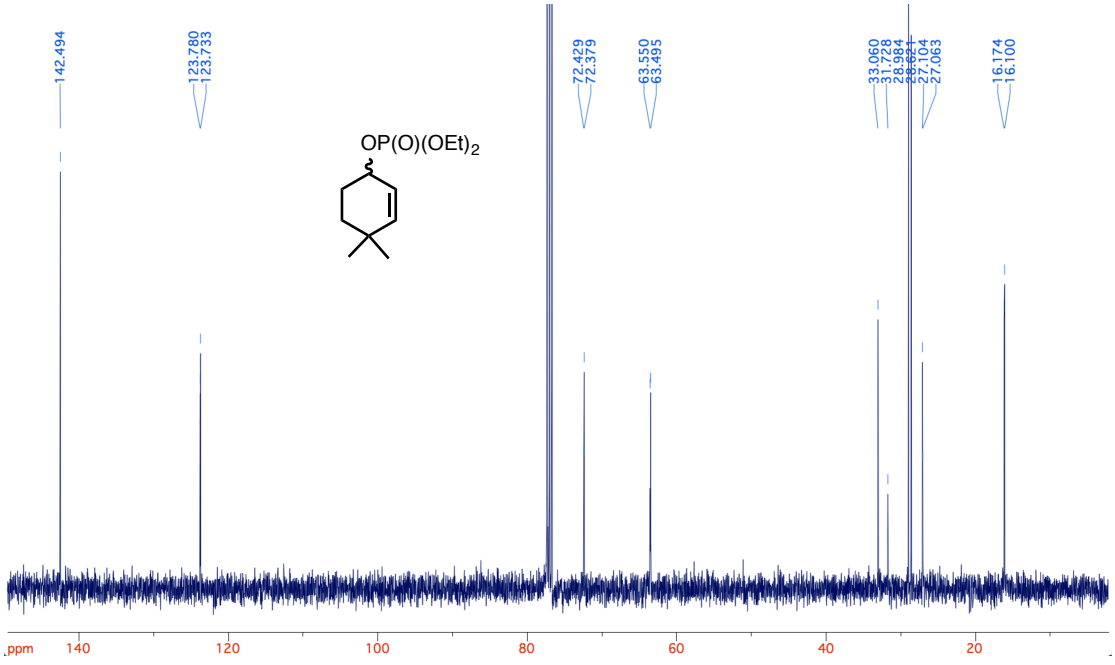
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 0.97 (s, 3 H), 1.03 (s, 3 H), 1.32-1.36 (m, 6 H), 1.43-1.46 (m, 1 H), 1.59-1.66 (m, 1 H), 1.82-1.91 (m, 1 H), 1.93-2.01 (m, 1 H), 4.07-4.14 (m, 4 H), 4.78-4.84 (m, 1 H), 5.59-5.66 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 16.1, 16.2, 27.1, 28.6, 29.0, 31.7, 33.1, 63.5, 63.6, 72.4, 123.8, 142.5

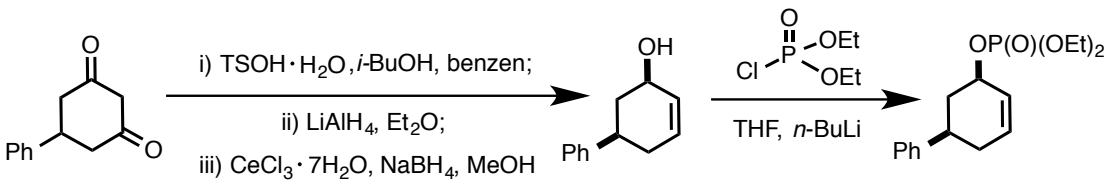
^{1}H NMR:



^{13}C NMR:



Diethyl ((1R,3R)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl) phosphate (3.9)



***cis*-alcohol,**

(a) In a 250 mL flame dried flask, 5-phenyl-1,3-cyclohexanedione (5.0 g, 26.50 mmol) was dissolved in *i*-BuOH (60 mL) and benzene (60 mL) under an argon atmosphere. Then *p*-toluenesulfonic acid (68 mg) was added, and the solution was refluxed in Dean-Stark device for overnight. The mixture was cooled to room temperature and concentrated in vacuo (~40 mL). The residue was diluted in Et_2O (100 mL), washed with NaOH (2M, 30 mL×3), brine (50 mL), dried over $MgSO_4$, and evaporated under reduced pressure.

(b) In another 500 mL flame dried flask, the residue was dissolved in Et_2O (150 mL), cooled in ice-bath. $LiAlH_4$ (5.2 mL, 4 M, 20.5 mmol) was added through syringe pump for 30 min. Then reaction flask was removed from the ice-bath and warmed to room temperature in air while stirring for another 2h. The reaction was quenched by slowly addition of HCl (100 mL, 10% aq.) with vigorous stirring. The phases were partitioned and aqueous phase was extracted with Et_2O (100 mL). The organic layer was combined and washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure.

(c) The resulting product was added to a solution of $CeCl_3.7H_2O$ (10g) in MeOH (200 mL) under an argon atmosphere in a 500 mL flame dried flask. After cooling to 0 ^oC in an ice-bath for around 15 min, $NaBH_4$ (1.0 g, 26 mmol) was added in portions over a period of 15 min. The ice-bath was left warm to room temperature and stirred for 3h. After concentrated the reaction in vacuo, the reaction was quenched with HCl (1 M, 50 mL), extracted with Et_2O (40×3 mL), resulting organic phase was washed with brine (50 mL), dried over $MgSO_4$, filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (EtOAc: Petrol, 20: 80; SiO_2) gave the *cis*-alcohol as light orange oil in 82% yield. (3.78 g, 21.73mmol).

***cis*-phosphate,**

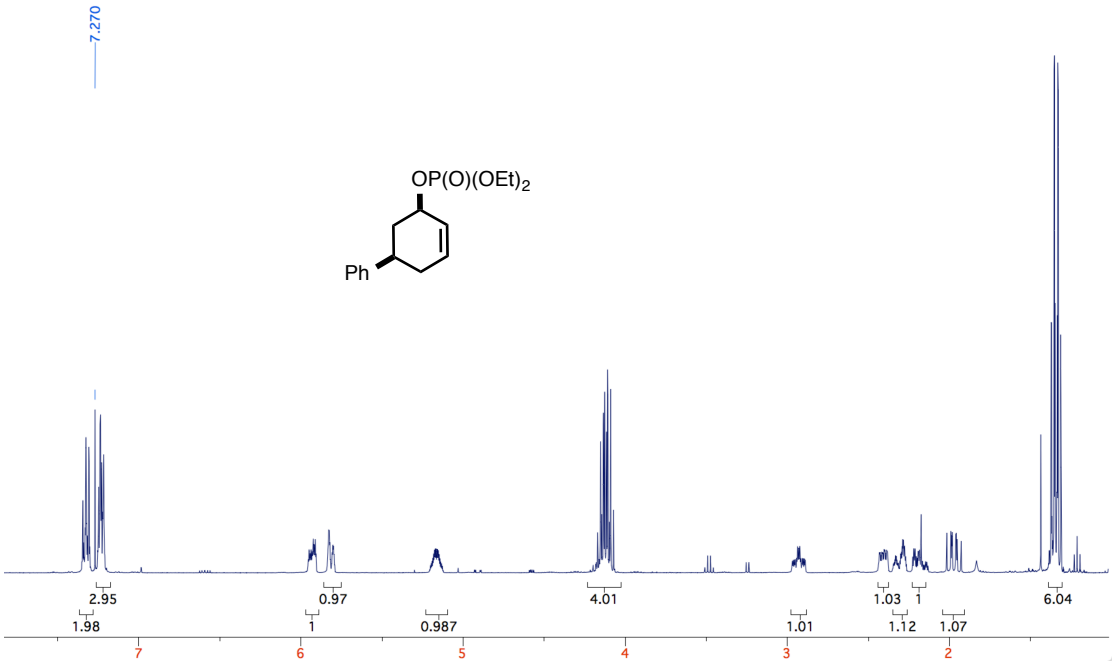
Same procedure refers to the preparation of ***(S)*-2-cyclohexenyl-diethyl phosphate (3.12)**

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.31-1.39 (m, 6 H), 1.92-2.02 (m, 1 H), 2.15-2.23 (m, 1 H), 2.27-2.34 (m, 1 H), 2.38-2.44 (m, 1 H), 2.93 (dddd, *J*=13.43, 10.92, 5.18, 2.47 Hz, 1 H), 4.07-4.18 (m, 4 H), 5.17 (m, 1 H), 5.80-5.84 (m, 1 H), 5.91-5.95 (m, 1 H), 7.21-7.25 (m, 3 H), 7.30-7.35 (m, 2 H).

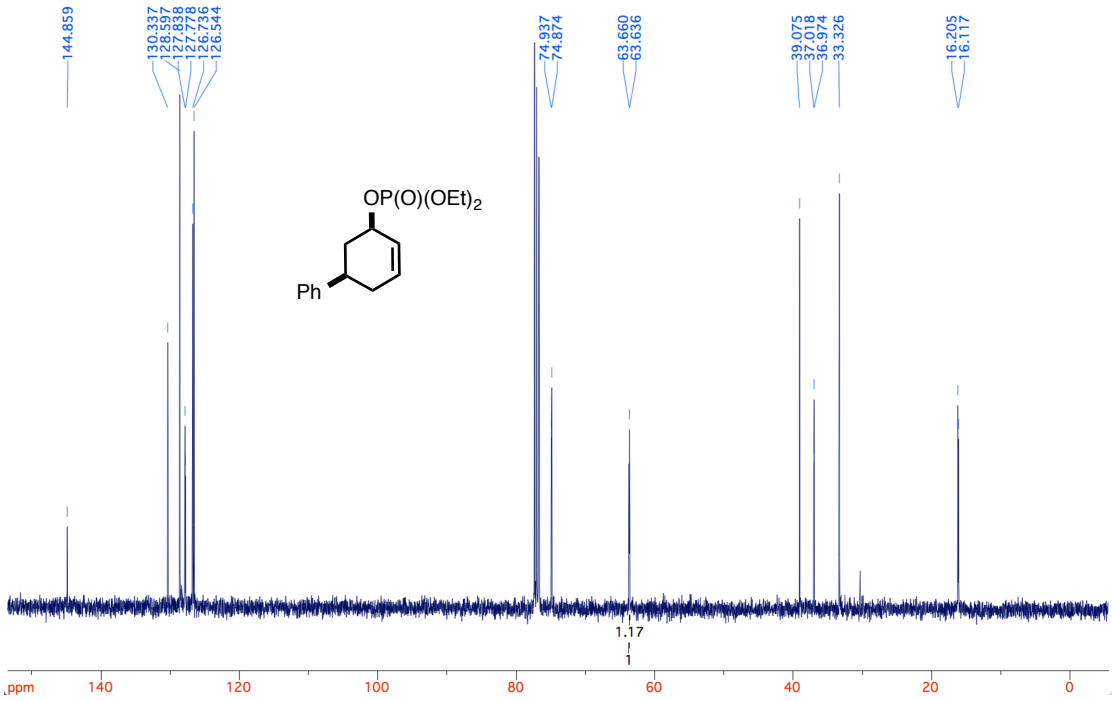
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 16.1, 16.2, 33.3, 37.0, 39.1, 63.6, 63.7, 74.9, 126.6, 126.7(2C), 127.8, 128.6(2C), 130.3, 144.8

^{31}P NMR: –1.08

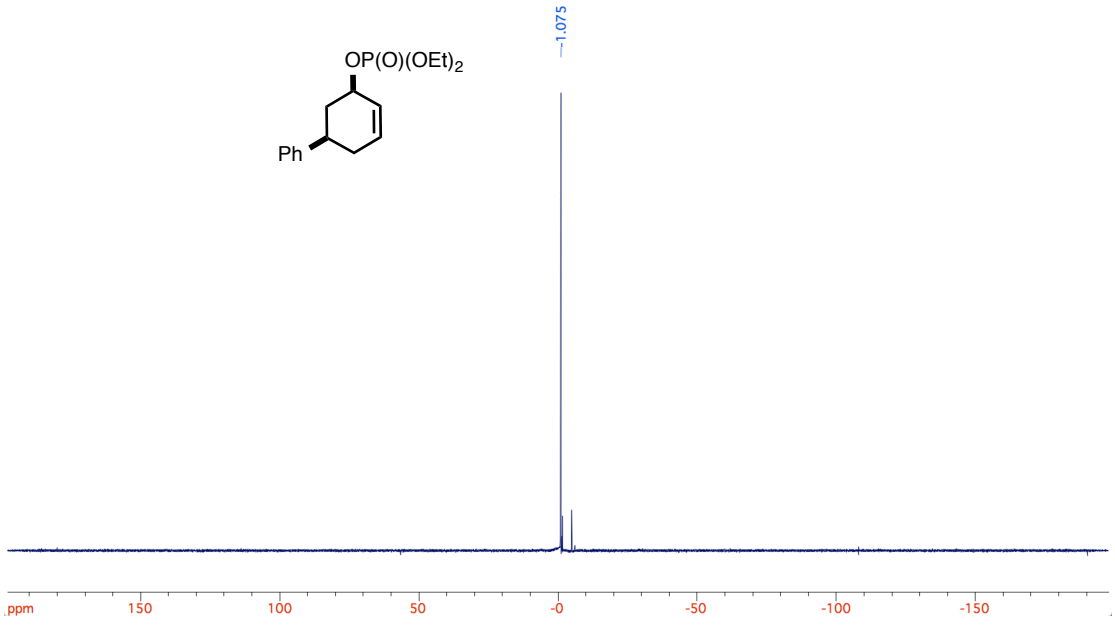
^{1}H NMR:



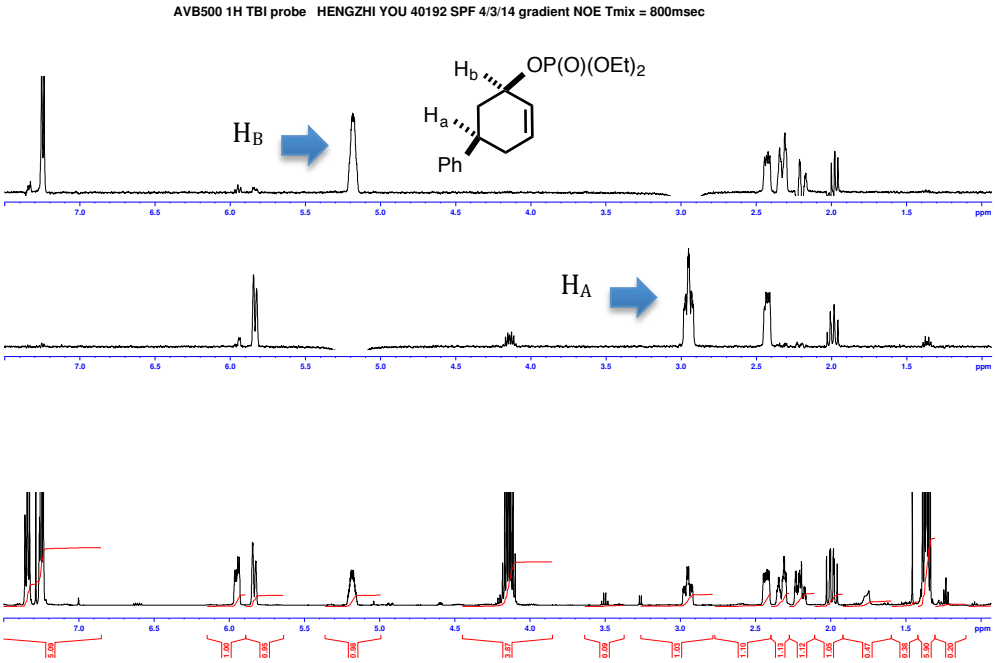
^{13}C NMR:


144.859
130.337
128.837
128.338
127.778
126.736
126.544
74.937
74.874
63.660
63.636
39.075
37.078
36.974
33.326
16.205
16.117
OP(O)(OEt)2
Ph
1.17
1
ppm
140
120
100
80
60
40
20
0

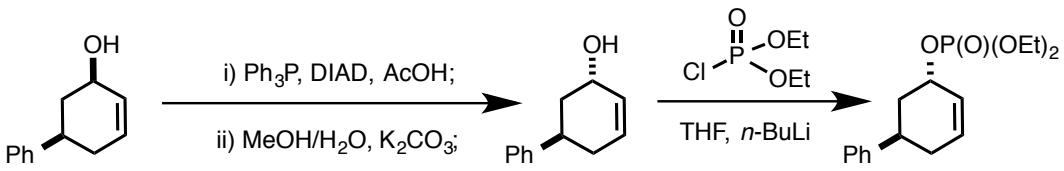
^{31}P NMR:


1.075
OP(O)(OEt)2
Ph
ppm
150
100
50
-0
-50
-100
-150

NOE:



Diethyl ((1R,3S)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl) phosphate (3.10)



trans-alcohol,

(a) In a 100 mL flame dried flask, *cis*-alcohol (2 g, 11.5 mmol) and triphenyl phosphine (4.5 g, 17.3 mmol) were dissolved in THF (50 mL). After cooling to 0 ^{o}C in an ice-bath for around 10 min, DIAD (2.95 ml, 14.9 mmol) and AcOH (0.85 ml, 14.9 mmol) were added. The ice-bath was left warm to room temperature and stirred for 1h. The reaction was quenched by water (30 mL), extracted with Et_2O (15×3 mL), resulting organic phase was washed with brine (50 mL), dried over $MgSO_4$, filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (Et_2O: Petrol, 5: 95; SiO_2) gave the intermediate product as colourless oil.

(b) In another 100 mL flame dried flask, the intermediate was dissolved in MeOH (30 mL) and water (30 mL) under an argon atmosphere. Then K_2CO_3 (0.9 g) was added, and the solution was stirred overnight. The reaction mixture was extracted with EtOAc (20×3 mL), dried over $MgSO_4$, filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (EtOAc: Petrol, 20: 80; SiO_2) gave *trans*-alcohol in 87% yield. (1.74 g, 10mmol).

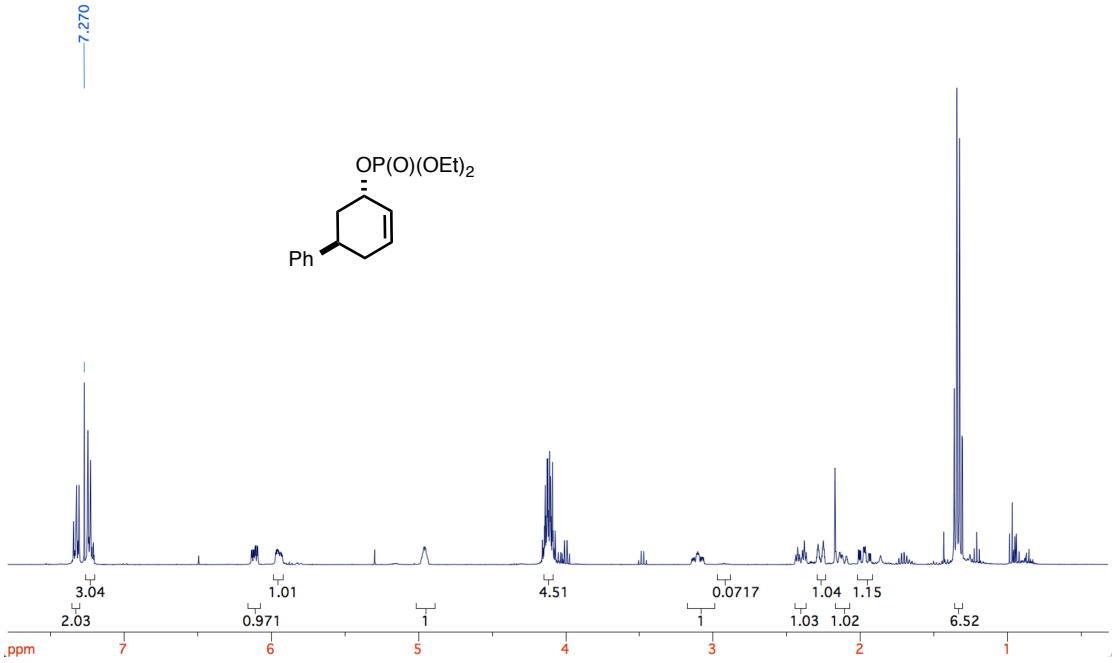
***trans*-phosphate,**

Same procedure refers to the preparation of ***(S)*-2-cyclohexenyl-diethyl phosphate (3.12)**

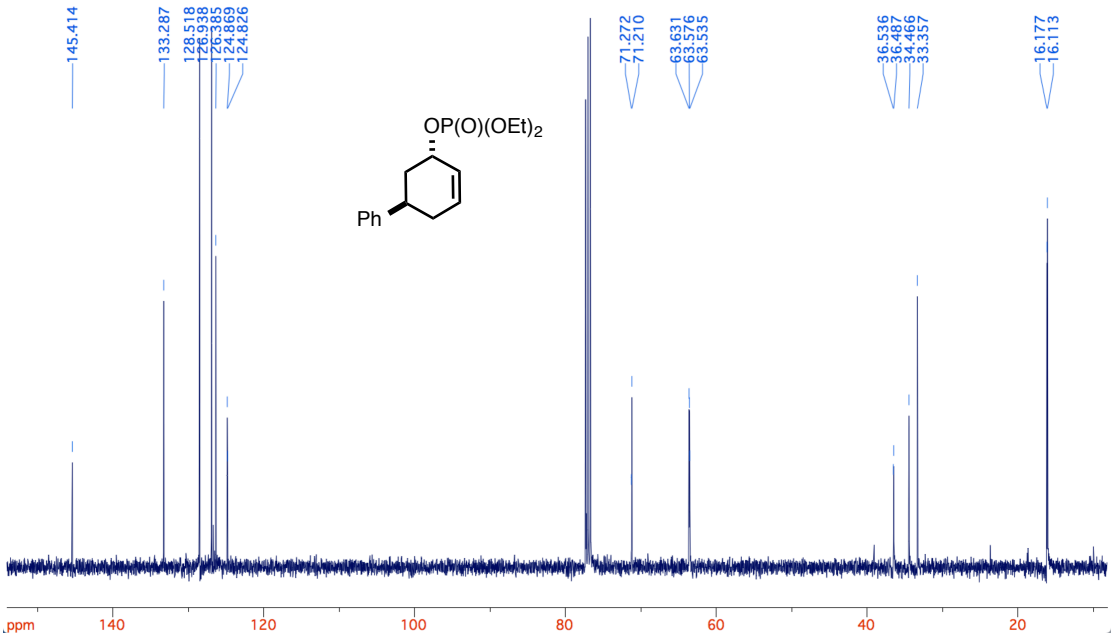
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.31-1.36 (m, 6 H), 1.97 (dddd, *J*=14.31, 12.87, 3.93, 1.64 Hz, 1 H), 2.14-2.17 (m, 1 H), 2.37-2.43 (m, 1 H), 3.06-3.14 (m, 1 H), 4.09-4.15 (m, 4 H), 4.96(m, 1 H), 5.92-5.97 (m, 1 H), 6.09-6.14 (m, 1 H), 7.20-7.25 (m, 3 H), 7.30-7.34 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 16.1, 16.2, 33.3, 34.5, 36.5, 63.6(2C), 71.2, 124.8, 126.4, 126.9(2C), 128.5 (2C), 133.3, 145.5

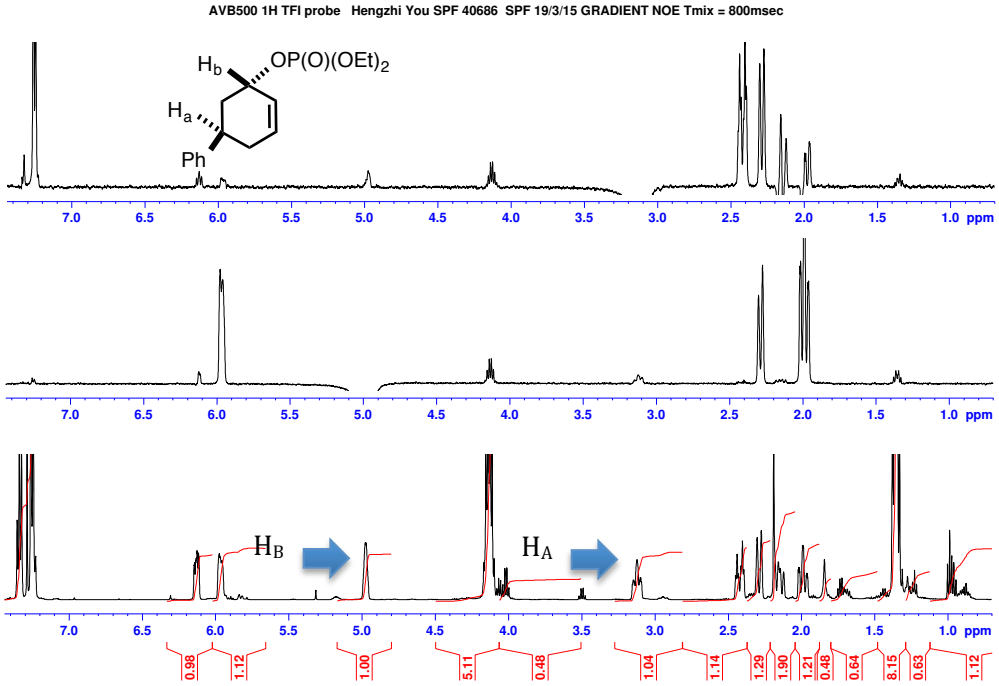
^{1}H NMR:


7.270
OP(O)(OEt)2
Ph
3.04
2.03
1.01
0.971
1
4.51
1
0.0717
1.04
1.03
1.15
1.02
6.52
ppm
7
6
5
4
3
2
1

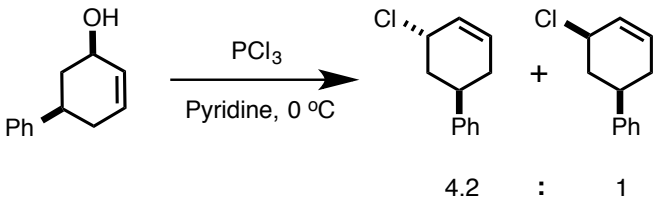
^{13}C NMR:


145.414
133.287
128.518
126.938
126.385
124.869
124.826
71.272
71.210
63.631
63.576
63.535
36.536
36.487
34.466
33.357
16.177
16.113
OP(O)(OEt)2
Ph
ppm
140
120
100
80
60
40
20

NOE:



(1R, 3S)-3-chloro-1,2,3,6-tetrahydro-1,1'-biphenyl; (1R,3R)-3-chloro-1,2,3,6-tetrahydro-1,1'-biphenyl (3.11)



Preparation of the *cis*-alcohol refers to **Diethyl ((1R, 3R)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3-yl) phosphate (3.9), *cis*-alcohol**.

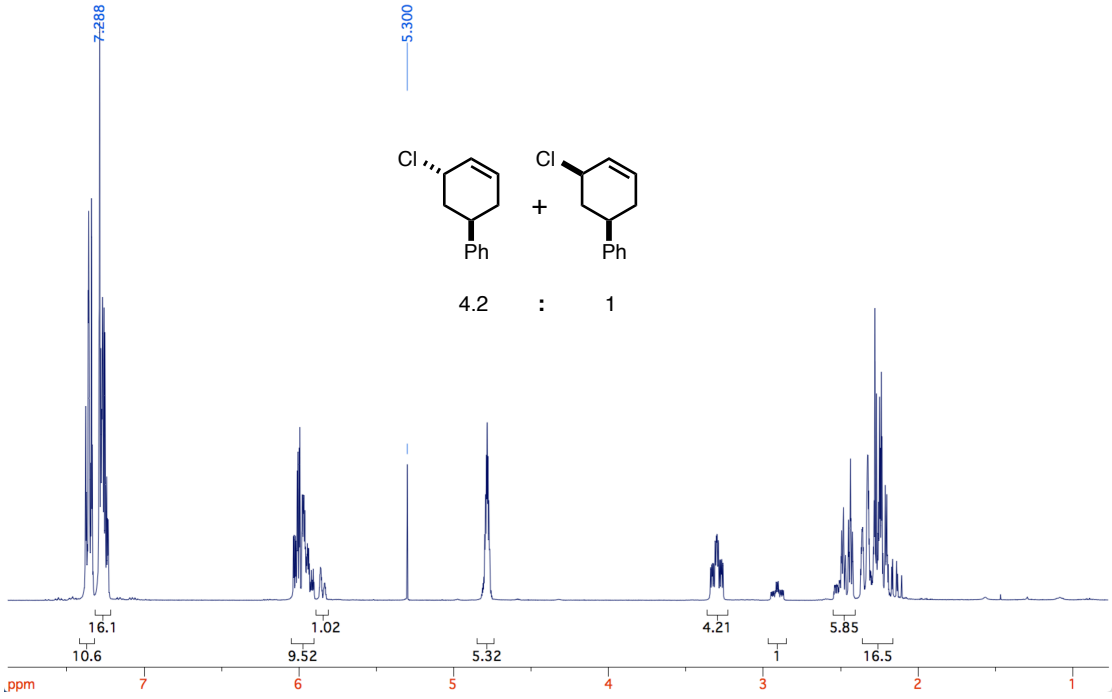
In a 10 mL flame dried flask, fresh distilled phosphorus trichloride (0.6 mL, 6.08 mmol, 0.4 eq) was added under an argon atmosphere. After cooling to 0 °C in an ice-bath for around 15 min, a mixture of *cis*-alcohol (2.64 g, 15.2 mmol, 1 eq) and pyridine (3 ml) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirring was continued

overnight. Then diluted the reaction with CH_2Cl_2, filtrated and the yellow solution was concentrated in vacuo. The residue was purified through flash column chromatography (Petrol: Et_3N, 99:1; SiO_2) to provide the product in 32% yield (0.94 g, 4.86 mmol) as colorless oil.

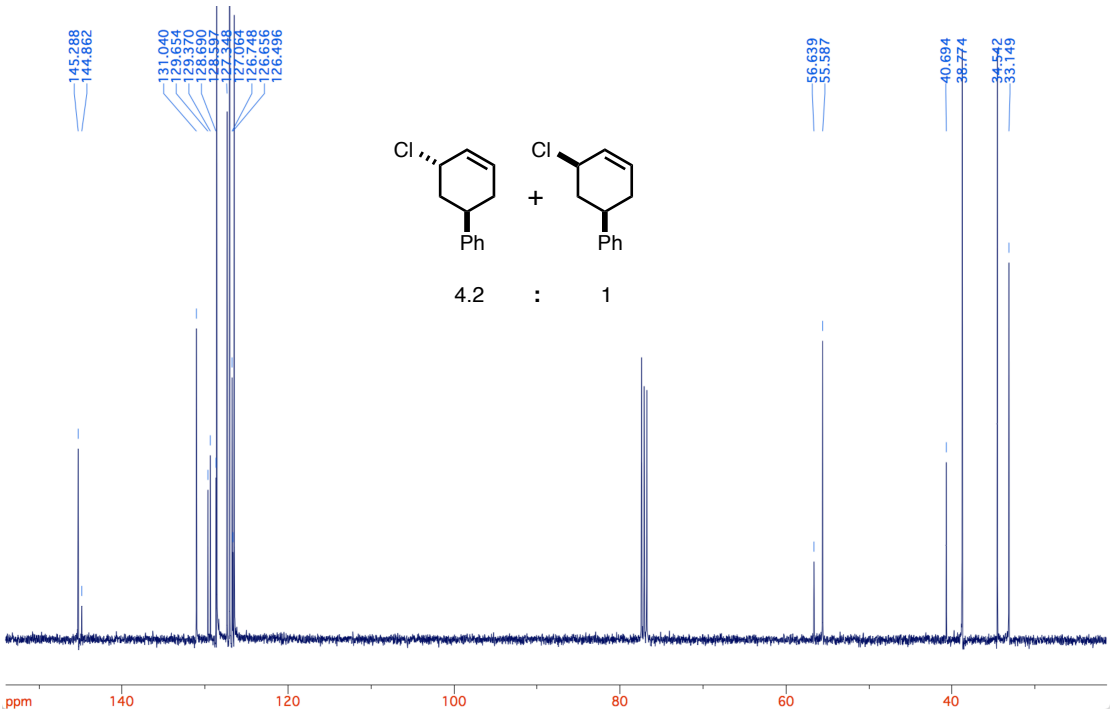
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 2.16-2.36 (m, 16H), 2.42-2.54 (m, 6H), 2.86-2.95 (m, 1H), 3.25-3.35 (m, 4H), 4.75-4.82 (m, 5H), 5.83-5.87 (m, 1H), 5.90-6.04 (m, 9H), 7.22-7.30 (m, 16H), 7.33-7.38 (m, 10H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 33.2, 34.5, 38.8, 40.7, 55.6, 56.6, 126.5, 126.7, 126.8, 127.1, 127.4, 128.6, 128.7, 129.4, 129.7, 131.0

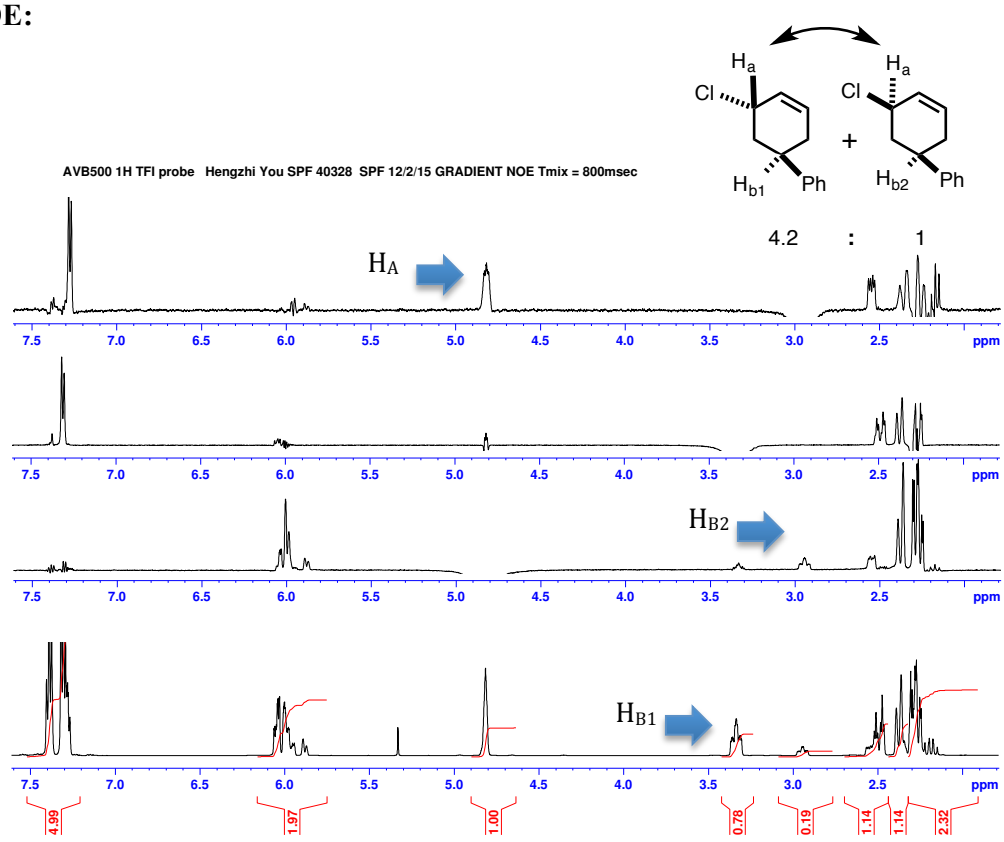
^{1}H NMR:



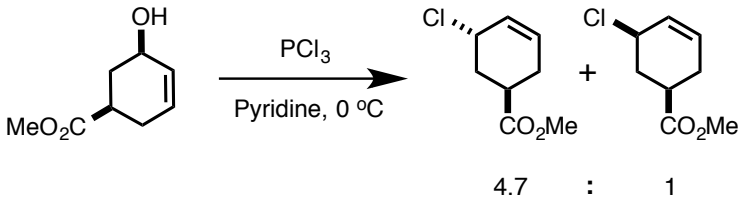
^{13}C NMR:


145.288
144.862
131.040
129.654
129.370
128.690
128.597
127.348
127.064
126.748
126.656
126.496
56.639
55.587
40.694
38.774
34.542
33.149
Cl
Ph
+
Cl
Ph
4.2 : 1
ppm
140
120
100
80
60
40

NOE:


Ha
Cl
Hb1
Ph
+
Ha
Cl
Hb2
Ph
4.2 : 1
AVB500 1H TFI probe Hengzhi You SPF 40328 SPF 12/2/15 GRADIENT NOE Tmix = 800msec
HA
HB2
HB1
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm
4.99
1.97
1.00
0.78
0.19
1.14
1.14
2.32

Methyl (1R, 5S)-5-chlorocyclohex-3-ene-1-carboxylate; Methyl (1R, 5R)-5-chlorocyclohex-3-ene-1-carboxylate (3.12)



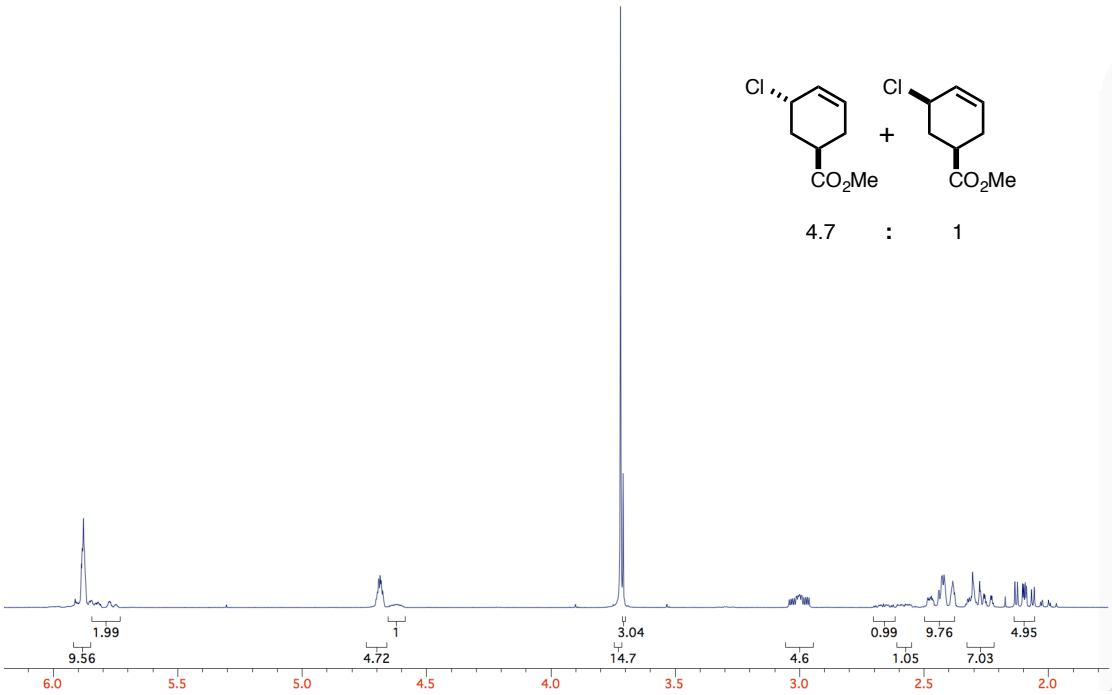
Preparation of the cis-alcohol refers to **Methyl (1R, 5R)-5-((diethoxyphosphoryl) oxy) cyclohex -3-ene-1-carboxylate (3.13)**.

In a 5 mL flame dried flask, fresh distilled phosphorus trichloride (0.17 mL, 1.72 mmol, 0.4 eq) was added under an argon atmosphere. After cooling to 0 ^{o}C in an ice-bath for around 15 min, a mixture of *cis*-alcohol (666 mg, 4.3 mmol, 1 eq) and pyridine (2 ml) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirring was continued overnight. Then diluted the reaction with CH_2Cl_2, filtrated and the yellow solution was concentrated in vacuo. The residue was purified through flash column chromatography (CH_2Cl_2: Et_3N, 99:1; SiO_2) to provide the product in 40% yield (294.1 mg, 1.68 mmol) as colorless oil.

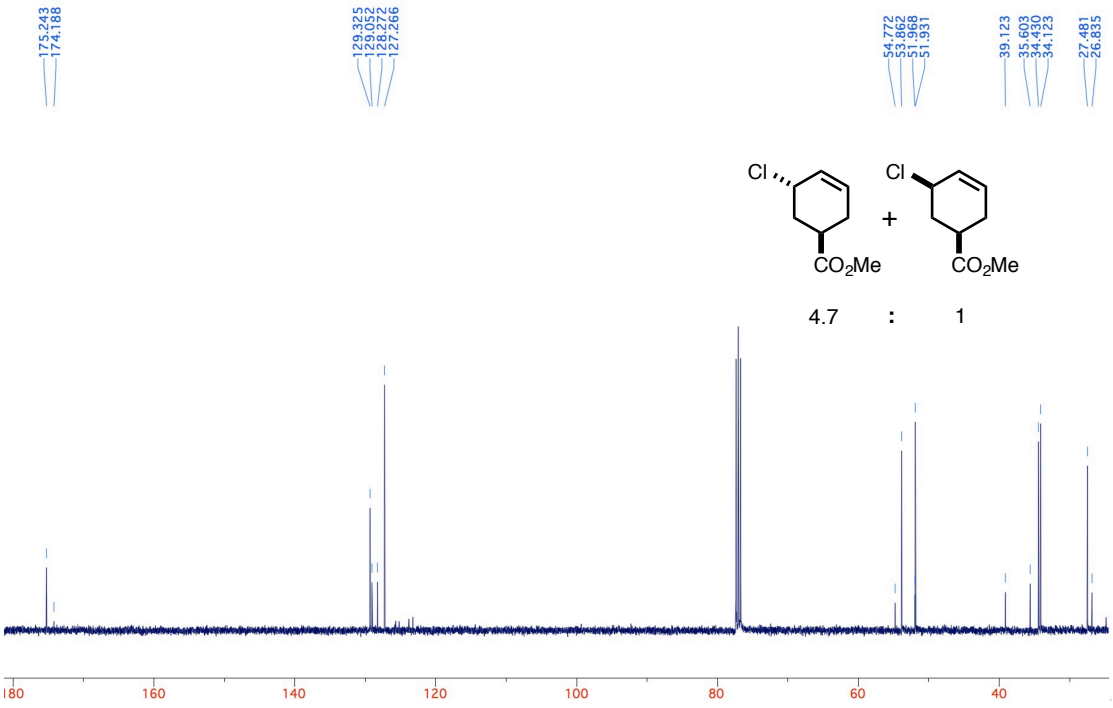
^{1}H NMR (400 MHz, $CDCl_3$): δ_H /ppm 2.06-2.14 (m, 5H), 2.22-2.32 (m, 7H), 2.38-2.50 (m, 10H), 2.55-2.61 (m, 1H), 2.62-2.70 (m, 1H), 2.96-3.04 (m, 5H), 3.71 (s, 3H), 3.72 (s, 15H), 4.59-4.65 (m, 1H), 4.67-4.71 (m, 5H), 5.73-5.84 (m, 2H), 5.85-5.92 (m, 10H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 26.8, 27.5, 34.1, 34.4, 35.6, 39.1, 51.9, 52.0, 53.9, 54.8, 127.3, 128.3, 129.1, 129.3.

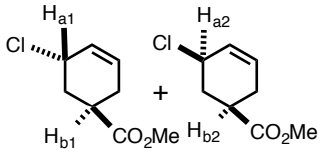
^{1}H NMR


Cl
Cl
+
CO2Me
CO2Me
4.7 : 1
1.99
1
3.04
0.99
9.76
4.95
9.56
4.72
14.7
4.6
1.05
7.03
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0

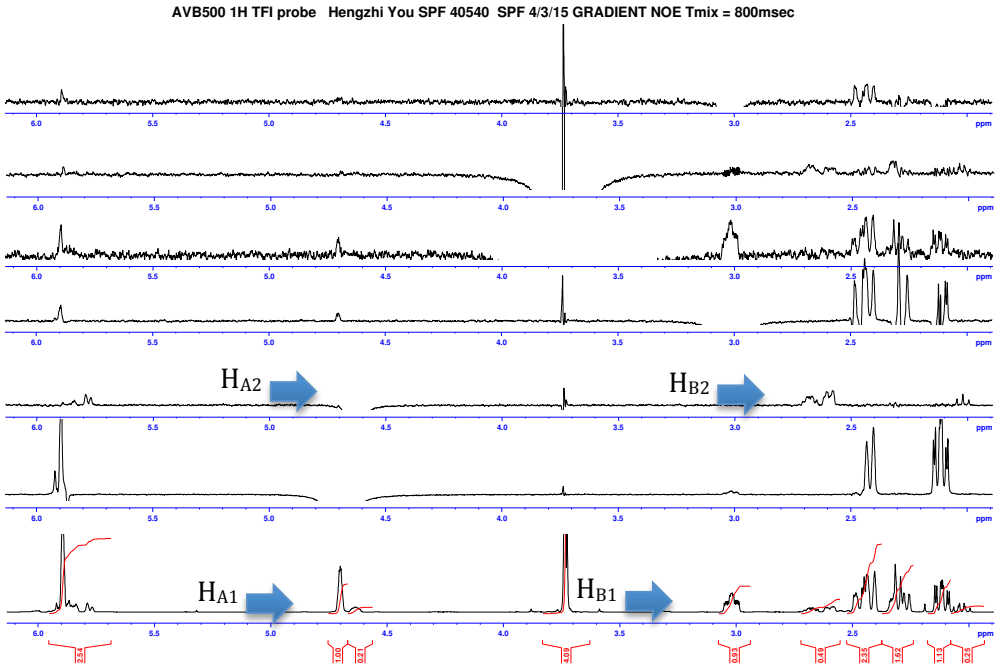
^{13}C NMR


175.243
174.188
129.325
129.052
128.272
127.266
54.772
53.862
51.968
51.931
39.123
35.603
34.430
34.123
27.481
26.835
Cl
Cl
+
CO2Me
CO2Me
4.7 : 1
180
160
140
120
100
80
60
40

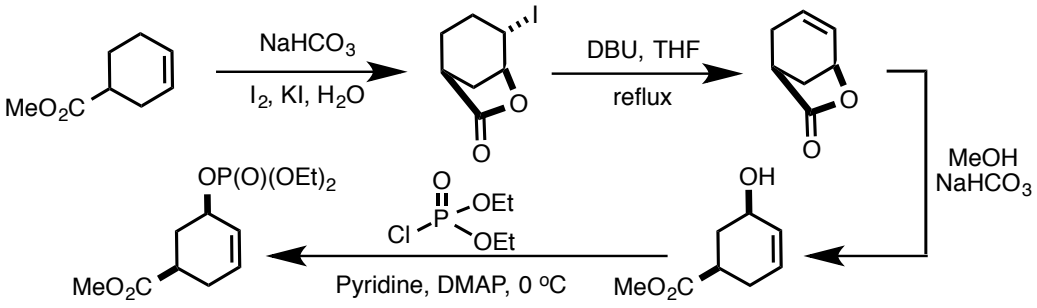
NOE:



4.7 : 1



Methyl (1R, 5R)-5-((diethoxyphosphoryl)oxy)cyclohex-3-ene-1-carboxylate (3.13)



Prepared in analogy to published procedure.

i) In a 500 mL flask, 3-cyclohexene-1-carboxylic acid (4.56g, 36.1 mmol, 1.00eq) was added dropwise to the stirring $NaHCO_3$ (9.12g, 108.6 mmol, 3.00eq) solution in water (150mL) for 20 mins. Then a solution of KI (36 g, 216.7 mol, 6.00eq) and I_2 (9.66 g,

38.0 mmol, 1.05eq) in water (90 mL) was added. The reaction was covered with foil and stirred overnight. The solution was extracted with CH_2Cl_2 (50 x 4mL) and the combined organic phase was washed with $Na_2S_2O_3$ (10% aq), NaHCO3 (10% aq), brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to afford the product (8.55g, 33.9 mmol, 93%).

ii) The resulting product (8.08g, 32.1 mmol, 1eq) was added to another 500 mL flame dried flask in THF (200 mL). DBU (1,8- diazabicyclo[5.4.0]undec-7-ene) (7.2 mL, 48.0 mmol, 1.5eq) was added and the solution was heated to reflux under an argon atmosphere overnight. Then the flask was cooled to room temperature, vacuum filtrated and the yellow solution was concentrated in vacuo. The residue was purified through flash column chromatography (Et_2O: Hexane, 80:20; SiO_2) to provide the product in 72% yield (2.87 g, 23.1 mmol) as orange oil.

iii) In a 100 mL flame dried flask, $NaHCO_3$ (4.03g, 48.0 mmol, 3.00eq) was added to a solution of above orange oil (2 g, 16 mmol, 1 eq) in MeOH (50 mL) under an argon atmosphere. After left stirring overnight, the reaction mixture was diluted with H_2O, extracted with Et_2O, and the organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified carefully through flash column chromatography (Et_2O: Petrol, 90:10; SiO_2) to provide the product in 58% yield (1.45 g, 9.28 mmol) as colorless oil.

iv) In a 10 mL flame dried flask, the responding alcohol (521 mg, 3.4 mmol, 1.0 eq) was dissolved in pyridine (5 mL) under an argon atmosphere. After cooling to 0 ^{o}C in an ice-bath for around 10 min, diethyl chlorophosphate (0.6 mL, 4.1mmol, 1.2 eq) was added dropwise. Then DMAP (83 mg, 0.68 mmol, 0.2 eq) was added, the reaction mixture was allowed to warm to room temperature and stirring was continued overnight. Afterwards, the reaction was diluted with CH_2Cl_2 (50 mL) and quenched

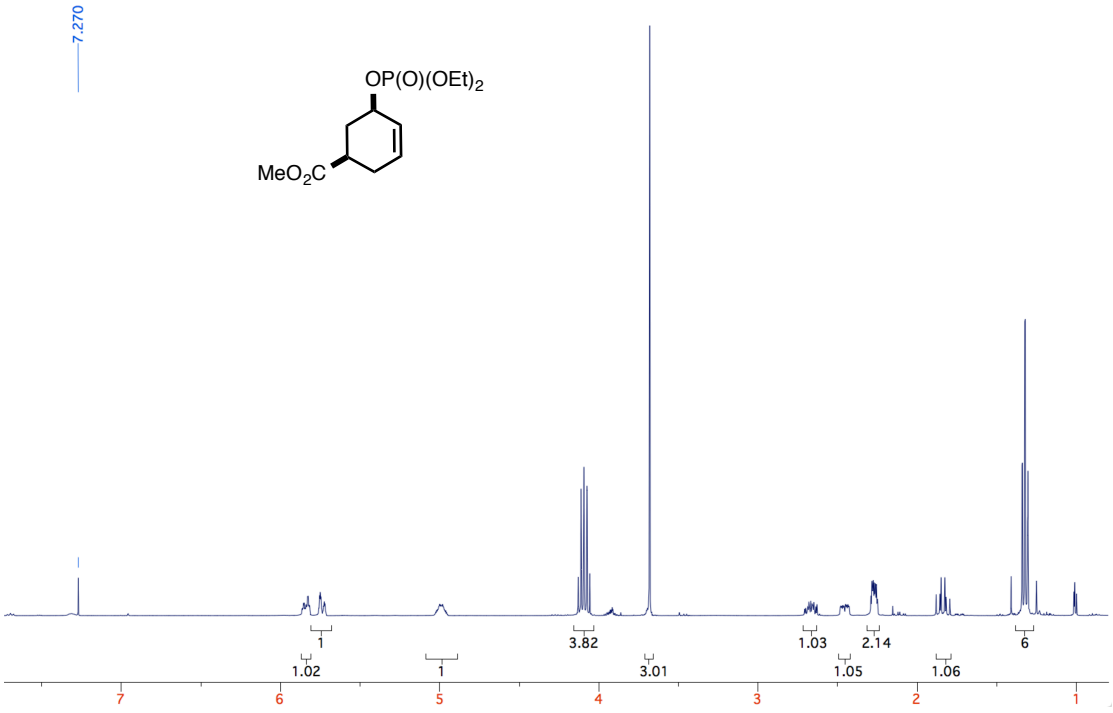
with H_2O (50 mL). The phases were partitioned and the organic phase was washed with sat. $CuSO_4$ (50 mL×2) and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified carefully through flash column chromatography (Et_2O: Et_3N, 99:1; SiO_2) to provide the product in 61% yield (606.2 mg, 2.07 mmol) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 1.30-1.34 (m, 6 H), 1.84 (m, 1 H), 2.27 (m, 2 H), 2.42-2.49 (m, 1 H), 2.62-2.71 (m, 1 H), 3.68 (s, 3 H), 4.06-4.13 (m, 4 H), 5.71-5.76 (m, 1 H), 5.81-5.87 (m, 1 H).

