Cu-catalyzed asymmetric conjugate additions of alkylzirconium species to various linear substrates

Zhenbo Gao



St Edmund Hall

University of Oxford

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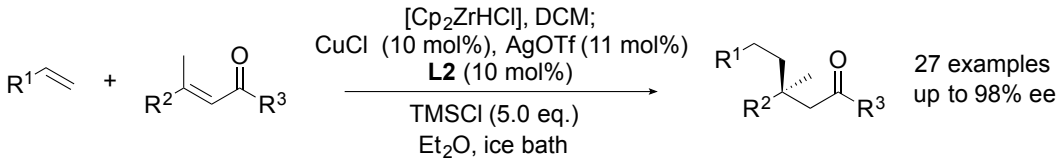
A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Organic Chemistry

Abstract

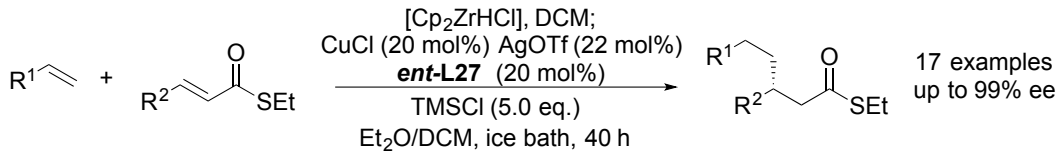
This thesis documents the development of the copper-catalyzed asymmetric conjugate addition (ACA) of alkylzirconium species to a range of linear Michael acceptors, constructing various chiral centres.

Chapter 1 gives an overview of the Cu-catalyzed asymmetric conjugate addition of various organometallic reagents to cyclic and noncyclic Michael acceptors.

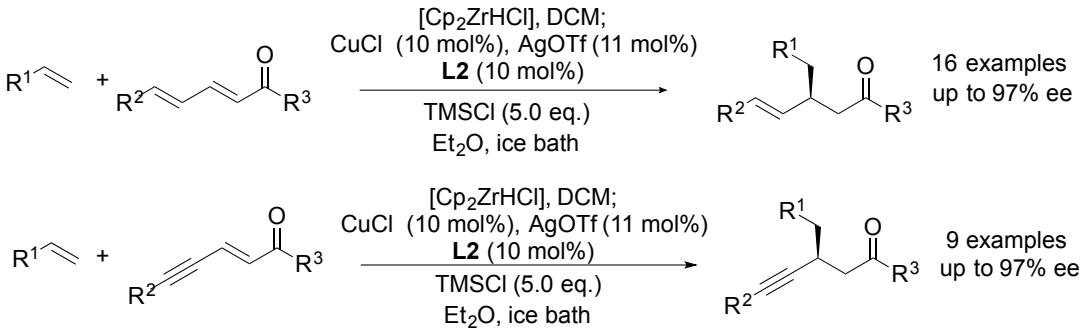
Chapter 2 illustrates Cu-catalyzed ACAs of alkylzirconium species to trisubstituted enones, forming acyclic quaternary centres efficiently.



Chapter 3 describes Cu-catalyzed ACAs to *α,β*-unsaturated thioesters, accessing several nonracemic fragrances and acyclic stereochemical arrays.



Chapter 4 discloses Cu-catalyzed ACAs to polyunsaturated substrates, constructing *β*- to carbonyl chiral centres from dienones, dienthioates, ynenones, and ynethioates.



Chapter 5 includes experimental procedures and data.

Declaration

The thesis has not been previously submitted for a degree, diploma or any other qualifications at the University of Oxford or elsewhere. I hereby declare that this thesis entitled “Cu-catalyzed asymmetric conjugate additions of alkylzirconium species to various linear substrates” is completed by myself for the degree of Doctor of Philosophy in Organic Chemistry under the supervision of Prof. Stephen Fletcher.

Three projects were completed in the thesis. The results and data detailed in Chapters 2-5 were obtained by myself, and have been published in three peer-reviewed papers (*Chemical Science* in 2017, *Chemical Communications* in 2017, and *Chemical Communications* in 2018). Contributions from group members are clearly stated.

Zhenbo Gao

May 2018

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Besides my supervisor, I would like to thank my colleagues. They taught me experimental skills, shared ideas, offered suggestions and discussed projects with me. Meanwhile, we shared many precious moments of pub crawl, singing karaoke, bowling, and sightseeing in Barcelona, Kyoto and Regensburg. I will never forget these happy moments with my lovely labmates.

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Last but not least I would like to gratefully acknowledge my family, my wife Huijie, my parents, and grandparents for their endless support, and encouragement regardless of conditions. They gave me the power to carry on whenever I wanted to give up. Without their backing, I would definitely not have been able to complete my DPhil in Oxford.

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Abbreviations

ACA	asymmetric conjugate addition
Ac	acetyl
Ar	aryl
BINAP	2, 2'-bis(diphenylphosphino)-1, 1'-binaphthyl
BINOL	1, 1′-Bi-2-naphthol
br.	broad
Bz	benzyl
Bu	butyl
ºC	degrees Celsius
cat.	catalyst
CI	chemical ionization
Cy	cyclohexyl
d	doublet or deuterated
DCM	dichloromethane
DIBAL	diisobutylaluminium hydride
dr	diastereomeric ratio
ee	enantiomeric excess
eq	equivalents
Et	ethyl
et al.	et alii (Latin: and others)
EWG	electron withdrawing group
g	gram(s)
h	hour(s)
Hex	*n*-hexyl

HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
^{i}Pr	*iso*-propyl
IR	infrared
J	coupling constant
L	ligand
LG	leaving group
LRMS	low resolution mass spectrometry
M	molar, mega or metal
m	milli (10^{-3}) or multiplet
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
min	minutes
mol	mole(s)
m.p.	melting point
MS	mass spectrometry
2-Me-THF	2-Methyltetrahydrofuran
MTBE	methyl tert-butyl ether
NMR	nuclear magnetic resonance
1-Nph	1-naphthyl
o	*ortho*
Oct	*n*-octyl
p	*para*
Pent	*n*-pentyl

Ph	phenyl
pin	pinacolato
ppm	parts per million
Pr	*n*-propyl
q	quartet
R	generic group/substituent
rac	racemic
RT	room temperature
s	singlet
t	triplet
^{t}Bu	*tert*-butyl
TC	thiophen-2-carboxylate
Tf	trifluoromethanesulfonate/triflate
TMSCl	trimethylsilyl chloride
Tol	Toluene
Tos	Tosyl
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet
δ	chemical shift
μ	micro (10^{-6})

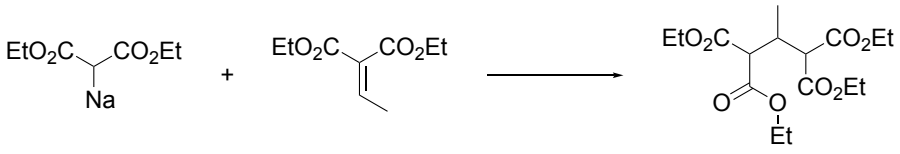
Chapter 1

Introduction

This chapter is divided into two parts. 1) Cu-catalyzed asymmetric conjugate addition (ACA) to cyclic Michael acceptors, and 2) Cu-catalyzed ACA to linear substrates. The first part is devoted to the construction of chiral tertiary and quaternary centres in cyclic systems. Different organometallic reagents applied in Cu-catalyzed ACAs are also reviewed. In the second part, previous work on Cu-catalyzed ACAs to linear acceptors has been summarized. There is much less research on linear systems than on cyclic systems, especially for the construction of quaternary centres.