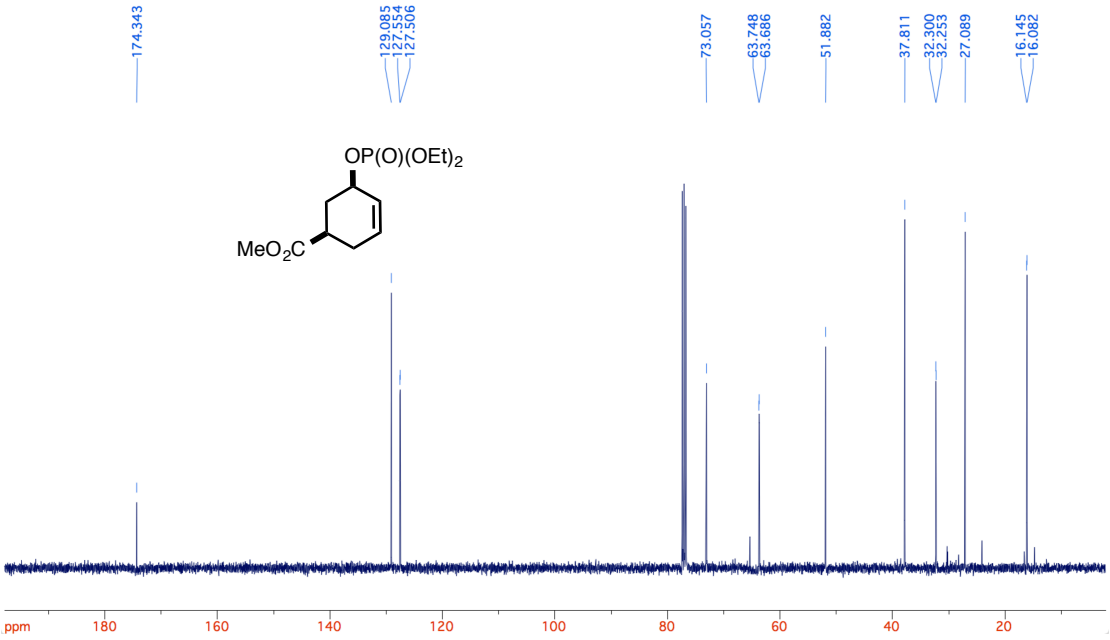
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 16.1, 16.2, 27.1, 32.3, 37.8, 51.9, 63.7, 63.8, 73.1, 127.5, 129.1, 174.3.

^{31}P NMR: –1.26

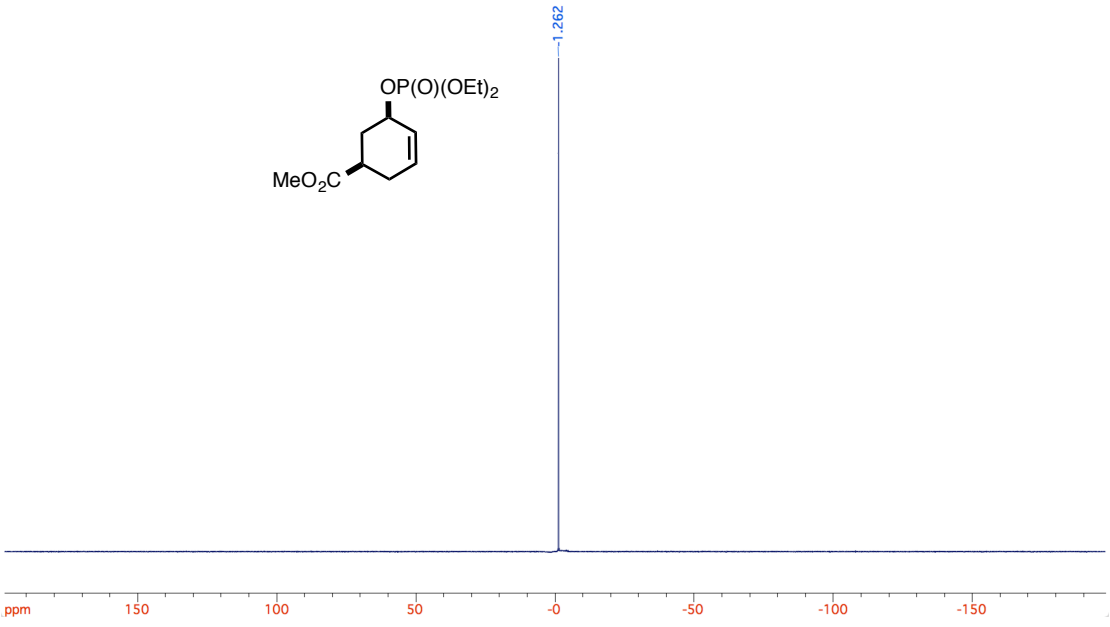
^{1}H NMR:



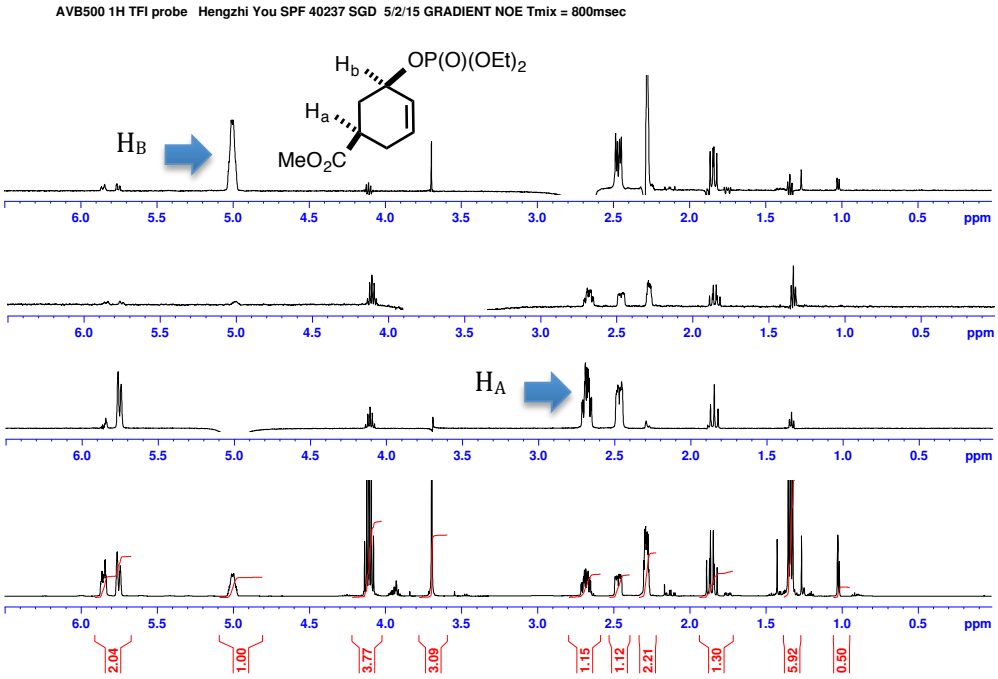
^{13}C NMR:


174.343
129.085
127.554
127.506
73.057
63.748
63.686
51.882
37.811
32.300
32.253
27.089
16.145
16.082
OP(O)(OEt)2
MeO2C
ppm
180
160
140
120
100
80
60
40
20

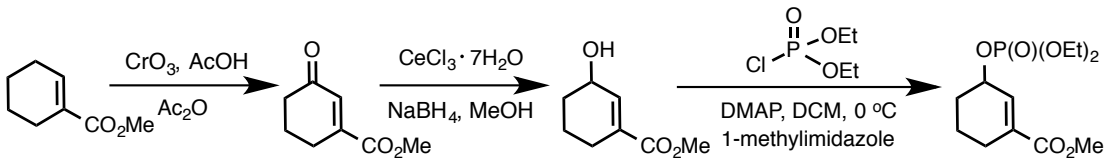
^{31}P NMR:


1.262
OP(O)(OEt)2
MeO2C
ppm
150
100
50
-0
-50
-100
-150

NOE:



Methyl 3-((diethoxyphosphoryl)oxy)cyclohex-1-ene-1-carboxylate (3.14)



Prepared in analogy to published procedure.

i) In a 100 mL flask, Ac_2O (14.5 mL) was added dropwise to the stirring CrO_3 (9.22 g, 60.7 mmol, 1.7 equiv) solution in AcOH (28.6 mL) and left stirring for 4h. In another 250 mL flask, the resulting CrO_3 solution was added dropwise through a syringe pump to the solution of methyl 1-cyclohexene-1-carboxylate (5.0 g, 35.7 mmol, 1 equiv) in CH_2Cl_2 (80mL). After stirring overnight, the reaction was cooled to 0 °C in an ice-bath, quenched by dropwise adding KOH (10 M, ~80 mL) until attain a pH ~8. The mixture

was diluted with water (200 mL), extracted with Et_2O (4 x 200 mL) and the combined organic phase was washed with saturated aqueous $NaHCO_3$ (2 x 200 mL), brine (200 mL), dried over $MgSO_4$, filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (EtOAc: Petrol, 30: 70; SiO_2) gave the product as yellow oil in 51 % yield. (2.78 g, 18.21mmol).

ii) The resulting product (2.67 g, 17.3 mmol, 1 eq) was added to a solution of $CeCl_3.7H_2O$ (7.8 g, 20.76 mmol, 1.2 eq) in MeOH (50 mL) under an argon atmosphere in a 100 mL flame dried flask. After cooling to 0 ^oC in an ice-bath for around 15 min, $NaBH_4$ (0.79g, 20.76 mmol, 1.2 eq) was added in portions over a period of 15 min. The ice-bath was left warm to room temperature and stirred for 3h. After concentrated the reaction in vacuo, the reaction was quenched with HCl (1 M, 30 mL), extracted with Et_2O (20×3 mL), resulting organic phase was washed with brine (50 mL), dried over $MgSO_4$, filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (EtOAc: Petrol, 10: 90; SiO_2) gave the alcohol as colourless oil in 83% yield. (2.25 g, 14.4 mmol).

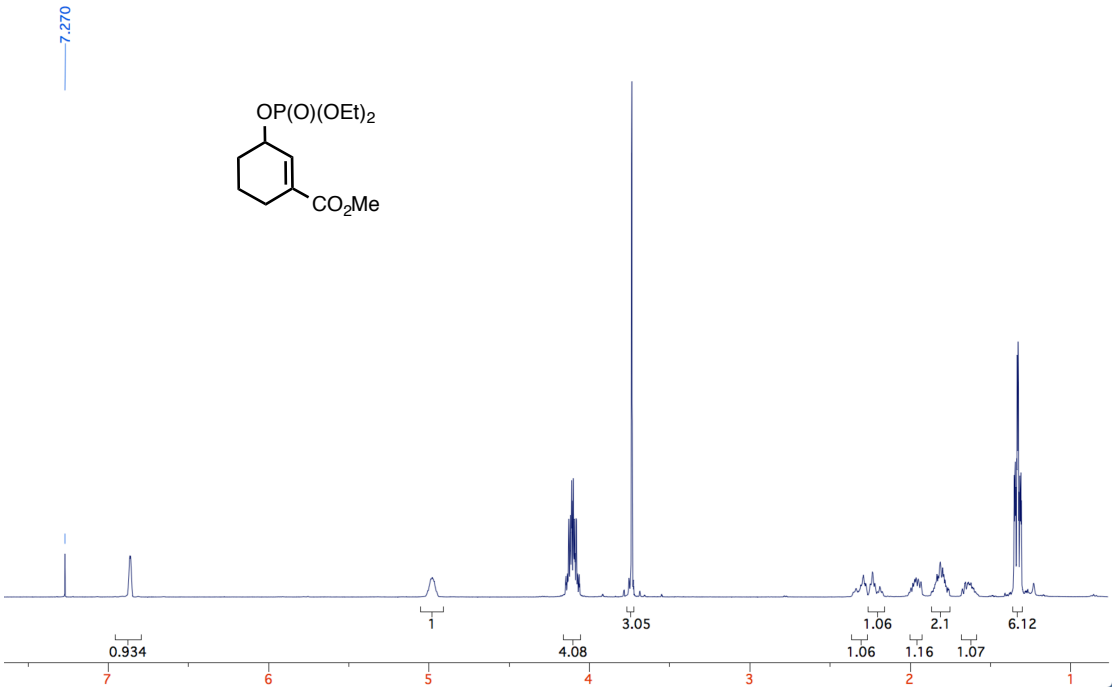
iii) In a 50 mL flame dried flask, 1-methylimidazole (1.3 mL, 16.3 mmol, 2.5 eq) was added to the solution of responding alcohol (1 g, 6.5 mmol, 1.0 eq) in CH_2Cl_2 (20 mL) under an argon atmosphere. After cooling to 0 ^oC in an ice-bath for around 10 min, diethyl chlorophosphate (1.87 mL, 13mmol, 2 eq) was added dropwise. Then DMAP (0.8 g, 6.5 mmol, 1 eq) was added, the reaction mixture was allowed to warm to room temperature and stirring was continued for 48h. Afterwards, the reaction was diluted with CH_2Cl_2 (50 mL) and quenched with HCl (50 mL). The phases were partitioned and the organic phase was washed with sat. $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified carefully through flash column chromatography (Et_2O: Hexane, 90:10; SiO_2) to provide the product in 43% yield (816 mg, 2.80 mmol) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm 1.30-1.36 (m, 6 H), 1.59-1.68 (m, 1 H), 1.76-1.87 (m, 2 H), 1.92-2.01 (m, 1 H), 2.18-2.25 (m, 1 H), 2.28-2.35 (m, 1 H), 3.72-3.76 (s, 3 H), 4.06-4.15 (m, 4 H), 4.94-5.02 (m, 1 H), 6.86 (d, *J*=1.70 Hz, 1 H).

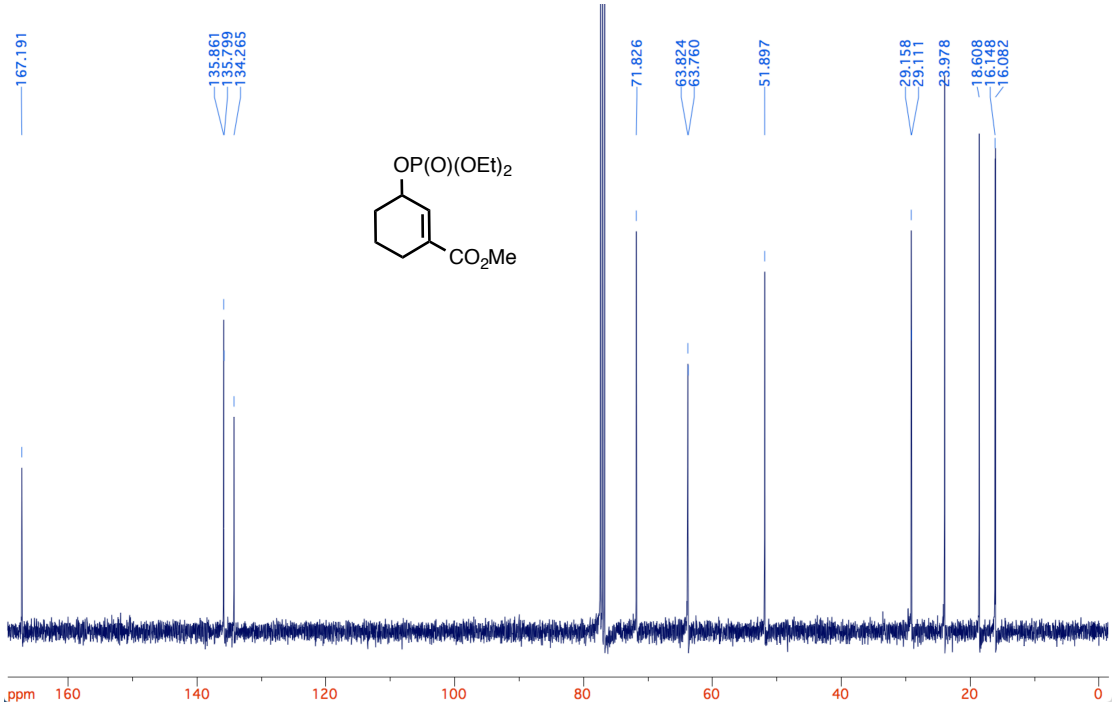
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm 16.1, 16.2, 18.6, 24.0, 29.1, 51.9, 63.7, 63.8, 71.8, 134.3, 135.8, 167.2.

^{31}P NMR: –1.36

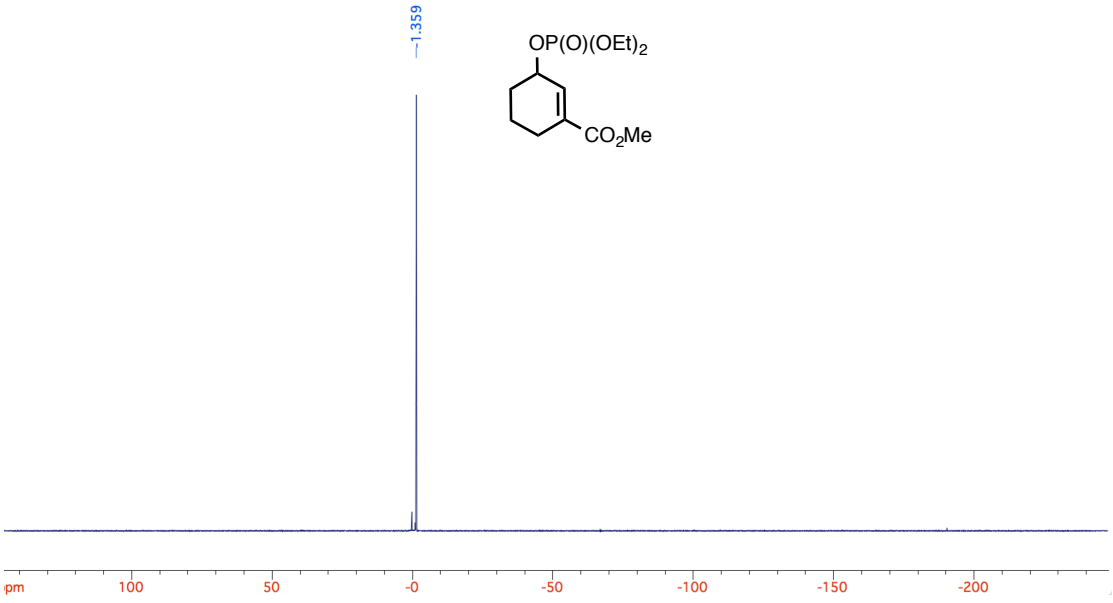
^{1}H NMR:



^{13}C NMR:

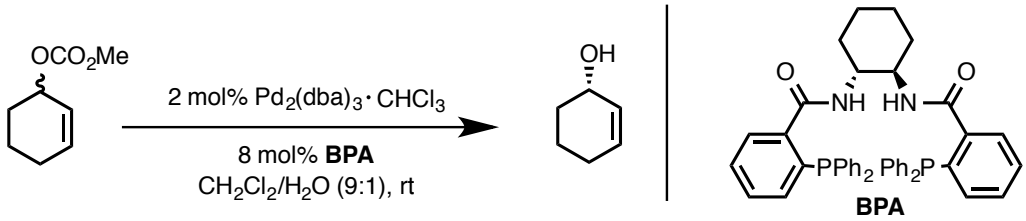


^{31}P NMR:



(S)-2-cyclohexenyl-diethyl phosphate (3.15)

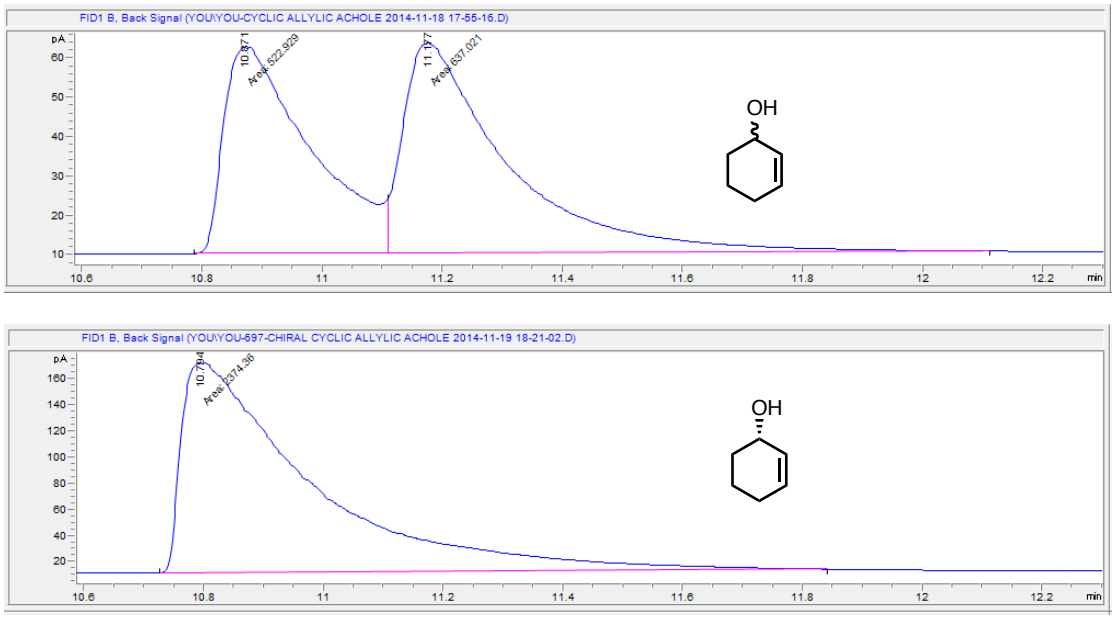
(S)-2-cyclohexenol



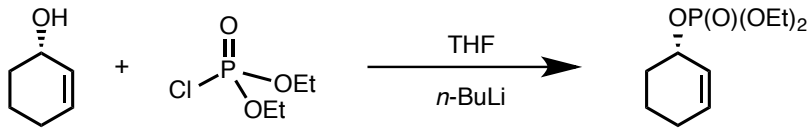
In a 250 mL flame dried flask, $Pd_2(dba)_3 \cdot CHCl_3$ (265 mg, 0.256 mmol, 2 mol %) and **BPA** (707mg, 1.03 mmol, 8 mol %) were dissolved in CH_2Cl_2 (90 mL) under an argon atmosphere. The resulting orange solution was stirred at room temperature for 15 min, then water (10 mL) and 2-cyclohexenyl methyl carbonate (2 g, 12.8 mmol) were added. After stirring the mixture at room temperature for 24 h, it was filtered through short pad column chromatography. The filtrate was dried (MgSO4) and concentrated in vacuo. Purification of the residue by chromatography on silica gel (pentane/ether, 1:1) afforded the product (1.09 g, 11.1 mmol) in 87% yield with 97% ee.

GC analysis of the product indicated an enantiomeric excess of 95% (Hydrodex 6-TBDM, 60-150^{o}C at 5 ^{o}C/min, 10psi); minor enantiomer t_R = 11.2 min; major enantiomer t_R = 10.9 min.

GC traces:



(S)-2-cyclohexenyl-diethyl phosphate

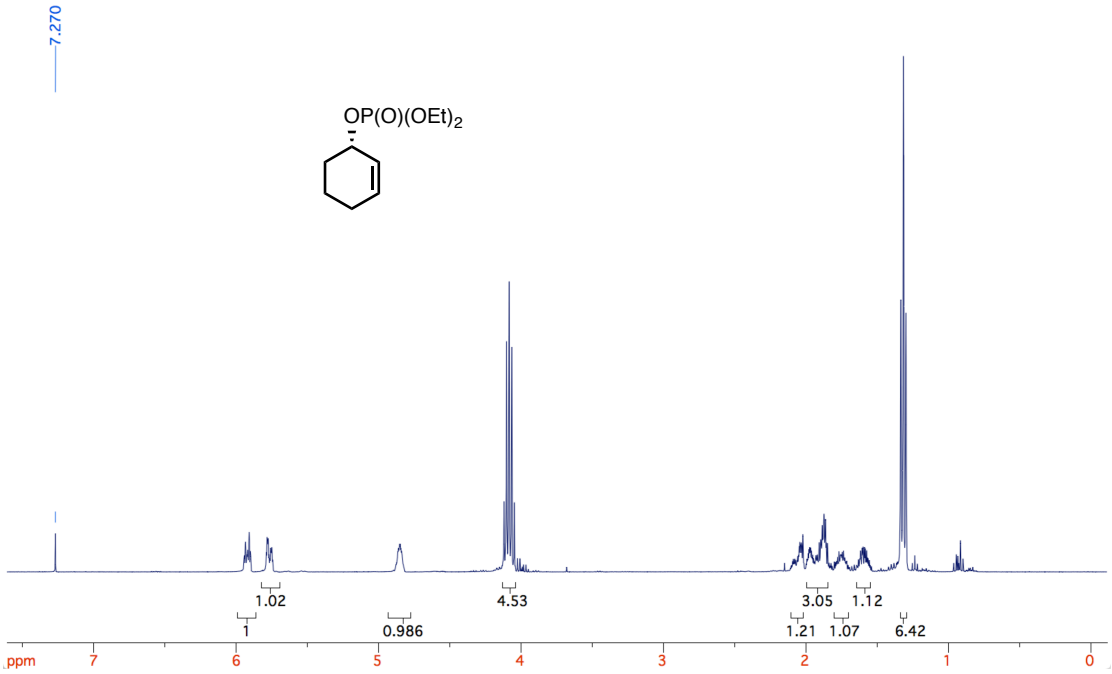


In a 250 mL flame dried flask, the responding chiral alcohol (651.5 mg, 6.6 mmol, 1 eq) was dissolved in THF (60 mL) under an argon atmosphere, *n*-BuLi (3.2 mL, 2.5 M in Hexane, 1.2eq) was added and the mixture was stirred at room temperature for 15 min before diethyl chlorophosphate (1.47 mL, 9.9 mmol, 1.5eq) was added dropwise. After stirring the mixture at room temperature for overnight, the reaction was quenched by water (20 mL), and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL), resulting organic phase was washed with brine (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified carefully through flash column chromatography (EtOAc: Hexane: Et_3N, 49: 49: 2; SiO_2) to provide the product in 76% yield (1.17 g, 5.02 mmol) as colorless oil.

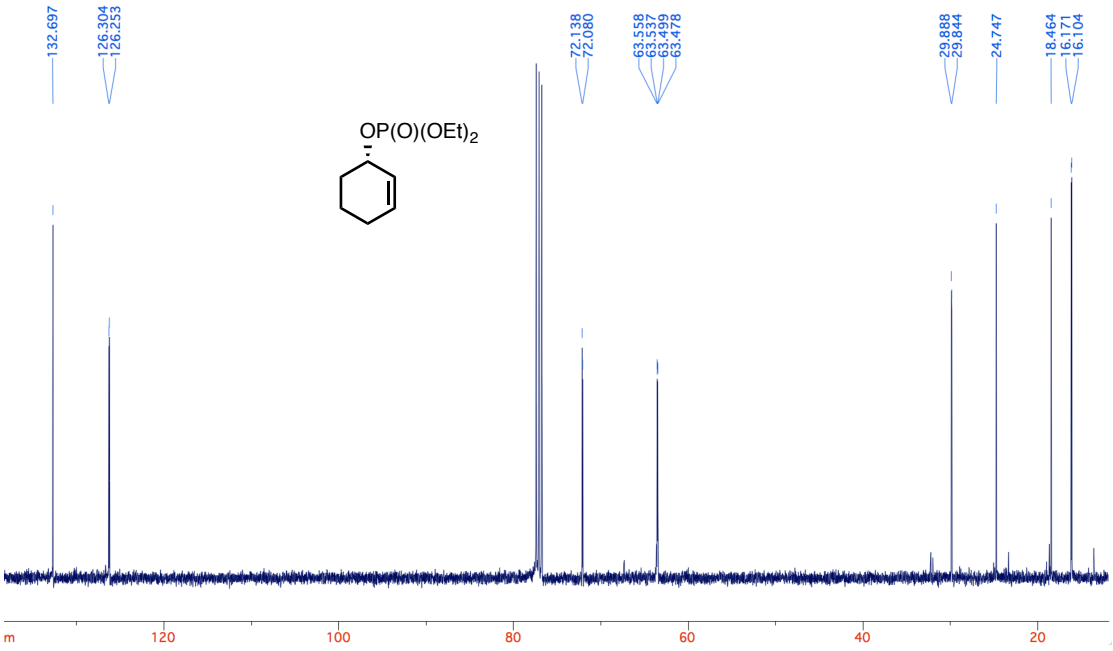
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.32 (t, *J*=7.08 Hz, 6 H), 1.53 - 1.61 (m, 1 H), 1.65 - 1.77 (m, 1 H) 1.82 - 1.97 (m, 3 H), 2.02 - 2.07 (m, 1 H), 4.06 (quint, *J*=7.32 Hz, 4 H), 4.83(brs, 1 H), 5.74 (m, 1 H), 5.93 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 16.1, 16.2, 18.5, 24.7, 29.9, 63.5, 63.6, 72.1, 126.3, 132.7.

^{1}H NMR:


7.270
OP(O)(OEt)2
1.02
4.53
3.05
1.12
1
0.986
1.21
1.07
6.42
ppm
7
6
5
4
3
2
1
0

^{13}C NMR:


132.697
126.304
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72.138
72.080
63.558
63.537
63.499
63.478
29.888
29.844
24.747
18.464
16.171
16.104
OP(O)(OEt)2
m
120
100
80
60
40
20

General synthesis of products

Procedure used in the synthesis of racemic products

In a 5ml flame dried flask, Cp_2ZrHCl (206 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkene (1.0 mmol, 2.5 eq) in CH_2Cl_2 (2.0 ml) under an argon atmosphere. After stirring for 20 to 40 min, $CuBr \cdot Me_2S$ (82 mg, 0.40 mmol 1.0 eq), was added to clear solution and the resulting black mixture was allowed to stir for an additional 10 min before a cyclic allylphosphate (0.40 mmol, 1.0 eq) was added via microsyringe over about 1 min. Stirring at room temperature was continued arbitrarily overnight before the reaction was diluted and quenched by addition of petrol (ca 3 ml) and then NH_4Cl (1M aq., ca 1.5 ml). The mixture was partitioned between water and petrol and the aqueous phase extracted with petrol (3 × 10 ml). The combined organic phase was washed with $NaHCO_3$ (aq. sat. ca 10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Flash column chromatography of the residue (EtOAc/petrol; SiO_2) gave the desired cyclic allylic product. In most cases, Kugelrohr distillation was used to remove excess starting alkene.

Procedure used in the synthesis of asymmetric products

Cu-catalyzed AAA chloride system (Method A)

CuI (7.7 mg, 0.04 mmol, 0.1 eq) and the phosphoramidite ligand **1** (21.2 mg, 0.04 mmol, 0.1 eq) were dissolved in $CHCl_3$ (0.8 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkene (1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 20 ~ 40 min, the resulting clear solution was transferred via syringe over about 1 min to the stirred solution containing the copper and ligand under an argon atmosphere. The resulting mixture was allowed to stir for an additional 10 min before

cyclic allylchloride (0.40 mmol, 1.0 eq) was added dropwise via a microsyringe. The reaction was stirred overnight. Afterwards, reaction was diluted and quenched by the addition of Petrol (ca 3 mL) and then NH_4Cl (1 M aq., ca 1.5 mL). The mixture was partitioned between water and Petrol and the aqueous phase extracted with Petrol (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat. ca 10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Flash column chromatography of the residue (EtOAc/petrol; SiO2) gave the desired cyclic allylic product. In most cases, further purification is needed to get ride of the extra alkene. The purification is done by distillation using a Kugelrohr, setting up conditions according to the boiling point of the alkene used in case.

Cu-catalyzed AAA chloride system (Method B)

CuI (7.7 mg, 0.04 mmol, 0.1 eq) and the phosphoramidite ligand **16** (19.8 mg, 0.04 mmol, 0.1 eq) were dissolved in $CHCl_3$ (0.8 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkene (1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 20 ~ 40 min, the resulting clear solution was transferred via syringe over about 1 min to the stirred solution containing the copper and ligand under an argon atmosphere. The resulting mixture was allowed to stir for an additional 10 min before cyclic allylchloride (0.40 mmol, 1.0 eq) was added dropwise via a microsyringe. The reaction was stirred overnight. Afterwards, reaction was diluted and quenched by the addition of Petrol (ca 3 mL) and then NH_4Cl (1 M aq., ca 1.5 mL). The mixture was partitioned between water and Petrol and the aqueous phase extracted with Petrol (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat. ca 10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Flash column chromatography of the residue (EtOAc/petrol; SiO2) gave the desired cyclic allylic product. In most cases, further purification is needed to

get ride of the extra alkene. The purification is done by distillation using a Kugelrohr, setting up conditions according to the boiling point of the alkene used in case.

Cu-catalyzed AAA phosphate system (Method C)

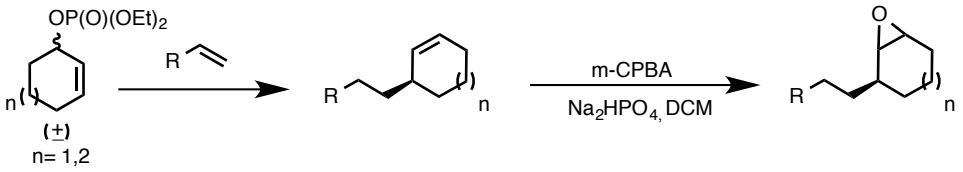
CuI (7.7 mg, 0.04 mmol, 0.1 eq) and the phosphoramidite ligand **16** (19.8 mg, 0.04 mmol, 0.1 eq) were dissolved in $CHCl_3$ (0.8 mL) under an argon atmosphere and allowed to stir for 1 h at room temperature. In another flask, Cp_2ZrHCl (206.0 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of alkene (1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.40 mL) under an argon atmosphere. After stirring for 20 ~ 40 min, the resulting clear solution was transferred via syringe over about 1 min to the stirred solution containing the copper and ligand under an argon atmosphere. The resulting mixture was allowed to stir for an additional 10 min before cyclic allylphosphate (93.7 mg, 0.40 mmol, 1.00 eq) was added dropwise via a microsyringe. Then, $TMSCl_4$ (43.5 mg, 0.40 mmol, 1.00 eq) was injected. The reaction was arbitrarily left stirring overnight. Afterwards, reaction was diluted and quenched by the addition of Petrol (ca 3 mL) and then NH_4Cl (1 M aq., ca 1.5 mL). The mixture was partitioned between water and Petrol and the aqueous phase extracted with Petrol (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat. ca 10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product. Flash column chromatography of the residue (EtOAc/petrol; SiO2) gave the desired cyclic allylic product. In most cases, further purification is needed to get ride of the extra alkene. The purification is done by distillation using a Kugelrohr, setting up conditions according to the boiling point of the alkene used in case.

Procedure used in selected optimization experiments

In a 5 mL flame dried flask, the copper reagent (0.02 mmol, 0.1 eq) and the phosphoramidite ligand (0.02 mmol, 0.1 eq) were dissolved in the selected solvent (0.4 ml) under an argon atmosphere and allowed to stir for 1 h at room temperature. In another flask, Cp_2ZrHCl (103

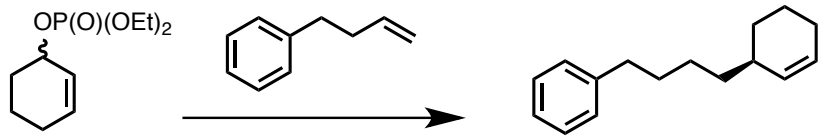
mg, 0.40 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 4-phenyl-1-butene (0.08 ml, 0.5 mmol, 2.5 eq) in CH_2Cl_2 (0.20 ml) under an argon atmosphere. After stirring for 20 min, the resulting clear yellow solution was transferred via syringe over about 1 min to the stirred solution containing the copper and ligand under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before cyclic allylic substrates (0.20 mmol, 1.00 eq) was added dropwise *via* a microsyringe. Then, additive (0.04 mmol, 0.20 eq) was injected. The reaction was stirred at room temperature arbitrarily for overnight before the reaction was diluted and quenched by addition of petrol (ca 3 ml) and then NH_4Cl (1 M aq., ca 1.5 ml). The mixture was partitioned between water and petrol and the aqueous phase extracted with petrol (3 × 10 ml). The combined organic phase was washed with $NaHCO_3$ (aq. sat. ca 10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. The enantiomeric excess was measured directly on the crude reaction products.

Derivatisation of products to the corresponding epoxides



In a 25 ml flame dried flask, the isolated product (1 eq) was dissolved in CH_2Cl_2 (6 ml, for 0.4 mmol scale reaction) under an argon atmosphere. m-CPBA (2 eq) and Na_2HPO_4 (3 eq) were added at room temperature and the reaction mixture was stirred arbitrarily for 2 h before being diluted and quenched by addition of Et_2O (10 ml) and an aqueous solution of saturated $Na_2S_2O_3$ (10 ml) . The organic layer was washed with NaOH (1 M aq., 3× 5ml), dried over Mg_2SO_4, filtered and concentrated under vacuum. The crude mixture of diastereoisomeric epoxides was directly analyzed by GC chromatography using a chiral non-racemic stationary phase [16].

(R)-(–)-4-(Cyclohex-2-en-1-yl) butyl) benzene (3.16, Method C)



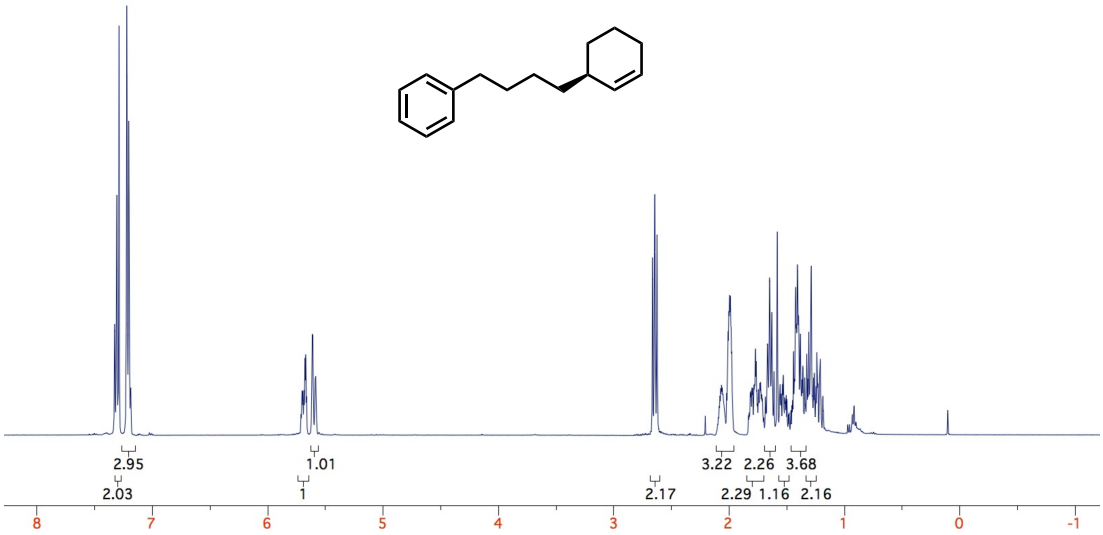
CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S*)- Ligand **L16** (19.8 mg, 0.04 mmol, 0.10 eq) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 4-Phenyl-1-butene (0.15ml, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.5 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, cyclohex-2-en-1-yl diethyl phosphate (93.7 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. Then, TMSCl (43.5 mg, 0.40 mmol, 1.00 eq) was injected. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (~1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr apparatus (T = 110 °C, 55 mbar) gave (R)-(–)-4- (cyclohex-2-en-1-yl) butyl) benzene (68.7 mg, 0.32 mmol) in 80% yield.

Enantiomeric excess of 89% was determined by HPLC [Chiralpak® IA; flow: 0.6 mL/min; hexane/i-PrOH: 99.9: 0.1; λ = 210 nm; major enantiomer t_R = 8.8 min; minor enantiomer t_R = 8.2 min].

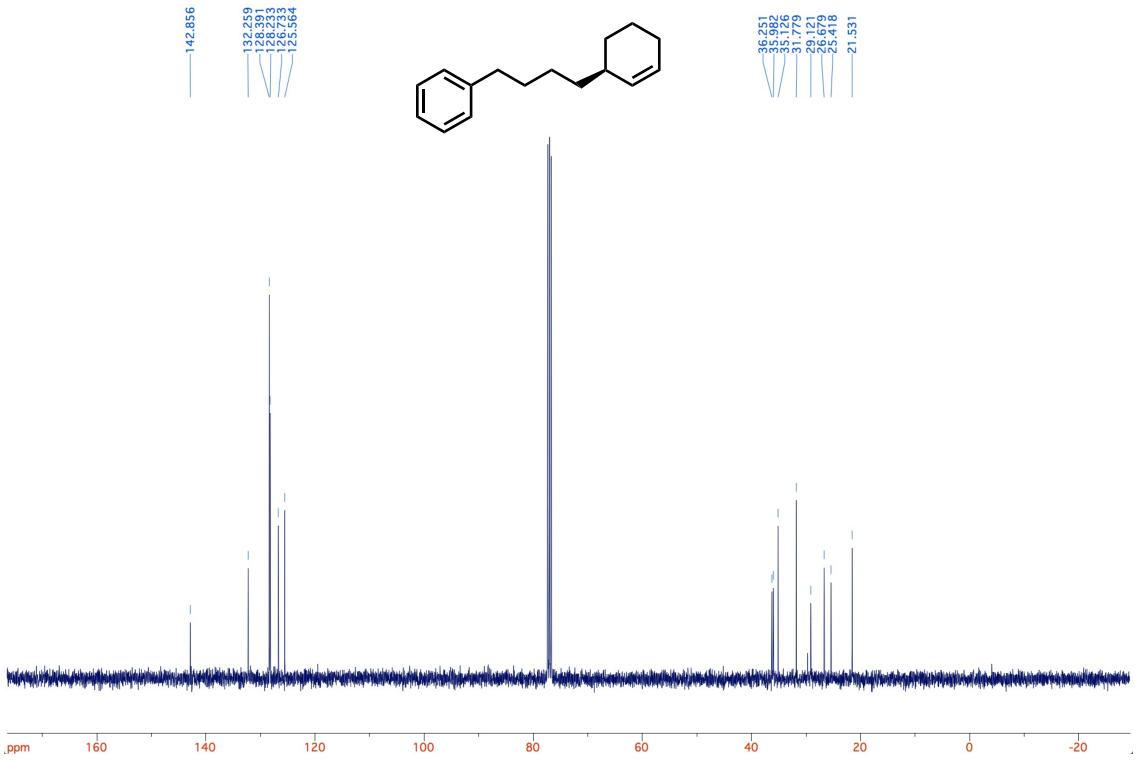
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.26 - 1.78 (m, 10 H), 1.99(m, 1 H), 2.07(m, 2 H), 2.62-2.67(m, 2 H), 5.58-5.62 (m, 1 H), 5.67-5.71 (m, 1 H), 7.20- 7.23 (m, 3 H), 7.28 - 7.31 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 21.5, 25.4, 26.7, 29.1, 31.8, 35.1, 35.9, 36.2, 125.6, 126.7, 128.2, 128.4, 132.3, 142.9.

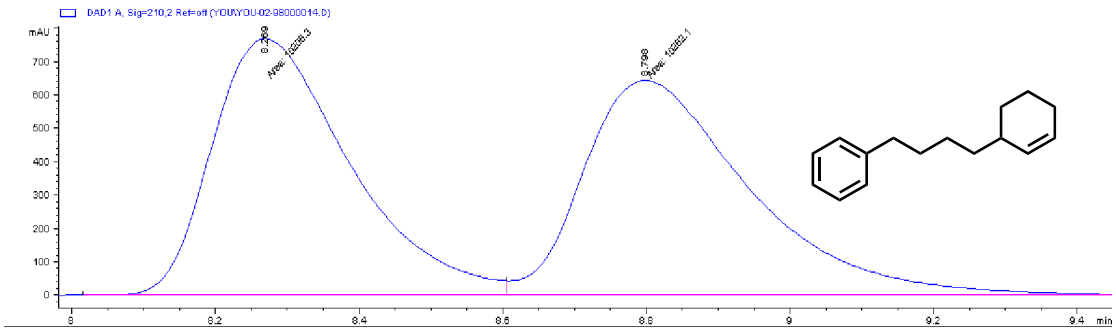
^{1}H NMR:

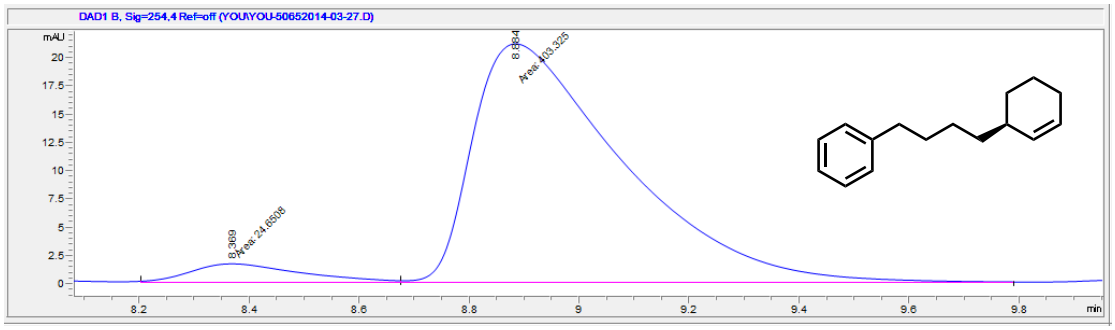


^{13}C NMR:

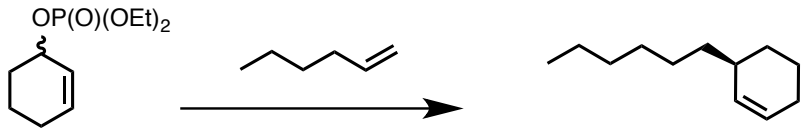


HPLC traces:





(R)-(−)-3-hexylcyclohex-1-ene (3.17)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S*)- Ligand **L16** (19.8 mg, 0.04 mmol, 0.10 eq) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 1-hexene (0.12 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.5 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 15 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, cyclohex-2-en-1-yl diethyl phosphate (93.7 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. Then, TMSCl (43.5 mg, 0.40 mmol, 1.00 eq) was injected. The reaction was

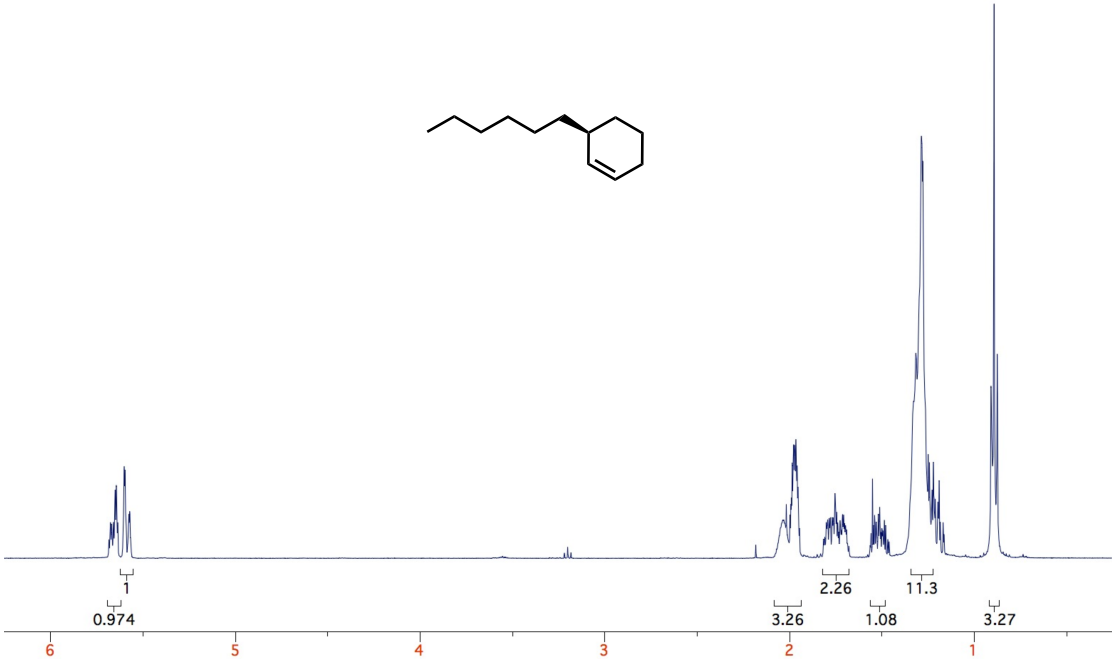
arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (~1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr apparatus (T = 30 °C and 100 mbar pressure) gave (*R*)-(–)-3-hexylcyclohex-1-ene (63.1 mg, 0.38mmol) in 95 % yield.

GC analysis of the crude mixture of epoxides derived from product indicated an enantiomeric excess of 85% (Hydrodex 6-TBDM, 60-170^{o}C at 1 ^{o}C/min, 10psi); minor enantiomer t_R = 62.1, 65.5 min; major enantiomer t_R = 62.7, 66.6 min.

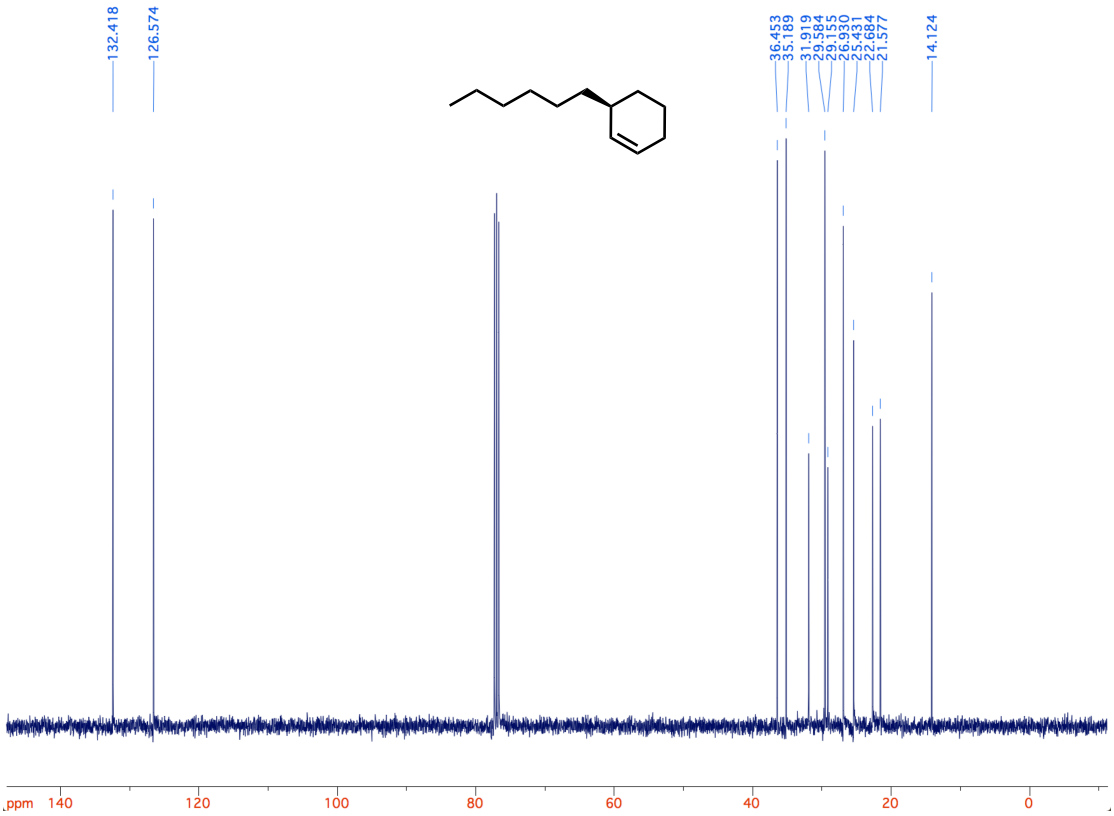
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 0.88-0.91 (t, 3 H, J =6.8 Hz), 1.25-1.31 (m, 11 H), 1.48-1.56(m, 1H), 1.69-1.81(m, 2 H), 1.95- 2.04 (m, 3 H), 5.57-5.60 (m, 1 H), 5.64-5.67 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 14.1, 21.6, 22.7, 25.4, 26.9, 29.2, 29.6，31.9，35.2，36.5，126.6, 132.4.

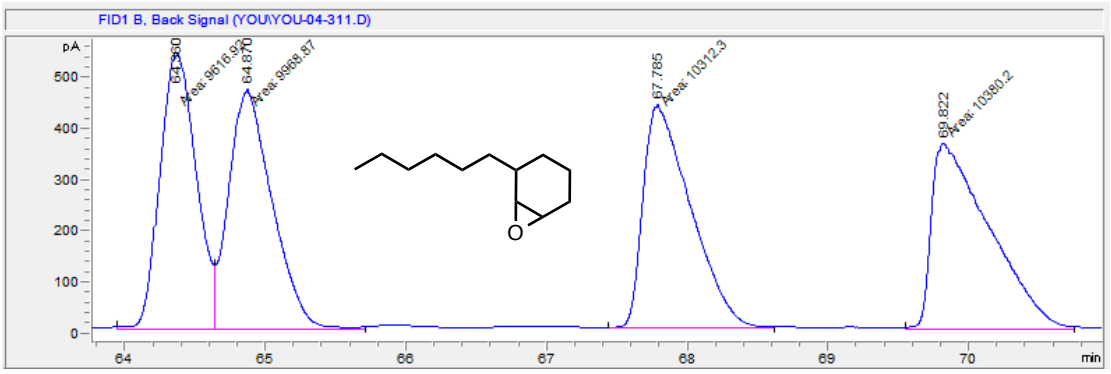
^{1}H NMR:

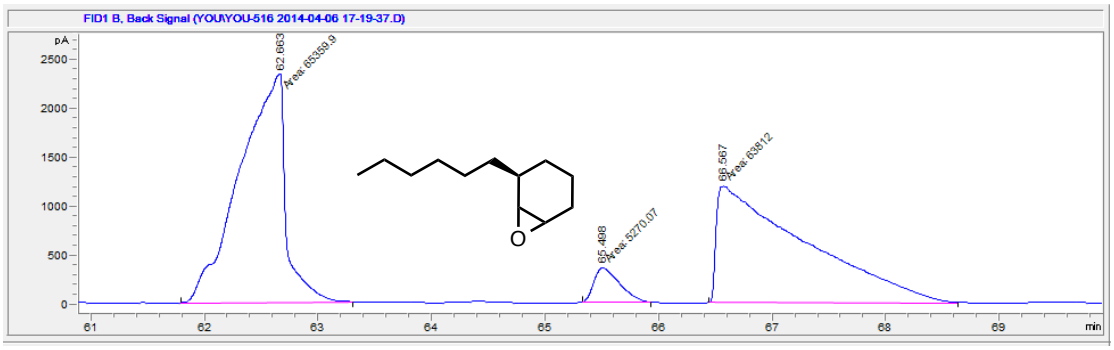


^{13}C NMR:

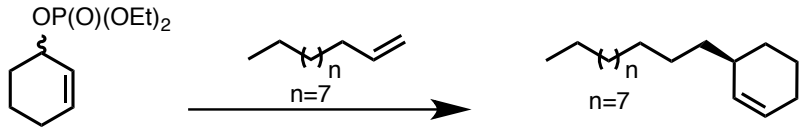


GC traces:





(R)-(−)-3-dodecylcyclohex-1-ene (3.18)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S*)- Ligand **L16** (19.8 mg, 0.04 mmol, 0.10 eq) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 1-dodecene (0.22 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.5 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, cyclohex-2-en-1-yl diethyl phosphate (93.7 mg, 0.40 mmol, 1.00 eq) was added dropwise via

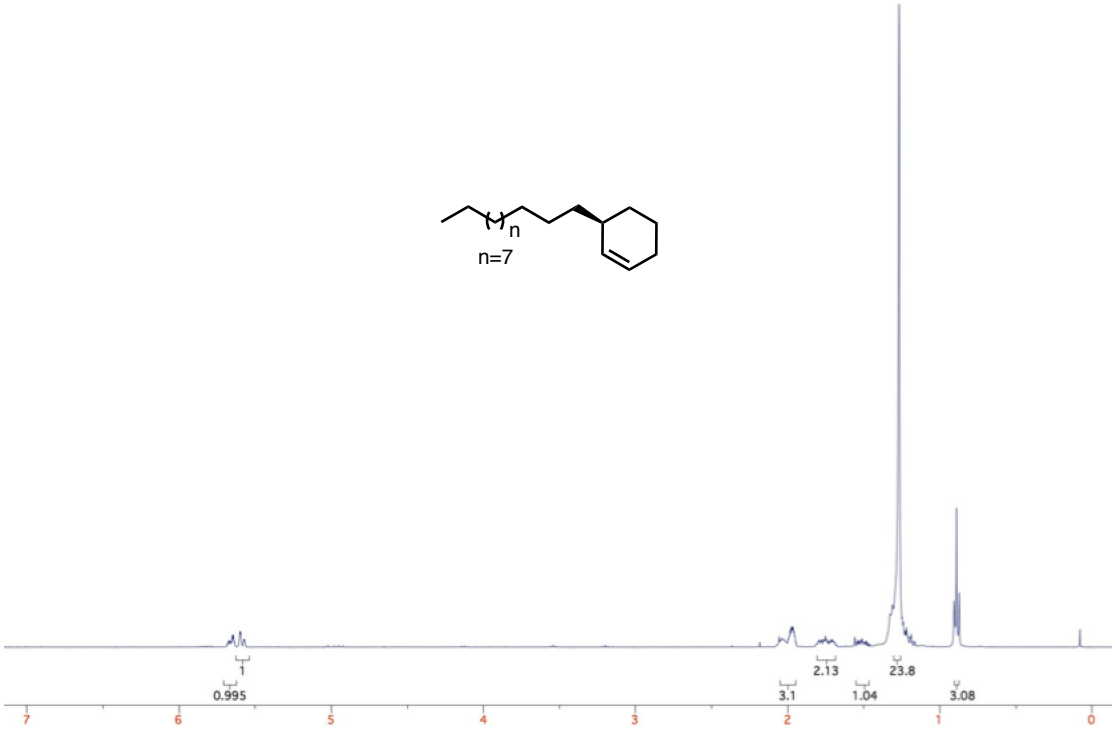
syringe. Then, TMSCl (43.5 mg, 0.40 mmol, 1.00 eq) was injected. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (~1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr apparatus (T = 150 °C and 50 mbar pressure) gave (*R*)-(–)-3- dodecylcyclohex-1-ene (77.1 mg, 0.31mmol) in 77 % yield.

GC analysis of the crude mixture of epoxides derived from product indicated an enantiomeric excess of 92% (Hydrodex 6-TBDM, 60-170^{o}C at 1 ^{o}C/min, hold for 70 min, 10psi); minor enantiomer t_R = 135.7min; major enantiomer t_R = 138.9 min.

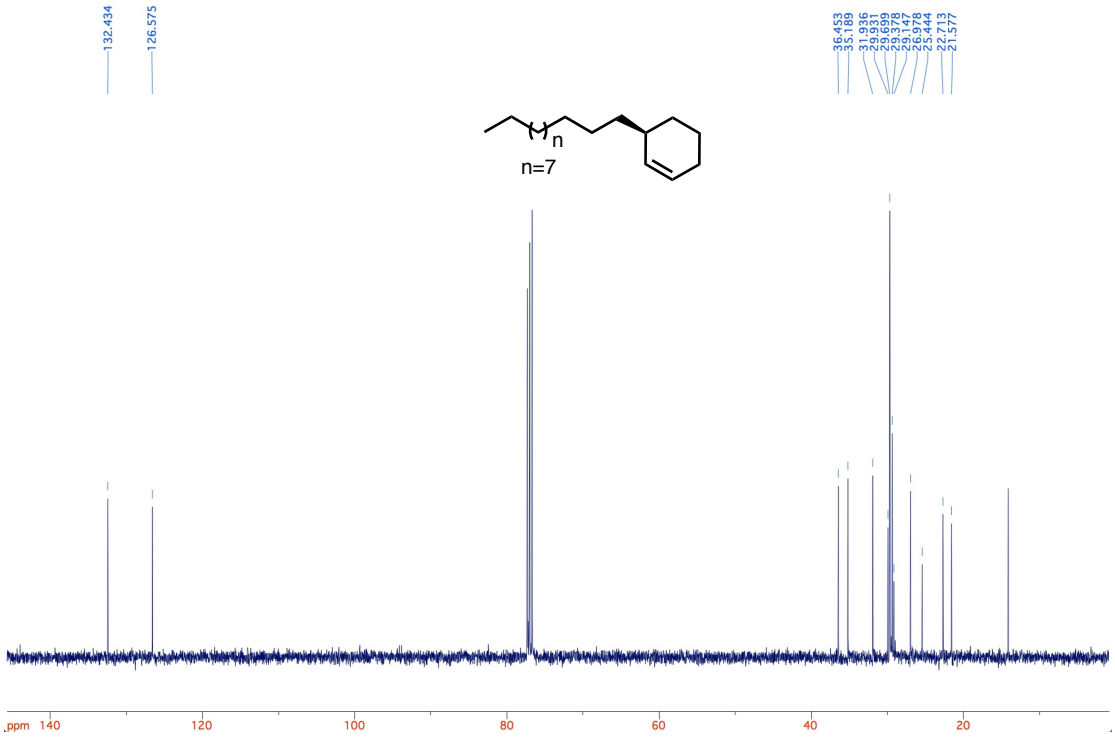
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 0.87-0.91 (t, 3 H, J =6.85 Hz), 1.22-1.32 (m, 23 H), 1.48-1.56 (m, 1 H), 1.71-1.81 (m, 2 H), 1.95-2.06 (m, 3 H), 5.57-5.60 (m, 1 H), 5.64-5.68 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 21.6, 22.7, 25.4, 27.0, 29.1, 29.3, 29.7 (br. m, 6C), 29.9, 31.9, 35.2, 36.5, 126.6, 132.4.

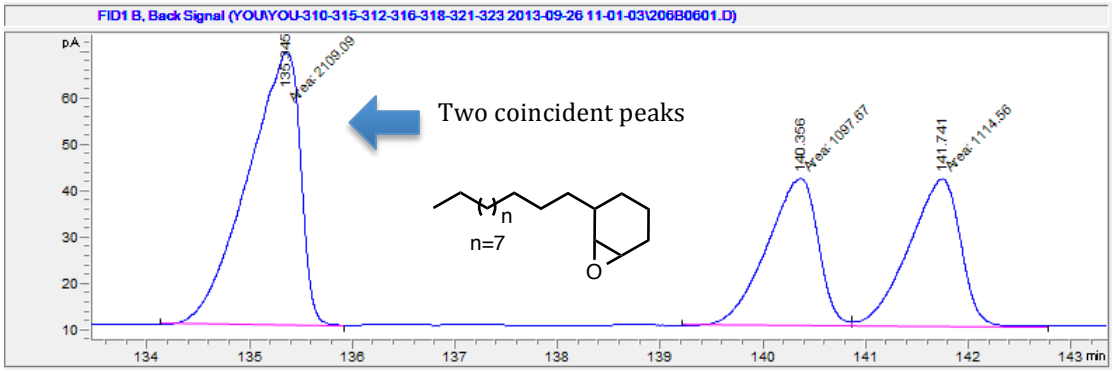
^{1}H NMR:

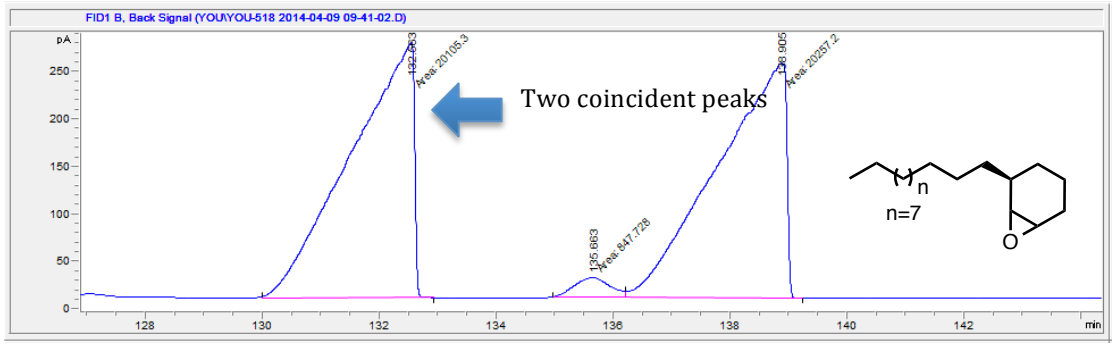


^{13}C NMR:

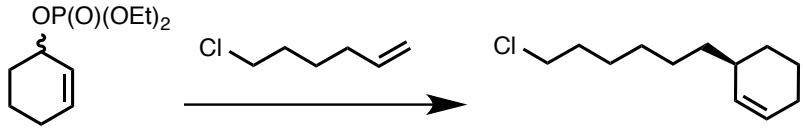


GC traces:





(R)-(–)-3-(6-chlorohexyl) cyclohex-1-ene (3.19)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S*)- Ligand **L16** (19.8 mg, 0.04 mmol, 0.10 eq) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 6-chlorohex-1-ene (106 µL, 1.0 mmol, 2.50 eq), CH_2Cl_2 (0.5 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, cyclohex-2-en-1-yl diethyl phosphate (93.7 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe.

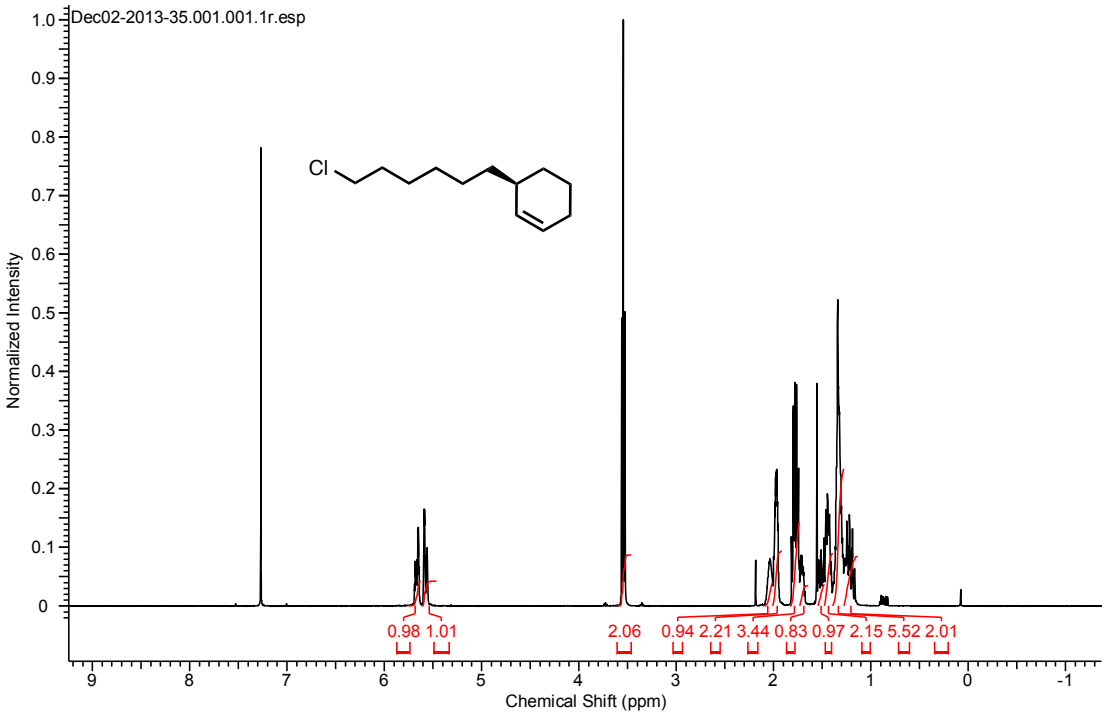
Then, TMSCl (43.5 mg, 0.40 mmol, 1.00 eq) was injected. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (~1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave (*R*)-(–)-3-(6-chlorohexyl) cyclohex-1-ene (35.4 mg, 0.18mmol) in 44 % yield.

GC analysis of the crude mixture of epoxides derived from product indicated an enantiomeric excess of 75% (Hydrodex 6-TBDM, 60-165^{o}C at 1 ^{o}C/min, hold for 30 min, 10psi); minor enantiomer t_R = 109.2min; major enantiomer t_R = 109.9 min.

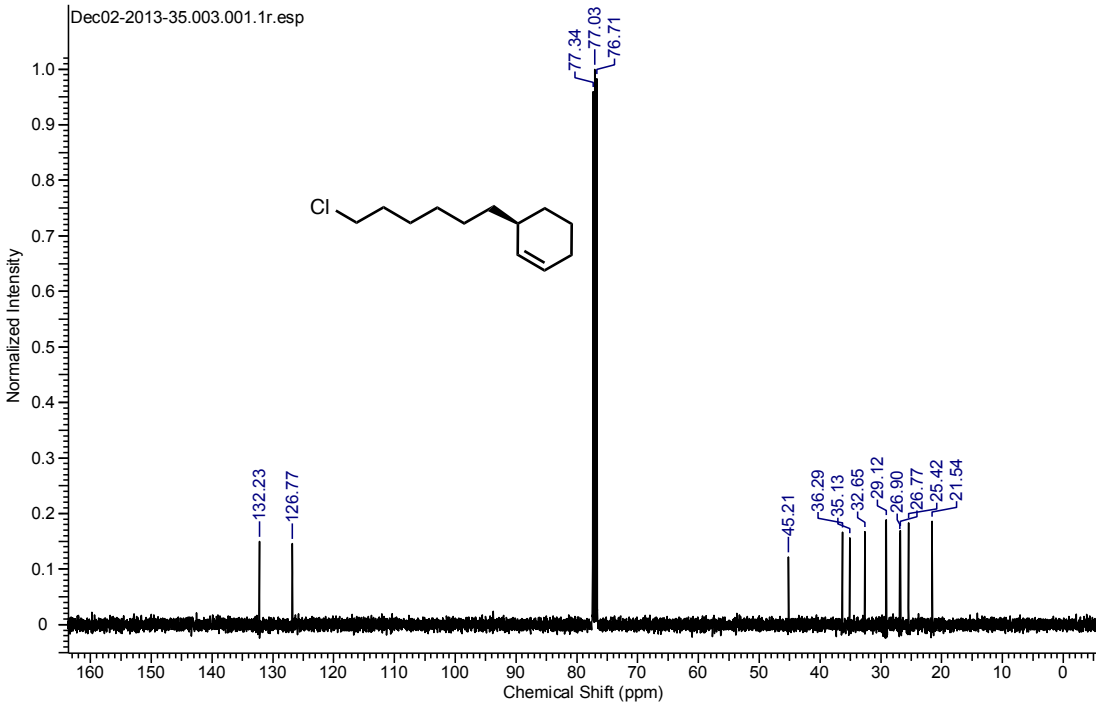
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 5.72-5.62 (m, 1H), 5.61-5.53 (m, 1H), 3.54 (t, *J*=6.8 Hz, 2H), 2.09-2.00 (m, 1H), 2.00-1.91 (m, 2H), 1.83-1.74 (m, 3H), 1.73-1.66 (m, 1H), 1.55-1.48 (m, 1H), 1.48-1.39 (m, 2H), 1.38-1.28 (m, 5H), 1.28-1.15 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 132.2, 126.8, 45.2, 36.3, 35.1, 32.6, 29.1, 29.1, 26.9, 26.8, 25.4, 21.5;

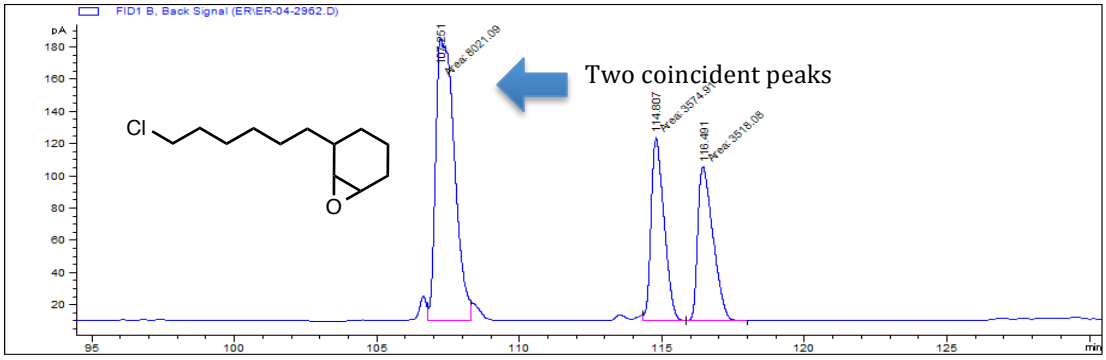
^{1}H NMR:

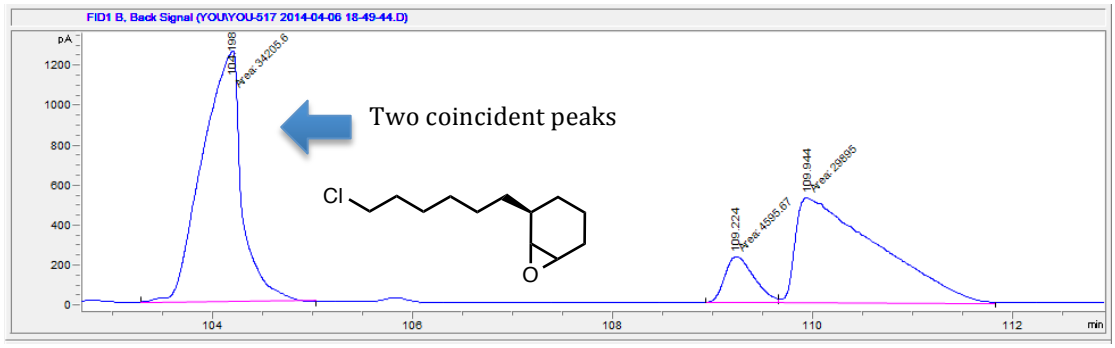


^{13}C NMR:

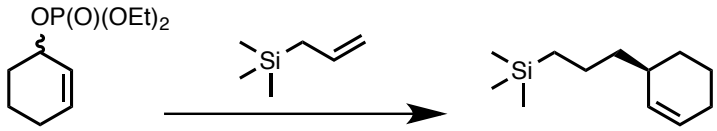


GC traces:





(R)-(−)-(3-(cyclohex-2-en-1-yl) propyl) trimethylsilane (3.20)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S*)- Ligand **L16** (19.8 mg, 0.04 mmol, 0.10 eq) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, Allyltrimethylsilane (0.16 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.5 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, cyclohex-2-en-1-yl diethyl phosphate (93.7 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. Then, TMSCl (43.5 mg, 0.40 mmol, 1.00 eq) was injected. The reaction was arbitrarily left

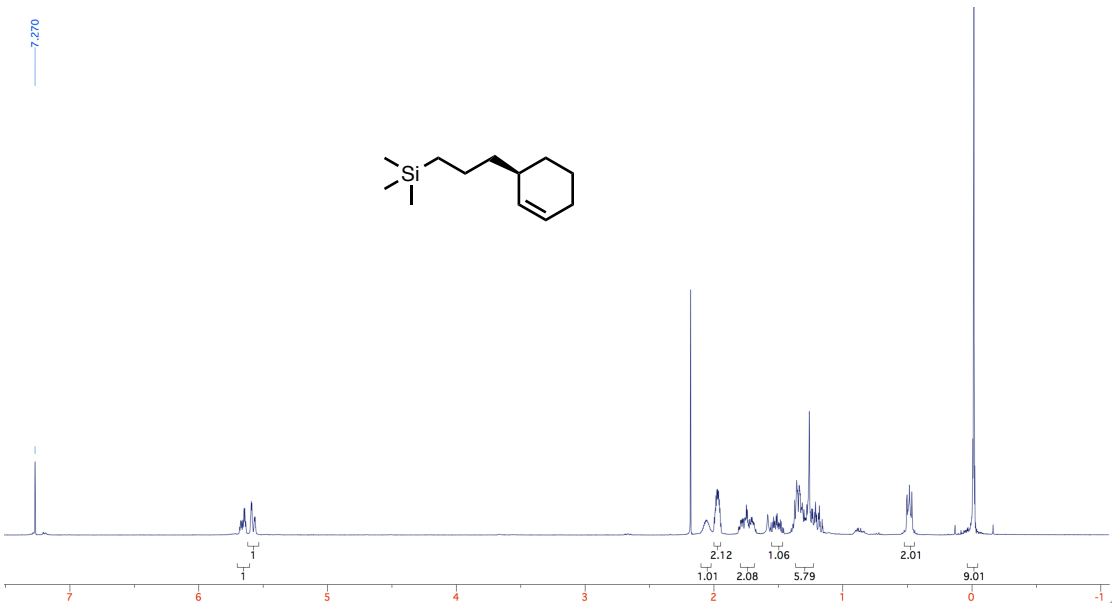
stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (~1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr apparatus (T = 40 °C and 40 mbar pressure) gave (*R*)-(–)-(3-(cyclohex-2-en-1-yl) propyl) trimethylsilane (21.6 mg, 0.11 mmol) in 28% yield.

GC analysis of the crude mixture of epoxides derived from product indicated an enantiomeric excess of 93% (Hydrodex 6-TBDM, 60-170^{o}C at 1 ^{o}C/min, 10psi); major enantiomer t_R = 63.4, 69.7 min; minor enantiomer t_R = 63.8, 67.5 min.

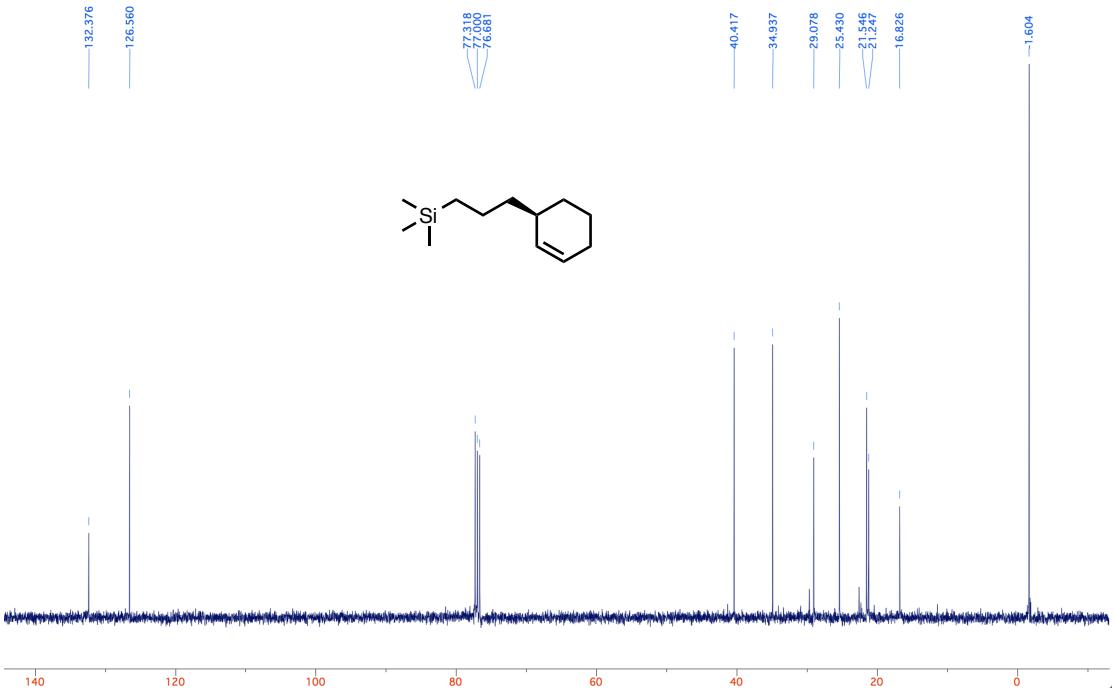
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 0.005 (s, 9H), 0.49-0.53 (m, 2 H), 1.23-1.39 (m, 5 H), 1.50-1.57 (m, 1 H), 1.72-1.82 (m, 2 H), 1.98-2.01 (m, 2 H), 2.06-2.10 (m, 1 H), 5.58-5.62 (m, 1H), 5.66-5.70 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: -1.6, 16.8, 21.2, 21.5, 25.4, 29.1, 34.9, 40.4, 126.6, 132.4.

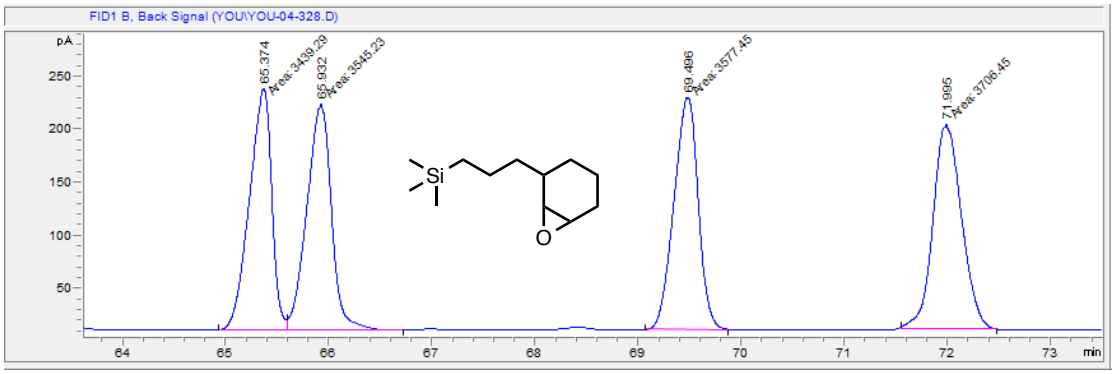
^{1}H NMR:

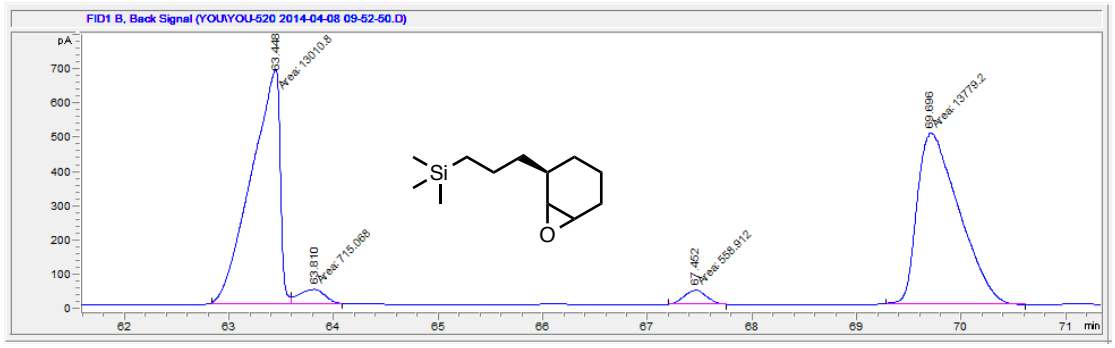


^{13}C NMR:

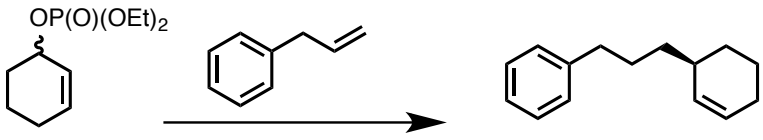


GC traces:





(R)-(–)-(3-(cyclohex-2-en-1-yl) propyl) benzene (3.21)



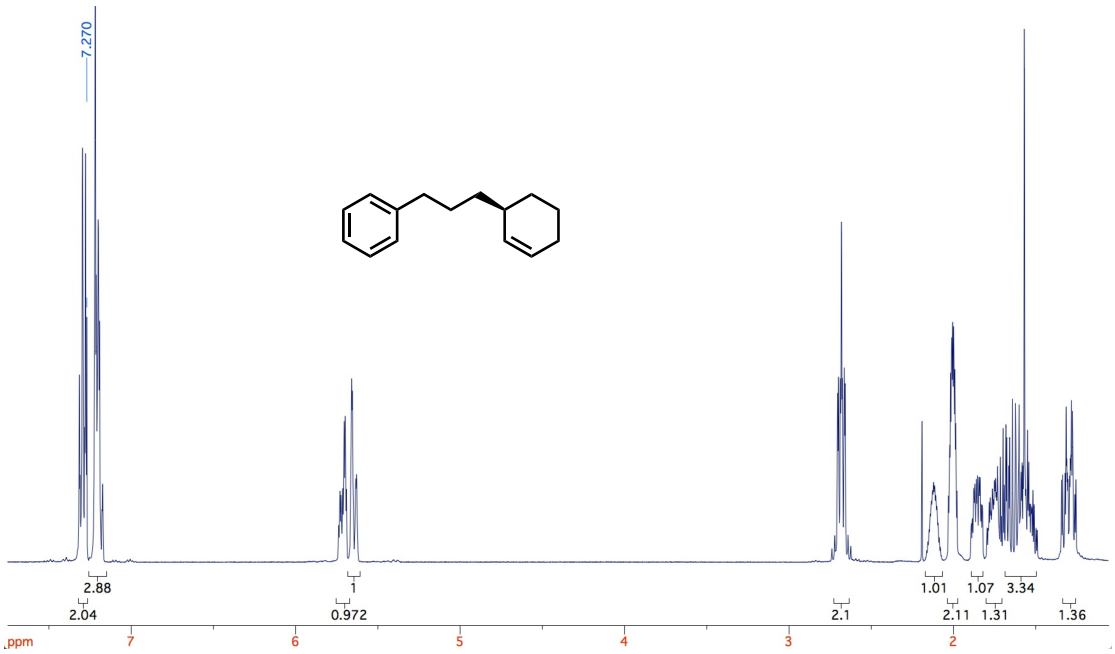
CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S*)- Ligand **L16** (19.8 mg, 0.04 mmol, 0.10 eq) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, allylbenzene (0.13 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.5 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, cyclohex-2-en-1-yl diethyl phosphate (93.7 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. Then, TMSCl (43.5 mg, 0.40 mmol, 1.00 eq) was injected. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (~1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr apparatus (T = 100 °C and 50 mbar pressure) gave (*R*)-(–)-(3-(cyclohex-2-en-1-yl) propyl) benzene (72.3 mg, 0.36mmol) in 91% yield.

GC analysis of the crude mixture of epoxides derived from product indicated an enantiomeric excess of 81% (Hydrodex 6-TBDM, 60-170^{o}C at 1 ^{o}C/min, hold for 70 min, 10psi); major enantiomer t_R = 112.5, 117.4 min; minor enantiomer t_R = 114.9 min.

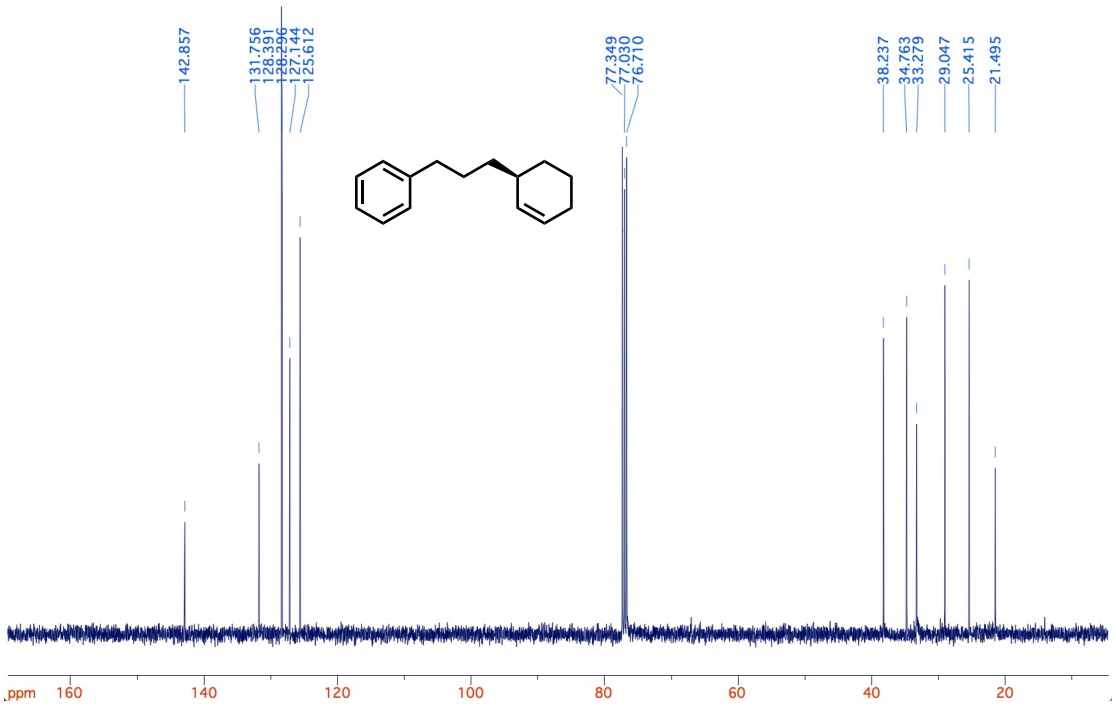
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.22-1.43 (m, 3H), 1.50-1.56 (m, 1 H), 1.68-1.83 (m, 4 H), 1.97-2.01 (m, 2 H), 2.08-2.13 (m, 1 H), 2.62-2.66 (t, 2 H, J =7.77 Hz), 5.58-5.62 (m, 1 H), 5.67-5.71 (m, 1H), 7.21-7.23 (m, 3H), 7.29-7.33 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 21.6, 25.4, 28.9, 29.1, 35.1, 36.1, 36.2, 125.6, 126.8, 128.3, 128.4, 132.1, 142.8.

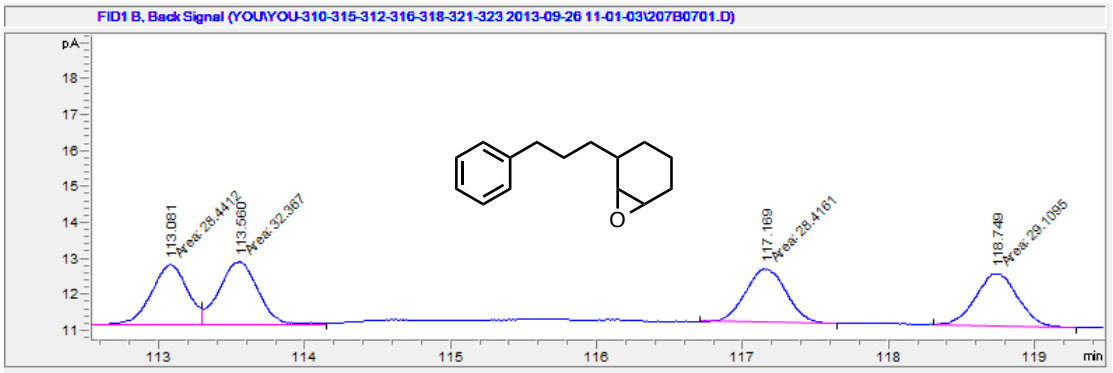
^{1}H NMR:

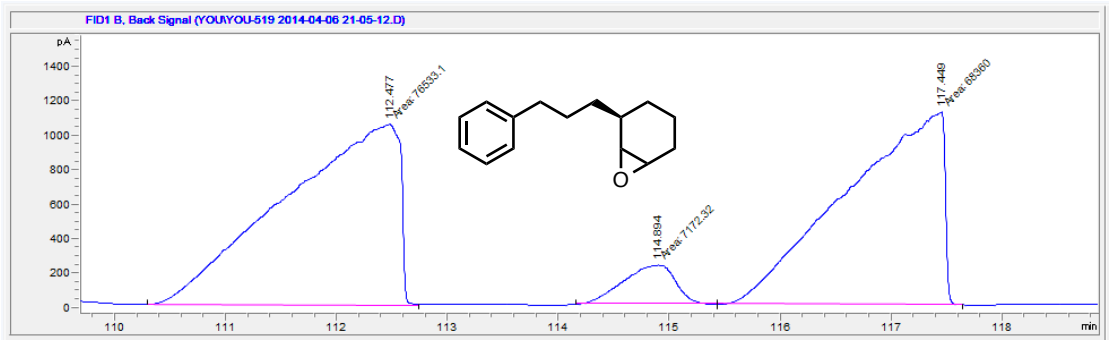


^{13}C NMR:

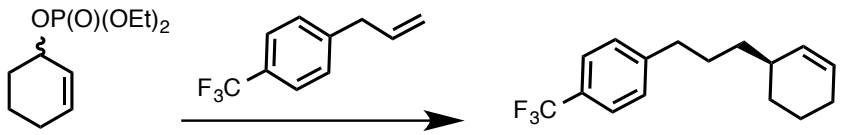


GC traces:





(*S*)-(–)-1-(3-(cyclohex-2-en-1-yl) propyl)-4-(trifluoromethyl) benzene (3.22)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S*)- Ligand **L16** (19.8 mg, 0.04 mmol, 0.10 eq) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 1-allyl-4-(trifluoromethyl)benzene (0.17ml, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.5 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional

minutes, cyclohex-2-en-1-yl diethyl phosphate (93.7 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. Then, TMSCl (43.5 mg, 0.40 mmol, 1.00 eq) was injected. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (~1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave (*S*)-(–)-1-(3-(cyclohex-2-en-1-yl) propyl)-4- (trifluoromethyl) benzene (93.1mg, 0.35mmol) in 86% yield.

GC analysis of the crude mixture of epoxides derived from product indicated an enantiomeric excess of 65% (Hydrodex 6-TBDM, 90-180^{o}C at 10 ^{o}C/min, hold for 10 min, 180-220^{o}C at 1 ^{o}C/min, 10psi); major enantiomer t_R = 28.4 min; minor enantiomer t_R = 27.4 min.

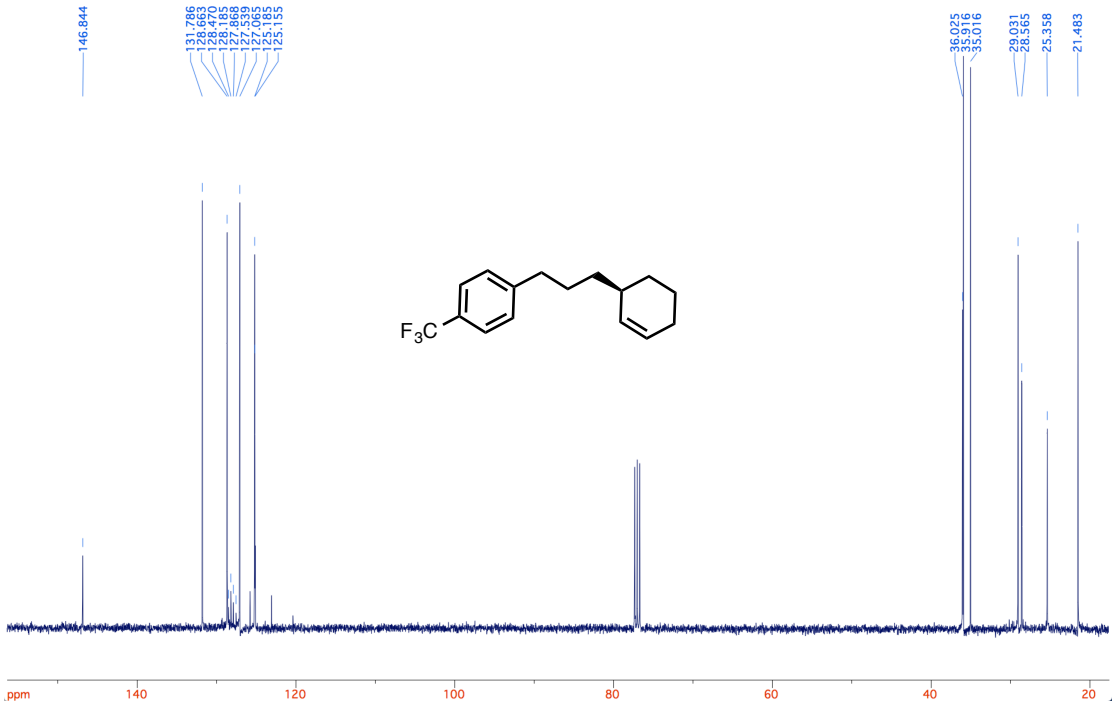
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.20-1.43 (m, 3H), 1.50-1.56 (m, 1 H), 1.68-1.74 (m, 3 H), 1.76-1.83 (m, 1 H), 1.96-2.00 (m, 2 H), 2.06-2.13 (m, 1 H), 2.66-2.70 (t, 2 H, J= 7.74 Hz), 5.56-5.60 (m, 1H), 5.66-5.71 (m, 1H), 7.29-7.32 (m. 2 H), 7.53-7.55 (d, 2H, J= 7.87 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 21.5, 25.4, 28.6, 29.0, 35.0, 35.9, 36.0, 125.2 (2C), 127.1, 128.0 (q, J (C, F)=31.0 Hz), 128.7, 131.8, 146.8.