A conjugate addition is the addition of a nucleophile to an acceptor-substituted alkene or alkyne. It is part of fundamental C-C and C-heteroatom bond-forming strategy in organic synthesis.[1] The first example of conjugate addition was reported by Komnenos in 1883, in which reaction of deprotonated diethyl malonate with diethyl 2-ethylidenemalonate formed a 1,4- adduct (Scheme 1-1).[2]

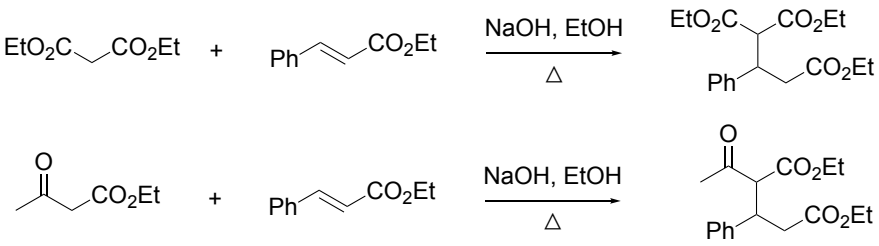
The Komnenos group



Scheme 1-1 An example of conjugate addition by Komnenos

This reaction was followed by Michael, whose work on this type of conjugate addition resulted in its additional name of Michael reaction or Michael addition (Scheme1-2).[3] In his research, he used NaOH as a strong base to activate the nucleophile, which was then added to a Michael acceptor, ethyl cinnamate, affording the product.

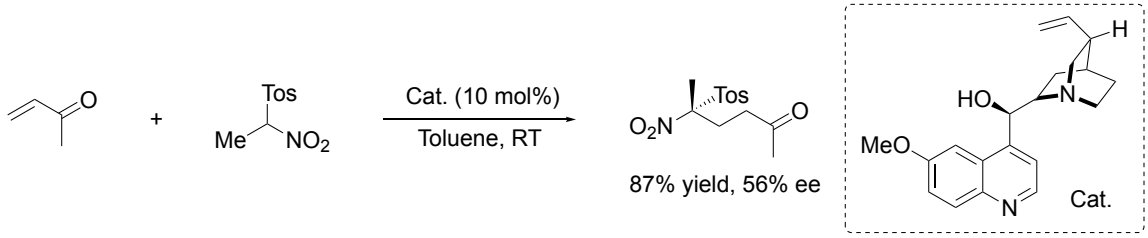
The Michael group



Scheme 1-2 Examples of conjugate additions by Michael

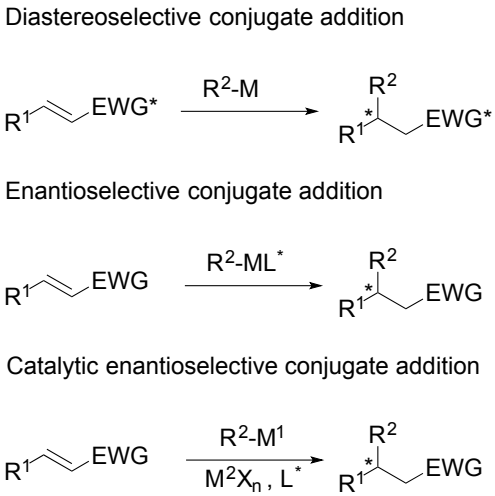
However, asymmetric Michael additions were not reported until nearly a hundred year later. In 1975, Wynberg and Helder published the first asymmetric conjugate addition (ACA).[4] In this study, nitrosulfone acted as a Michael donor, while methyl vinyl ketone worked as a Michael acceptor, catalyzed by quinine (Scheme1-3). The reaction afforded 87% yield with 56% ee. Since then, ACA has been investigated by a variety of groups.