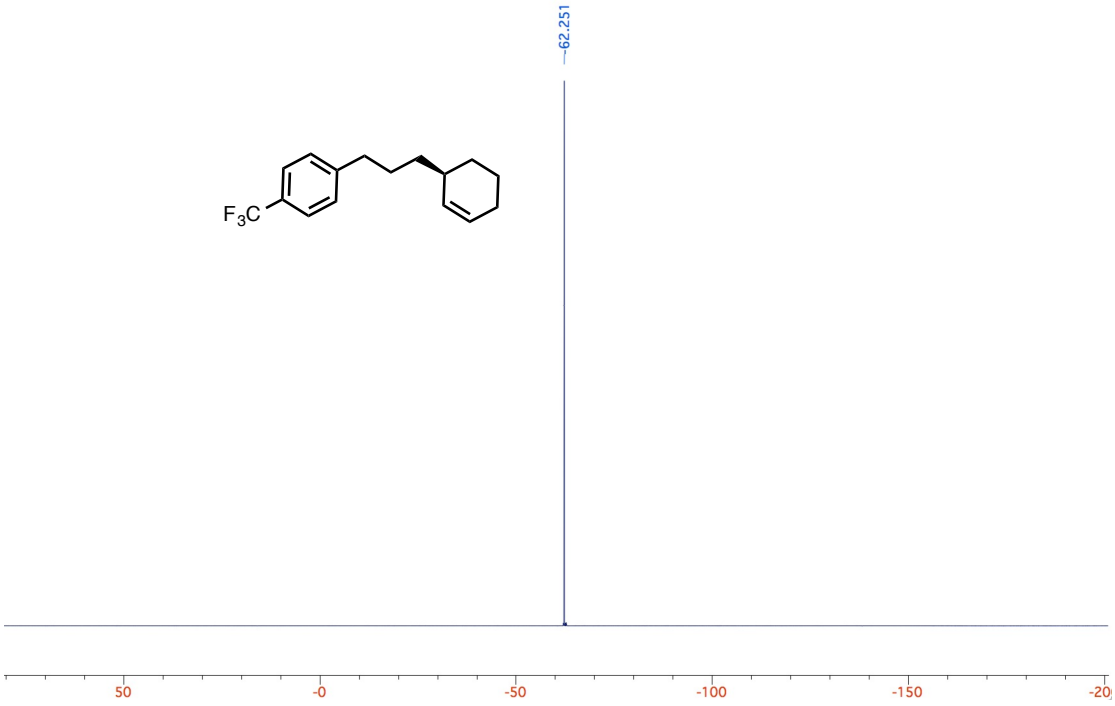
^{19}F NMR (380 MHz, $CDCl_3$) δ_F /ppm: –62.3.

^{1}H NMR:

^{13}C NMR:



^{19}F NMR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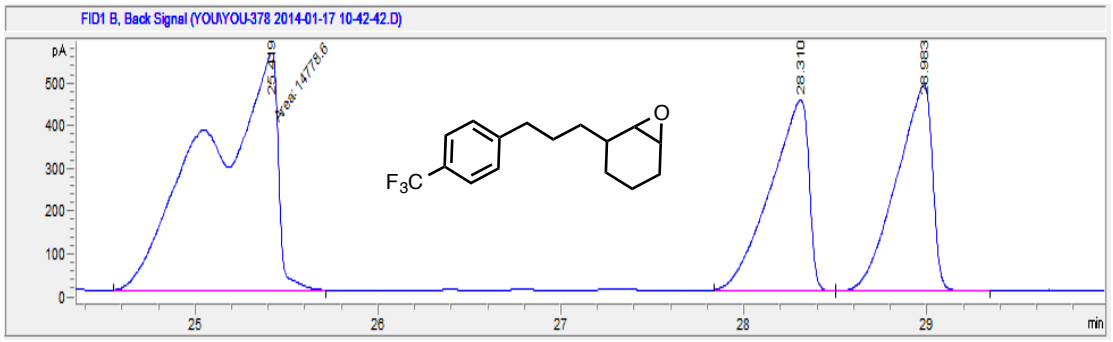
-50
-100
-150
-20

GC traces: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O
F3C
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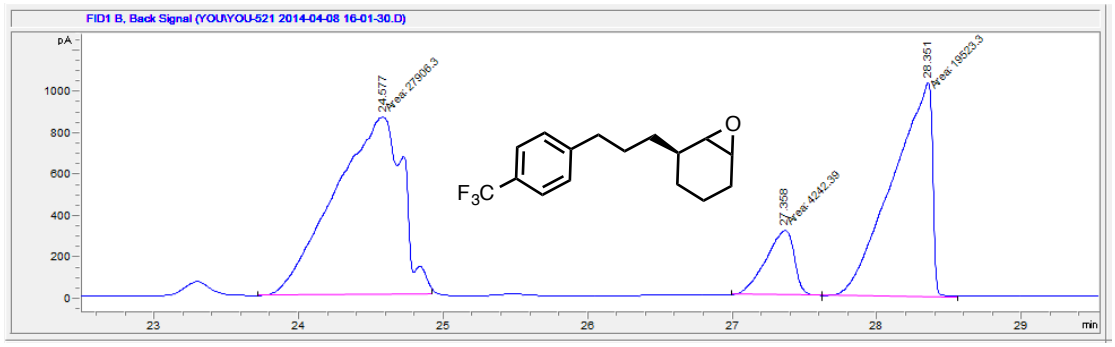
28
29
min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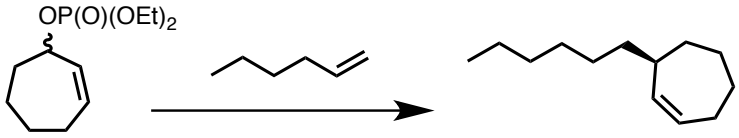
O
F3C
23
24
25
26
27
28
29
min

(R)-3-(4-phenylbutyl) cyclohept-1-ene (3.23, Method C)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S*)- Ligand **L16** (19.8 mg, 0.04 mmol, 0.10 eq) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 1-hexene (0.12 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.5 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, cyclohept-2-en-1-yl diethyl phosphate (99.4 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. Then, TMSCl (43.5 mg, 0.40 mmol, 1.00 eq) was injected. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (~1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave the product (46.4 mg, 0.26 mmol) in 65% yield.

GC analysis of crude mixture of epoxides derived from the products indicated an enantiomeric excess of 90% (Hydrodex ß-3P, 60-110^{o}C at 5 ^{o}C/min, 110-140^{o}C at 10 ^{o}C/min, hold for 10 min, 140-170^{o}C at 10 ^{o}C/min, hold for 10 min, 10psi); major enantiomer t_R = 30.9, 31.1 min; minor enantiomer t_R = 30.5, 31.3 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 0.88-0.91 (m, 3 H), 1.24-1.40 (m, 12 H), 1.53-1.70 (m, 3 H), 1.91-1.98 (m, 1 H), 2.08-2.19 (m, 3 H), 5.57(m, 1 H), 5.76 (m, 1 H).

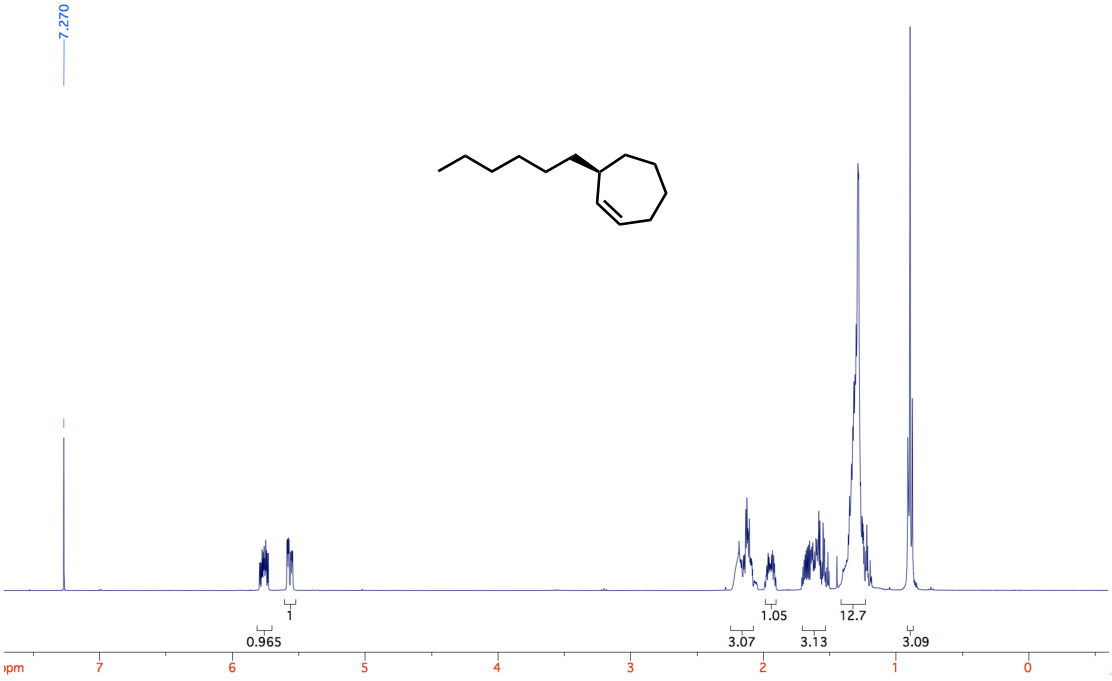
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 14.1, 22.7, 27.1, 27.3, 28.8, 29.6, 30.7, 31.9, 33.6, 37.0, 39.7, 130.9, 138.4.

HRMS (ESI) *m*/z calcd for $C_{13}H_{24}$ $[M]^+$: 180.1878, found: 180.1875.

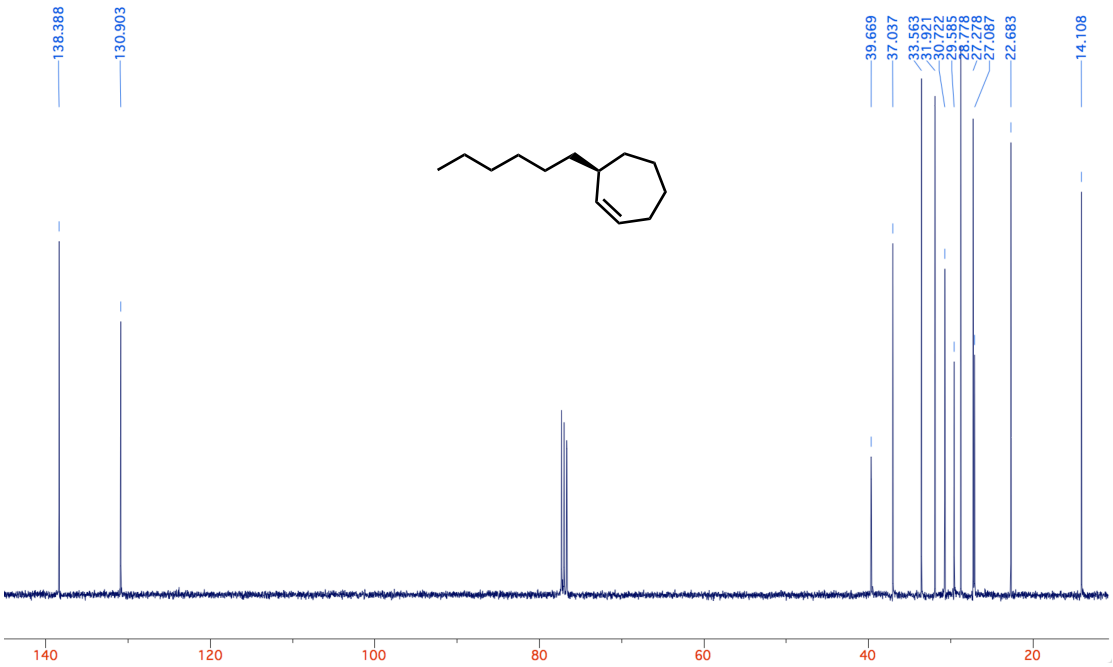
IR (ATR) ν (cm^{-1}, $CHCl_3$): 690, 1217, 1366, 1445, 1739, 2853, 2922.

$[\alpha]^{20}_{589}$ = –11.19 (c=1.34 in $CHCl_3$, 90% ee).

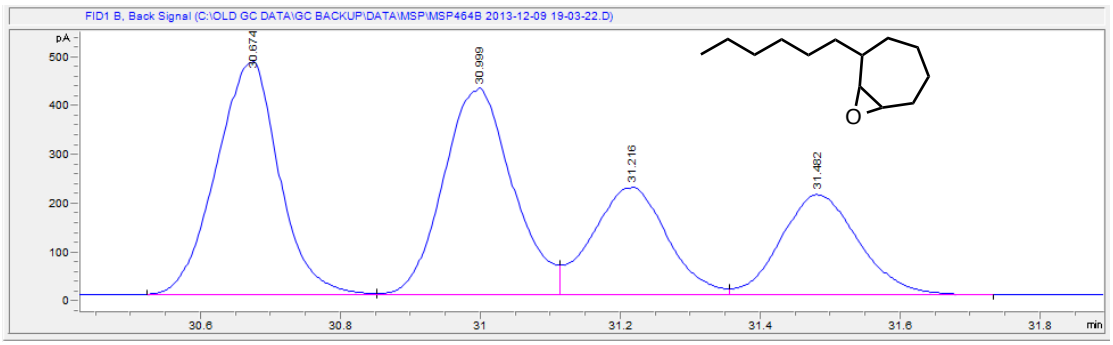
^{1}H NMR:



^{13}C NMR:


138.388
130.903
39.669
37.037
33.563
31.321
30.585
28.778
27.278
27.087
22.683
14.108
140
120
100
80
60
40
20

GC traces:


FID1 B, Back Signal (C:\OLD GC DATA\GC BACKUP\DATA\MSP\MSP464B 2013-12-09 19-03-22.D)
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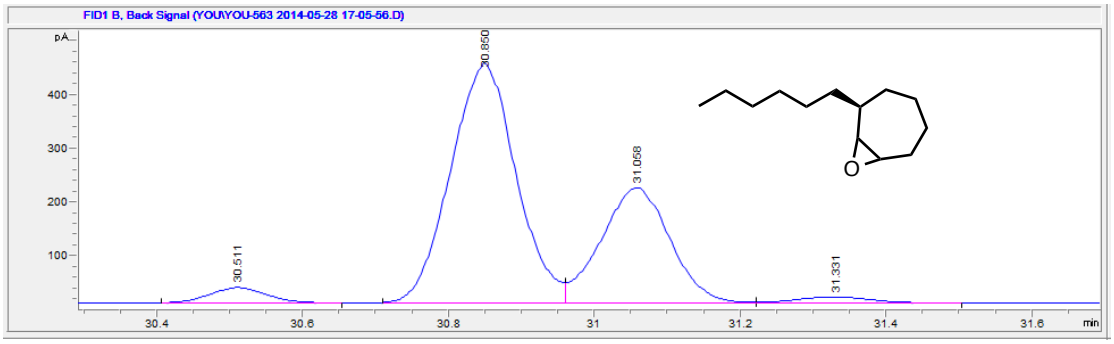
30.999
31.216
31.482
O
min


FID1 B, Back Signal (YOU\YOU-563 2014-05-28 17-05-56.D)
pA
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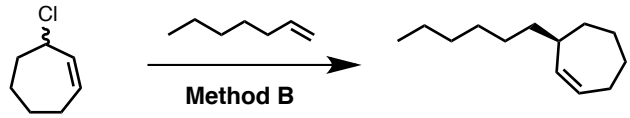
30.850
31.058
31.331
O
min

(R)-3-(4-phenylbutyl) cyclohept-1-ene (3.23, Method B)



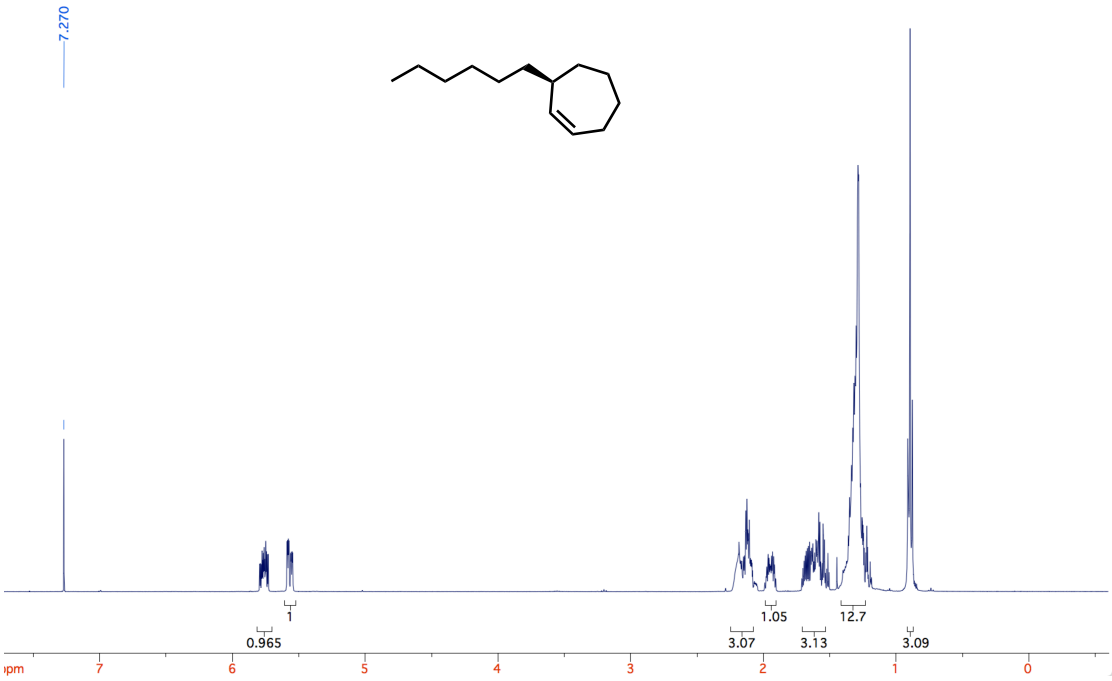
CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S*)- Ligand **L16** (19.8 mg, 0.04 mmol, 0.10 eq) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 1-hexene (0.12 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.5 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, 3-chlorocycloheptene (52.3 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (~1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave the product (49.1 mg, 0.27 mmol) in 68% yield.

GC analysis of crude mixture of epoxides derived from the products indicated an enantiomeric excess of 94% (Hydrodex ß-3P, 60-110^{o}C at 5 ^{o}C/min, 110-140^{o}C at 10 ^{o}C/min, hold for 10 min, 140-170^{o}C at 10 ^{o}C/min, hold for 10 min, 10psi); major enantiomer t_R = 30.9, 31.1 min; minor enantiomer t_R = 30.5, 31.3 min.

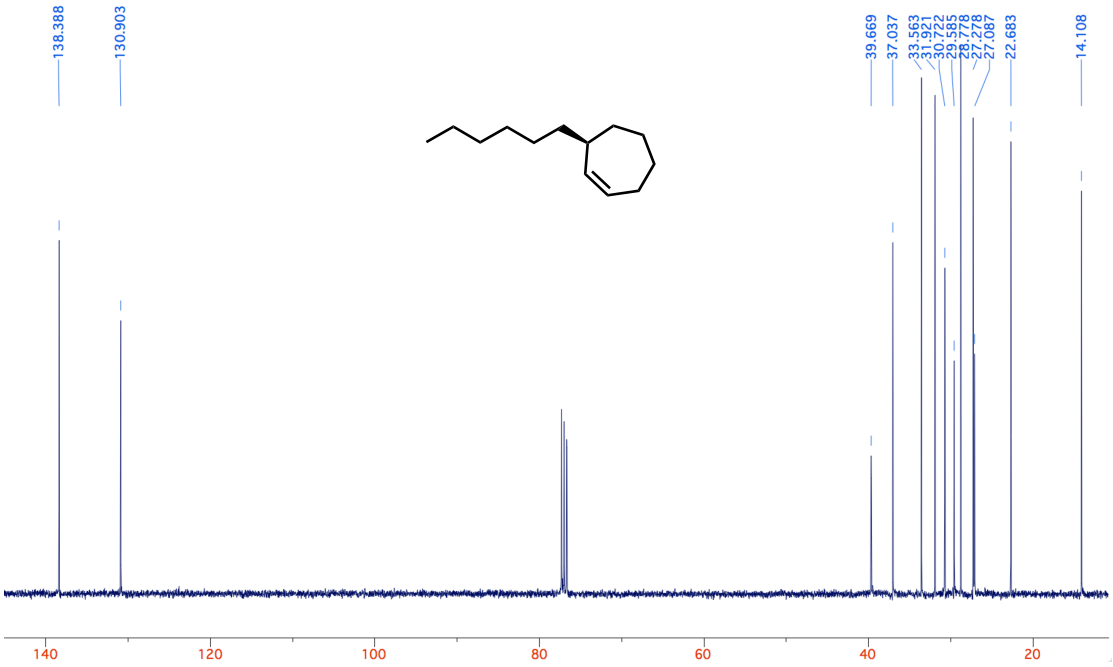
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 0.88-0.91 (m, 3 H), 1.24-1.40 (m, 12 H), 1.53-1.70 (m, 3 H), 1.91-1.98 (m, 1 H), 2.08-2.19 (m, 3 H), 5.57(m, 1 H), 5.76 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 14.1, 22.7, 27.1, 27.3, 28.8, 29.6, 30.7, 31.9, 33.6, 37.0, 39.7, 130.9, 138.4.

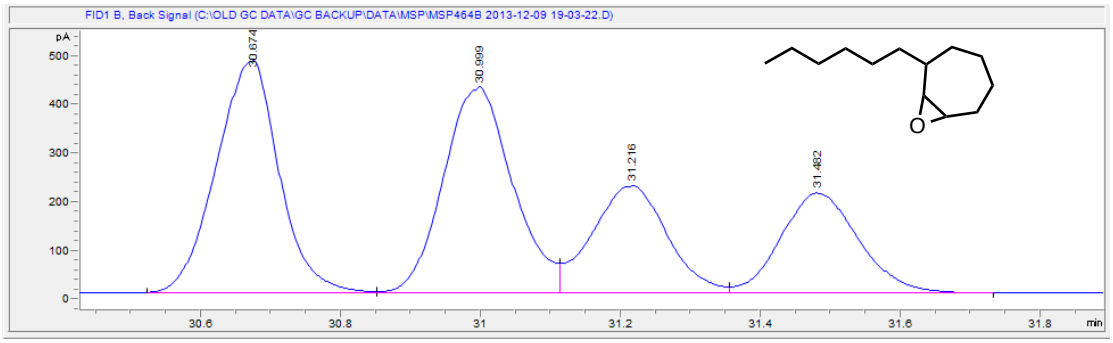
^{1}H NMR:

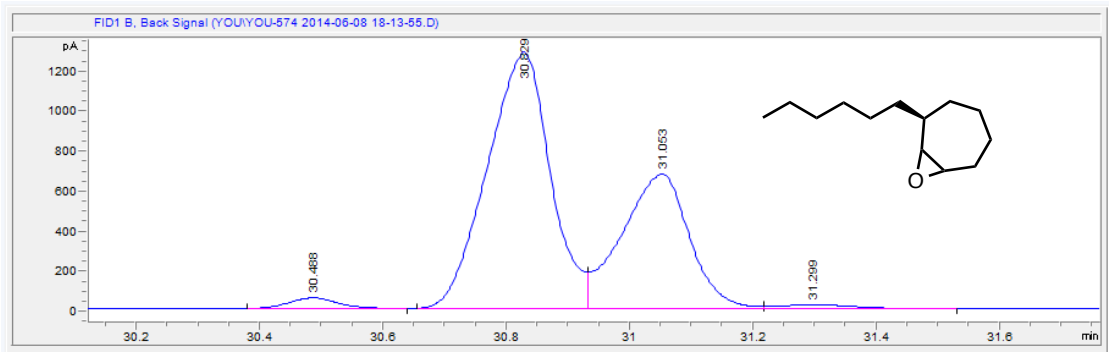


^{13}C NMR:

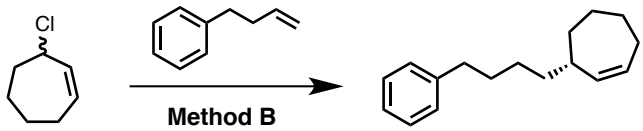


GC traces:





(S)-(–)-3-(4-Phenylbutyl) cyclohept-1-ene (3.24)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R*)- Ligand **L16** (19.8 mg, 0.04 mmol, 0.10 eq) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 4-phenyl-1-butene (0.15 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.5 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, 3-chlorocycloheptene (52.3 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was

arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (~1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave the product (86.2 mg, 0.38 mmol) in 95% yield.

HPLC analysis indicated an enantiomeric excess of 94% (Chiralpak® IE Hexane 0.4 mL/min); minor enantiomer t_R = 17.8 min; major enantiomer t_R = 18.0 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 7.35 – 7.26 (m, 2H), 7.21 (m, 3H), 5.78 (m, 1H), 5.57 (m, 1H), 2.70 – 2.59 (m, 2H), 2.25 – 2.04 (m, 3H), 1.95 (m, 1H), 1.75 – 1.49 (m, 7H), 1.49 – 1.36 (m, 4H), 1.32 (m, 2H), 1.28 – 1.18 (m, 1H).

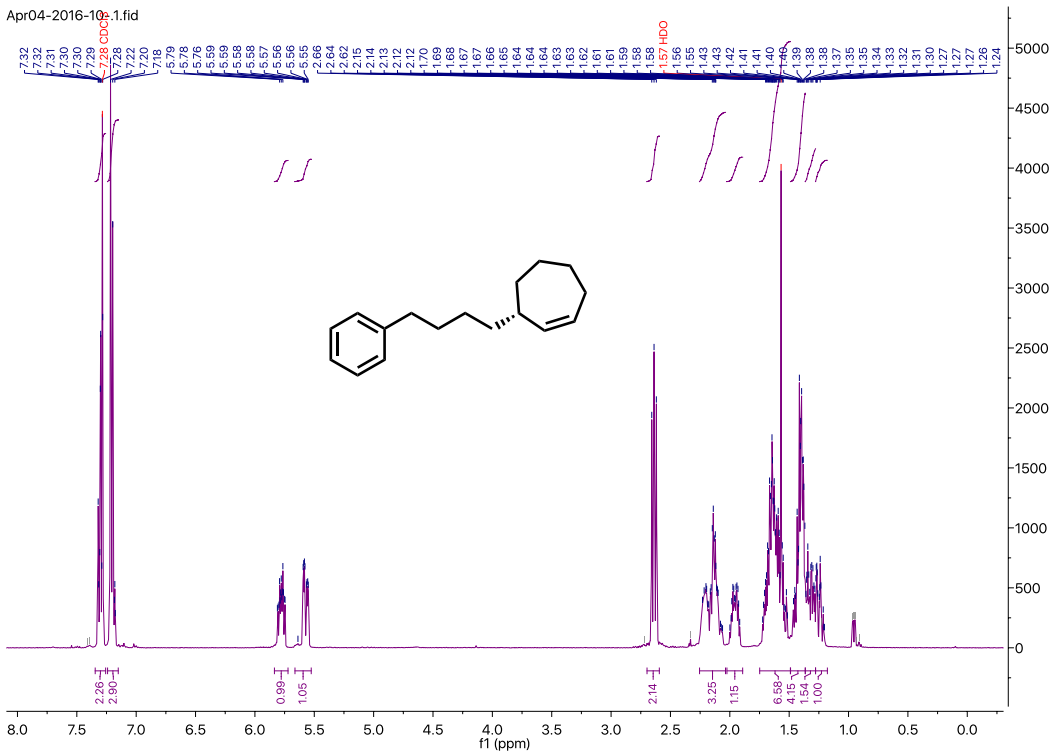
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 142.9, 138.2, 131.1, 128.4, 128.2, 125.6, 39.6, 36.9, 36.0, 33.6, 31.8, 30.7, 28.8, 27.1, 27.0.

HRMS (ESI) *m*/z calcd for $C_{17}H_{24}$ $[M]^+$: 228.1878, found: 228.1881.

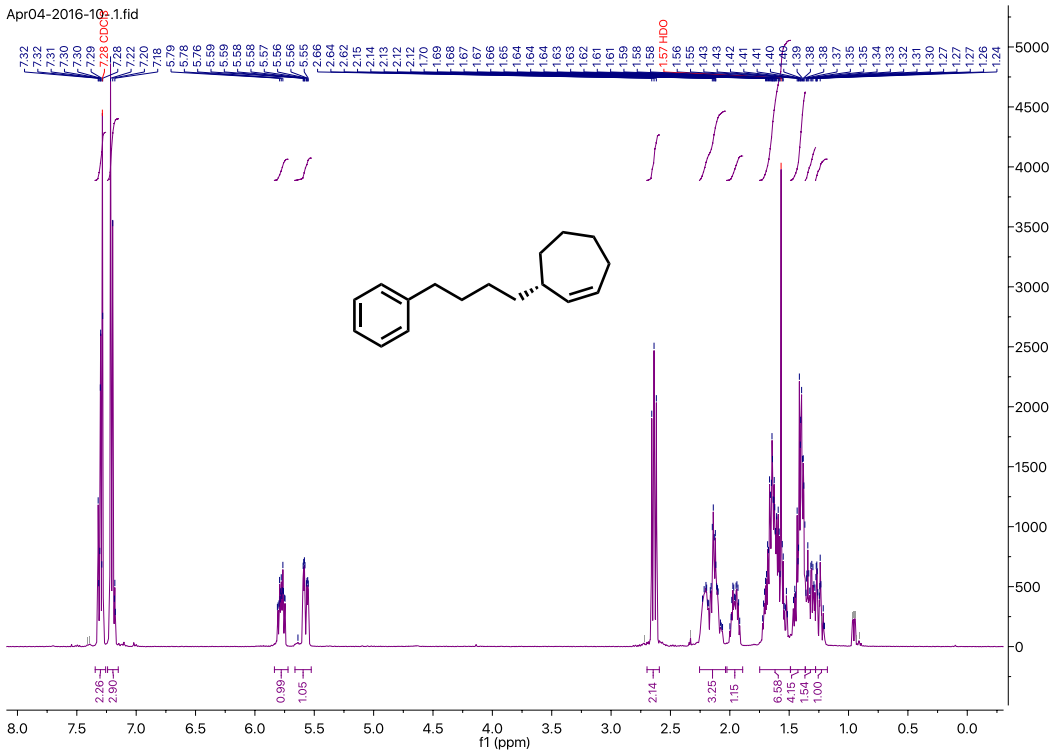
IR (ATR) ν (cm^{-1}, $CHCl_3$): 1496, 1604, 2853, 2920, 3024

$[\alpha]^{20}_{589}$ = +18.3 (c=1.09 in $CHCl_3$, 94% ee).

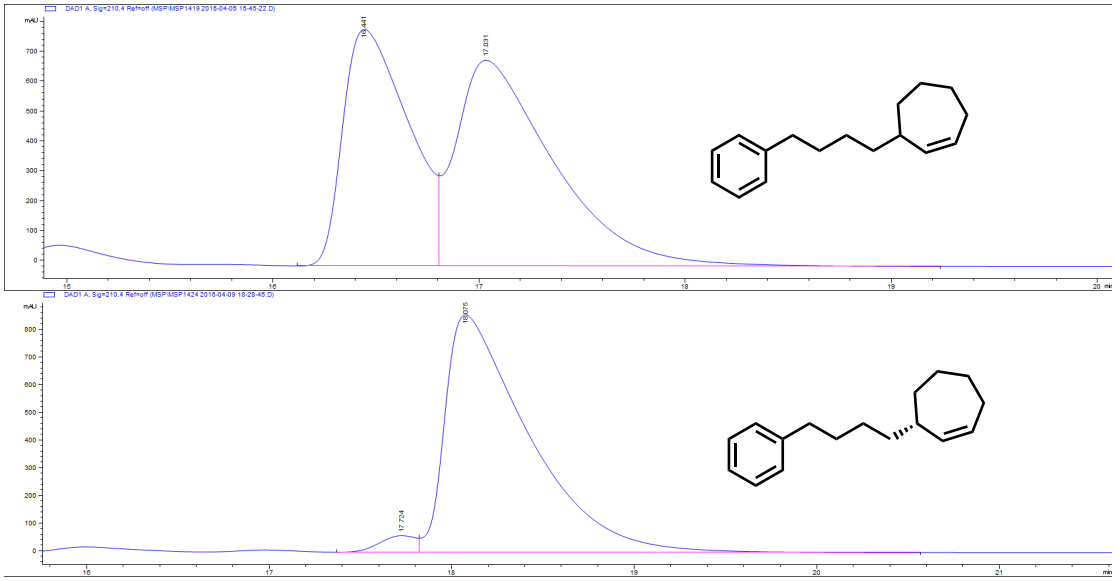
^{1}H NMR:



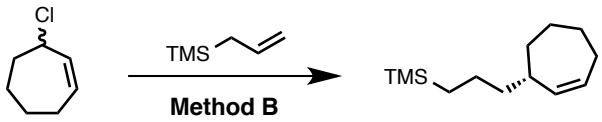
^{13}C NMR:



HPLC traces:



(S)-(–)-3-(Trimethylsilylpropyl)cyclohept-1-ene (3.25)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*R,R*)- Ligand **L1** (19.8 mg, 0.04 mmol, 0.10 eq) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 4-phenyl-1-butene (0.15 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.5 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, 3-chlorocycloheptene (52.3 mg, 0.40 mmol, 1.00 eq) was added dropwise. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (~1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered

and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave the product (70.2 mg, 0.33 mmol) in 83% yield.

GC analysis of crude mixture of epoxides derived from the products indicated an enantiomeric excess of 95% (Hydrodex ß-3P, 50-200°C at 1°C/min, 10psi); major enantiomer t_R = 30.9, 31.1 min; minor enantiomer t_R = 30.5, 31.3 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.81 – 5.70 (m, 1H), 5.60 – 5.50 (m, 1H), 2.20 – 2.01 (m, 2H), 2.00 – 1.74 (m, 1H), 1.72 – 1.47 (m, 3H), 1.45 – 1.34 (m, 2H), 1.34 – 1.27 (m, 3H), 1.27 – 1.14 (m, 2H), 0.56 – 0.39 (m, 2H), 0.005 (s, 9H).

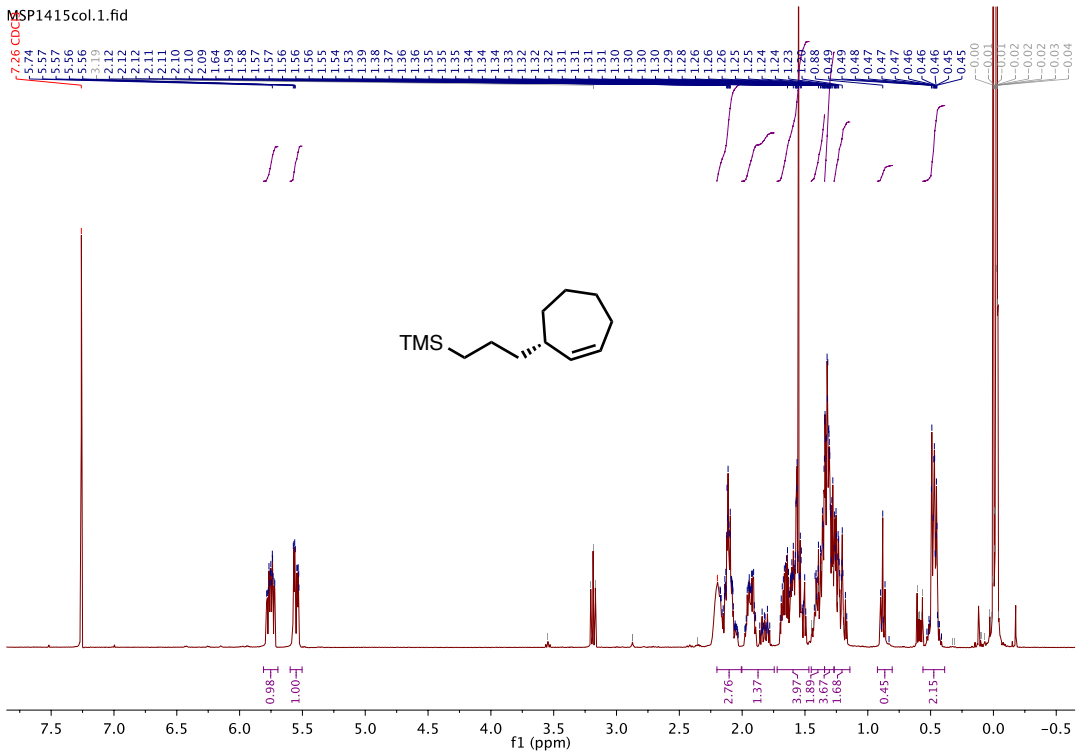
^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 139.9, 132.6, 78.8, 42.7, 42.7, 41.1, 35.2, 32.4, 30.4, 30.4, 28.7, 25.4, 23.2, 18.5.

HRMS (ESI) *m*/z calcd for $C_{13}H_{26}Si$ $[M]^+$: 210.1804, found: 210.1808.

IR (ATR) ν (cm^{-1}, $CHCl_3$): 1613, 2855, 2921.

$[\alpha]^{20}_{589}$ = +19.2 (c=0.41 in $CHCl_3$, 95% ee).

^{1}H NMR:



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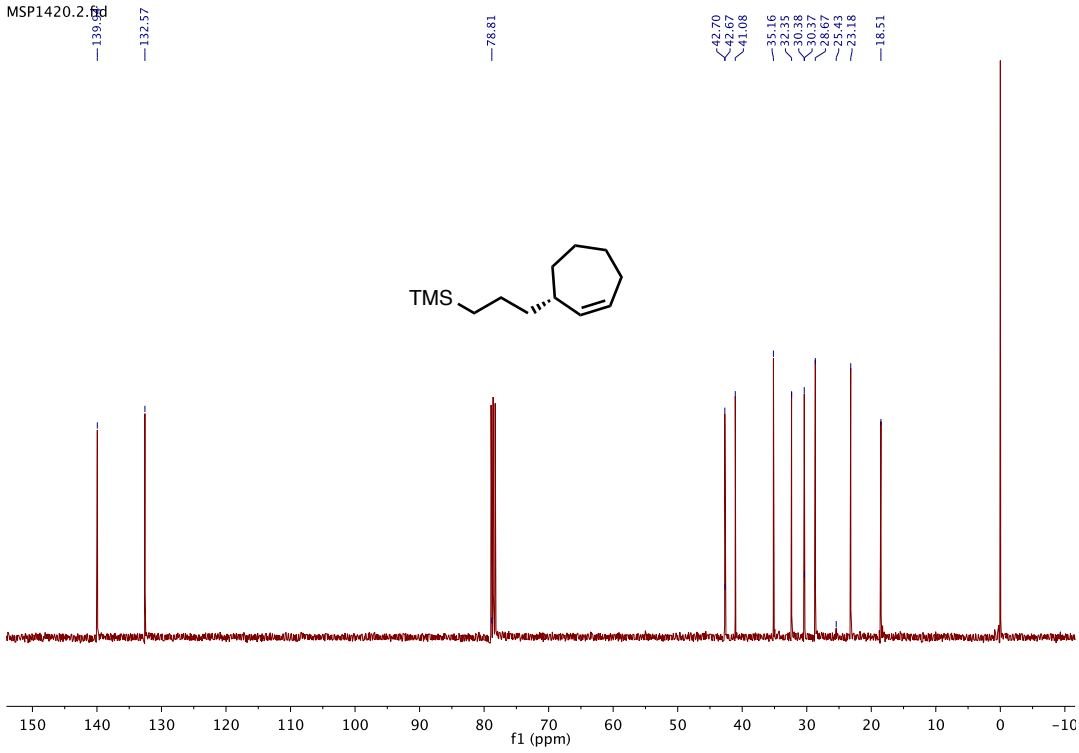
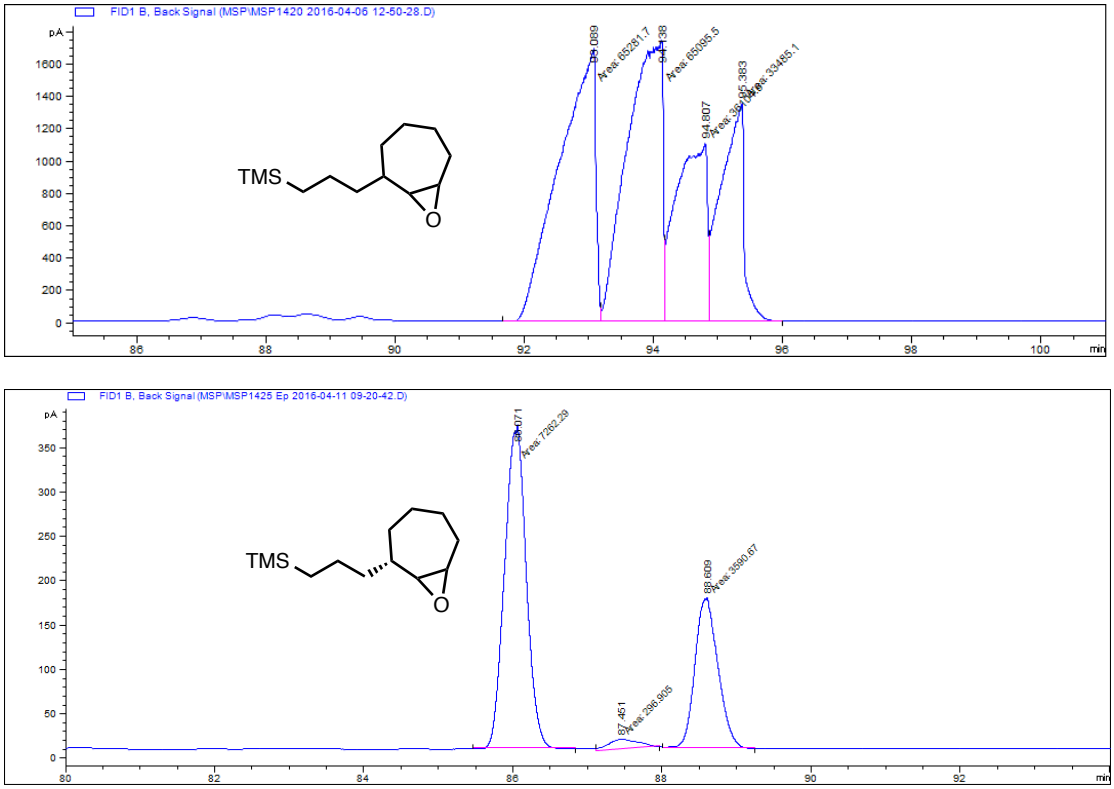
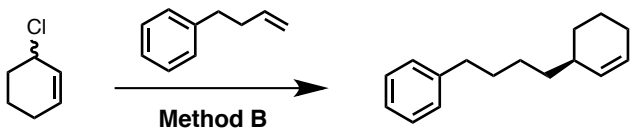


GC traces:



(S)-(4-(cyclohex-2-en-1-yl)butyl)benzene (3.16, Method B)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S*)- Ligand **L16** (19.8 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 4-Phenyl-1-butene (0.15ml, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional

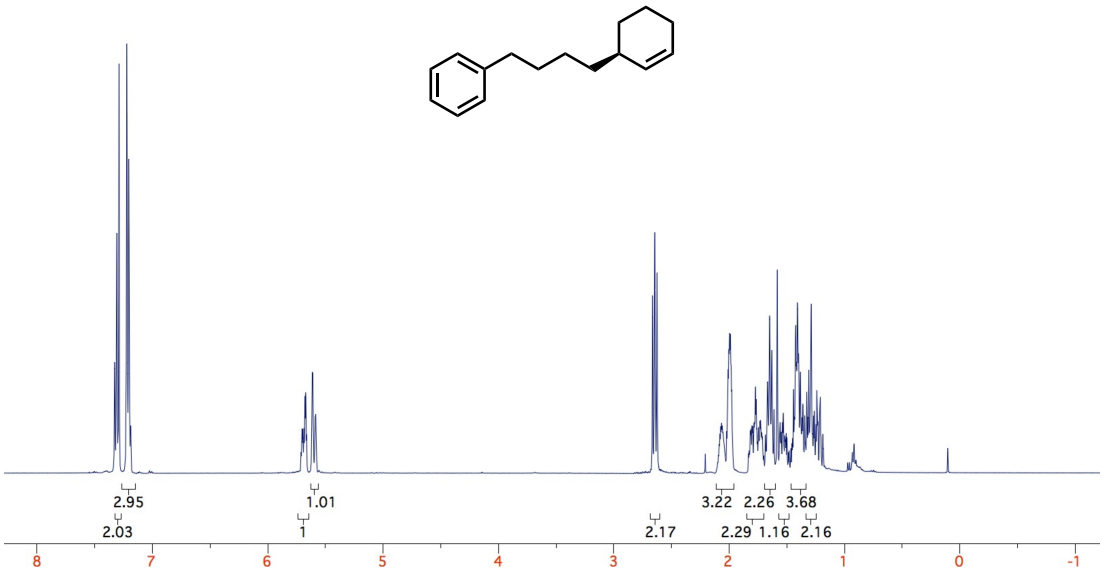
minutes, 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr apparatus (T = 110 °C, 55 mbar) gave (*S*)-(–)-4-(cyclohex-2-en-1-yl) butyl) benzene (61.4 mg, 0.29 mmol) in 72% yield

Enantiomeric excess of 95% was determined by HPLC [Chiralpak® IA; flow: 0.6 mL/min; hexane/i-PrOH: 99.9: 0.1; λ = 210 nm; major enantiomer tR = 8.8 min; minor enantiomer tR = 8.2 min].

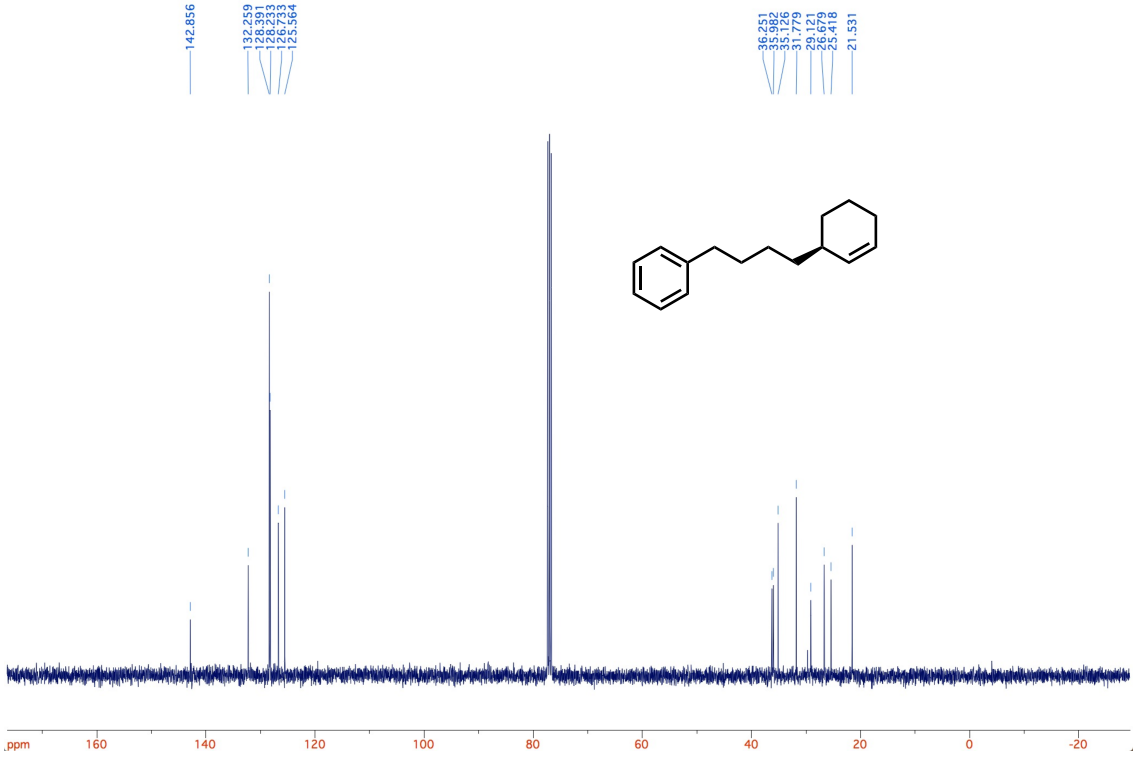
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 1.26 - 1.78 (m, 10 H), 1.99(m, 1 H), 2.07(m, 2 H), 2.62-2.67(m, 2 H), 5.58-5.62 (m, 1 H), 5.67-5.71 (m, 1 H), 7.20- 7.23 (m, 3 H), 7.28 - 7.31 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 21.5, 25.4, 26.7, 29.1, 31.8, 35.1, 35.9, 36.2, 125.6, 126.7, 128.2, 128.4, 132.3, 142.9

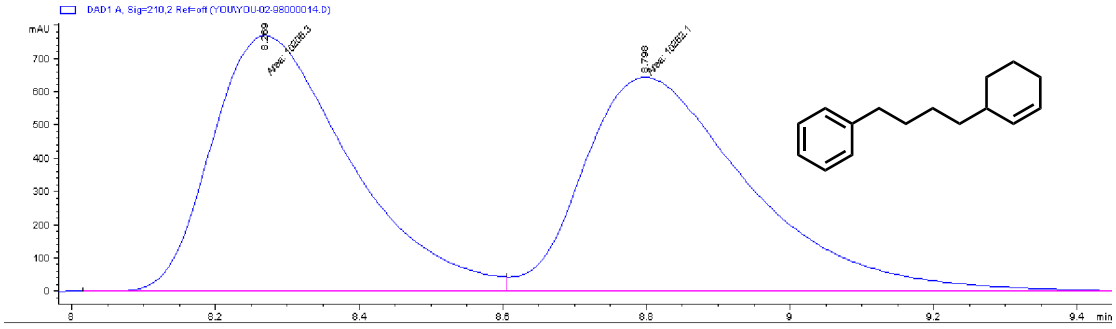
^{1}H NMR:

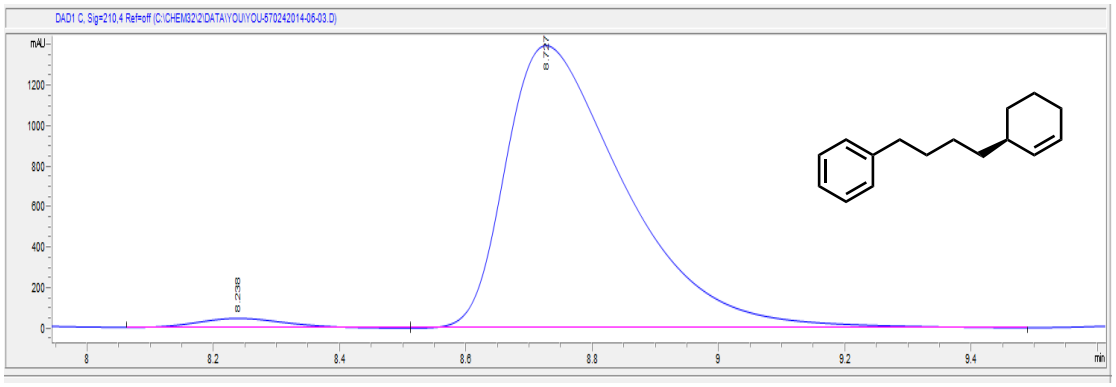


^{13}C NMR:

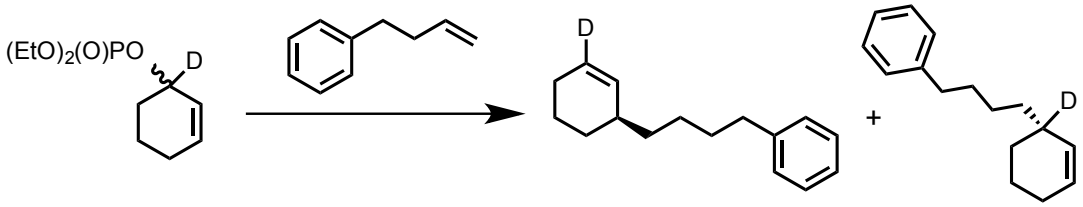


HPLC traces:





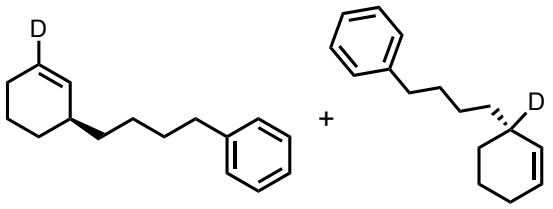
Cu-catalyzed AAA with Deuterated cyclic phosphate (3.26-3.27)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S*)- Ligand **L16** (19.8 mg, 0.04 mmol, 0.10 eq) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 4-Phenyl-1-butene (0.15ml, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.5 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes,

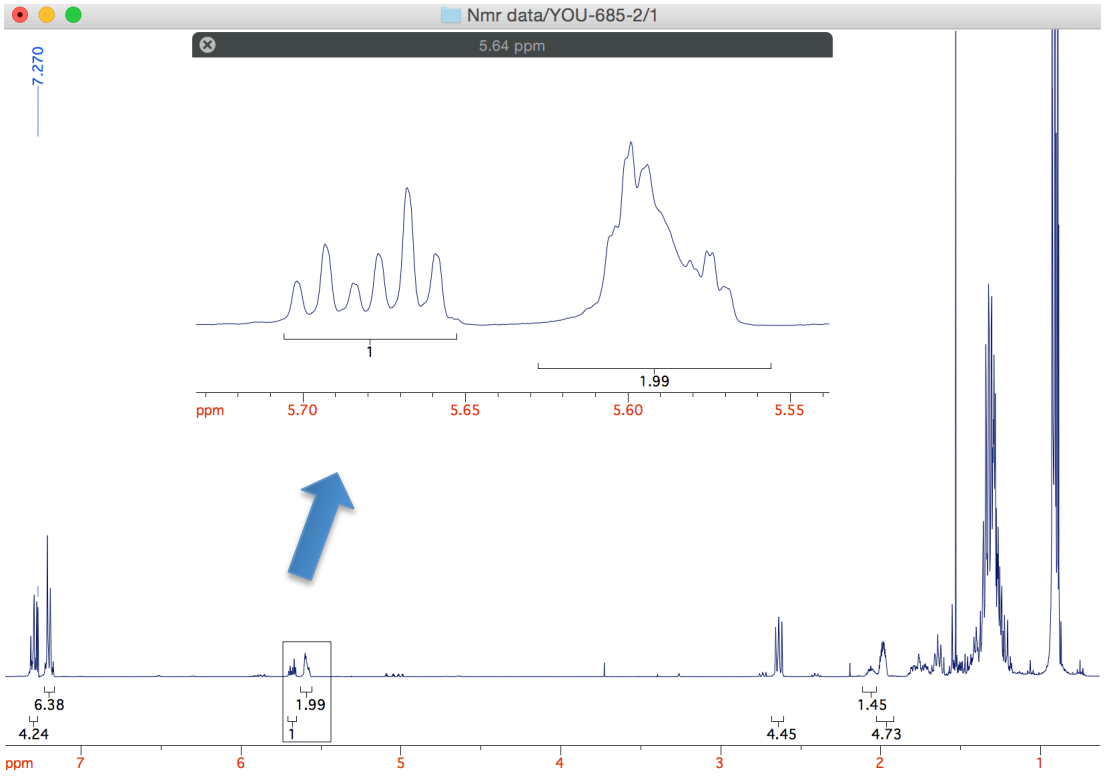
Deuterated cyclohex-2-en-1-yl diethyl phosphate (94.1 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. Then, TMSCl (43.5 mg, 0.40 mmol, 1.00 eq) was injected. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (~1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) and further distillation by Kugelrohr apparatus (T = 110 °C, 55 mbar) gave the products (67.2 mg, 0.31 mmol) in 78% yield.