The Wynber and Helder groups



Scheme 1-3 First example of asymmetric conjugate addition

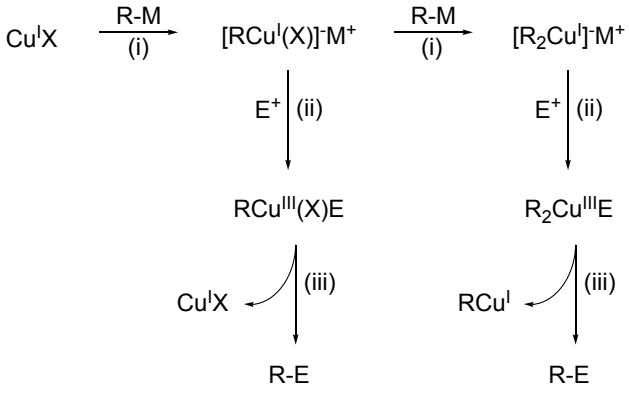
Three methods of asymmetric conjugate addition using organometallic reagents have been explored, namely, diastereoselective conjugate addition, enantioselective conjugate addition and catalytic enantioselective conjugate addition (Scheme 1-4). Copper catalyzed enantioselective conjugate addition is described in detail in the following section.



Scheme 1-4 Three potential strategies for ACA

Copper is a metal of choice in organometallic chemistry due to its high abundance and low cost. It is one of the first metals to be extensively used in organic synthesis, and most organocopper compounds appear in the form of nucleophilic organocopper reagents, generated *in situ* from a copper(I) complex and organometallic reagents.[1] The general mechanism of organocopper(I)-mediated C-C bond formation includes three elementary steps, namely, (i) transmetalation between a Cu(I) salt and an organometallic reagent; (ii) oxidative

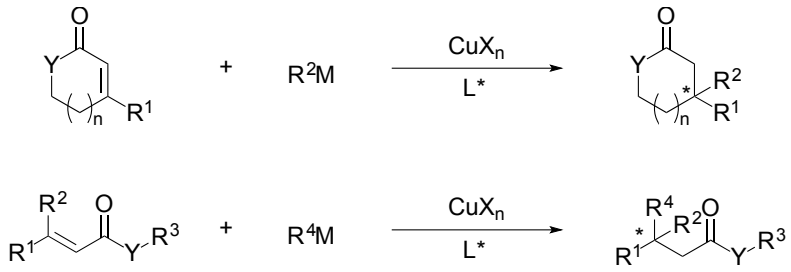
addition of an electrophile to the Cu(I) complex; and (iii) reductive elimination of the Cu(III) intermediate to obtain the desired product (R-E) and the Cu(I) species (scheme 1-5).[5] The transmetalation between organometallic reagents and Cu(I) complexes generally proceeds well, because the metal "M" is less electronegative than copper, and carbon-M bonds are weaker than carbon-Cu bonds.[6] Oxidative addition and reductive elimination are also favoured for most organocopper reactions. Since the 3d orbitals of copper atom are polarizable and high-energy, the d^{10} electronic configuration in Cu(I) enables charge transfer upon interaction with electrophiles, forming a Cu(III) intermediate, in a process of oxidative addition. The instability of the d^8 electronic configuration in Cu(III) leads to C-C bond formation, namely a reductive elimination.[5]



Scheme 1-5 General mechanism of organocopper(I)-mediated C-C bond formation

Numerous research groups have developed the Cu-catalyzed enantioselective Michael reaction into one of the most robust and widely applied synthetic methods.[7–12] The greatest advancement in the last decade is the development of phosphoramidite ligands, capable of affording excellent enantioselectivities with a variety of Michael acceptors.[13, 14] Meanwhile, several different organometallic reagents, such as Grignard reagents,[15] organozincs,[16, 17] alkylaluminium reagents,[18] organoboron reagents,[19] and alkylzirconium species,[20] have been progressively explored in combination with various copper-chiral

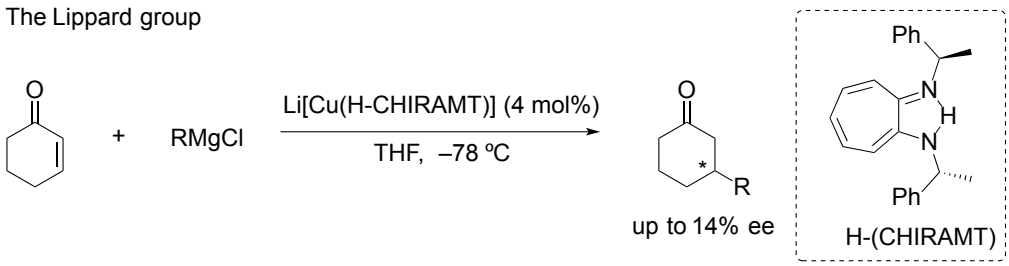
ligand complexes. We will discuss the advancement of Cu-catalyzed enantioselective conjugate additions based on two different types of Michael acceptors, cyclic (Scheme 1-6 top) and noncyclic acceptors (Scheme 1-6 bottom).



Scheme 1-6 Cu-catalyzed 1,4-addition of organometallics to cyclic and noncyclic Michael acceptors

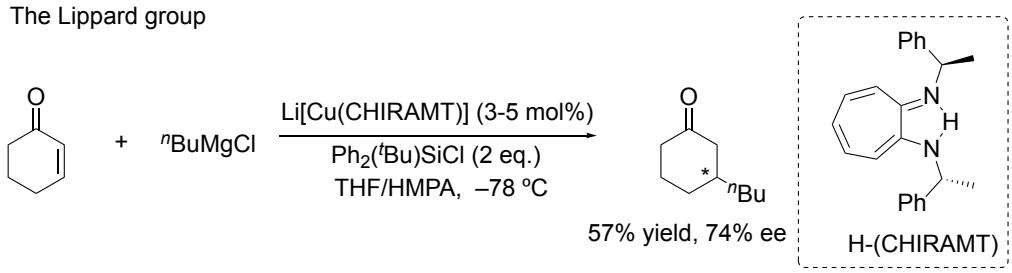
1.1 Copper catalyzed asymmetric 1,4-addition to cyclic systems

1.1.1 Cu-catalyzed asymmetric conjugate addition with Grignard reagents



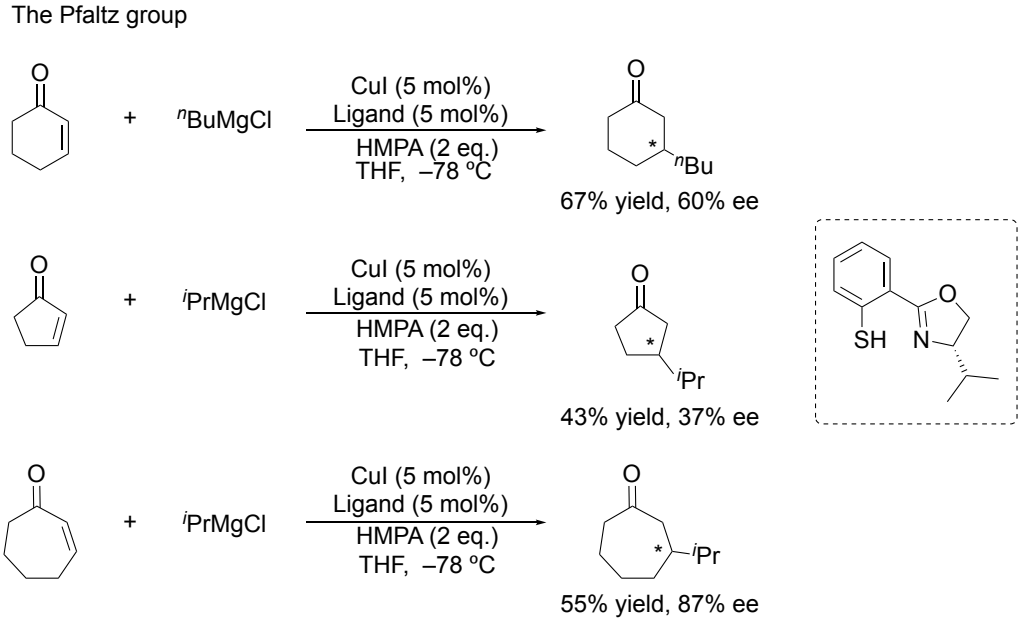
Scheme 1-7 The first reported Cu-catalyzed ACAs to cyclic acceptors