Enantiomeric excess of overall 89% was determined by HPLC [Chiralpak® IA; flow: 0.6 mL/min; hexane/i-PrOH: 99.9: 0.1; λ = 210 nm; major enantiomer t_R = 8.8 min; minor enantiomer t_R = 8.2 min].

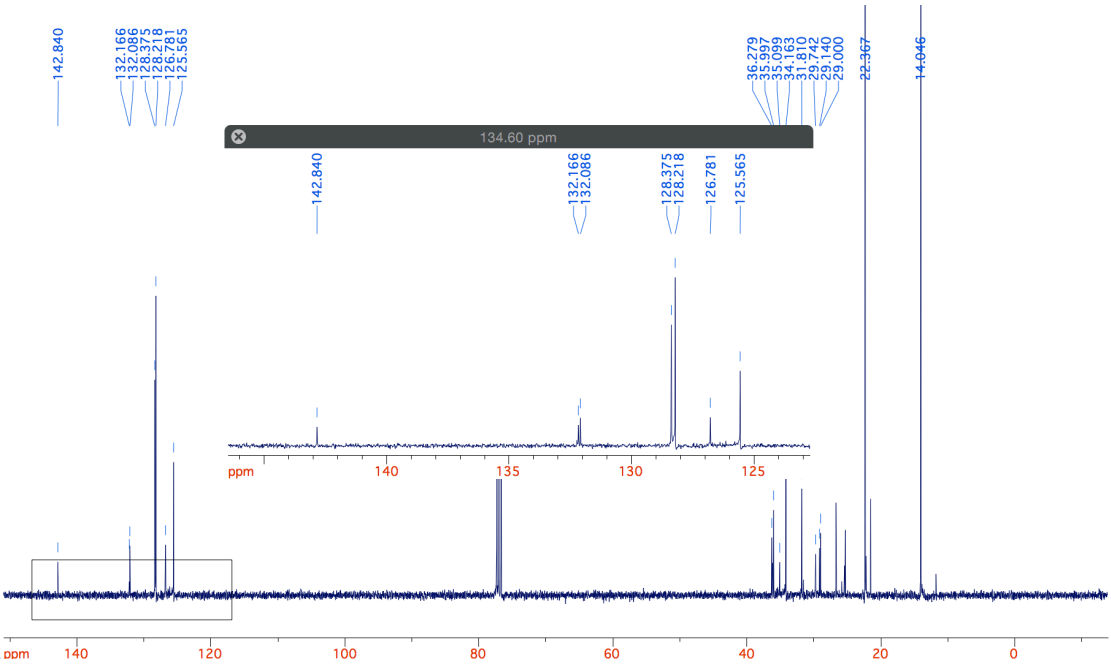


γ/α substitution products ratio, 3.41 : 1

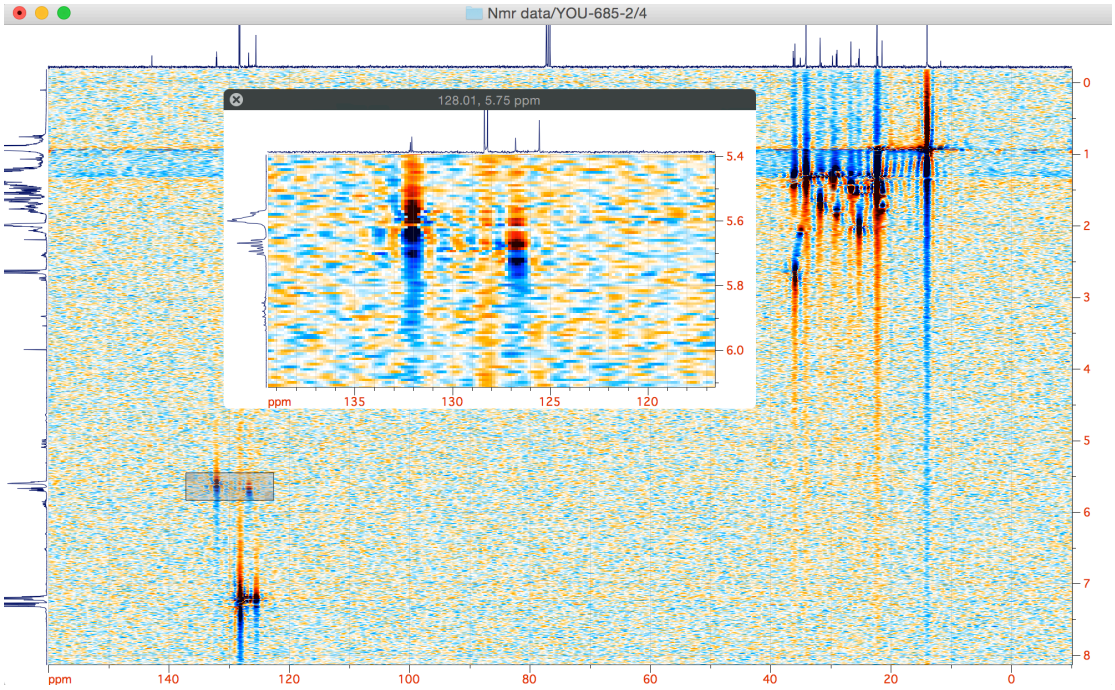
^{1}H NMR:



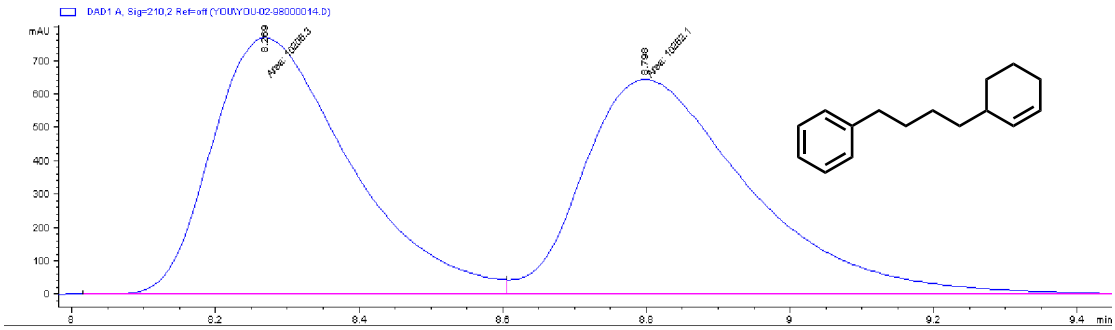
^{13}C NMR:

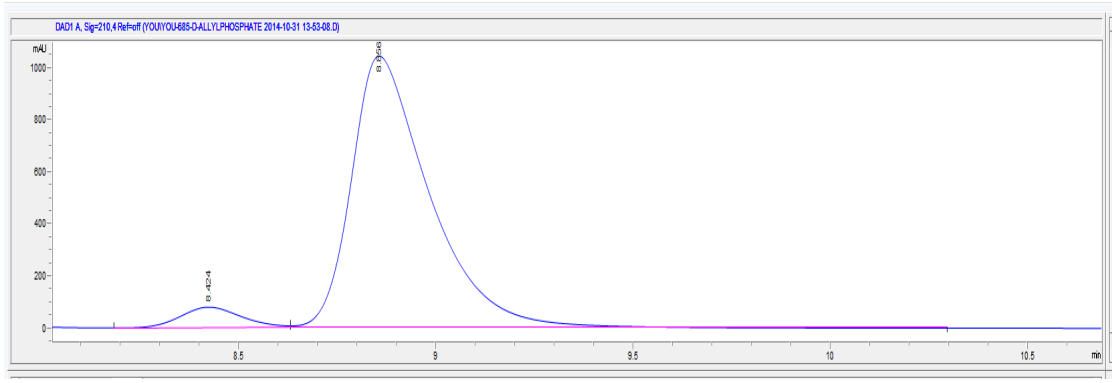


HSQC, NMR:


Nmr data/YOU-685-2/4
128.01, 5.75 ppm
ppm
140
120
100
80
60
40
20
0

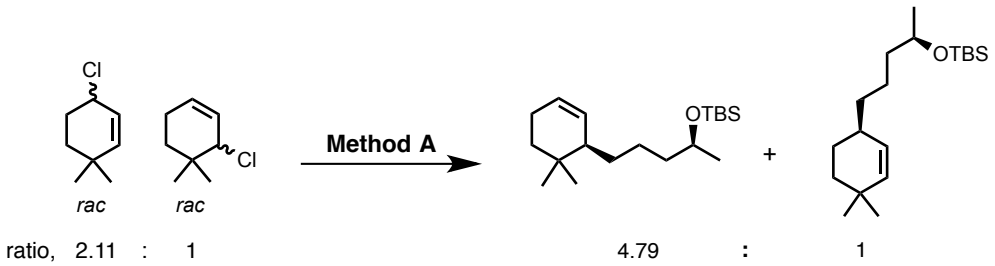
HPLC traces:


DAD1 A, Sig=210,2 Ref=off (YOUYOU-02-98000014.D)
mAU
min

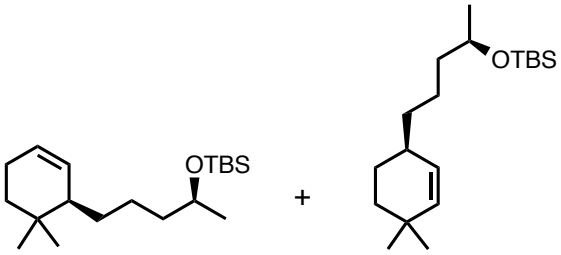

DAD1 A, Sig=210,4 Ref=off (YOUYOU685-D-ALLYLPHOSPHATE 2014-10-31 13-53-08.D)
mAU
min

Cu-catalyzed AAA with non-symmetrical substrates

Method A: chloride system (3.28-3.29)



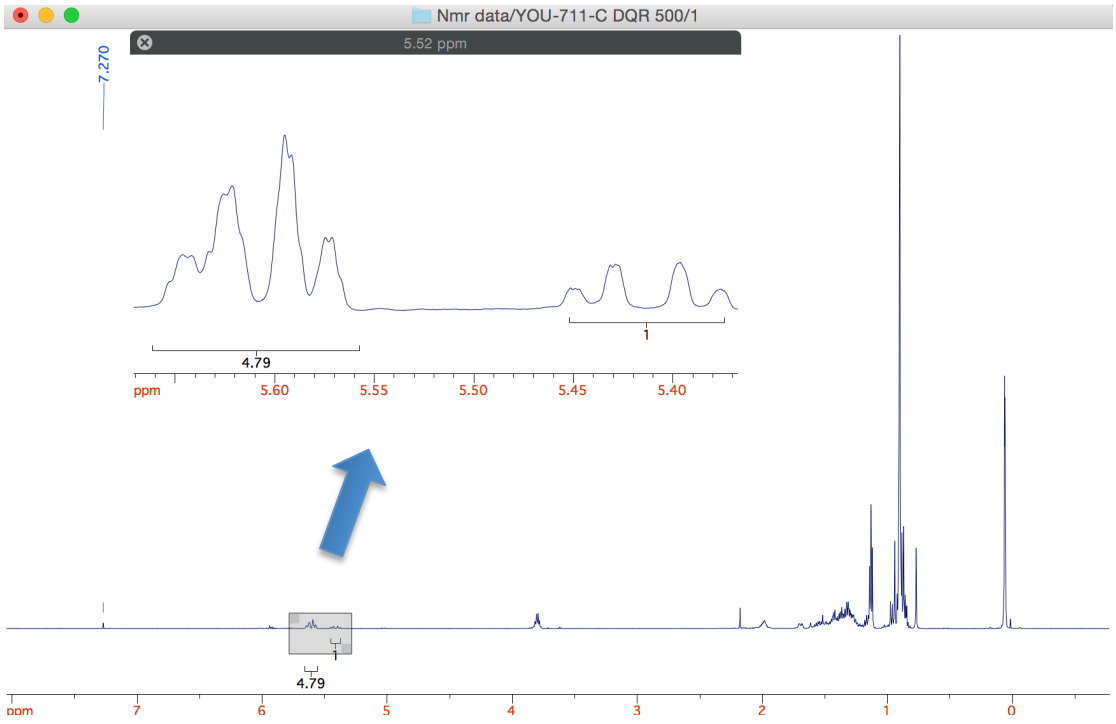
CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S,S*)- Ligand **L1** (21.6 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, (*S*)-tert-butyldimethyl(pent-4-en-2-yloxy)silane (200 mg, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, 4,4-disubstituted cyclic chloride (57.9 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave the mixture products (69.6 mg, 0.22 mmol) in 56% yield.



Ratio selectivity, 4.79 : 1

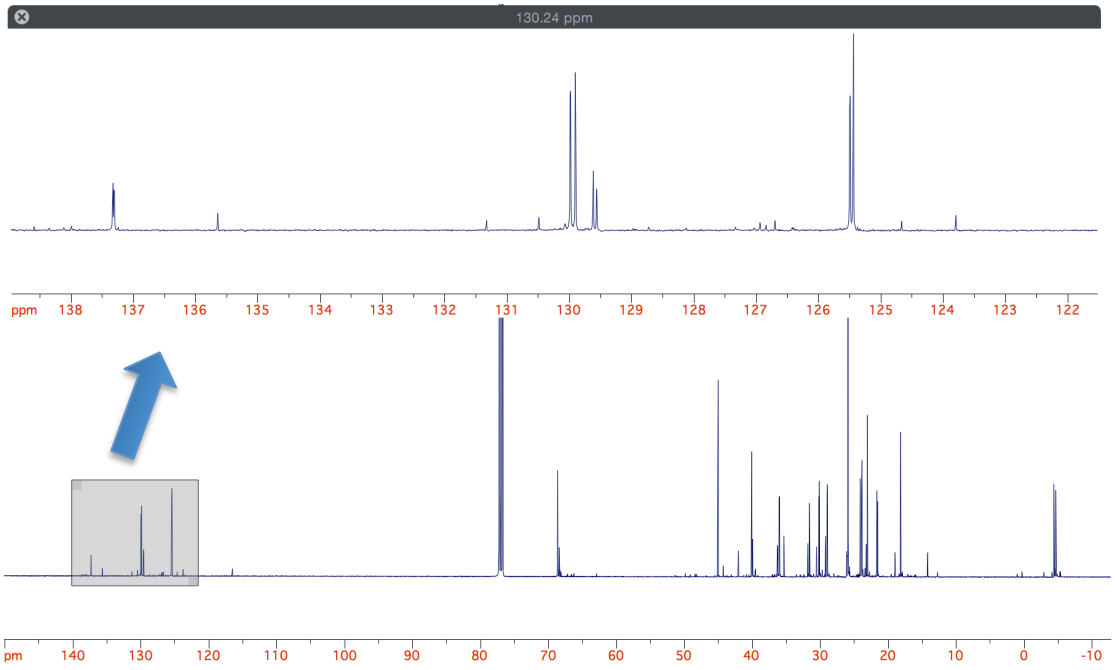
Diastereo selectivity, 51% ; 18%

^{1}H NMR:

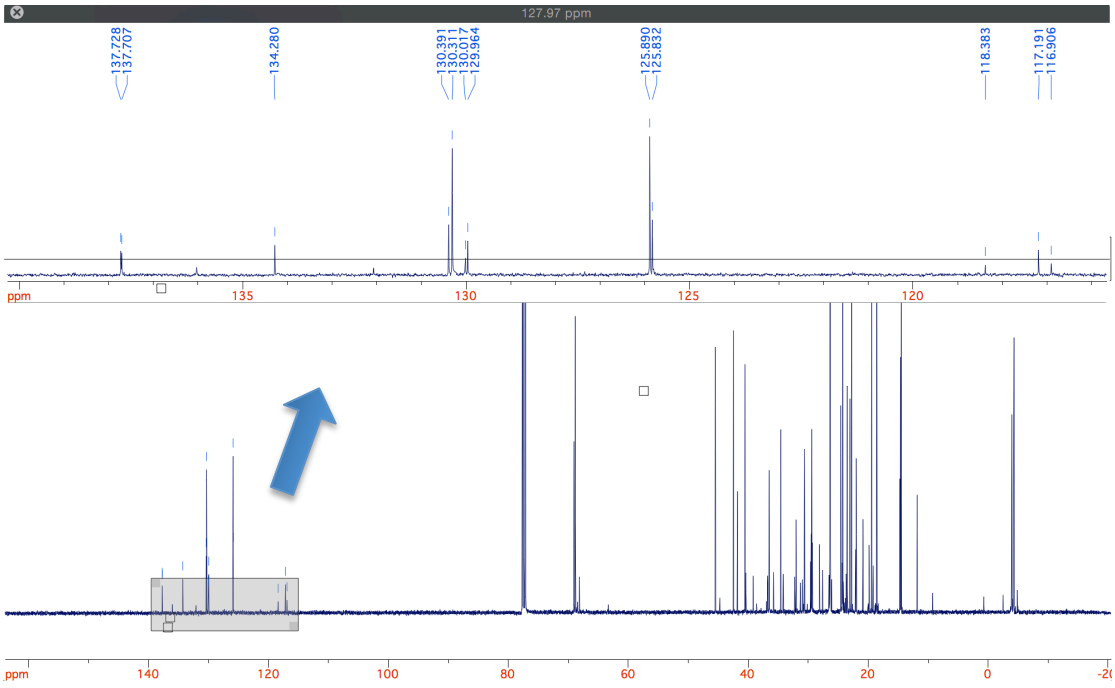


^{13}C NMR:

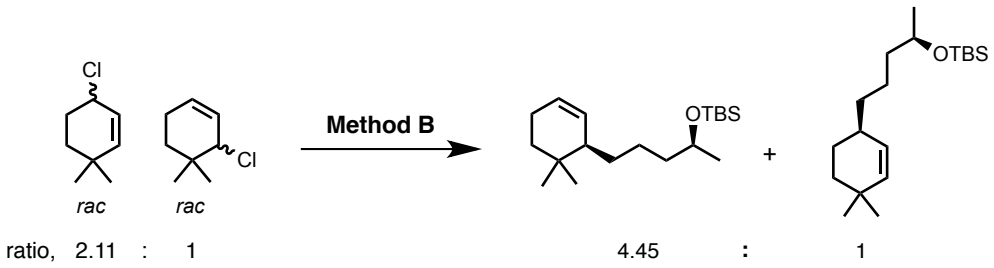
Racemic,


130.24 ppm
ppm 138 137 136 135 134 133 132 131 130 129 128 127 126 125 124 123 122
pm 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

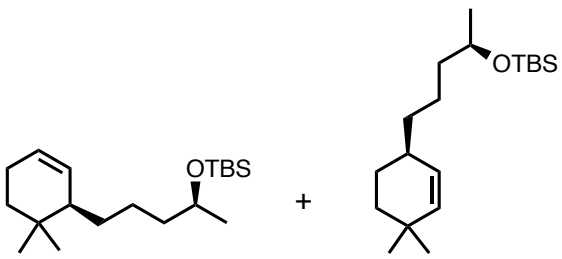
Asymmetric,


127.97 ppm
137.728
137.707
134.280
130.391
130.311
130.017
129.964
125.890
125.832
118.383
117.191
116.906
ppm 135 130 125 120
ppm 140 120 100 80 60 40 20 0

Method B: chloride system (3.28-3.29)



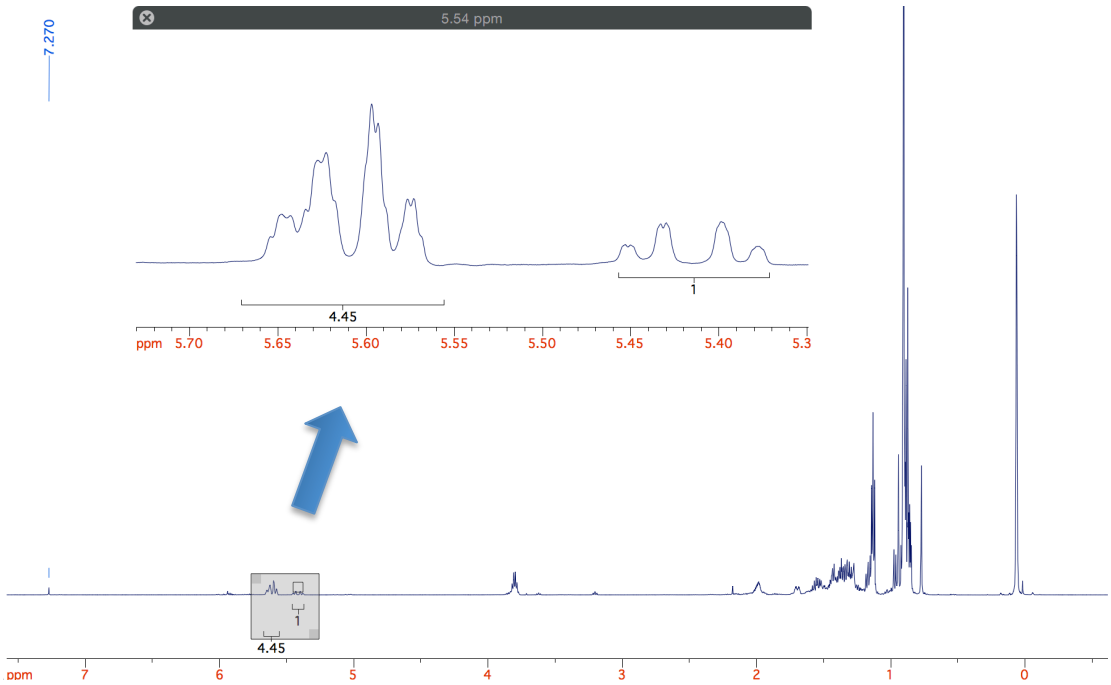
CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S*)- Ligand **L16** (19.8 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, (*S*)-tert-butyldimethyl(pent-4-en-2-yloxy)silane (200 mg, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, 4,4-disubstituted cyclic chloride (57.9 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave the mixture products (53.5 mg, 0.17 mmol) in 43% yield.



Ratio selectivity, 4.45 : 1

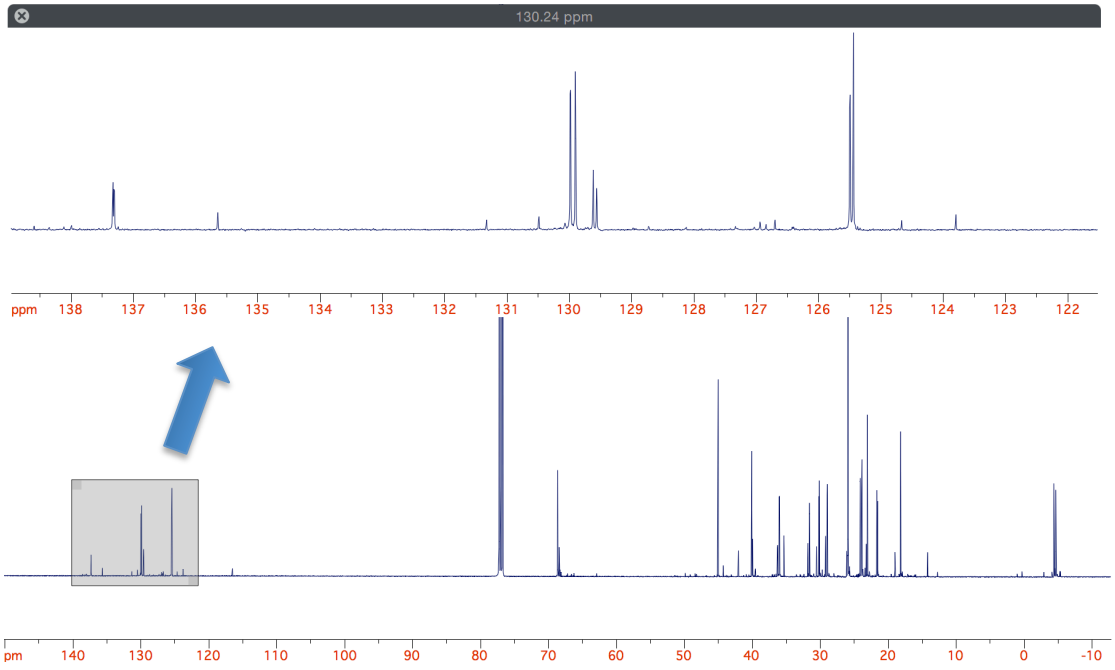
Diastereo selectivity, 72% ; 53%

^{1}H NMR:

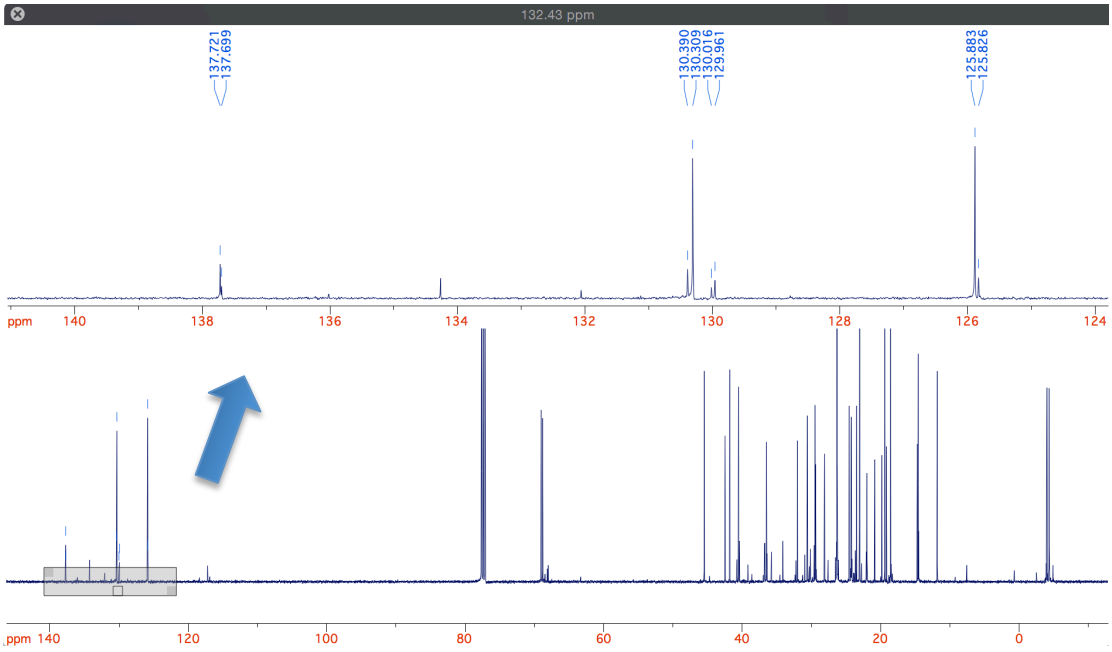


^{13}C NMR:

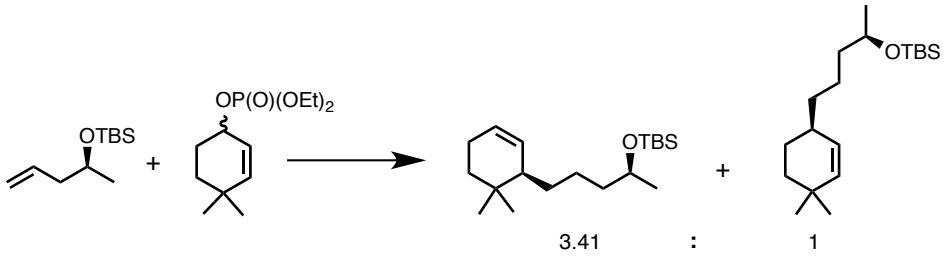
Racemic:



Asymmetric:

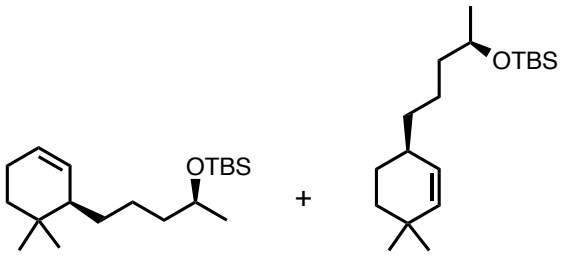


Method C: phosphate system (3.28-3.29)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S*)- Ligand **L16** (19.8 mg, 0.04 mmol, 0.10 eq) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, (*S*)-tert-butyldimethyl(pent-4-en-2-yloxy)silane (200 mg, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.5 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution. The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, 4,4-dimethylcyclohexenyl diethyl phosphate (105 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. Then, TMSCl (43.5 mg, 0.40 mmol, 1.00 eq) was injected. The reaction

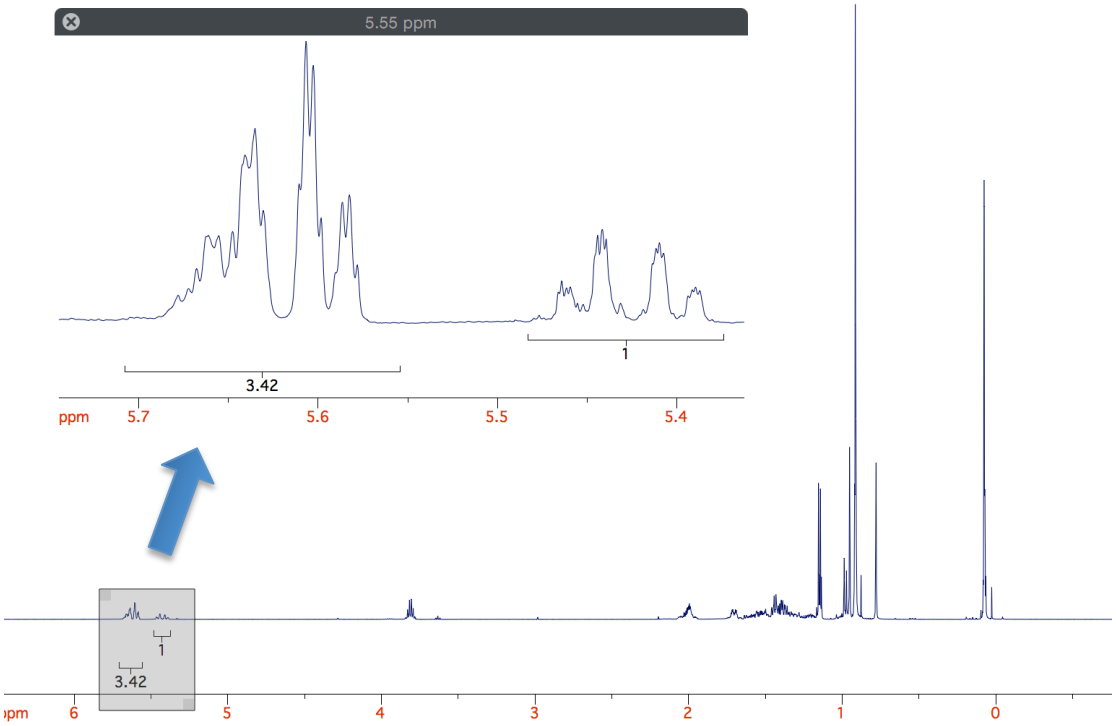
was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (~1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave the product (79 mg, 0.25 mmol) in 83% yield.



Ratio selectivity, 3.41 : 1

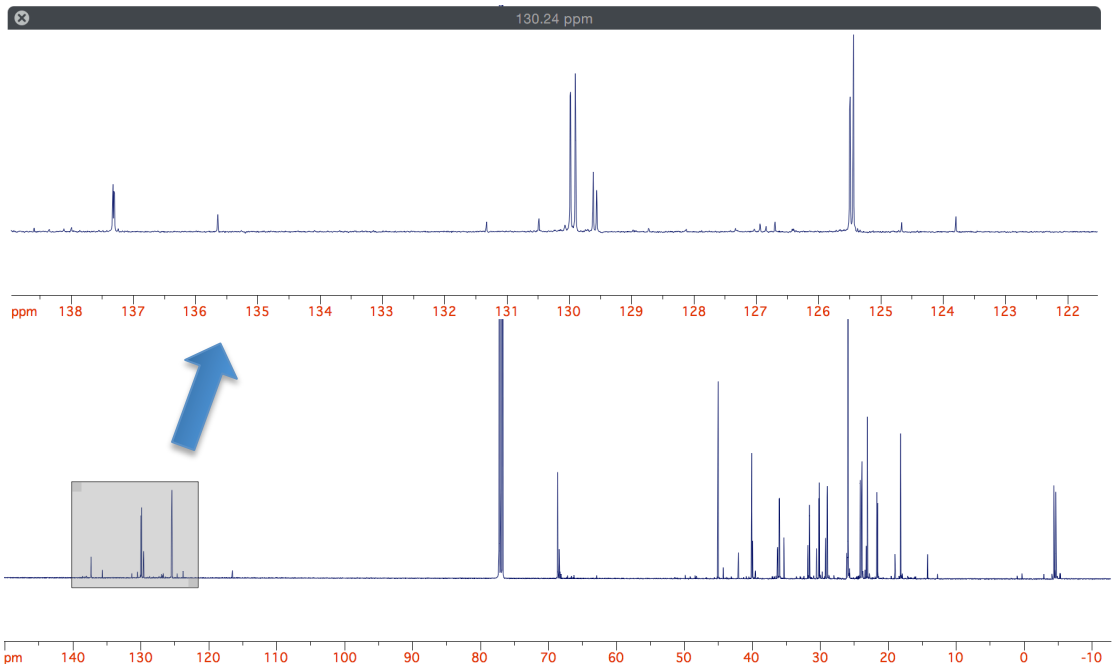
Diastereo selectivity, 61% ; 33%

^{1}H NMR:

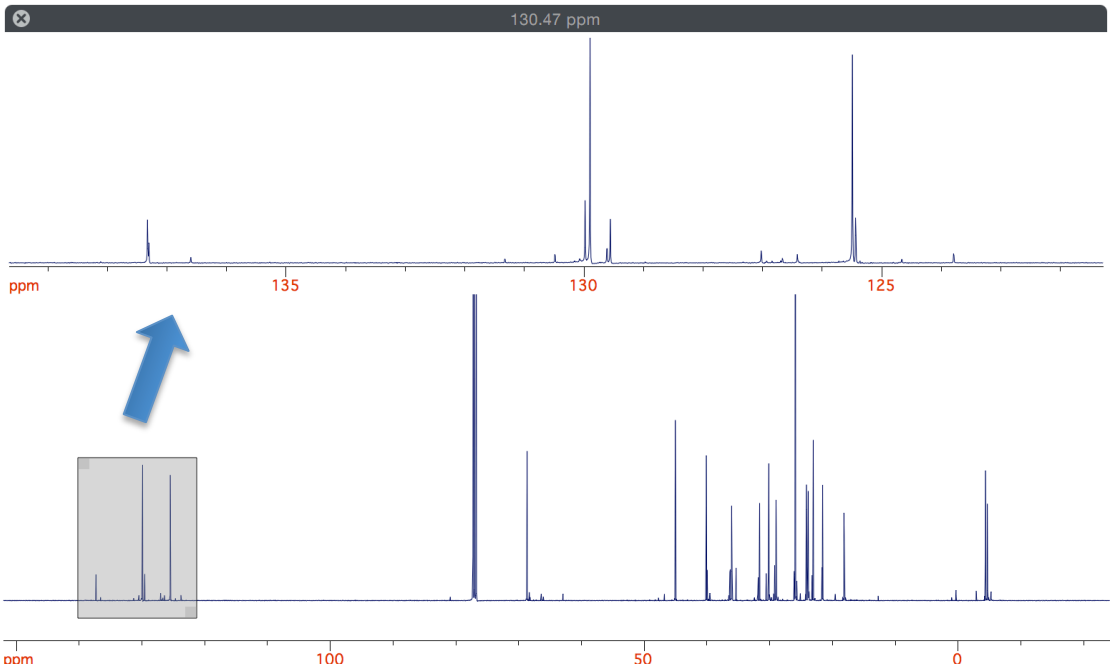


^{13}C NMR:

Racemic,

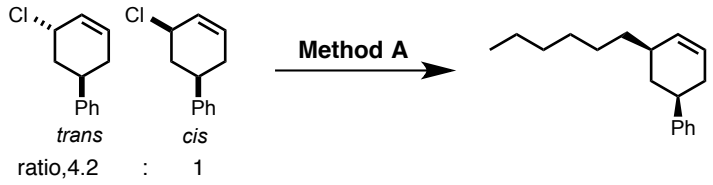


Asymmetric,



Cu-catalyzed AAA with 5-phenol substituted substrates

Method A: chloride system (3.30)



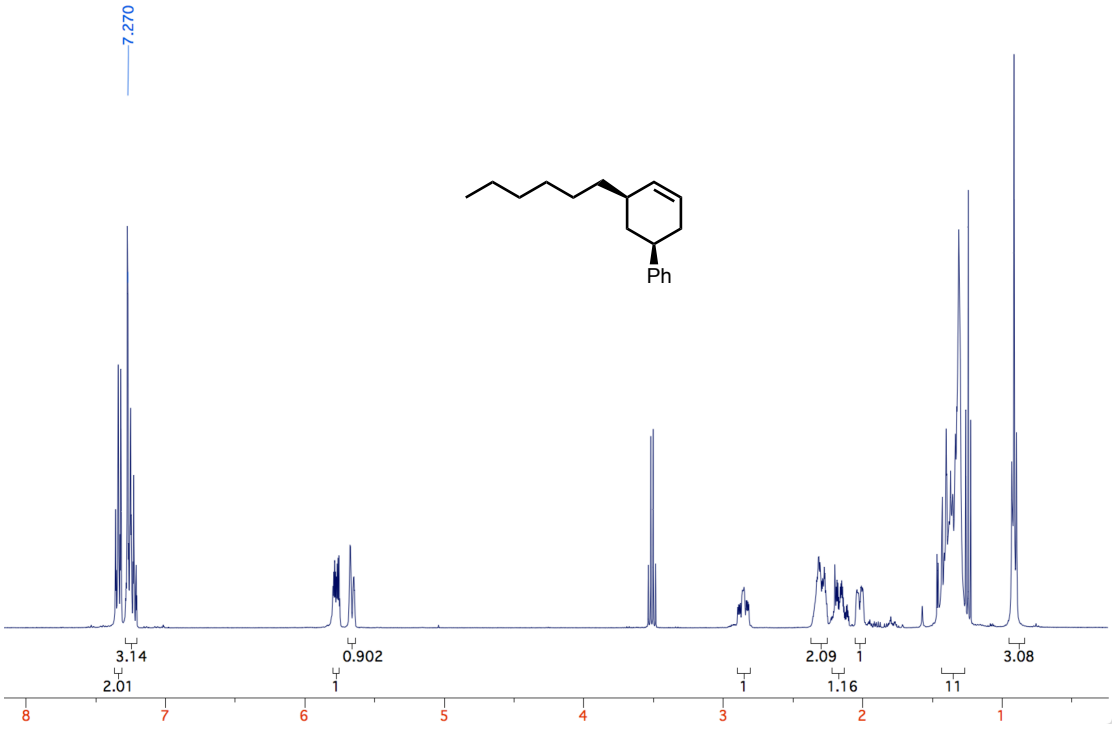
CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S,S*)- Ligand **L1** (21.6 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 1-hexene (0.12 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, 5-substituted cyclic chloride (77.1 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave the product (64.1 mg, 0.26 mmol) in 66% yield.

Enantiomeric excess of 95% was determined by HPLC [Chiralpak® IE; flow: 0.3 mL/min; hexane ; λ = 210 nm; major enantiomer t_R = 22.3 min; minor enantiomer t_R = 18.7, 21.7 min].

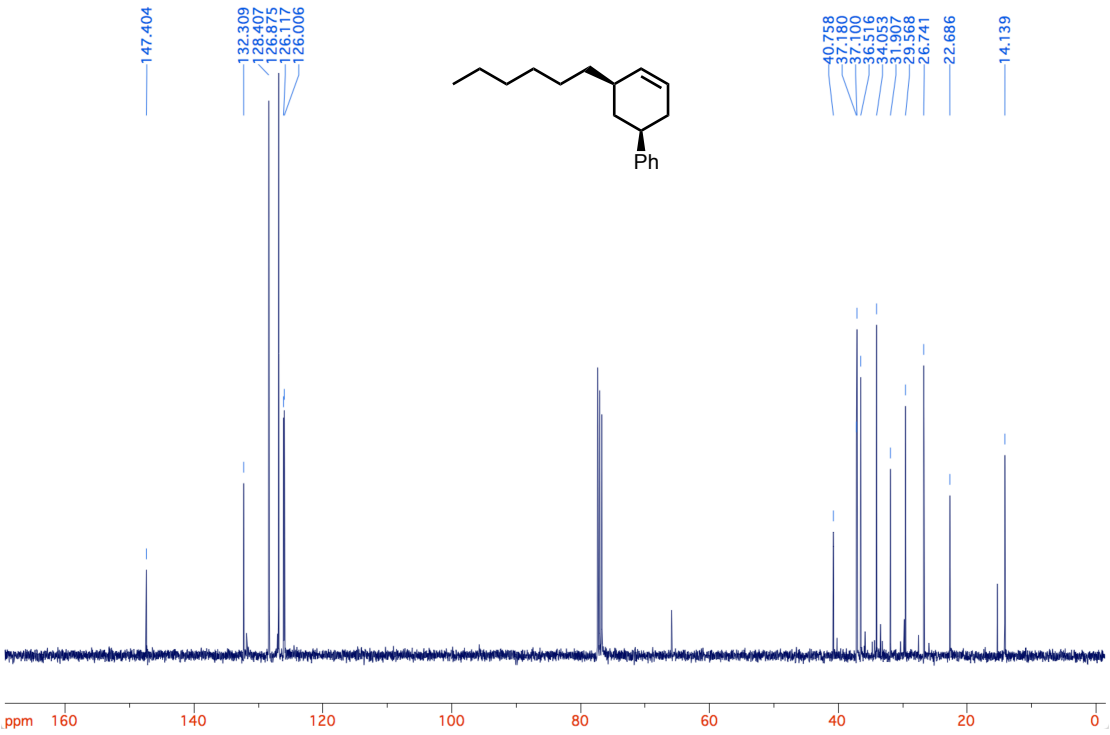
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 7.31-7.36 (m, 2 H), 7.21-7.28 (m, 3 H), 5.75-5.80 (m, 1 H), 5.65-5.68 (m, 1 H), 2.82-2.90 (m, 1 H), 2.26-2.36 (m, 2 H), 2.13-2.22 (m, 1 H), 1.99-2.05 (m, 1 H), 1.31-1.43 (m, 11 H), 0.92 (m, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 14.1, 22.7, 26.7, 29.6, 31.9, 34.1, 36.5, 37.1, 37.2, 40.8, 126.0, 126.1, 126.9 (2C), 128.4 (2C), 132.3, 147.4.