In 1988, the Lippard group[21] explored the Cu-catalyzed ACA of Grignard reagents to 2-cyclohexen-1-one using H-(CHIRAMT) as a chiral ligand to control stereochemistry, achieving the adduct with only 14% ee (Scheme1-7). Later, the reaction was further optimized by the use of HMPA and a silyl reagent, $Ph_2(^tBu)SiCl$. The results were optimized to over 57% yield and 74% ee when adding ^{n}BuMgCl to 2-cyclohexen-1-one (Scheme 1-8).[22]



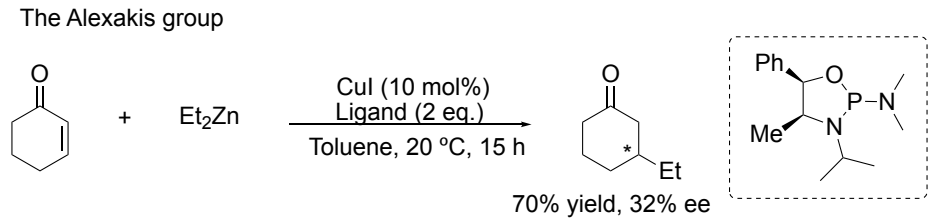
Scheme 1-8 The first reported Cu-catalyzed ACAs to cyclohexanone

Then the cyclic acceptors were expanded from 2-cyclohexenone to 2-cyclopentenone and 2-cycloheptenone. Pfaltz and Zhou synthesized a series of chiral single enantiomer mercaptoaryl-oxazolines, whose use in enantioselective 1,4-additions resulted in a range of adducts with moderate to good yields and up to 87% ee (Scheme 1-9).[23] Since only moderate yield and enantioselectivity were achieved in these reactions, most groups then went on to explore the less reactive dialkylzinc reagents in 1,4-additions.



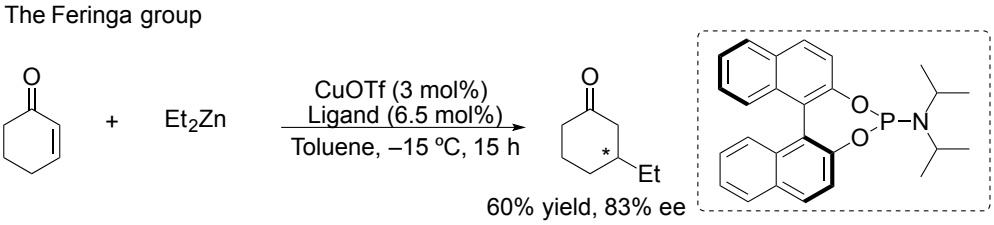
Scheme 1-9 Cu-catalyzed ACAs to 5-, 6-, and 7-membered cyclic acceptors

1.1.2 Cu-catalyzed asymmetric conjugate addition with dialkylzinc reagents



Scheme 1-10 The first Cu-catalyzed ACAs using organozincs

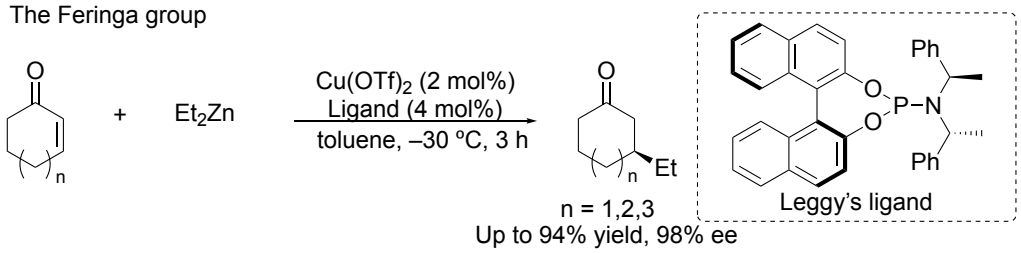
Alexakis *et al.* combined dialkylzinc reagents with the cyclic acceptor, 2-cyclohexen-1-one in Cu-catalyzed ACAs, and achieved enantioselectivity (Scheme 1-10).[24] CuI (10 mol%), associated with a nonracemic trivalent phosphorus ligand (2 eq.) allowed ACAs of diethylzinc reagents to 2-cyclohexen-1-one with 70% yield and 32% ee. Later, they found that the ACA could be accelerated either by $Cu(OTf)_2$ or trivalent phosphorus ligands.[25] After optimizing the conditions for the Cu-catalyzed ACA to cyclohexenone with $Cu(OTf)_2$ (0.5 mol%) and TADDOL-based phosphorus ligands (1 mol%) using dialkylzinc reagents, they finally obtained the 1,4- adduct, 3-ethylcyclohexan-1-one with 96% ee.[26]