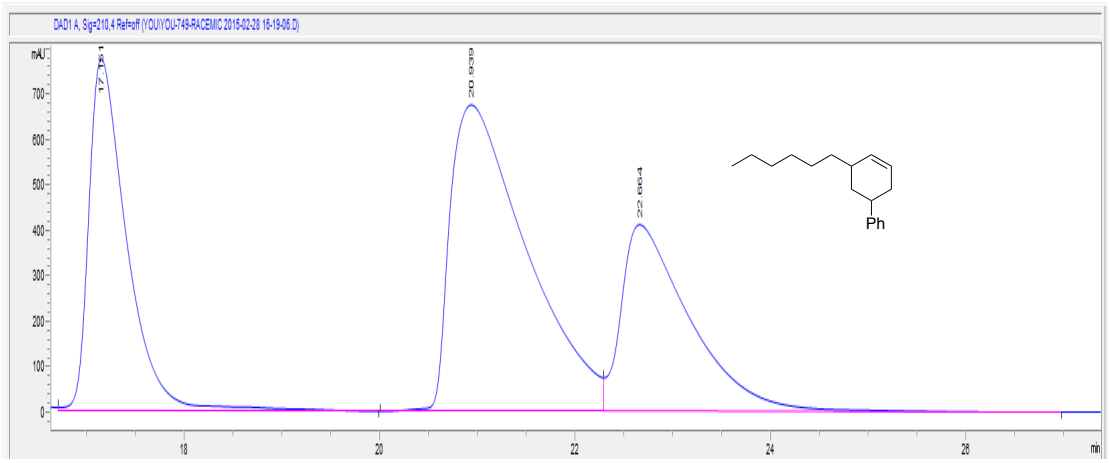
^{1}H NMR:



^{13}C NMR:


147.404
132.309
128.407
126.875
126.117
126.006
40.758
37.180
37.100
36.516
34.053
31.907
29.568
26.741
22.686
14.139
Ph
ppm 160 140 120 100 80 60 40 20 0

HPLC traces: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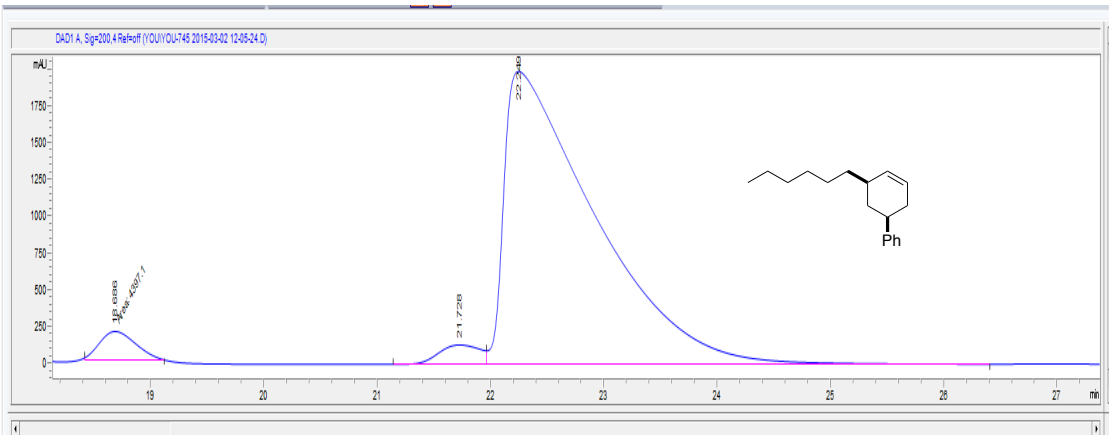
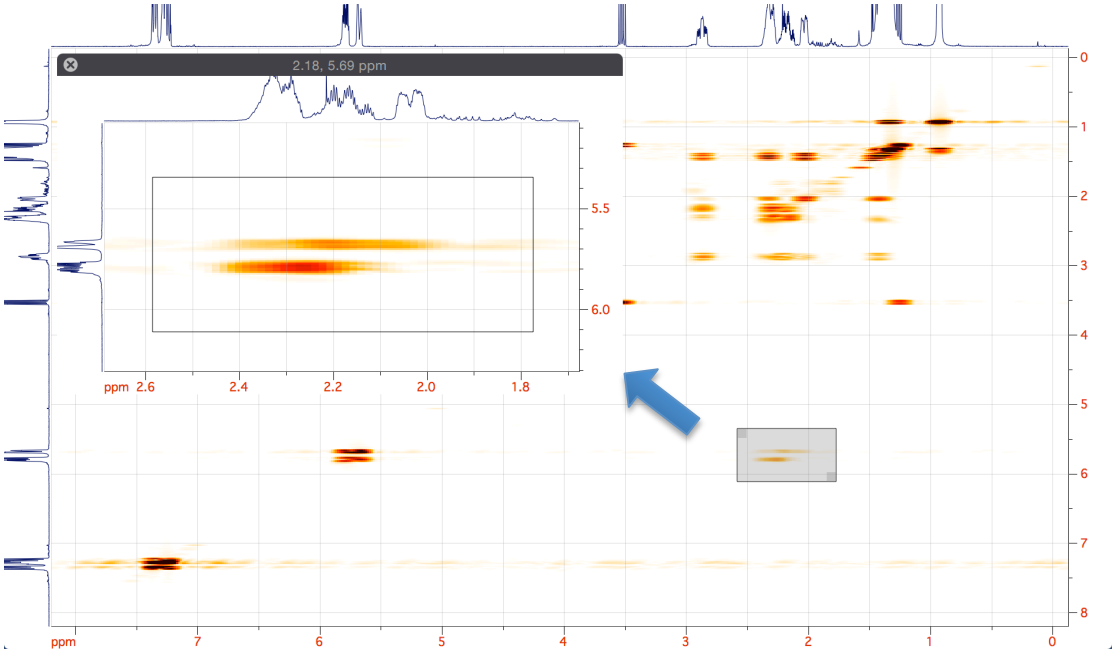
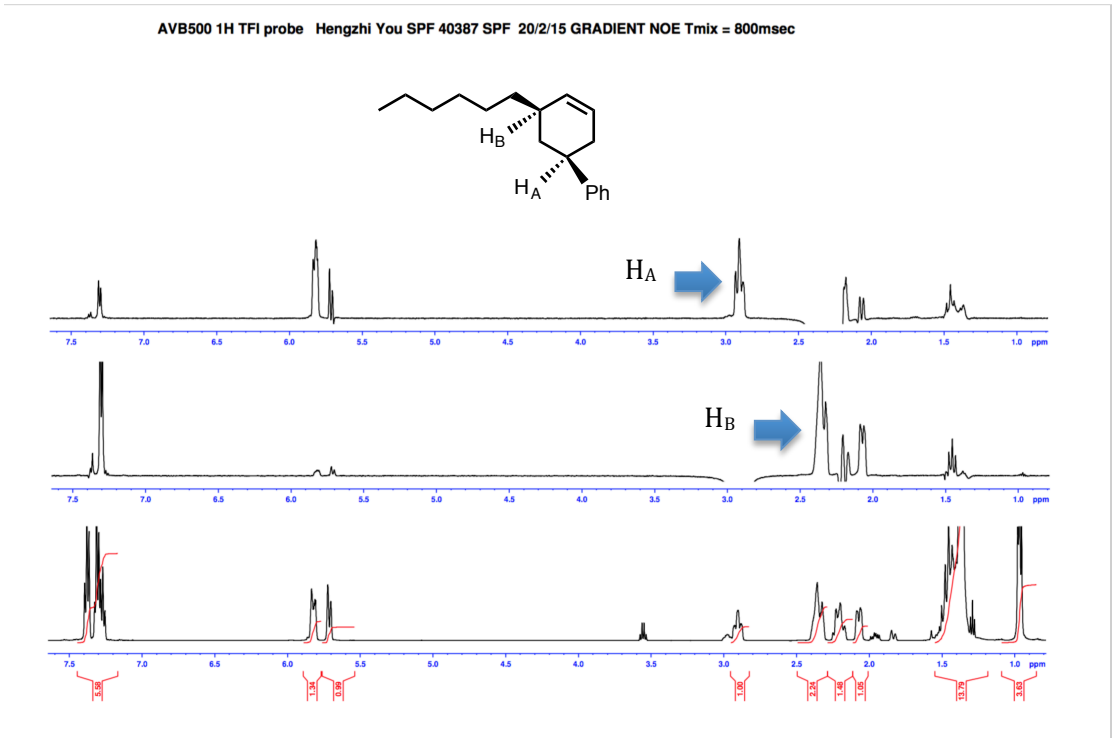
mAU
17.961
20.939
22.664
Ph
18 20 22 24 26 min


DAD1 A, Sig=200,4 Ref=off (YOUYOU-745 2015-03-02 12-05-24.D)
mAU
18.686
19.487
21.729
22.749
Ph
19 20 21 22 23 24 25 26 27 min

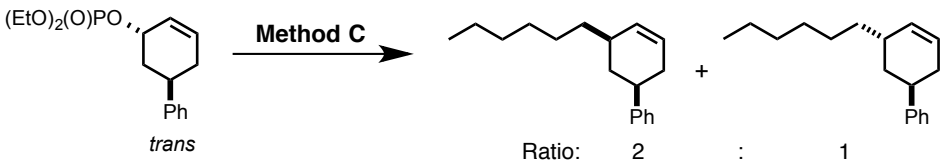
COSY, NMR:



NOESY, NMR:

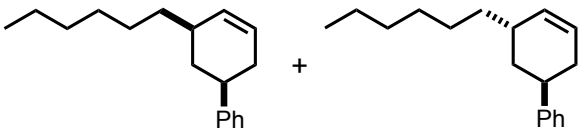


Method C: *trans*-phosphate system (3.30 -3.31)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S*)- Ligand **L16** (19.8 mg, 0.04 mmol, 0.10 eq) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 1-hexene (0.12 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.5 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution. The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, *trans*-5-substituted cyclic phosphate (124.2 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. Then, TMSCl (43.5 mg, 0.40 mmol, 1.00 eq) was injected. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (~1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave the products (79.5 mg, 0.33 mmol) in 82% yield.

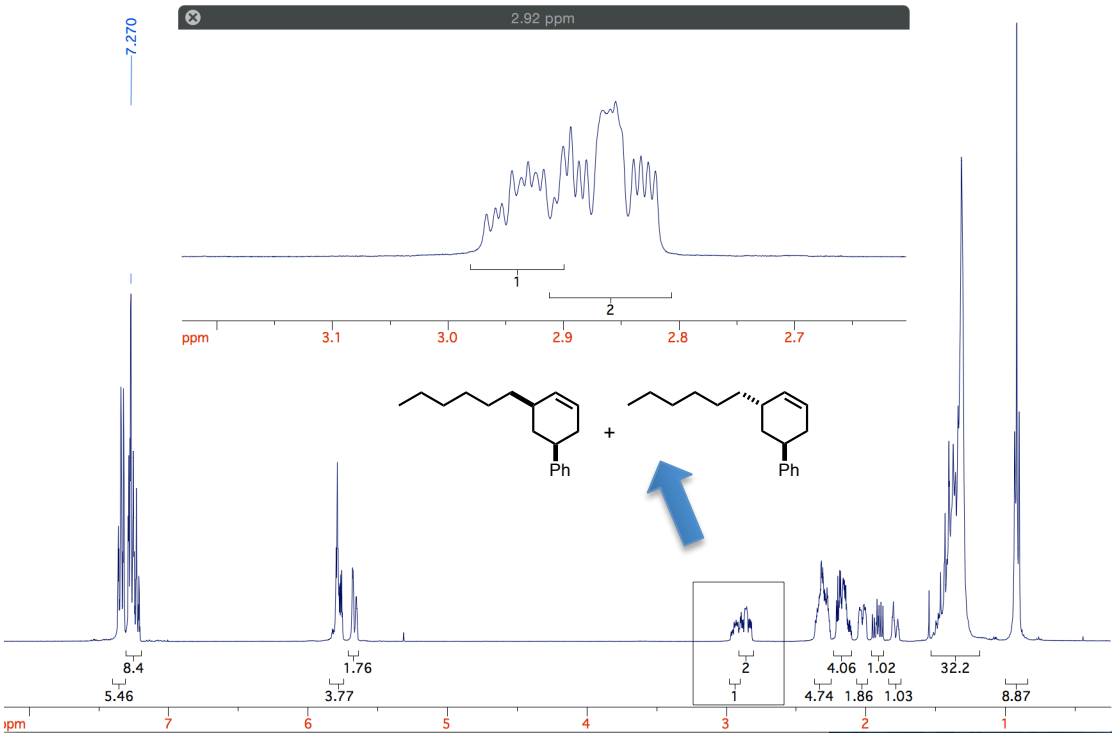
Enantiomeric excess was determined by HPLC [Chiralpak® IE; flow: 0.3 mL/min; hexane ; λ = 210 nm; major enantiomer t_R = 20.1 min; minor enantiomer t_R = 16.8, 22.1 min].



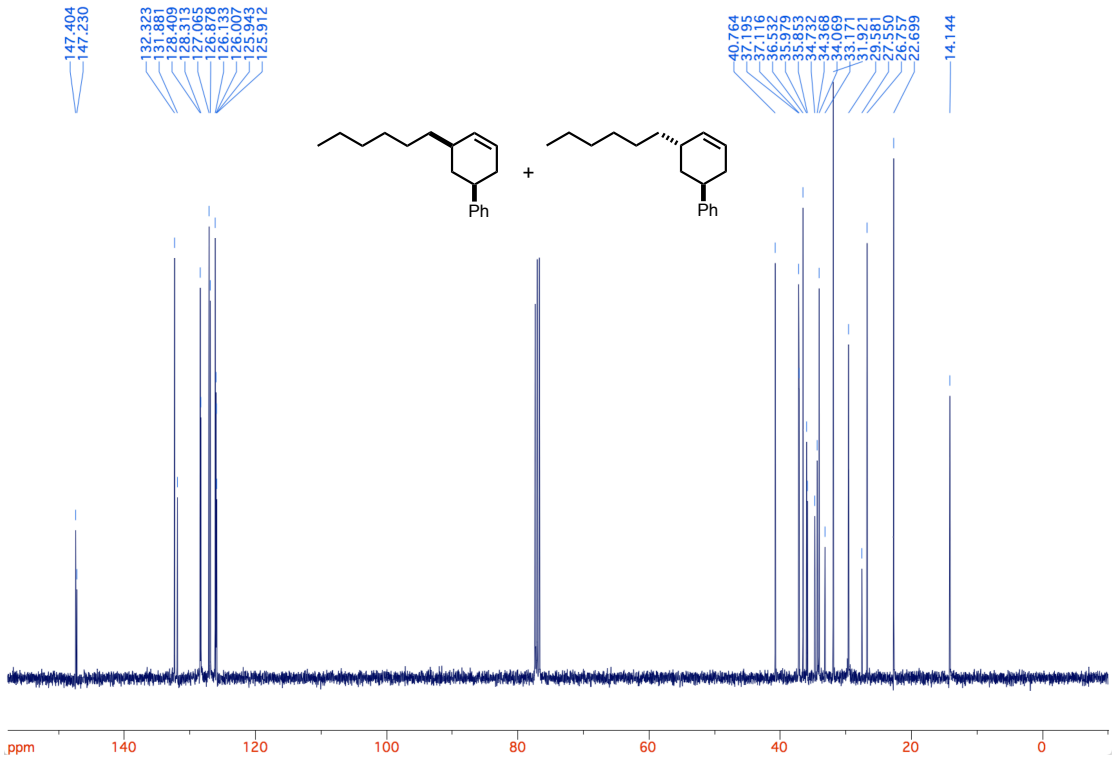
Ratio selectivity, 2 : 1

Enantioselectivity, 44% ; 19%

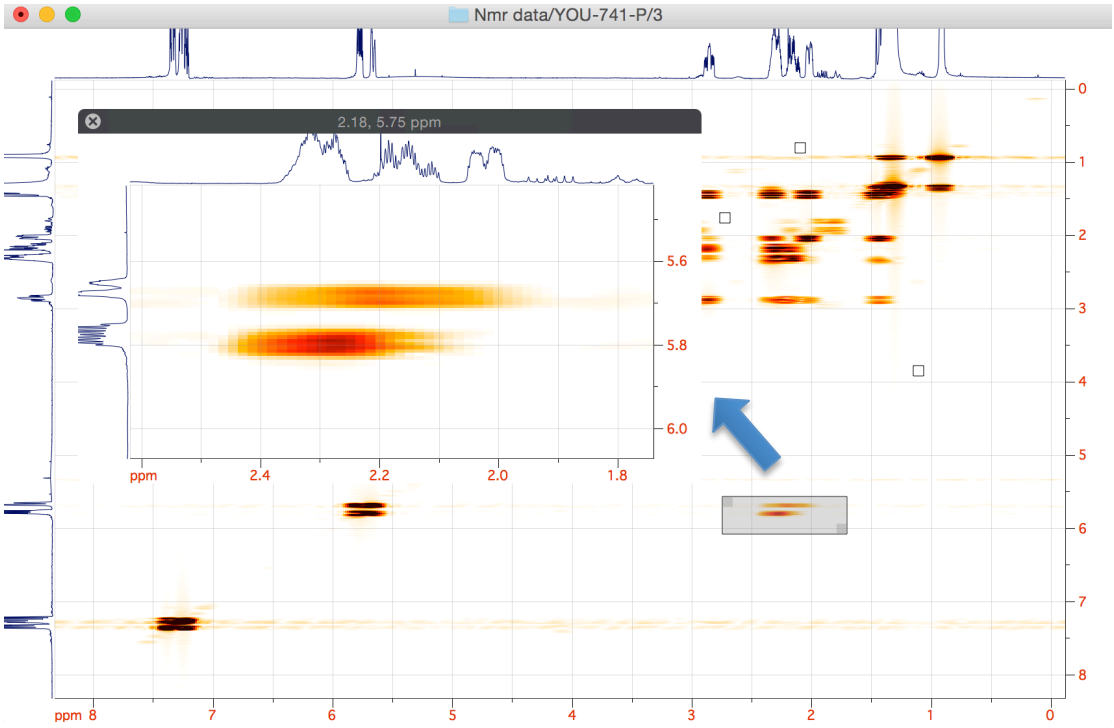
^{1}H NMR ($CDCl_3$):



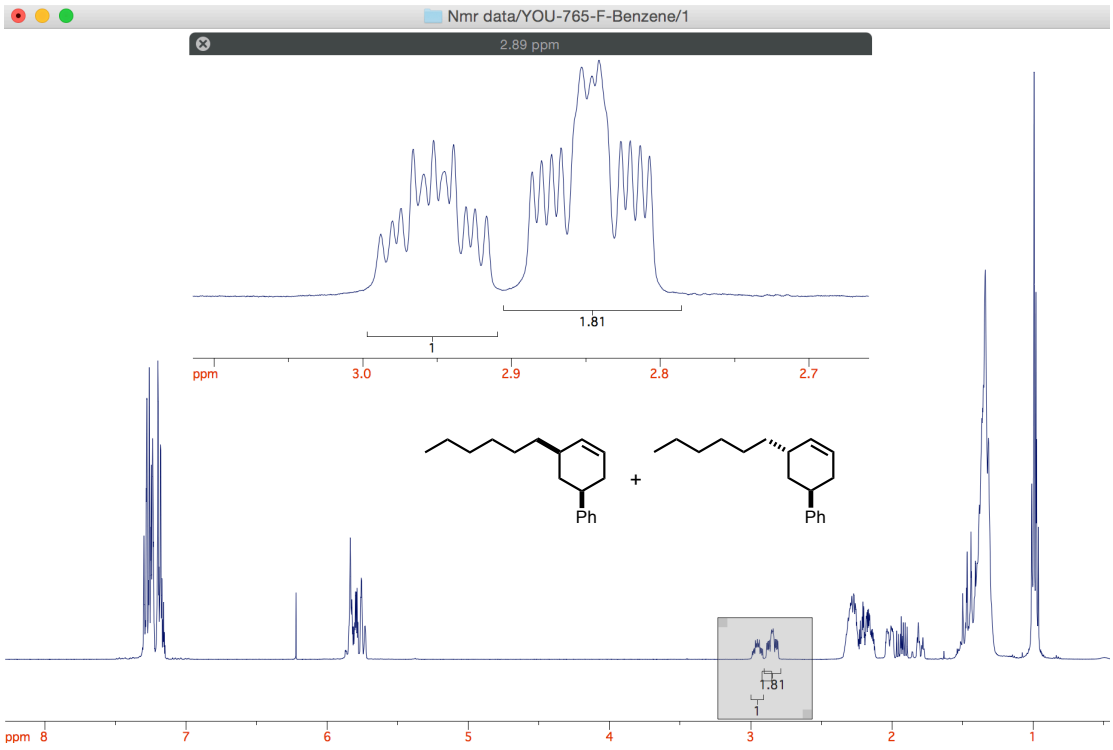
^{13}C NMR ($CDCl_3$):



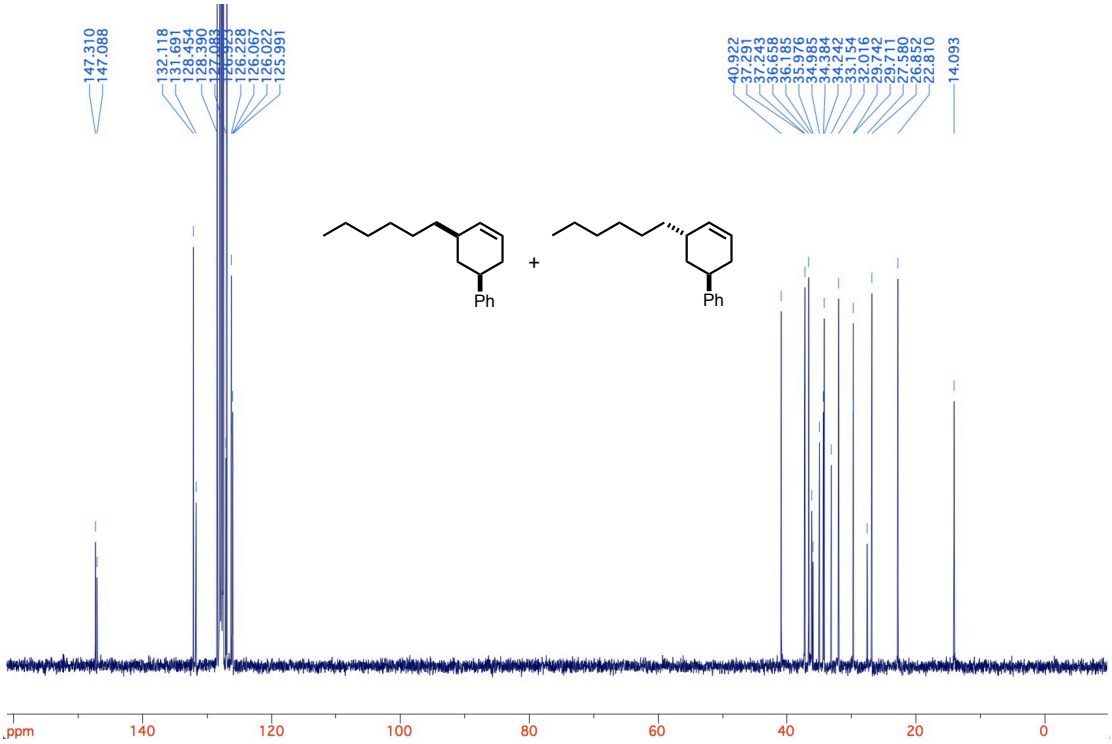
COSY, NMR ($CDCl_3$):



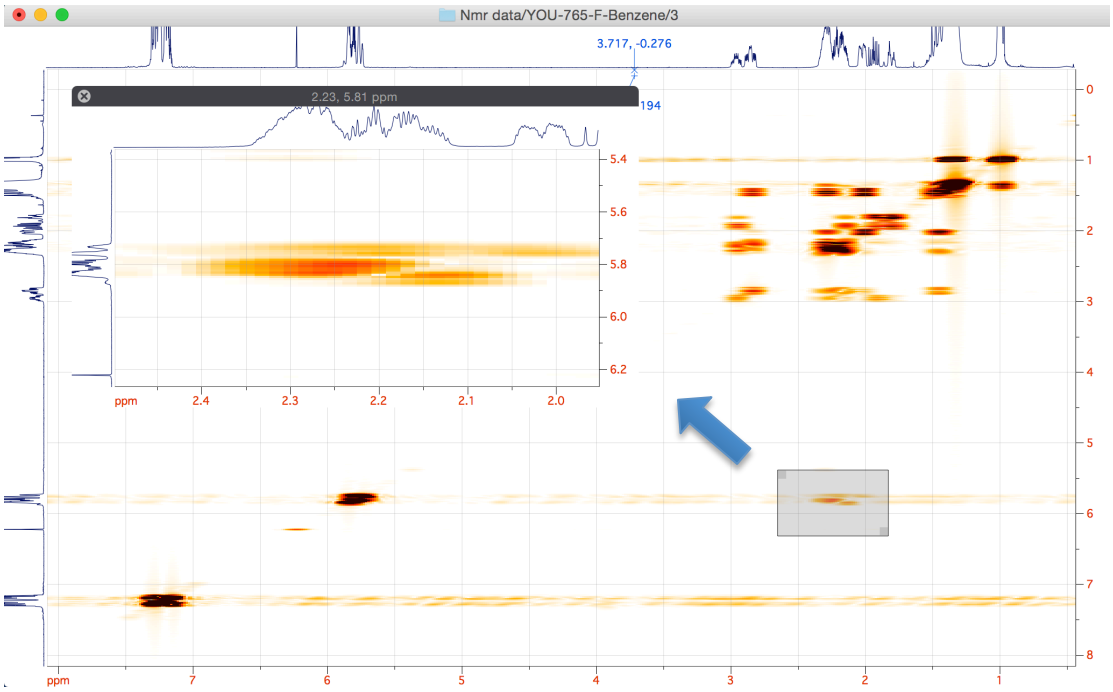
^{1}H NMR (Benzene-d6),



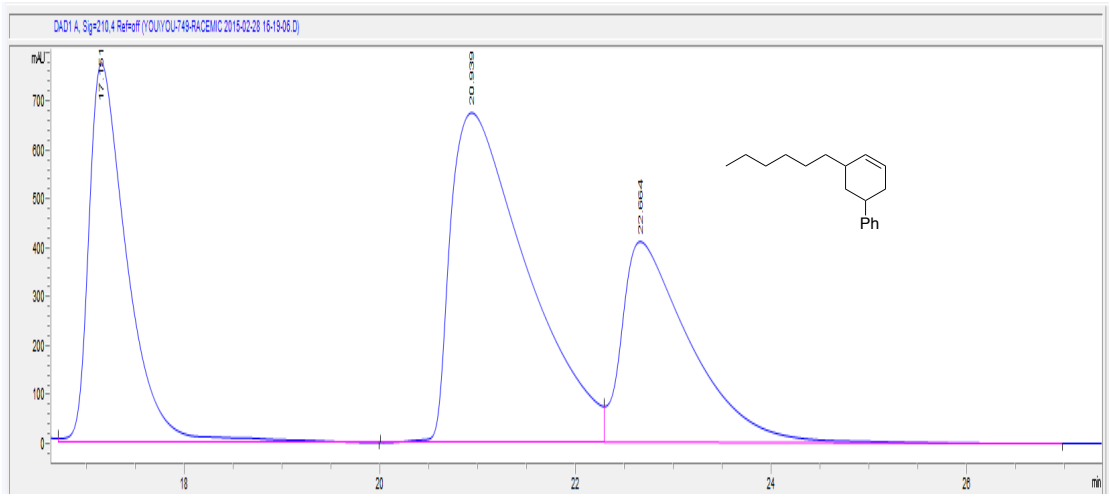
^{13}C NMR (Benzene-d6),

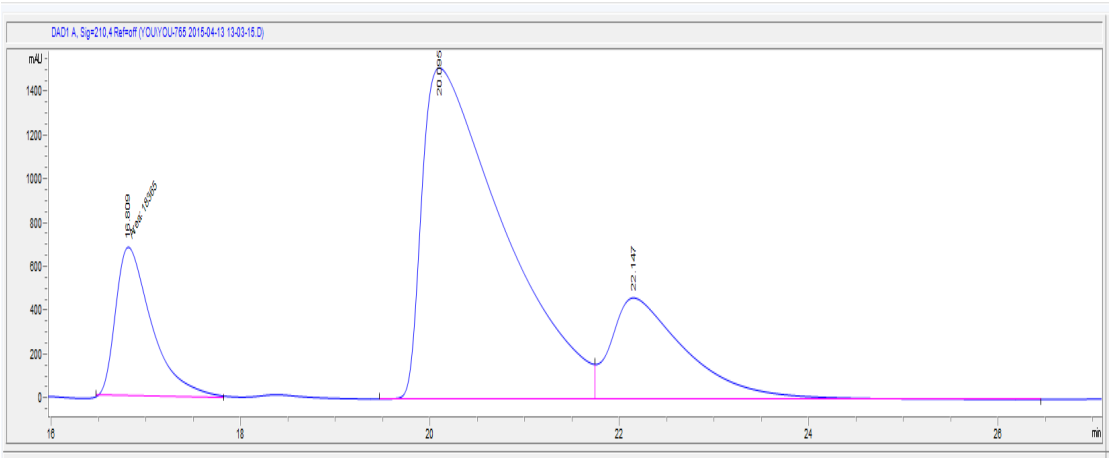


COSY, NMR (Benzene-d6):

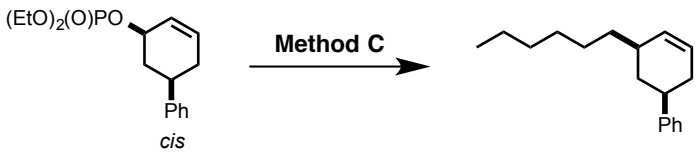


HPLC traces:





Method C: *cis*-phosphate system (3.30)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S*)- Ligand **L16** (19.8 mg, 0.04 mmol, 0.10 eq) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 1-hexene (0.12 mL, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.5 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution. The resulting

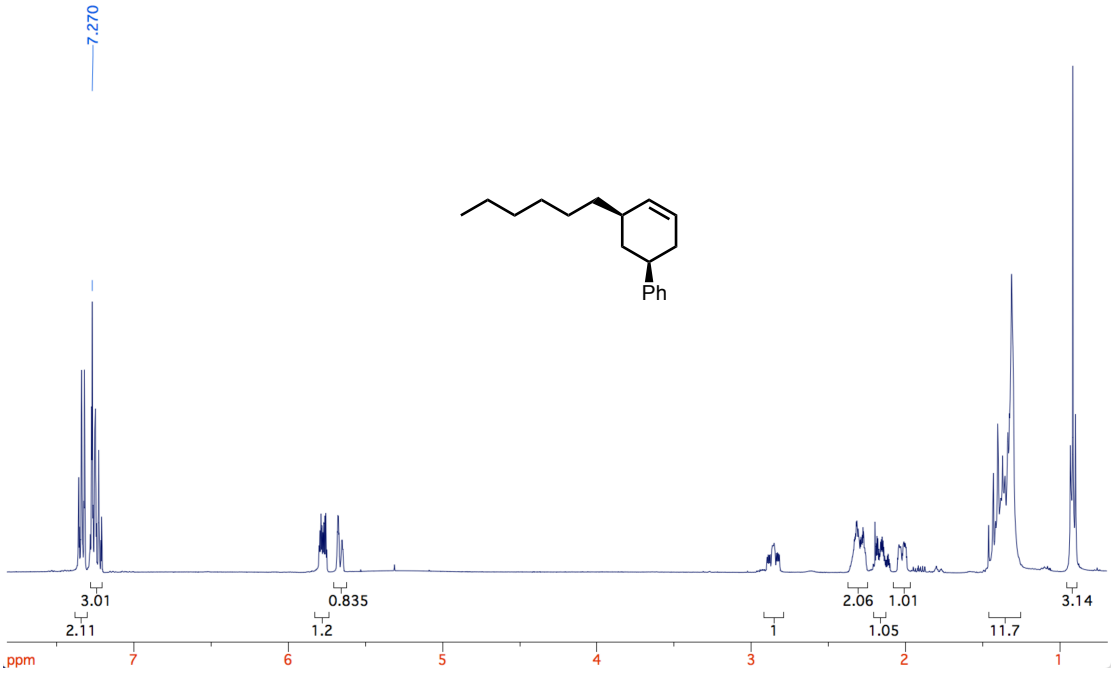
organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, *cis*-5-substituted cyclic phosphate (124.2 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. Then, TMSCl (43.5 mg, 0.40 mmol, 1.00 eq) was injected. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (~1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave the product (69.8 mg, 0.29 mmol) in 72% yield.

Enantiomeric excess of 82% was determined by HPLC [Chiralpak® IE; flow: 0.3 mL/min; hexane ; λ = 210 nm; major enantiomer t_R = 20.6 min; minor enantiomer t_R = 18.6, 22.9 min].

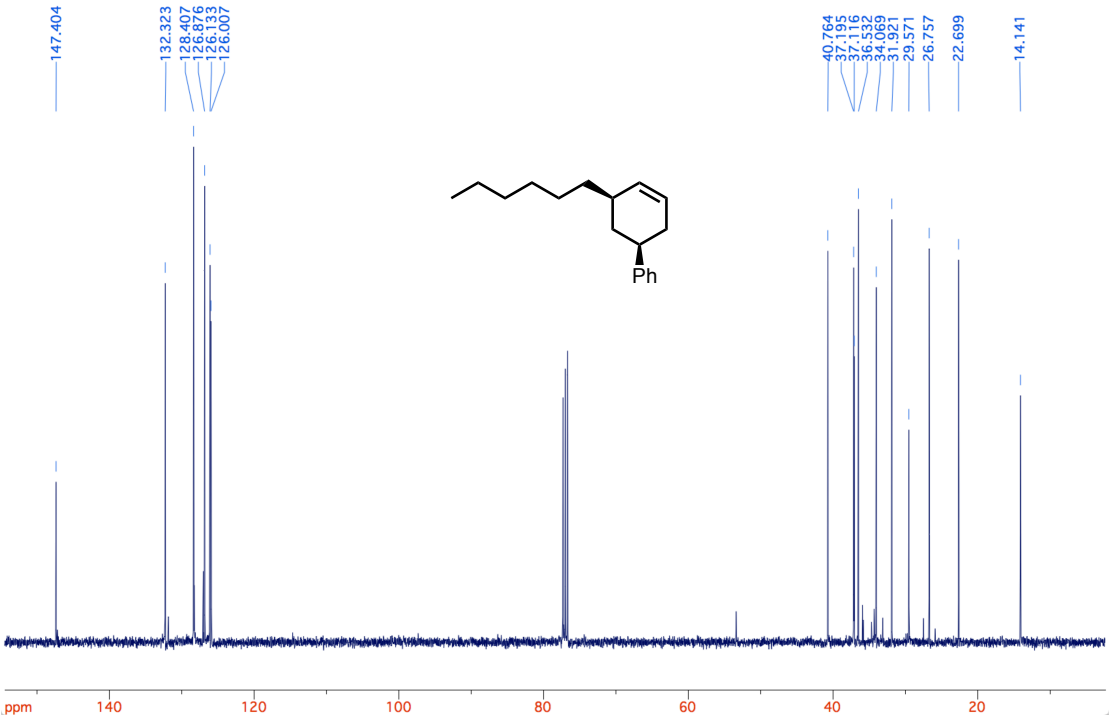
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 7.31-7.36 (m, 2 H), 7.21-7.28 (m, 3 H), 5.75-5.80 (m, 1 H), 5.65-5.68 (m, 1 H), 2.82-2.90 (m, 1 H), 2.26-2.36 (m, 2 H), 2.13-2.22 (m, 1 H), 1.99-2.05 (m, 1 H), 1.31-1.43 (m, 11 H), 0.92 (m, 3 H)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 14.1, 22.7, 26.7, 29.6, 31.9, 34.1, 36.5, 37.1, 37.2, 40.8, 126.0, 126.1, 126.9 (2C), 128.4 (2C), 132.3, 147.4.

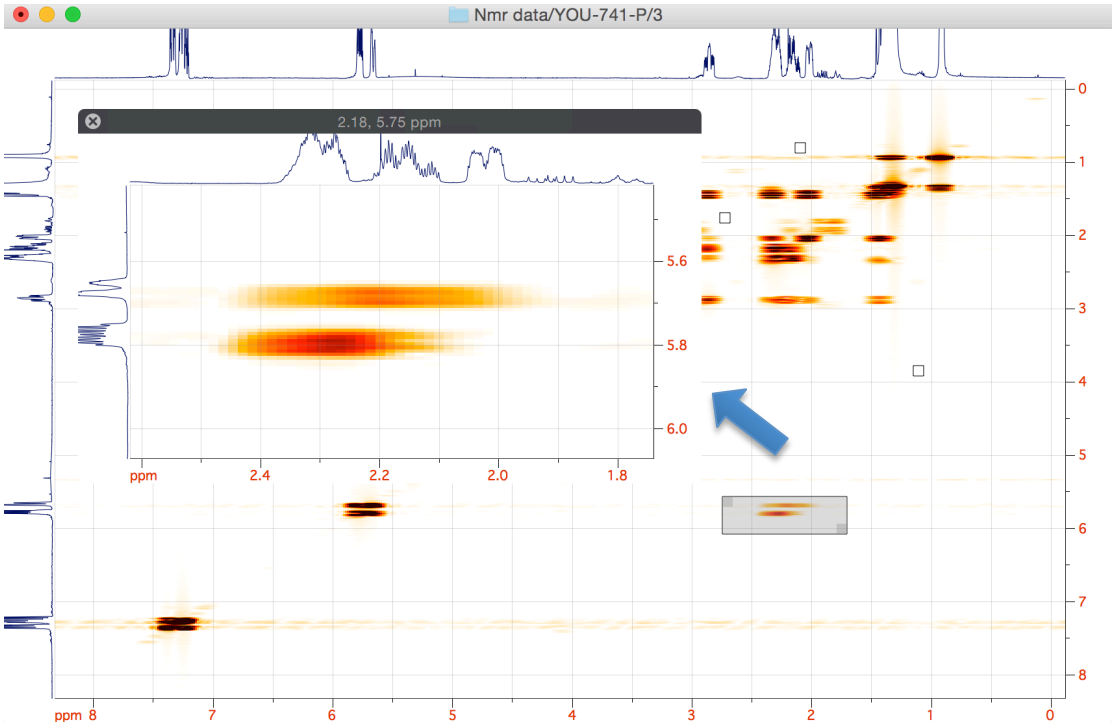
^{1}H NMR:



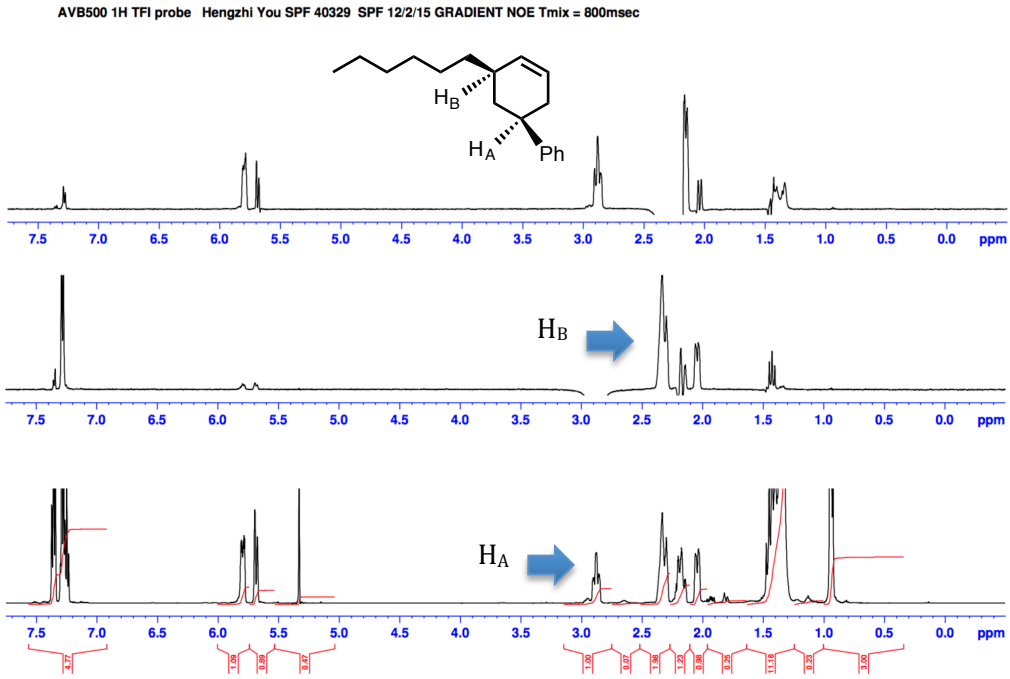
^{13}C NMR:



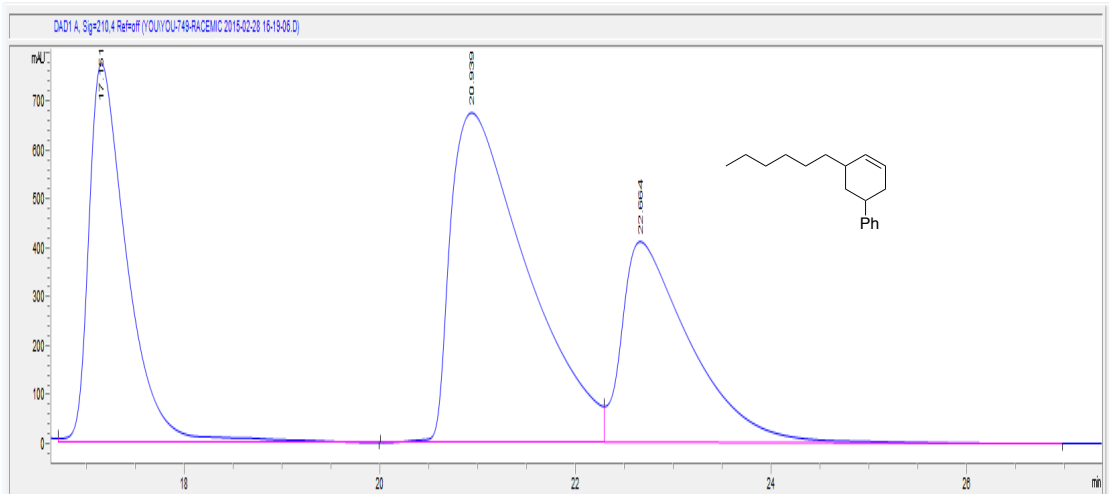
COSY, NMR:

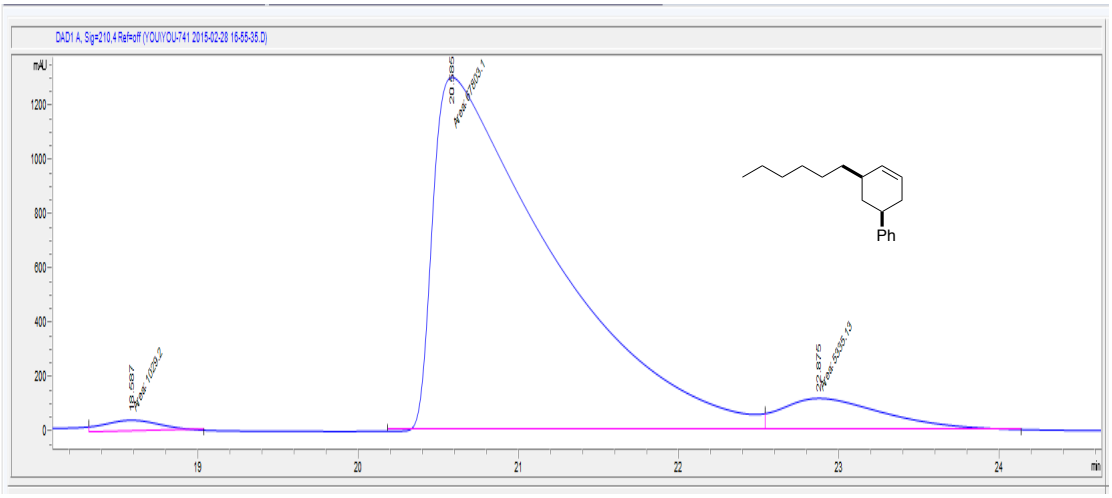


NOESY, NMR:



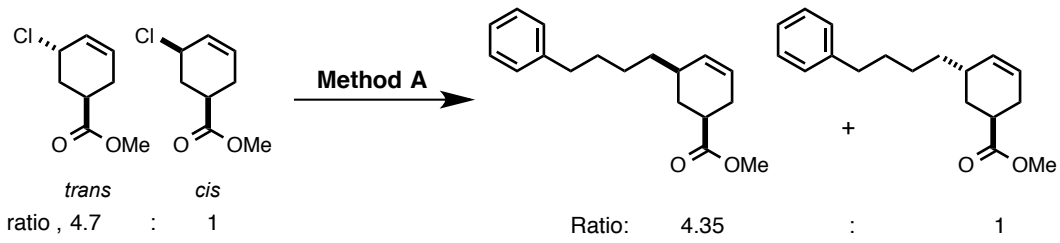
HPLC traces:





Cu-catalyzed AAA with 5-carboxylate substituted substrates

Method A: chloride system (3.31-3.32)



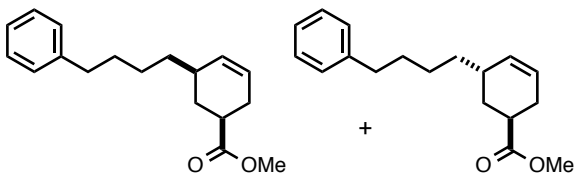
trans *cis*

ratio , 4.7 : 1

Ratio: 4.35 : 1

CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S,S*)- Ligand **L1** (21.6 mg, 0.04 mmol, 0.10 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 4-phenyl-1-butene (0.15 ml, 1.0 mmol, 2.5 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, 5-substituted cyclic chloride (70 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave the products (65.4 mg, 0.24 mmol) in 60% yield.

Enantiomeric excess was determined by HPLC [Chiralpak® IA; flow: 1.2 mL/min; hexane/i-PrOH: 99.6: 0.4;λ = 210 nm; major enantiomer t_R = 43.0, 75.5 min; minor enantiomer t_R = 37.1, 55.2 min].



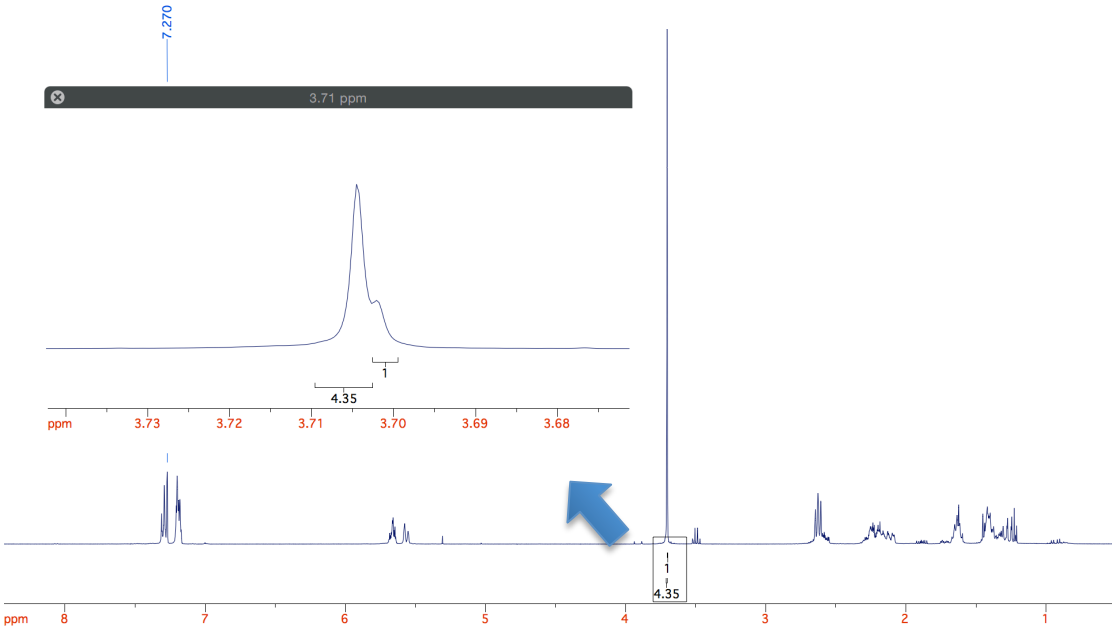
Ratio selectivity, 4.35 : 1

Enantioselectivity, 11% ; 8%

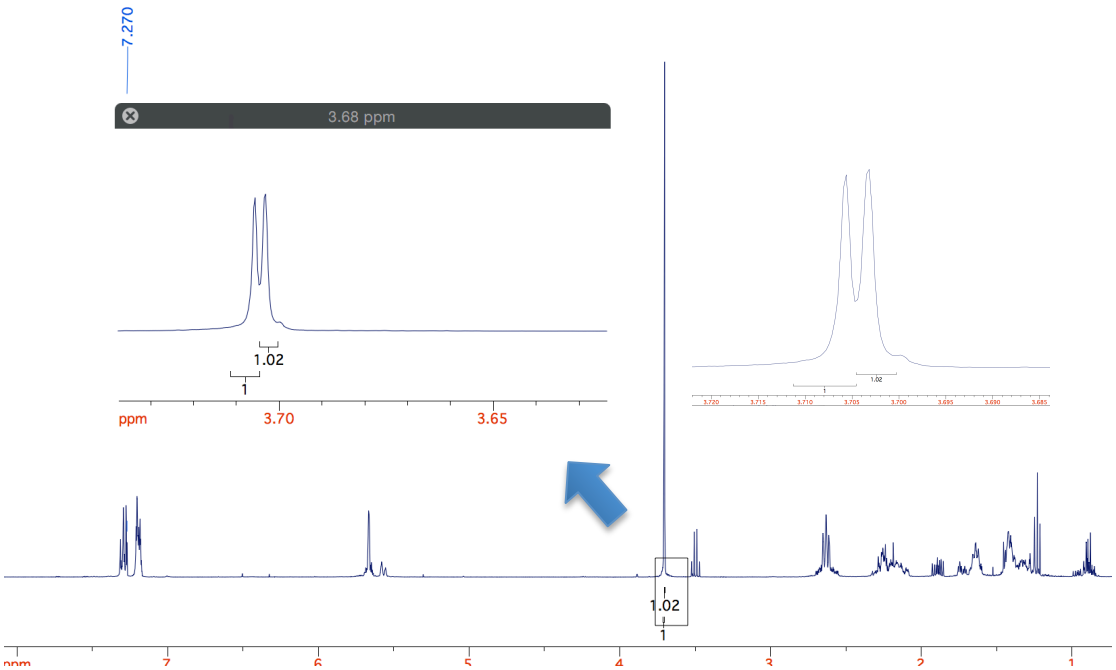
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 7.31-7.27 (m, 2H), 7.21-7.16 (m, 3H), 5.67-5.65 (m, 1H), 5.59-5.54 (m, 1H), 3.7 (s, 3H), 2.65-2.55 (m, 3H), 2.26-2.13 (m, 4H), 1.65-1.61 (m, 2H), 1.44-1.38 (m, 3H), 1.35-1.21 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 26.3, 27.9, 31.7, 32.3, 36.0, 39.9, 51.6, 124.7, 125.6, 128.3(2C), 128.4(2C), 131.9, 142.7, 176.4

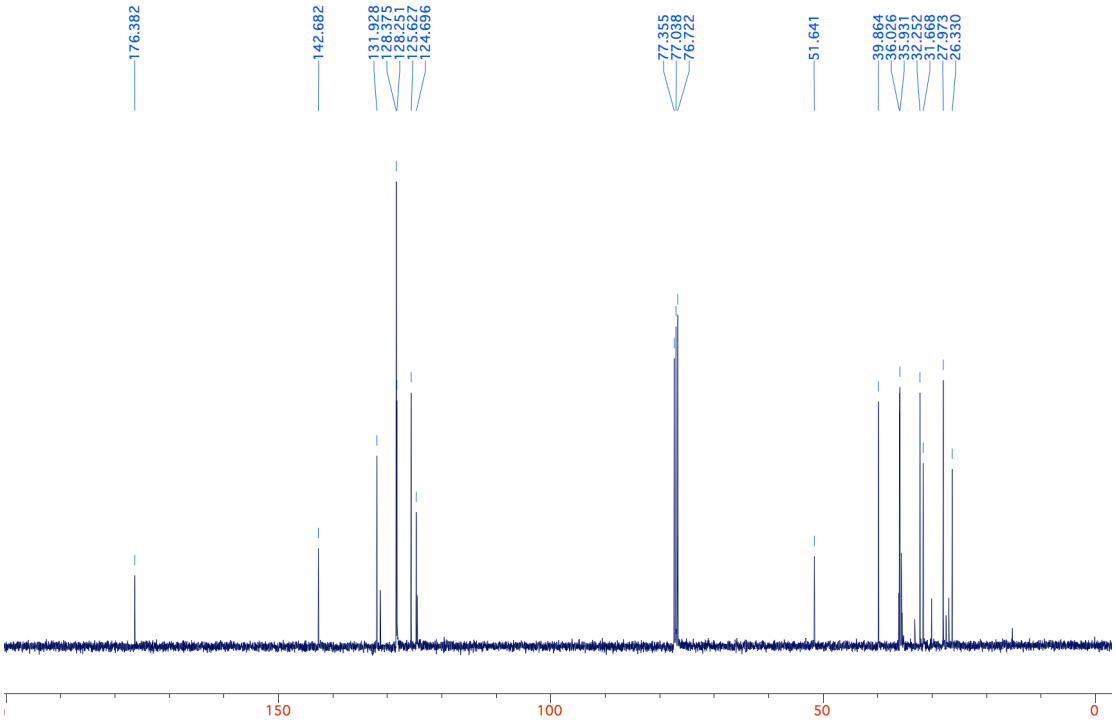
^{1}H NMR (Asymmetric)



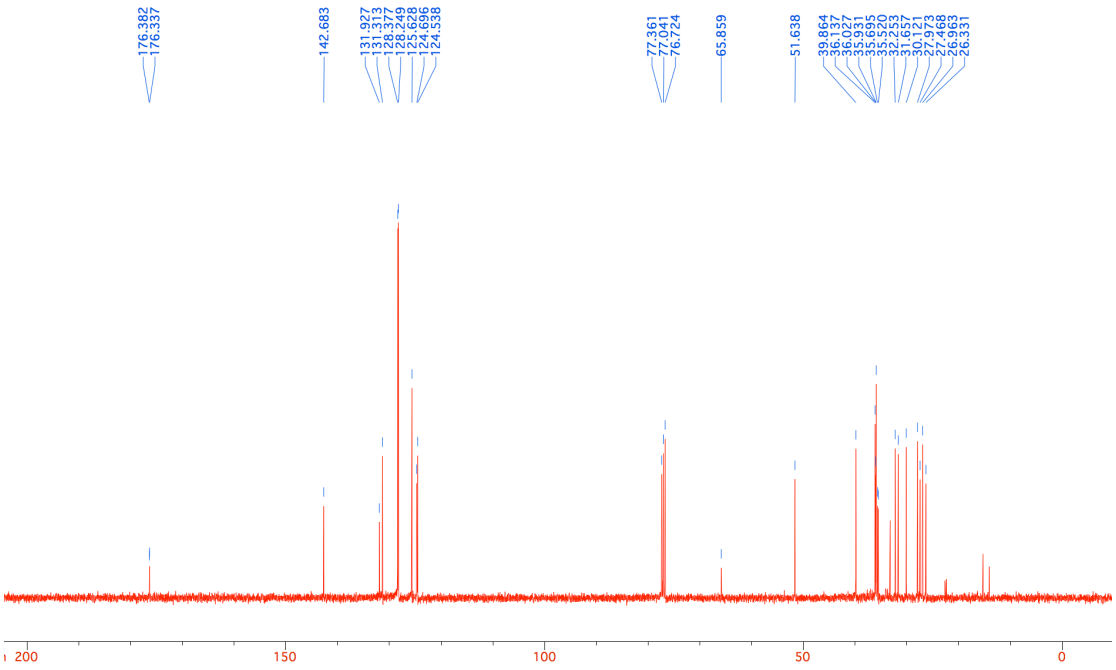
^{1}H NMR (Racemic)



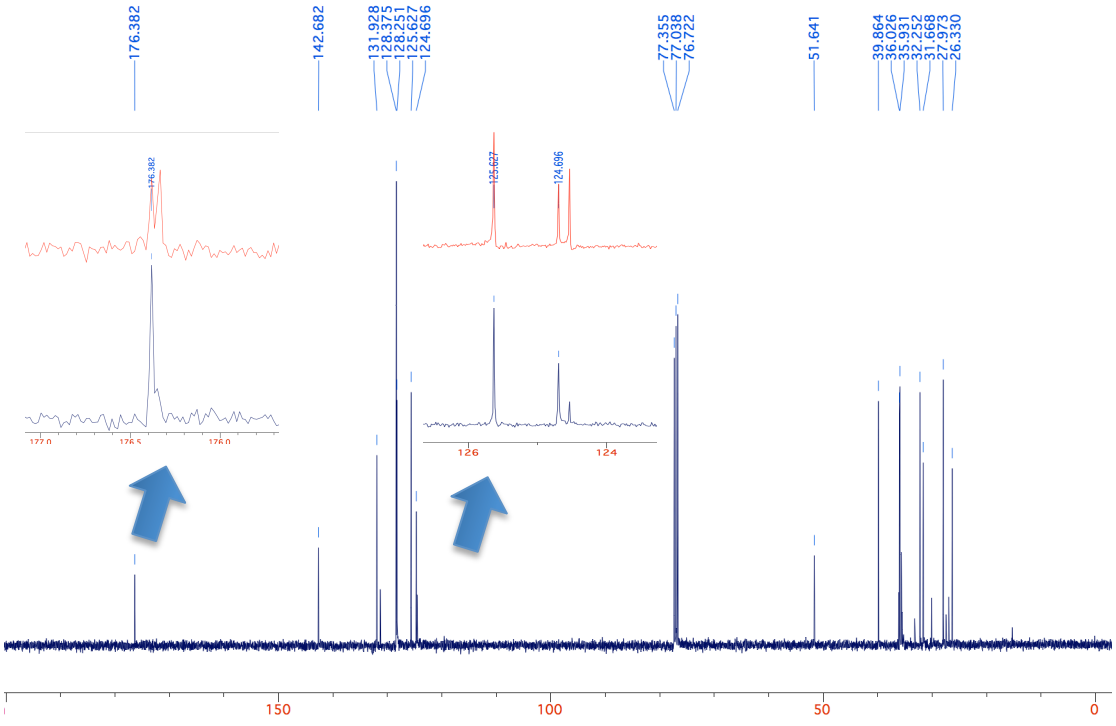
^{13}C NMR (Asymmetric)



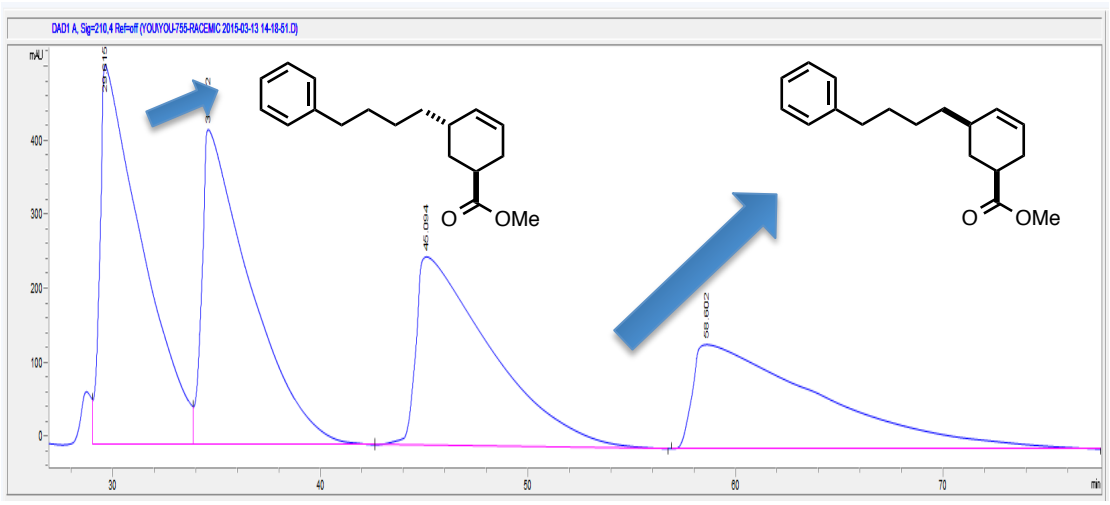
^{13}C NMR (Racemic):

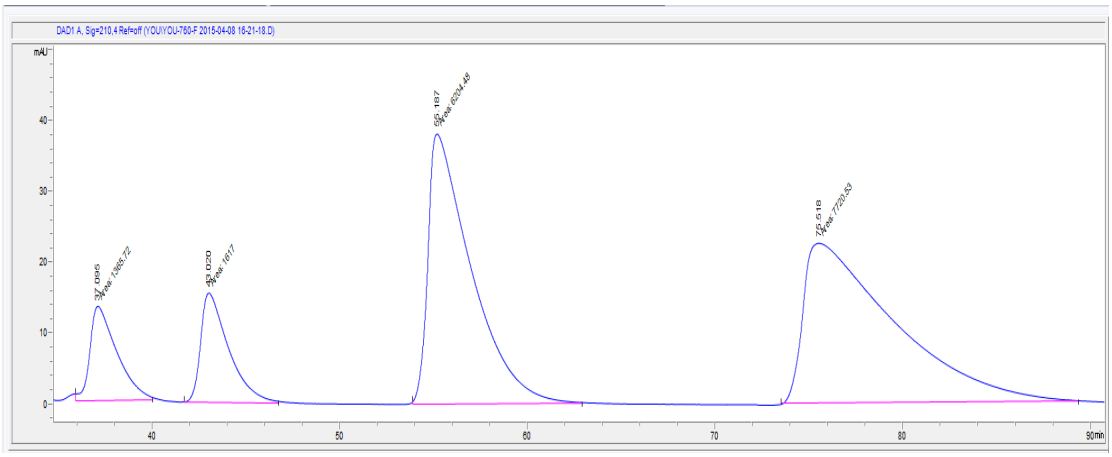


^{13}C NMR (Overlay)

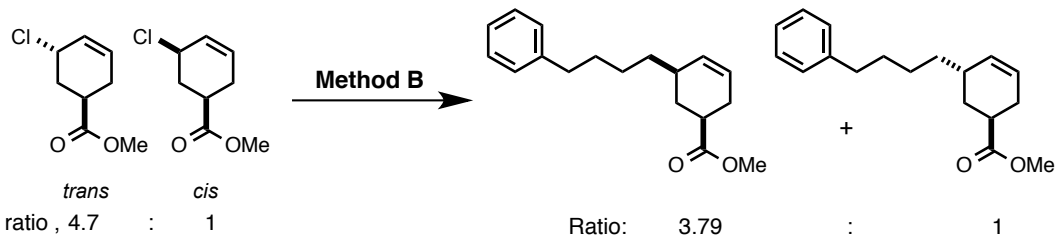


HPLC traces:





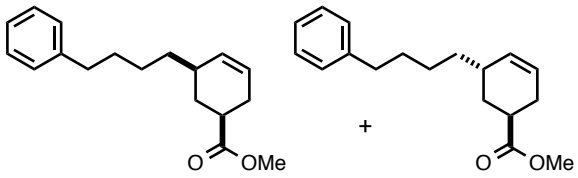
Method B: chloride system(3.31-3.32)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S,*)- Ligand **16** (19.8 mg, 0.04 mmol, 0.1 eq) and then $CHCl_3$ (0.8 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 4-phenyl-1-butene (0.15 ml, 1.0 mmol, 2.5 eq), CH_2Cl_2 (0.4

mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, 5-substituted cyclic chloride (70 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave the products (69.7 mg, 0.26 mmol) in 64% yield.

Enantiomeric excess was determined by HPLC [Chiralpak® IA; flow: 1.2 mL/min; hexane/i-PrOH: 99.6: 0.4;λ = 210 nm; major enantiomer t_R = 38.1, 62.1 min; minor enantiomer t_R = 34.2, 48.6 min].



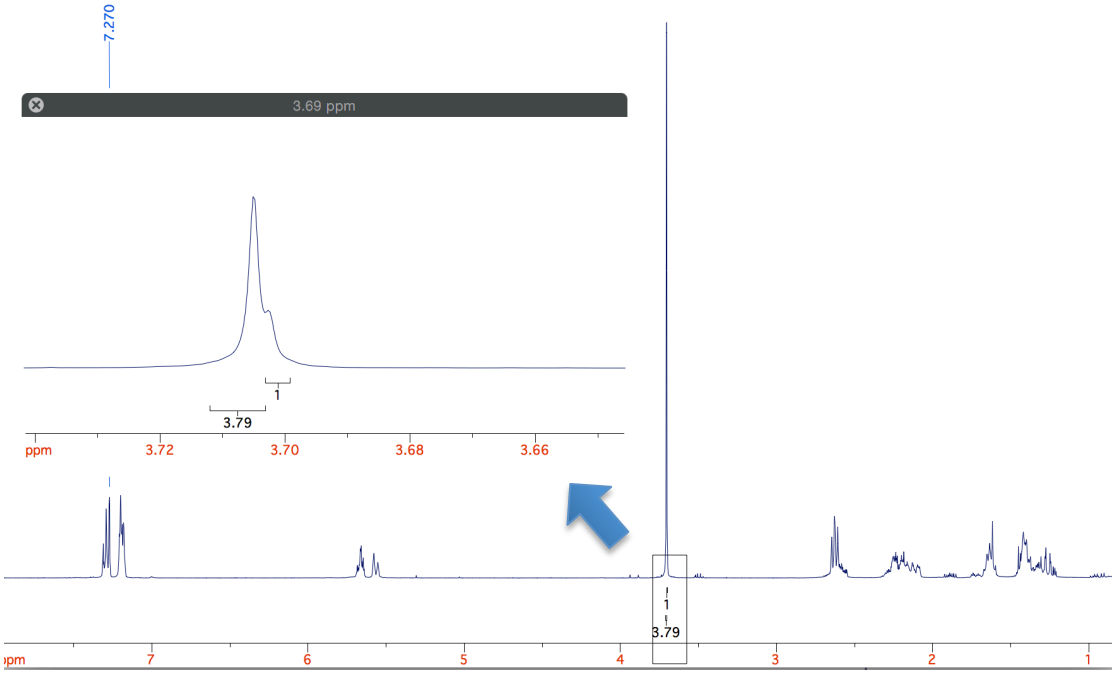
Ratio selectivity, 3.79 : 1

Enantioselectivity, 29% ; 42%

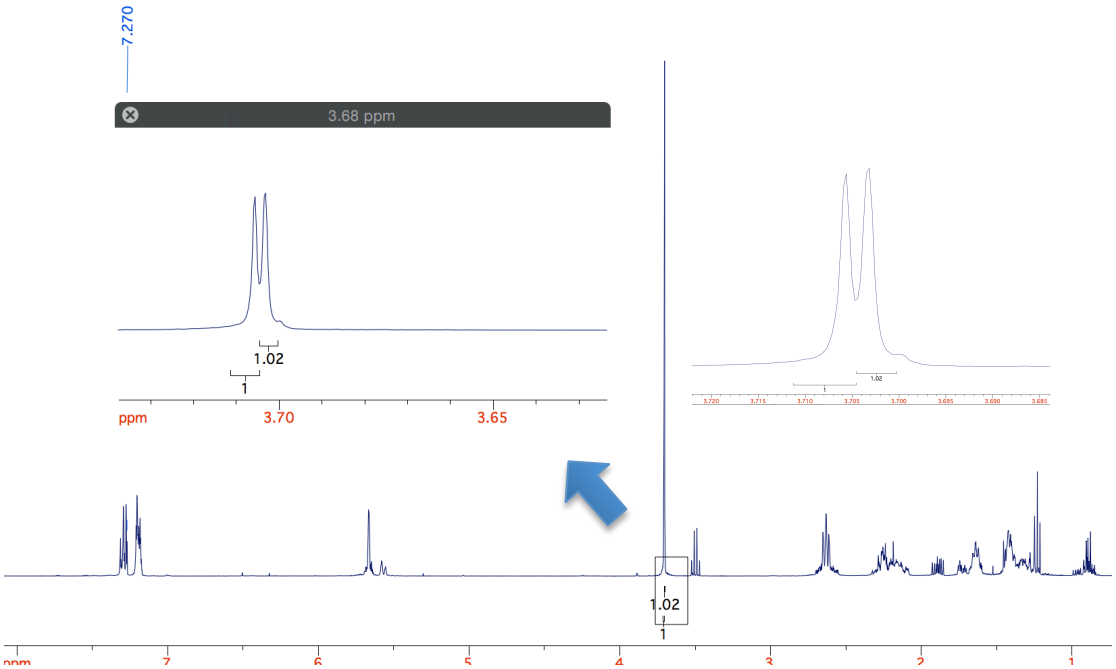
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 7.31-7.27 (m, 2H), 7.21-7.16 (m, 3H), 5.67-5.65 (m, 1H), 5.59-5.54 (m, 1H), 3.7 (s, 3H), 2.65-2.55 (m, 3H), 2.26-2.13 (m, 4H), 1.65-1.61 (m, 2H), 1.44-1.38 (m, 3H), 1.35-1.21 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 26.3, 27.9, 31.7, 32.3, 36.0, 39.9, 51.6, 124.7, 125.6, 128.3(2C), 128.4(2C), 131.9, 142.7, 176.4

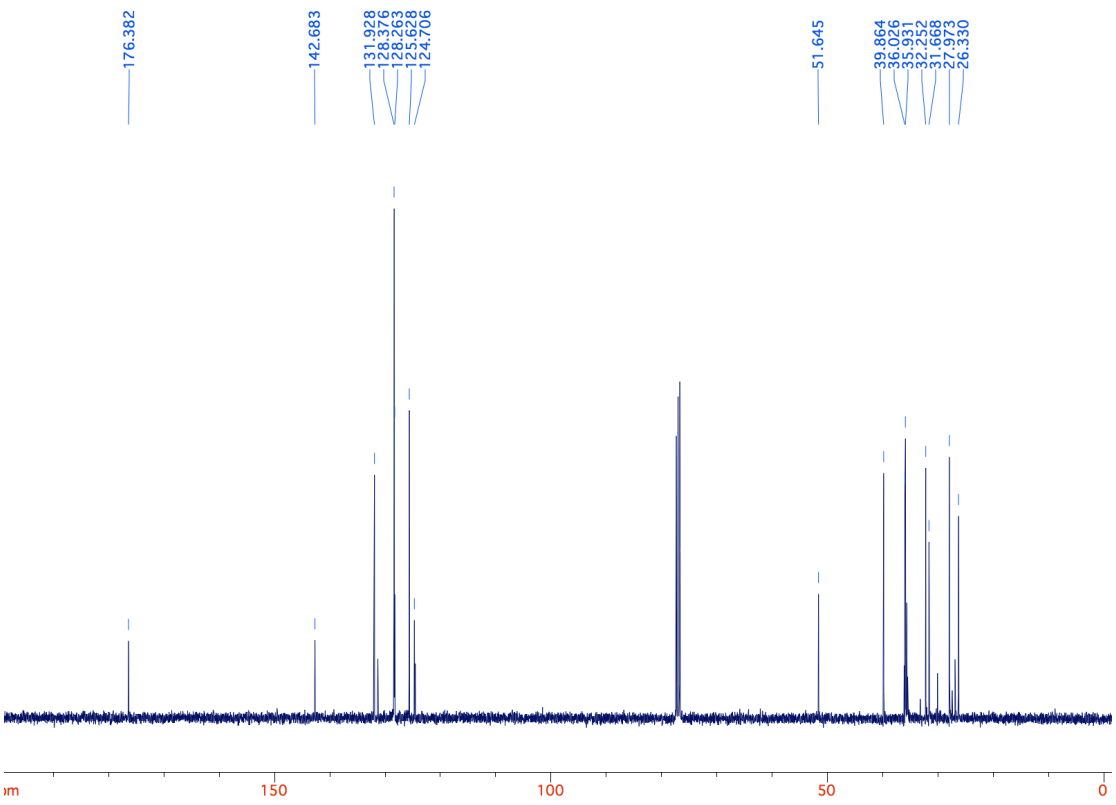
^{1}H NMR (Asymmetric):



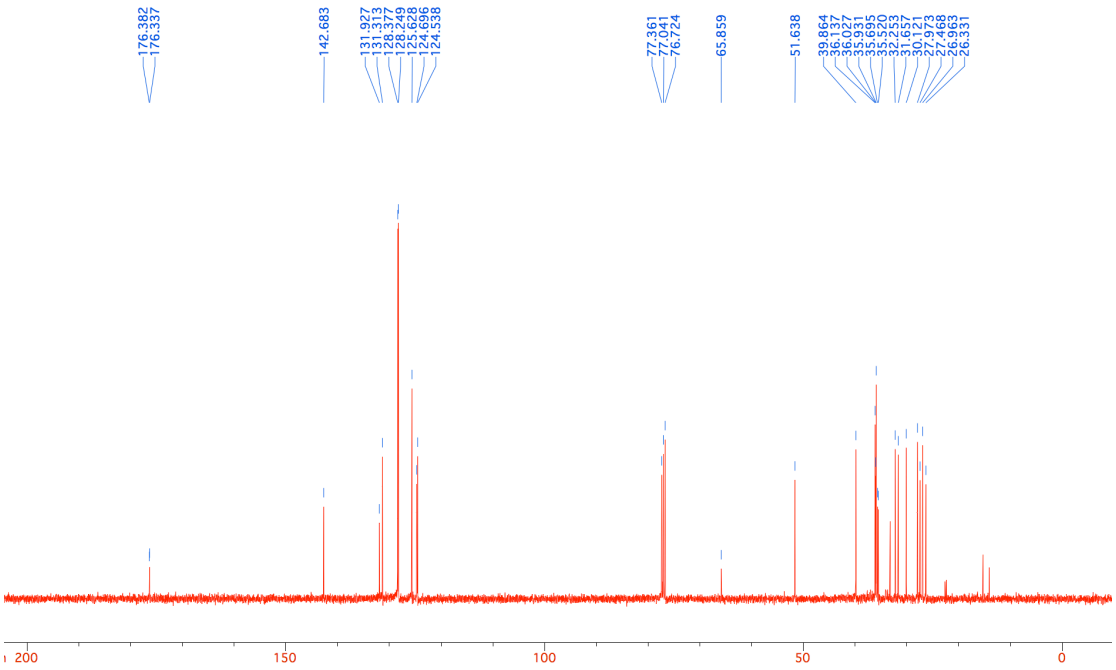
^{1}H NMR (Racemic):



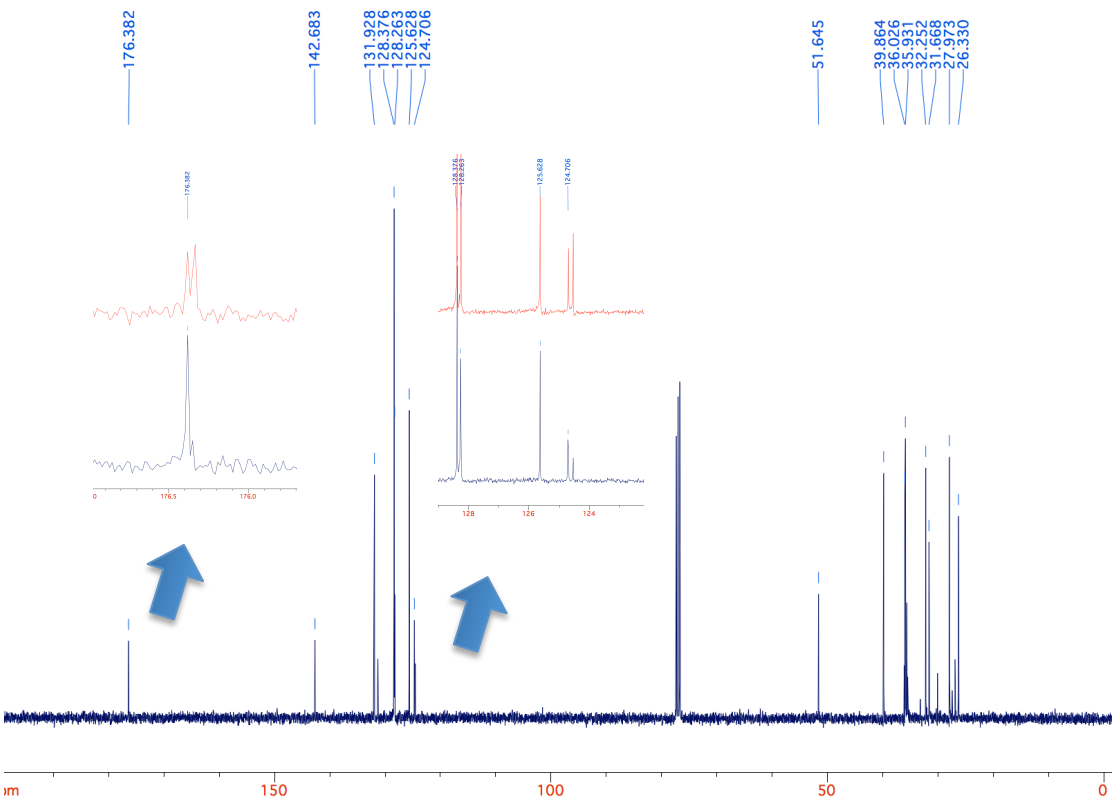
^{13}C NMR (Asymmetric):



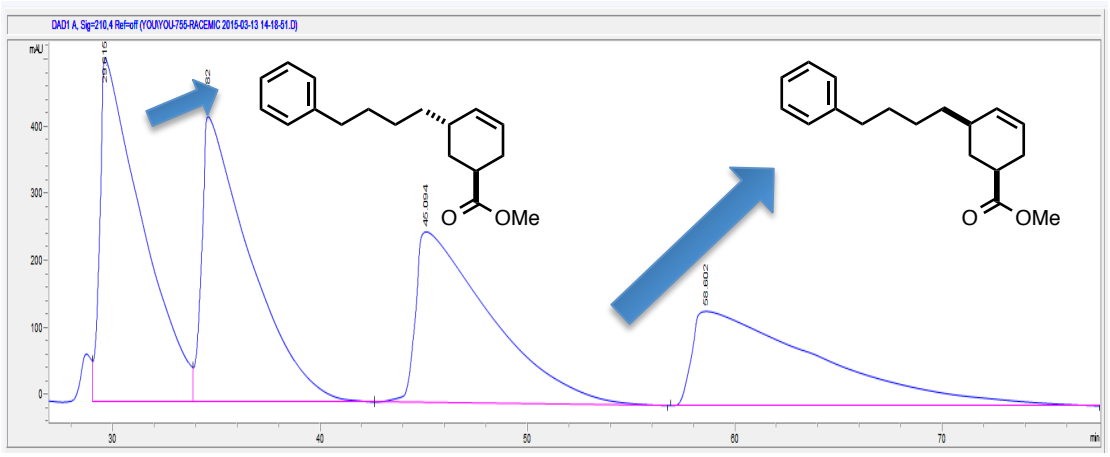
^{13}C NMR (Racemic):



^{13}C NMR (Overlay)


176.382
142.683
131.928
128.376
128.263
125.628
124.706
51.645
39.864
36.026
35.931
32.252
31.668
27.973
26.330
150
100
50
0

HPLC traces: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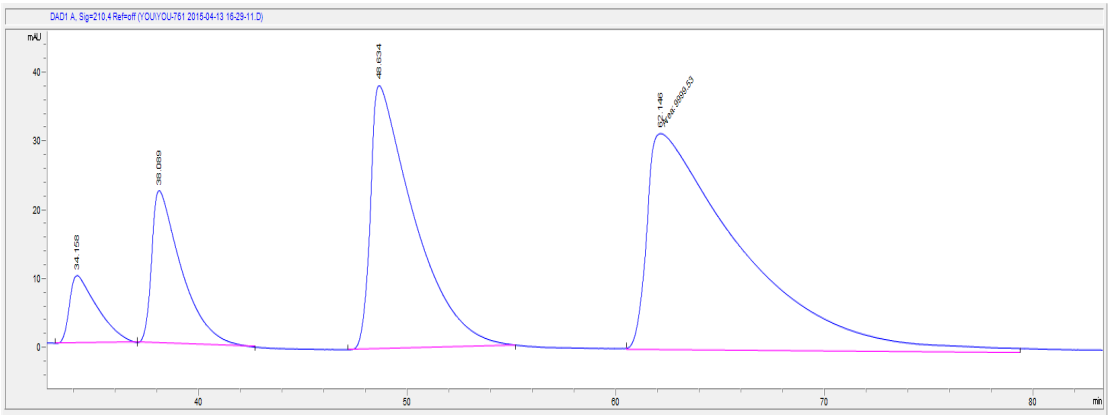
min
O
OMe
O
OMe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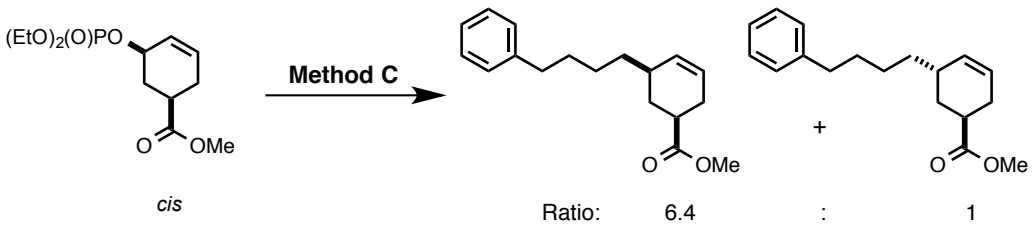
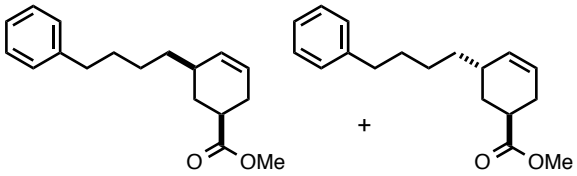
min

Method C: phosphate system (3.31-3.32)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S*)- Ligand **L16** (19.8 mg, 0.04 mmol, 0.10 eq) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 4-phenyl-1-butene (0.15 ml, 1.0 mmol, 2.5 eq), CH_2Cl_2 (0.5 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution. The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, *cis*-5-substituted cyclic phosphate (117 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. Then, TMSCl (43.5 mg, 0.40 mmol, 1.00 eq) was injected. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (~1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave the products (62.1 mg, 0.23 mmol) in 57% yield.

Enantiomeric excess was determined by HPLC [Chiralpak® IA; flow: 1.2 mL/min; hexane/i-PrOH: 99.6: 0.4;λ = 210 nm; major enantiomer t_R = 36.1, 54.2 min; minor enantiomer t_R = 32.4, 44.0 min].



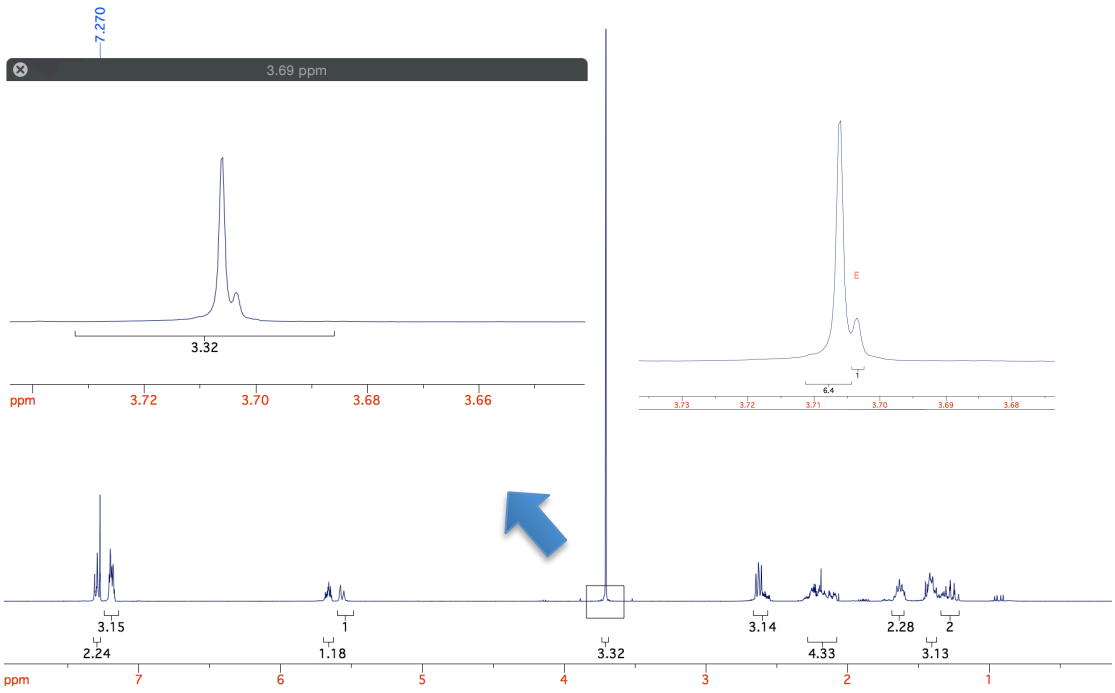
Ratio selectivity, 6.4 : 1

Enantioselectivity, 26% ; 16%

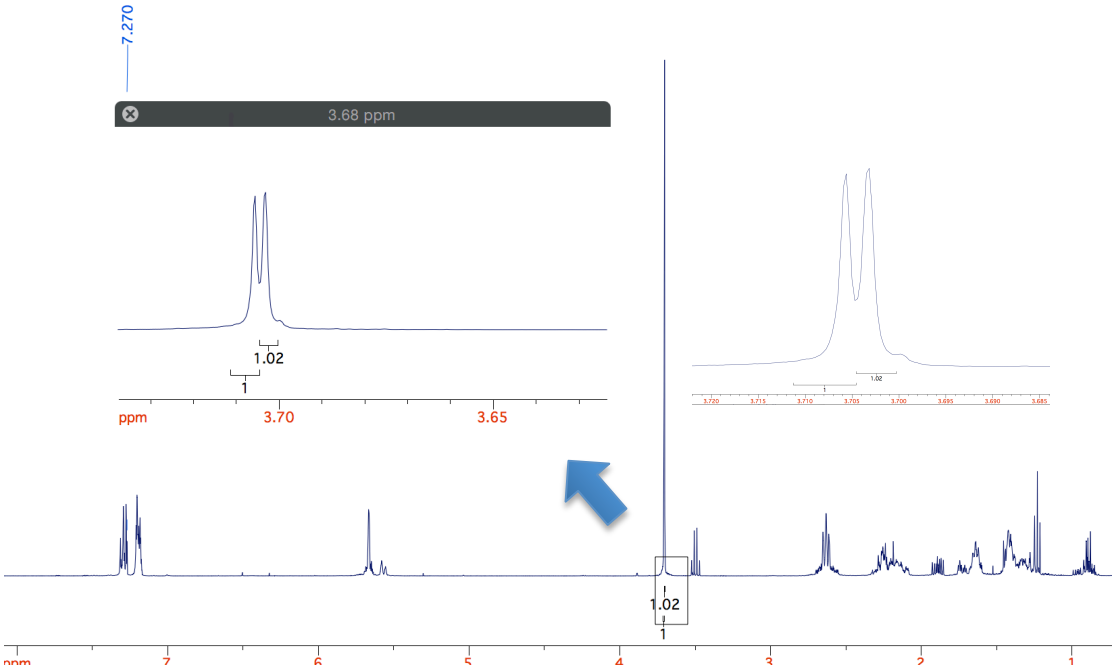
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 7.31-7.27 (m, 2H), 7.21-7.16 (m, 3H), 5.67-5.65 (m, 1H), 5.59-5.54 (m, 1H), 3.7 (s, 3H), 2.65-2.55 (m, 3H), 2.26-2.13 (m, 4H), 1.65-1.61 (m, 2H), 1.44-1.38 (m, 3H), 1.35-1.21 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 26.3, 27.9, 31.7, 32.3, 36.0, 39.9, 51.6, 124.7, 125.6, 128.3(2C), 128.4(2C), 131.9, 142.7, 176.4

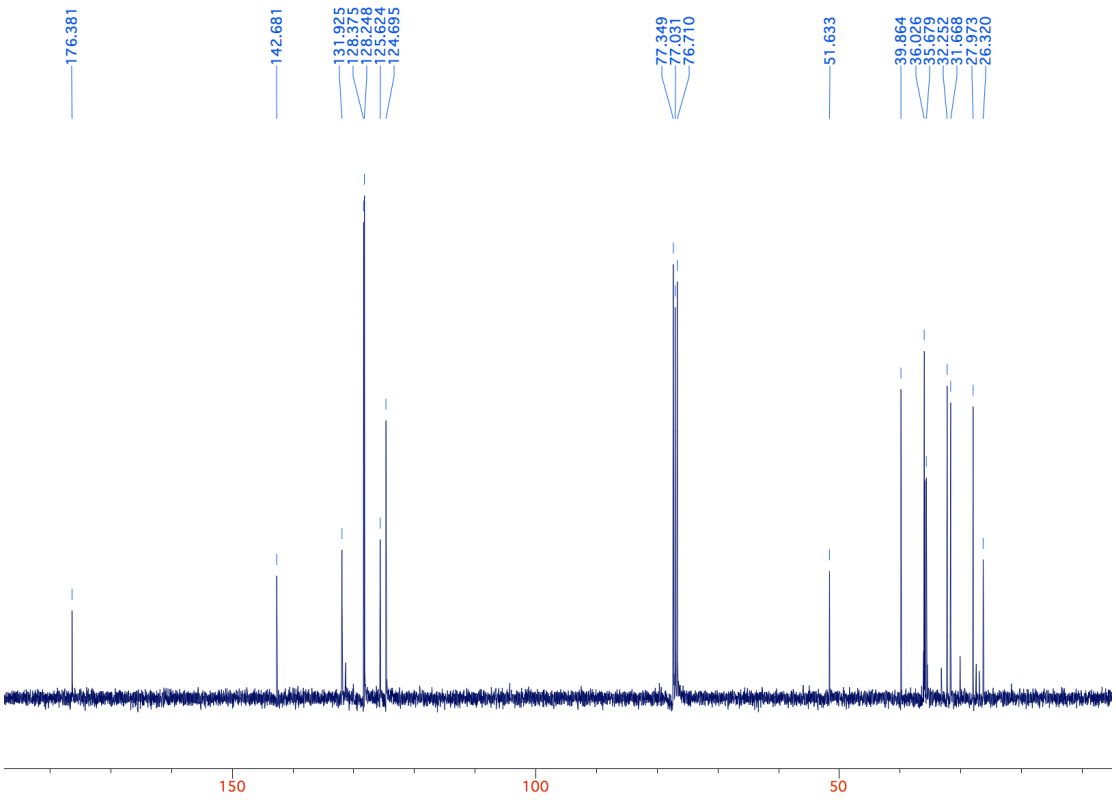
^{1}H NMR (Asymmetric):



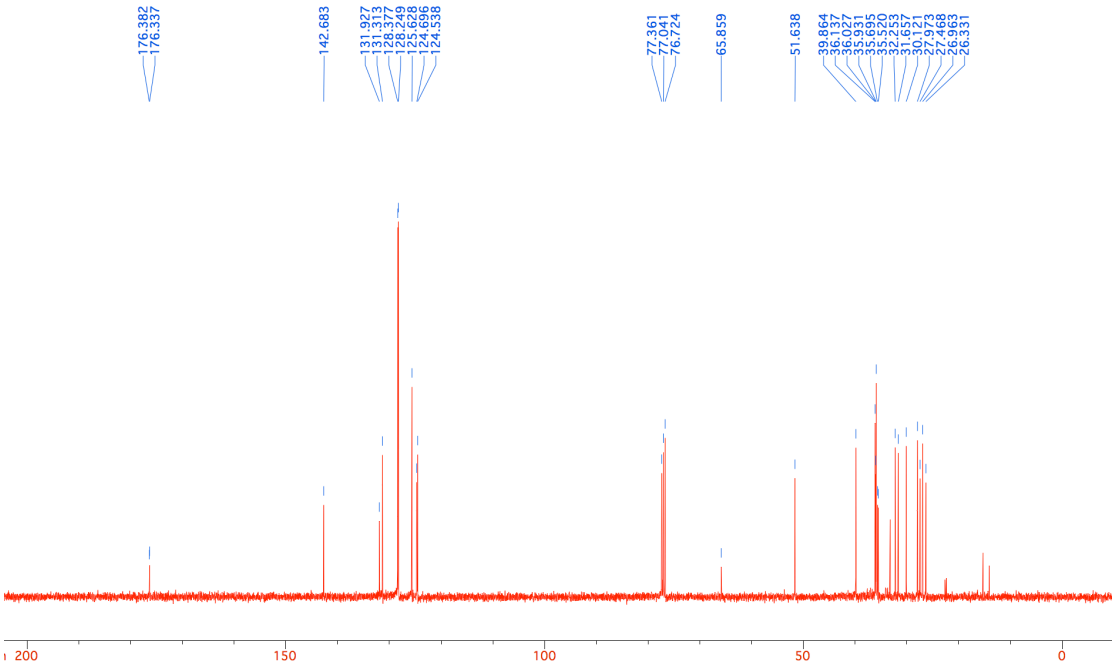
^{1}H NMR (Racemic):



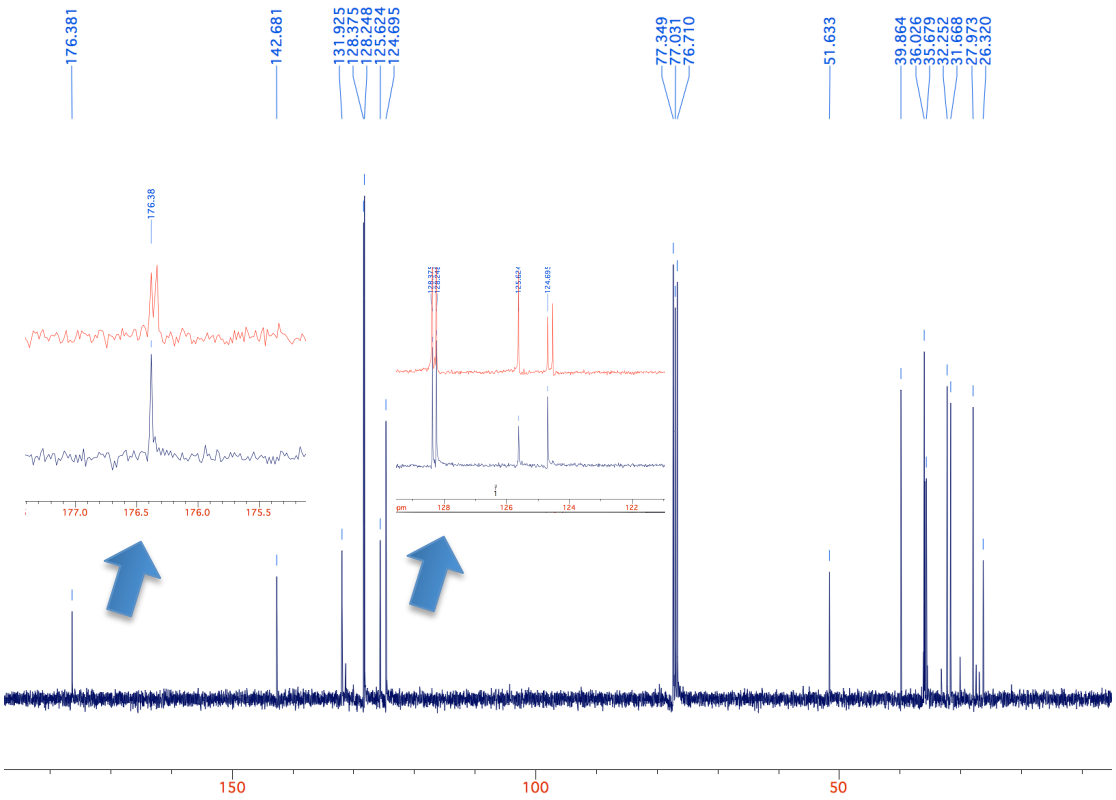
^{13}C NMR (Asymmetric):



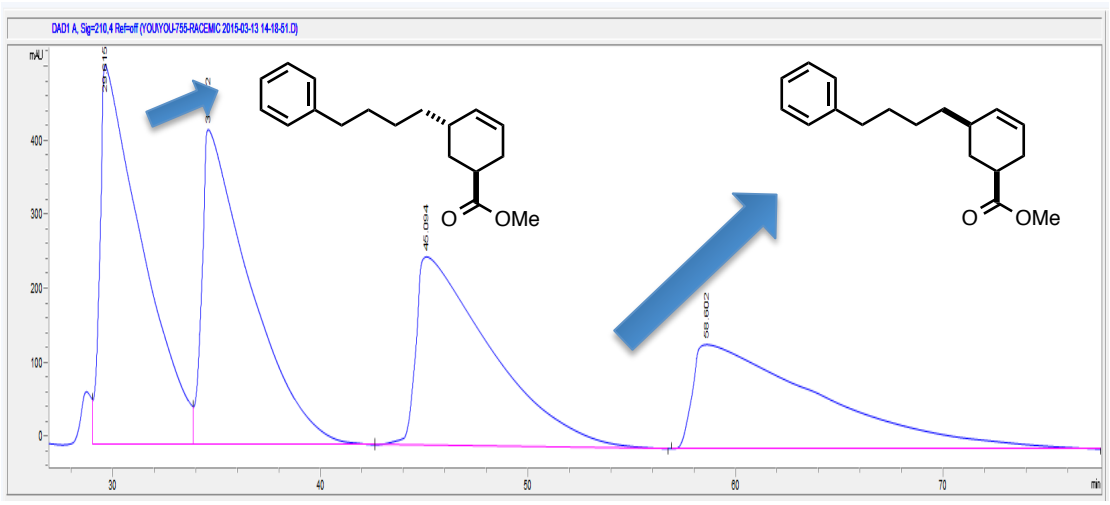
^{13}C NMR (Racemic):

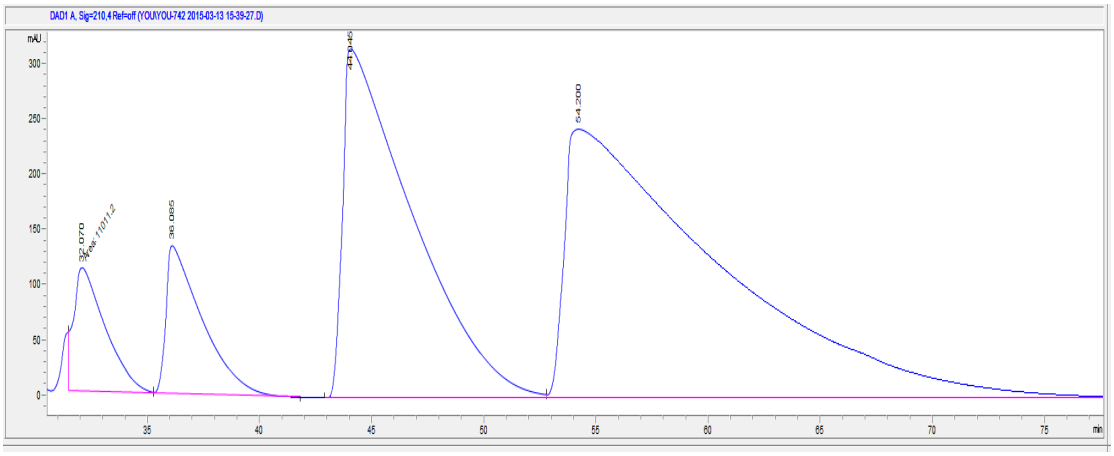


^{13}C NMR (Overlay)



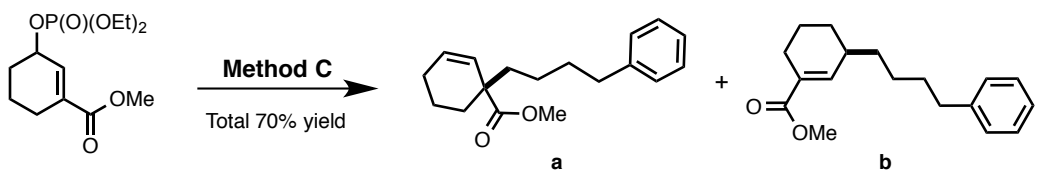
HPLC traces:





Cu-catalyzed AAA with 3-carboxylate substituted substrates

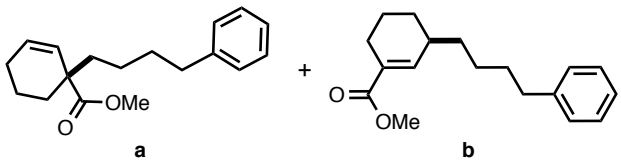
Method C: phosphate system (3.33-3.34)



a **b**

Ratio: 1.8 : 1

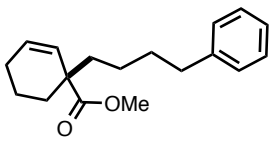
CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S*)- Ligand **L16** (19.8 mg, 0.04 mmol, 0.10 eq) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 4-phenyl-1-butene (0.15 ml, 1.0 mmol, 2.5 eq), CH_2Cl_2 (0.5 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear solution. The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, 3-substituted cyclic phosphate (117 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. Then, TMSCl (43.5 mg, 0.40 mmol, 1.00 eq) was injected. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (~1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. Flash column chromatography of the residue (pentane; SiO_2) gave the isolated products, **a** methyl-1-(4-phenylbutyl)cyclohex-2-ene-1-carboxylate (48.7 mg, 0.18 mmol) in 45% yield; **b** (27.5 mg, 0.10 mmol) in 25 % yield. (Total 70% yield).



a **b**

Ratio selectivity,	1.8	:	1
Enantioselectivity,	3%	;	7%

Methyl-1-(4-phenylbutyl)cyclohex-2-ene-1-carboxylate (3.33)

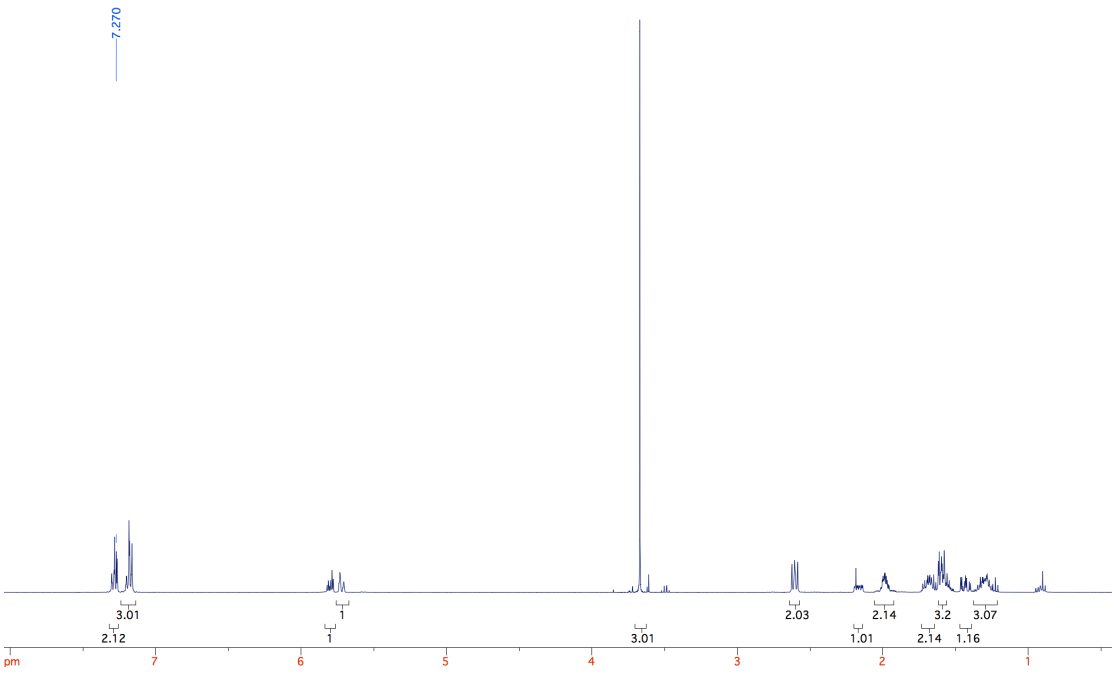


Enantiomeric excess 3% was determined by HPLC [Chiralpak® IA; flow: 0.6 mL/min; hexane; λ = 210 nm; major enantiomer t_R = 36.8 min; minor enantiomer t_R = 32.6 min].

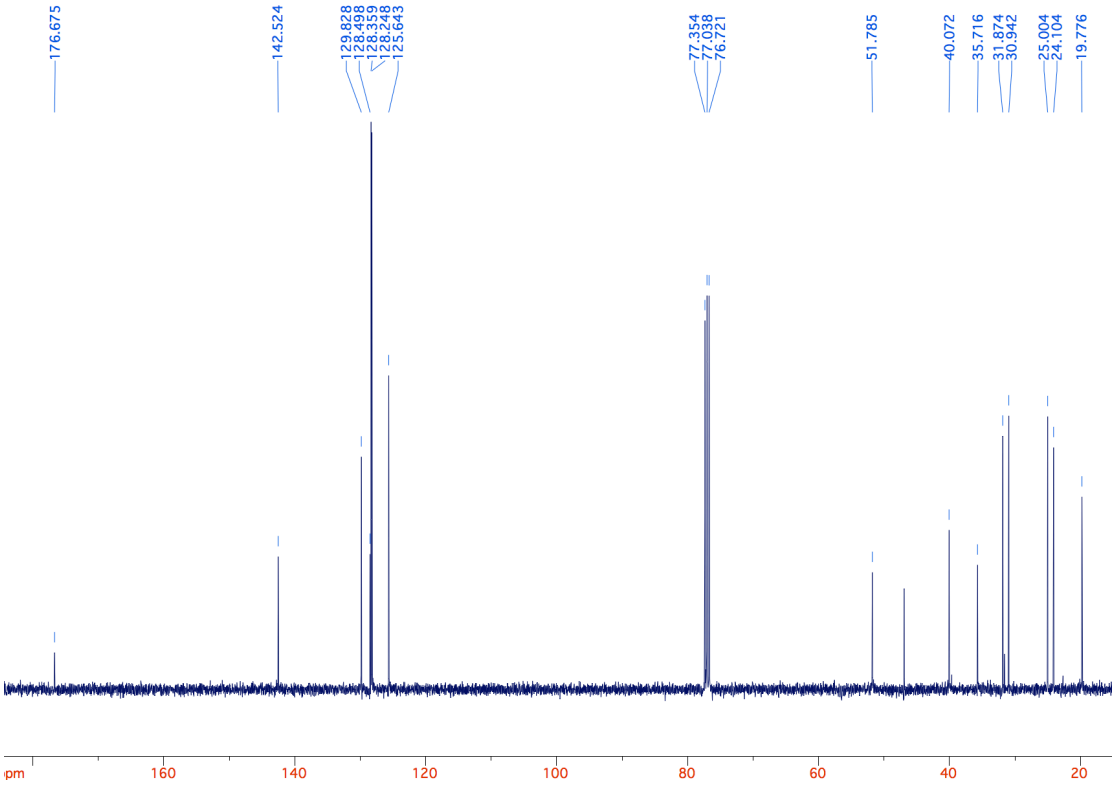
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 7.31-7.26 (m, 2H), 7.21-7.15 (m, 3H), 5.83-5.77 (m, 1H), 5.74-5.71 (m, 1H), 3.67 (s, 3H), 2.61 (t, 3 H, *J* =7.8 Hz), 2.20-2.13 (m, 1H), 2.05-1.91 (m, 2H), 1.73-1.65 (m, 2H), 1.62-1.56 (m, 3H), 1.47-1.39 (m, 1H), 1.33-1.23 (m, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 19.8, 24.1, 25.0, 30.9, 31.9, 35.7, 40.1, 51.8, 125.6, 128.3, 128.4(2C), 128.5(2C), 129.8, 142.5, 176.7

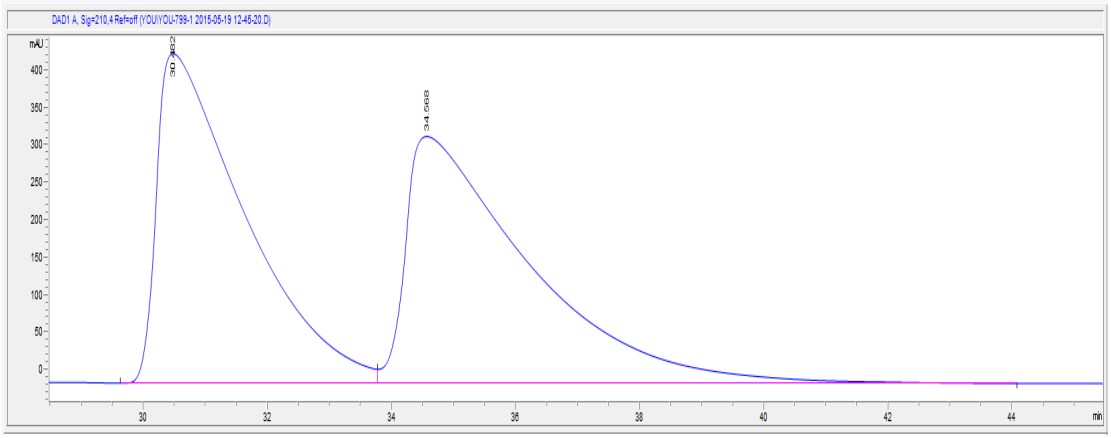
^{1}H NMR:



^{13}C NMR


176.675
142.524
129.828
128.498
128.359
128.248
125.643
77.354
77.038
76.721
51.785
40.072
35.716
31.874
30.942
25.004
24.104
19.776
ppm
160
140
120
100
80
60
40
20

HPLC traces: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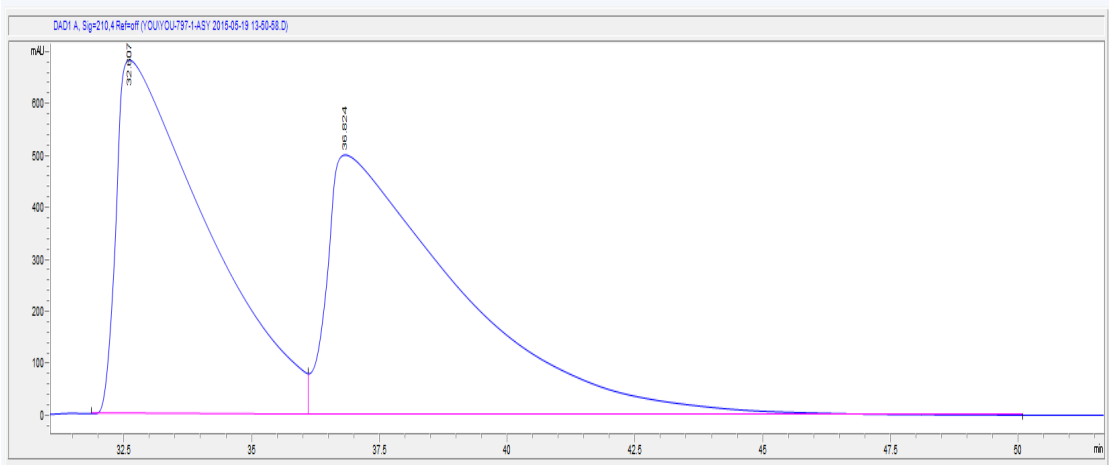
30.382
34.668
min


DAD1 A, Sig=210,4 Ref=off (YOUYOU-797-1-ASY 2015-05-19 13-50-58.D)
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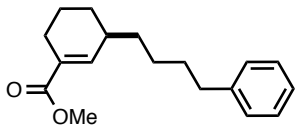
36.824
min

Methyl-3-(4-phenylbutyl)cyclohex-1-ene-1-carboxylate (3.34)

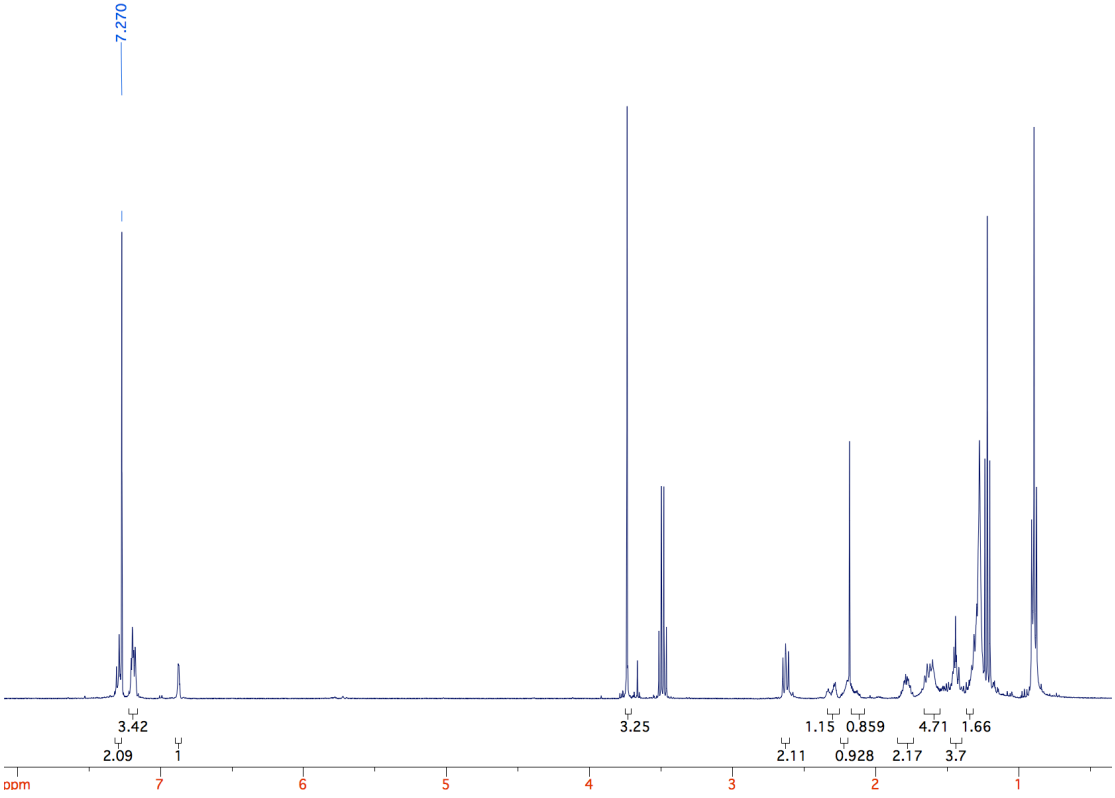


Enantiomeric excess 7% was determined by HPLC [Chiralpak® IA; flow: 1.2 mL/min; hexane/i-PrOH: 99.5: 0.5;; λ = 210 nm; major enantiomer t_R = 19.4 min; minor enantiomer t_R = 22.8 min].

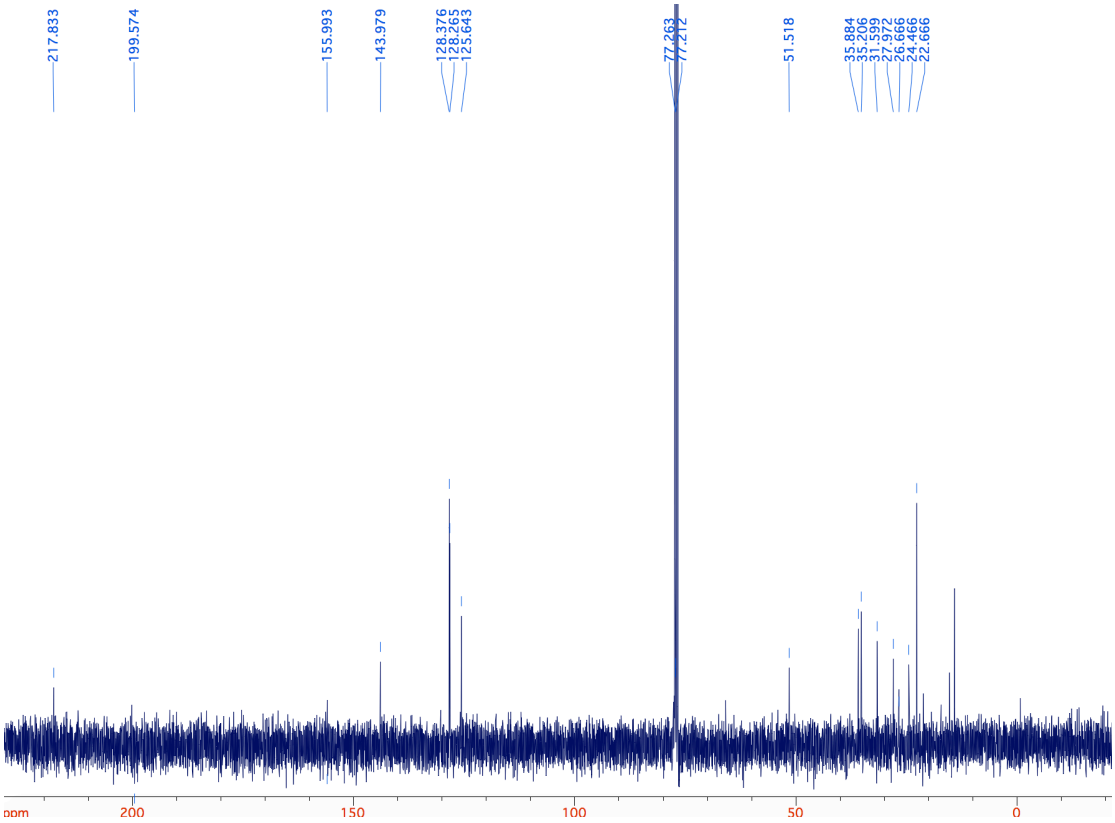
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 7.31-7.28 (m, 2H), 7.20-7.17 (m, 3H), 6.88-5.87 (m, 1H), 3.74 (s, 3H), 2.63 (t, 2 H, *J* =7.8 Hz), 2.35-2.27 (m, 1H), 2.24-2.10 (m, 2H), 1.85-1.74 (m, 2H), 1.66-1.56 (m, 4H), 1.47-1.39 (m, 3H), 1.36-1.31 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm:, 22.7, 24.5, 26.7, 27.9, 31.6, 35.2, 35.9, 51.5, 125.6, 128.3, 128.4(2C), 128.5(2C), 143.9, 155.9, 199.6

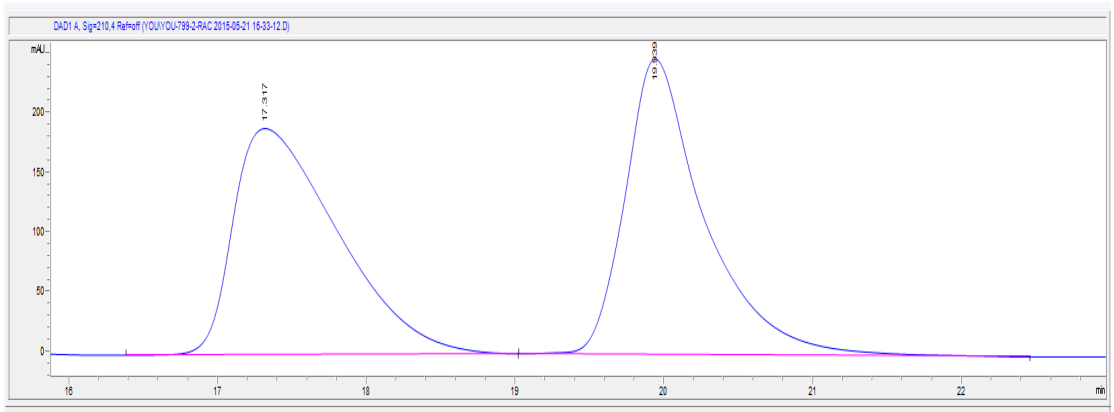
^{1}H NMR:

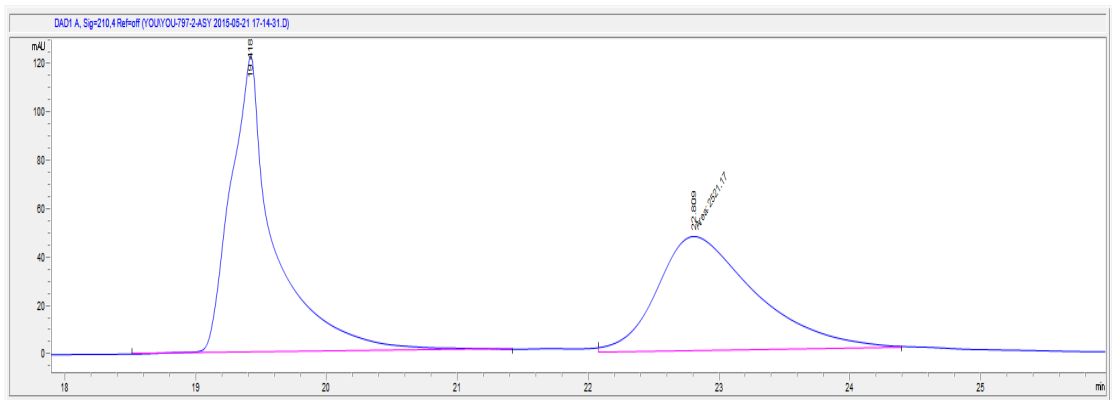


^{13}C NMR



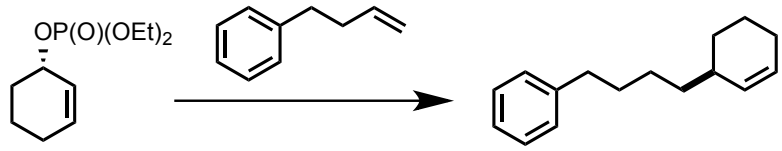
HPLC traces:





Ligand effect on enantioselectivity:

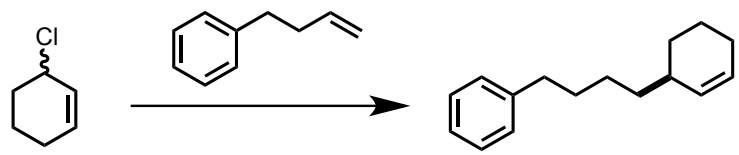
Enantiopure phosphate



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S*)- Ligand **L16** (19.8 mg, 0.04 mmol, 0.10 eq) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 4-Phenyl-1-butene (0.15ml, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.5 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, enantiopure cyclohex-2-en-1-yl diethyl phosphate (93.7 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. Then, TMSCl (43.5 mg, 0.40 mmol, 1.00 eq) was injected.

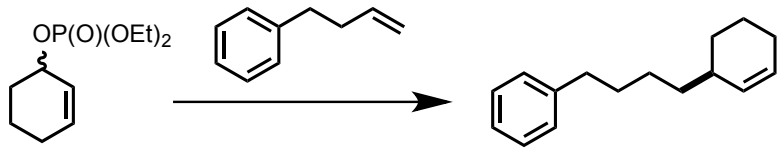
The reactions were arbitrarily left stirring: 30 min; 2h and 30 min; 4 h; overnight. Before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (~1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. The crude was injected to the HPCL directly to detect the enantiomeric excess of products.

Ee of product (Chloride system)



CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S,S*)- Ligand **L1** and (*R,R,R*)- Ligand **L1** were mixed into an enantiomeric excess of ligand 20% ee, 40% ee, 60% ee, 80% ee, 100% ee separately (21.6 mg, 0.04 mmol, 0.10 eq)) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 4-Phenyl-1-butene (0.15ml, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.4 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, 3-chlorocyclohex-1-ene (46.6 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. The reaction was arbitrarily left stirring overnight before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. The crude was injected to the HPCL directly to detect the enantiomeric excess of products.

Ee of product (Phosphate system)



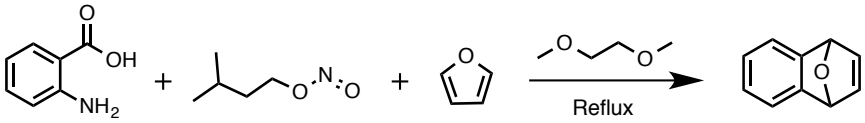
CuI (7.6 mg, 0.04 mmol, 0.10 eq), (*S,S*)- Ligand **L16** and (*R,R*)- Ligand **L16** were mixed into an enantiomeric excess of ligand 20% ee, 40% ee, 60% ee, 80% ee, 100% ee separately (19.8

mg, 0.04 mmol, 0.10 eq) and then CH_2Cl_2 (1 mL) were added to a flame dried round-bottom flask and then stirred for 1 h at room temperature. Meanwhile, 4-Phenyl-1-butene (0.15ml, 1.00 mmol, 2.50 eq), CH_2Cl_2 (0.5 mL) and Cp_2ZrHCl (206.2 mg, 0.80 mmol, 2.00 eq) were added to another flame-dried flask and smoothly stirred at room temperature until it became a clear yellow solution (approx. 20 min). The resulting organozirconium species was transferred to the copper-ligand solution using a syringe over about 1 minute. After stirring at room temperature for 5 additional minutes, cyclohex-2-en-1-yl diethyl phosphate (93.7 mg, 0.40 mmol, 1.00 eq) was added dropwise via syringe. Then, TMSCl (43.5 mg, 0.40 mmol, 1.00 eq) was injected. The reactions were arbitrarily left stirring overnight. Before being quenched by addition of NH_4Cl (1M, aq. ~1.0 mL) and diluted by addition of CH_2Cl_2 (~1.0 mL). The phases were partitioned and the organic phase was washed with $NaHCO_3$ (sat. aq. *ca.* 2.0 mL), water (2.0 mL), dried ($MgSO_4$), filtered and carefully concentrated under vacuum. The crude was injected to the HPCL directly to detect the enantiomeric excess of products.

5.5 Cu-catalyzed Enantioselective desymmetri-sation of meso compounds

Synthesis of starting materials

Oxabicycle (4.1)



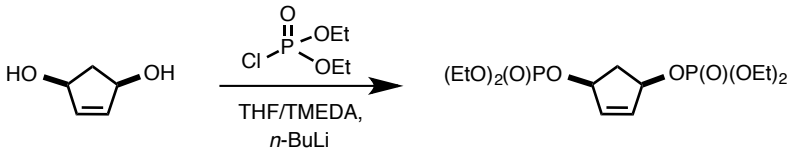
To a 100 mL round bottom flask with straight condenser tube 10 mL furan and 10 mL DME were added. Taking two 25 mL dropping bottles, one with 4 mL isoamyl nitrite and 10 mL

DME (A), the other with 2.75 g (20.06 mmol) 2-aminobenzoic acid dissolved by 10 mL DME (B). Then 1 mL of A and then 1 mL B were added to the refluxing furan solution over 4 min. The solution became red brown, giving off gas when the reagents were added. Heating was continued until the solution did not release gas (about 15 min). Then 25 mL of 2% sodium hydroxide was added to the mixture and transferred to a separating funnel to rinse, the phases were separated and the aqueous phase extracted three times with 15 mL petroleum ether (bp 30–60 °C). The combined organic phases were washed with water (15 mL × 4) and dried with magnesium sulphate and concentrated in vacuo. The crude material was purified by flash chromatography with 20% ethyl acetate in petrol to give the product as a yellow solid (1.72 g, 60%). Further crystallization gave white crystals (1.32 g, 77%) [22].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 7.27 (m, 2H), 7.04 (m, 2H), 6.99 (m, 2H), 5.73 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 148.9(2C), 143.0(2C), 125.0(2C), 120.0(2C), 82.3(2C)

meso-4-Cyclopentene-1,3-bisdiethylphosphate (4.4)



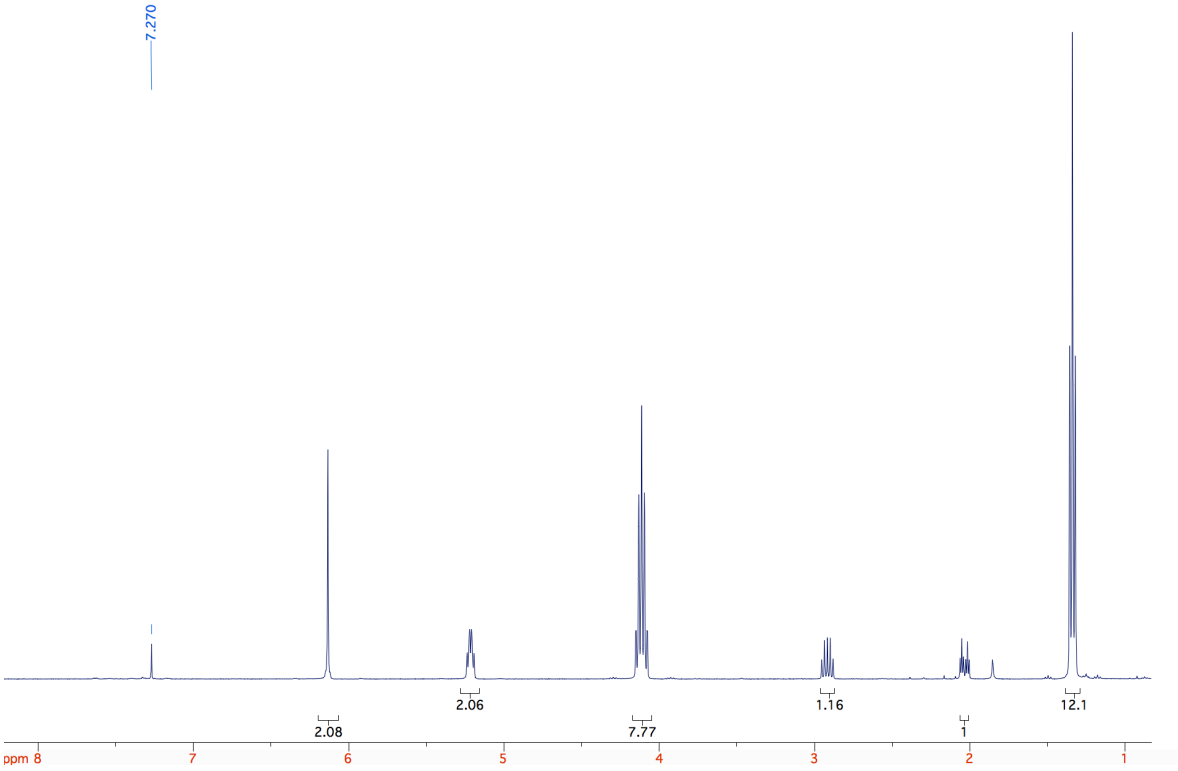
In a 250 mL flame dried flask, the responding *cis*-4-cyclopentene-1,3-diol alcohol (1 g, 10 mmol, 1 eq) was dissolved in THF/TMEDA (4:1, 70 mL) under an argon atmosphere at -40 ^{o}C . *n*-BuLi (8.4 mL, 2.5 M in Hexane, 2.1 eq) was added dropwise and the mixture was stirred for 15 min before diethyl chlorophosphate (3.26 mL, 22 mmol, 2.2 eq) was added dropwise. After stirring the mixture at -40 ^{o}C for 3 hours, it was left to warm up to room temperature. Then the reaction was quenched with brine (20 mL), and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL), resulting organic phase was washed with brine (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified carefully through flash column

chromatography (EtOAc: MeOH, 97: 3; SiO_2) to provide the product in 87% yield (3.24 g, 8.7 mmol) as colorless oil [23].

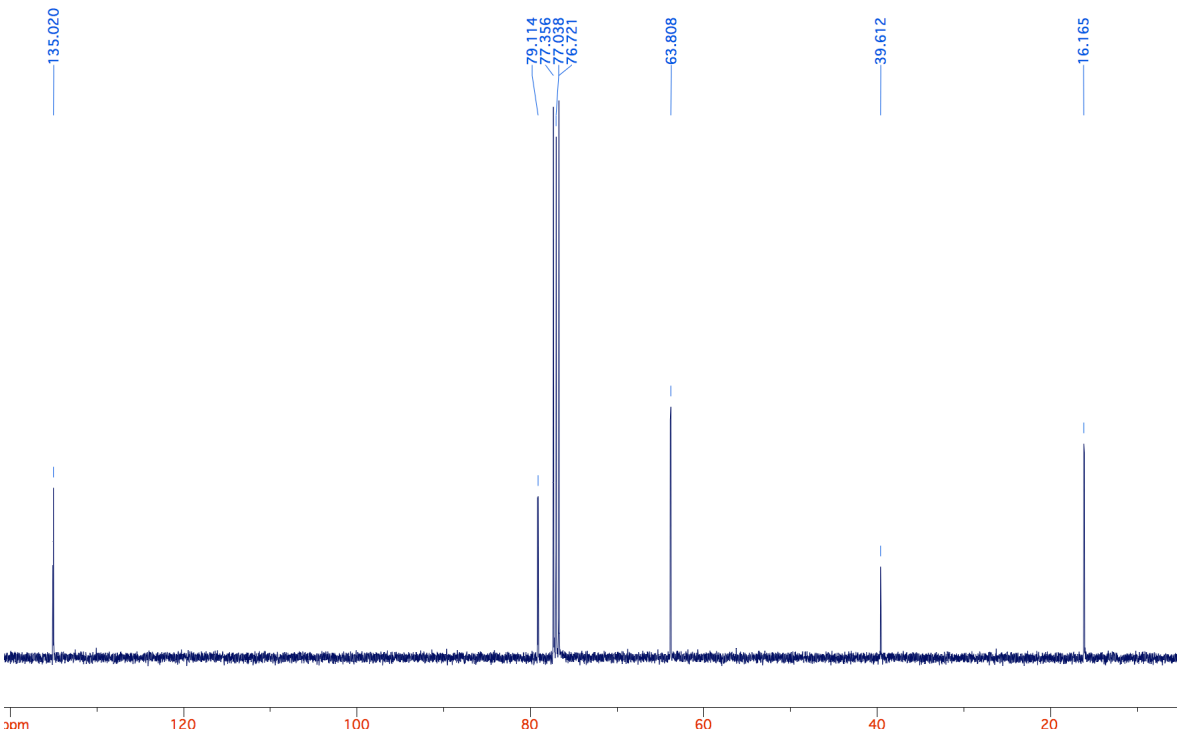
^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 6.12 (m, 2H), 5.21 (m, 2H), 4.10 (m, 8H), 2.91 (m, 1H), 2.03 (m, 1H), 1.33 (t, J = 7.1 Hz, 12H) ;

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 135.0(2C), 79.1(2C), 63.8(4C), 39.6, 16.2.(4C)

^{1}H NMR:



^{13}C NMR



General synthesis of products

Procedure used in the synthesis of racemic products

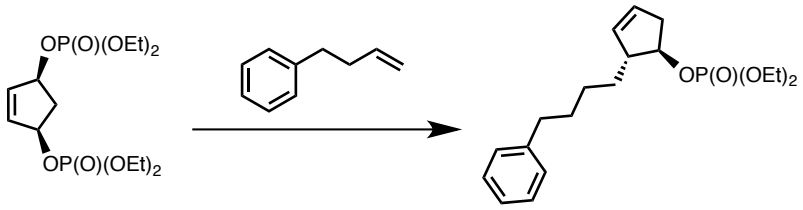
In a 5 mL flame dried flask, CuI (7.7 mg, 0.04 mmol, 0.1 eq) and the non-chiral phosphoramidite ligand **L1** (21.6 mg, 0.04 mmol, 0.1 eq) were dissolved in CH_2Cl_2 (0.8 ml) under an argon atmosphere and allowed to stir for 1 h at room temperature. In another flask, Cp_2ZrHCl (206.3 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of corresponding alkene (1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.50 ml) under an argon atmosphere. After stirring for 20 to 40 min, the resulting clear solution was transferred via syringe over about 1 min to the stirred solution containing the copper and ligand under an argon atmosphere. The resulting dark mixture was allowed to stir for an additional 10 min before *meso*-4-cyclopentene-1,3- bisdiethylphosphate (148mg, 0.40 mmol, 1.0 eq) was added dropwise *via* microsyringe and the reaction was arbitrarity stirred overnight. Afterwards, the reaction mixture was diluted and quenched by addition of petrol (ca 3 ml) and then NH_4Cl (1 M aq., ca

1.5 ml). The mixture was partitioned between water and petrol and the aqueous phase extracted with petrol (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat. ca 10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Flash column chromatography of the residue (EtOAc/petrol; SiO_2) gave the desired cyclic allylic product.

Procedure used in the synthesis of asymmetric products

In a 5 mL flame dried flask, CuCl (3.8 mg, 0.04 mmol, 0.1 eq) and the phosphoramidite ligand **L18** (26.1 mg, 0.048 mmol, 0.12 eq) were dissolved in CH_2Cl_2 (1.5 ml) under an argon atmosphere and allowed to stir for 1 h at room temperature. In another flask, Cp_2ZrHCl (206.3 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of corresponding alkene (1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.80 ml) under an argon atmosphere and stirred for 20 to 40 min. Then to the solution of CuCl and ligand was added $AgNTf_2$ (18.7 mg, 0.048 mmol, 0.12 eq) and the resulting mixture was left to stir for 15 min. The mixture was then added to the alkylzirconium flask using a syringe filter. The resulting mixture was left to stir for additional 10 min before the *meso*-4-cyclopentene-1,3- bisdiethylphosphate (148mg, 0.40 mmol, 1.0 eq) was added dropwise *via* microsyringe and the reaction was arbitrarity stirred overnight. Afterwards, the reaction mixture was diluted and quenched by addition of petrol (ca 3 ml) and then NH_4Cl (1 M aq., ca 1.5 ml). The mixture was partitioned between water and petrol and the aqueous phase extracted with petrol (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat. ca 10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Flash column chromatography of the residue (EtOAc/petrol; SiO_2) gave the desired product.

Diethyl ((1R,2R)-2-(4-phenylbutyl)cyclopent-3-en-1-yl) phosphate (4.5)



In a 5 mL flame dried flask, CuCl (3.8 mg, 0.04 mmol, 0.1 eq) and the (*S*, *S*)-phosphoramidite ligand **L18** (26.1 mg, 0.048 mmol, 0.12 eq) were dissolved in CH_2Cl_2 (1.5 ml) under an argon atmosphere and allowed to stir for 1 h at room temperature. In another flask, Cp_2ZrHCl (206.3 mg, 0.80 mmol, 2.0 eq) was added to a stirred, room temperature, solution of 4-phenyl-1-butene (0.15 ml, 1.0 mmol, 2.5 eq) in CH_2Cl_2 (0.80 ml) under an argon atmosphere and stirred for 20 min. Then to the solution of CuCl and ligand was added $AgNTf_2$ (18.7 mg, 0.048 mmol, 0.12 eq) and the resulting mixture was left to stir for 15 min. The mixture was then added to the alkylzirconium flask using a syringe filter. The resulting mixture was left to stir for additional 10 min before the *meso*-4-cyclopentene-1,3- bisdiethylphosphate (148mg, 0.40 mmol, 1.0 eq) was added dropwise *via* microsyringe and the reaction was arbitrarity stirred overnight. Afterwards, the reaction mixture was diluted and quenched by addition of petrol (ca 3 ml) and then NH_4Cl (1 M aq., ca 1.5 ml). The mixture was partitioned between water and petrol and the aqueous phase extracted with petrol (3 × 10 mL). The combined organic phase was washed with $NaHCO_3$ (aq. sat. ca 10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product. Flash column chromatography of the residue (EtOAc/petrol, 45: 55; SiO_2) gave the desired product in 75% yield (105.7 mg, 0.3 mmol).

Enantiomeric excess of 85% was determined by HPLC [Chiralpak® IA; flow: 1 mL/min; hexane/i-PrOH: 95: 5; λ = 210 nm; major enantiomer t_R = 8.3 min; minor enantiomer t_R = 10.8 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H /ppm: 7.30 – 7.25 (m, 2H), 7.20 – 7.15 (m, 3H), 5.70 – 5.63 (m, 2H), 4.71 – 4.65 (m, 1H), 4.09 (q, *J* = 7.32 Hz, 4H), 2.80 – 2.73 (m, 2H), 2.62 (t, *J* = 7.76 Hz, 2H), 2.48-2.54 (m, 1H), 1.70 – 1.60 (m, 2H), 1.50 – 1.36 (m, 4H), 1.33 (t, J = 7.1 Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ_C /ppm: 142.6, 132.6, 128.3(2C), 128.2(2C), 127.2, 125.6, 83.0, 63.5, 52.9, 39.8, 35.8, 32.5, 31.6, 27.1, 16.2.

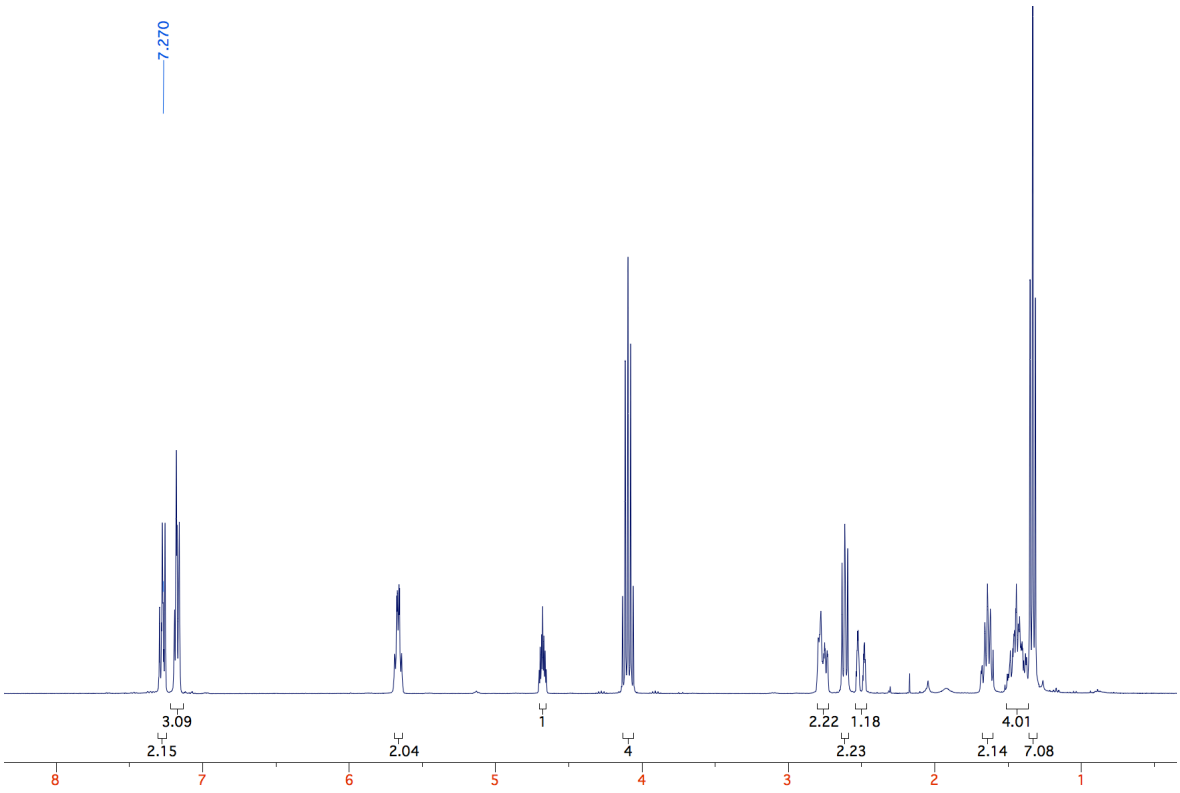
^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm: −1.46

HRMS (ESI) *m*/z calcd for $C_{19}H_{29}O_4P$ $[M+H]^+$: 353.1803, found: 353.1883

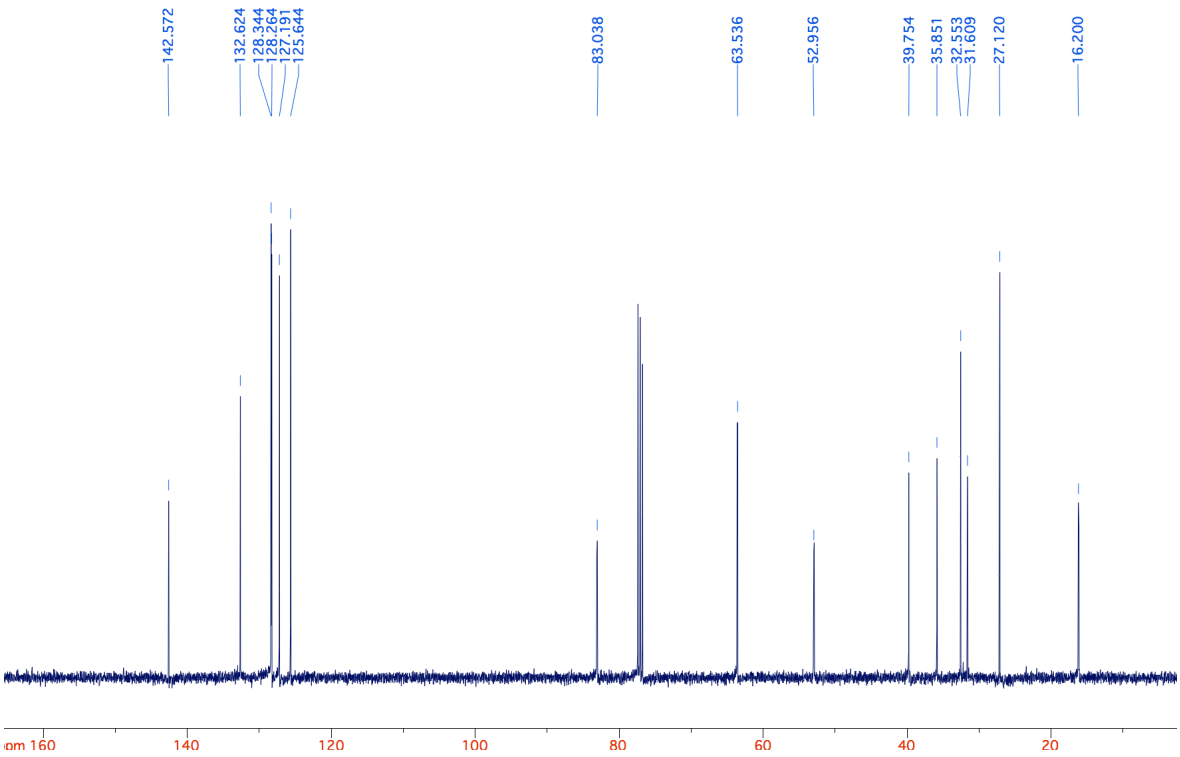
IR (ATR) ν (cm^{-1}, $CHCl_3$): 2931, 2587, 1454, 1370, 1264, 1167, 1029, 976, 821, 748, 700

$[\alpha]^{20}_{589}$ = -68.1 (c=0.82 in $CHCl_3$, 85% ee).

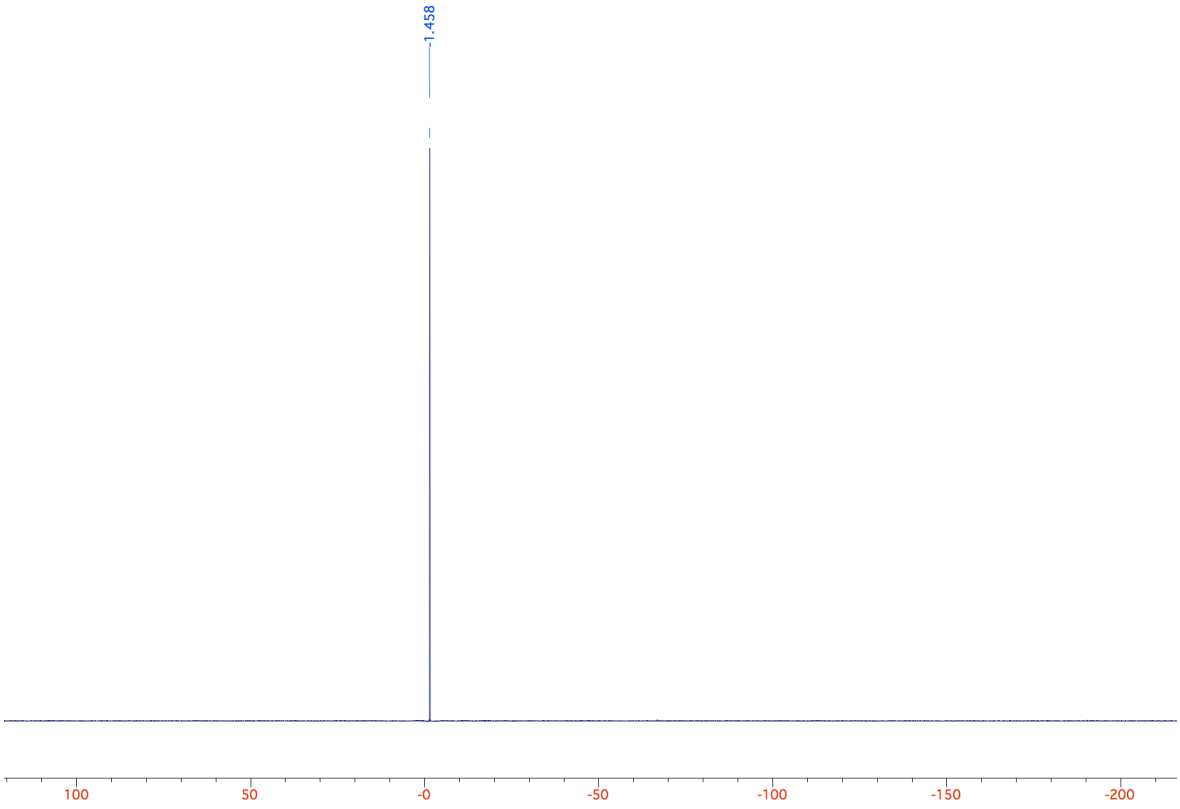
^{1}H NMR:



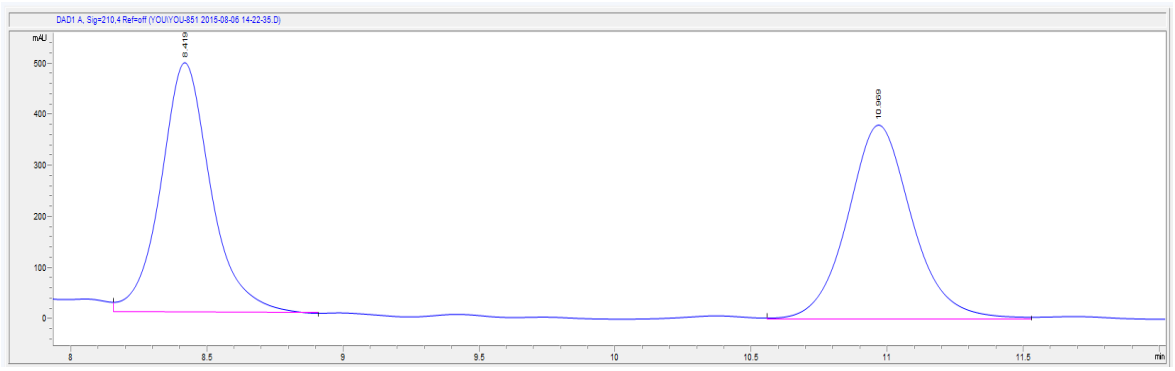
^{13}C NMR:

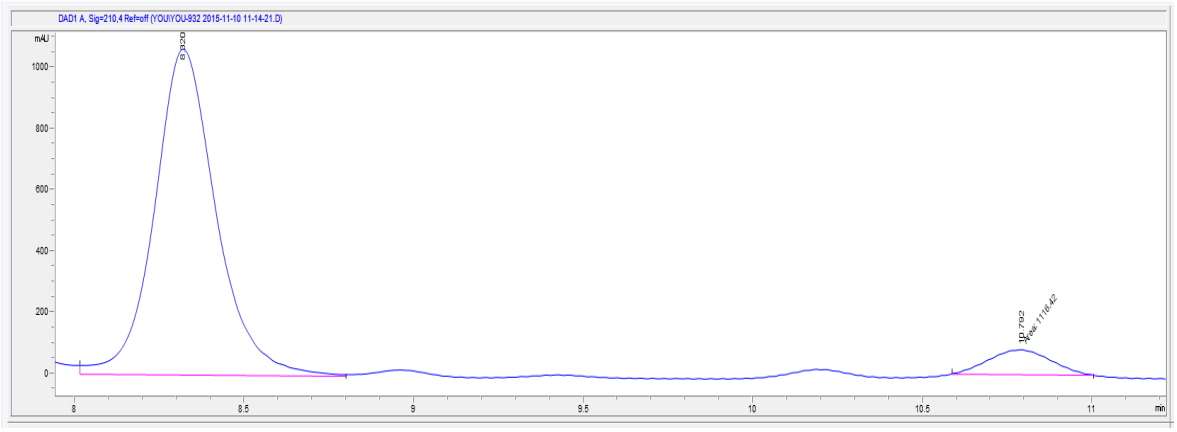


^{31}P NMR:



HPLC traces:





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