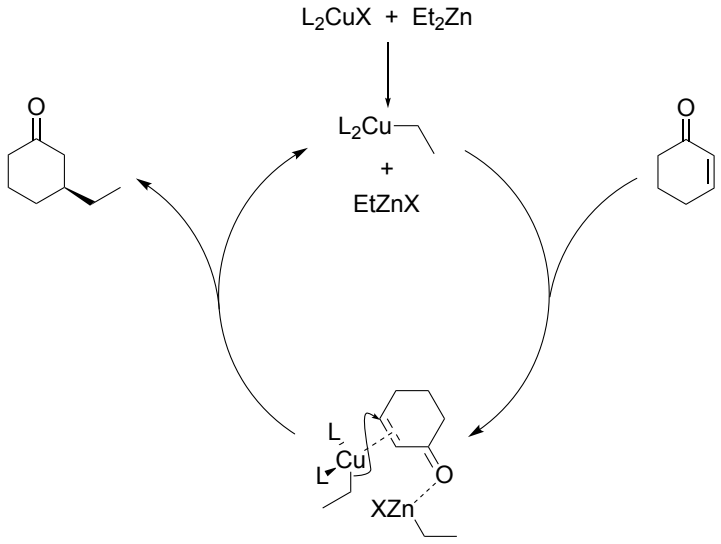
S**cheme 1-11** Cu-catalyzed ACAs using organozincs with phosphoramidites

In 1996, Feringa *et al.* introduced another ACA of Et_2Zn to 2-cyclohexen-1-one, using a catalytic amount of CuOTf (3.5 mol%) and a novel BINOL-based phosphorus ligand (6.5 mol%). This new approach successfully accessed the chiral product with over 60% yield and 83% ee (Scheme 1-11).[27] The following year, they disclosed a new phosphoramidite ligand, which showed a significant

improvement on their previous results. This ligand is now commonly known as Leggy's ligand. A combination of the Leggy's ligand (2 mol%) and $Cu(OTf)_2$ (2 mol%) could afford products with excellent results (up to 94% yield, 98% ee) after a reaction time of 3 hours (Scheme 1-12).[28] For the first time, the complete enantiocontrol for the addition of dialkylzinc species to a range of cyclic enones could be observed. Furthermore, this novel class of nonracemic ligands later proved to be extremely effective for controlling the enantioselectivity in the reaction of various cyclic and acyclic Michael acceptors.[17]

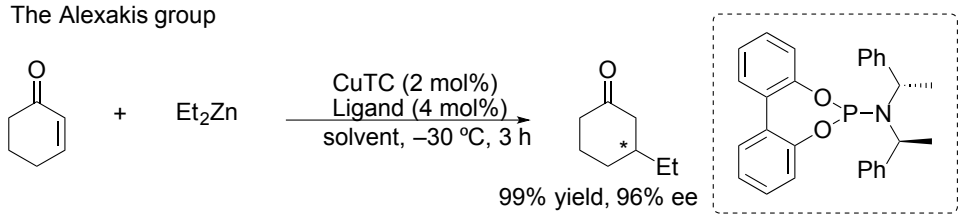


Scheme 1-12 Cu-catalyzed ACAs using organozincs with phosphoramidites



Scheme 1-13 Proposed catalytic cycle of the ACA

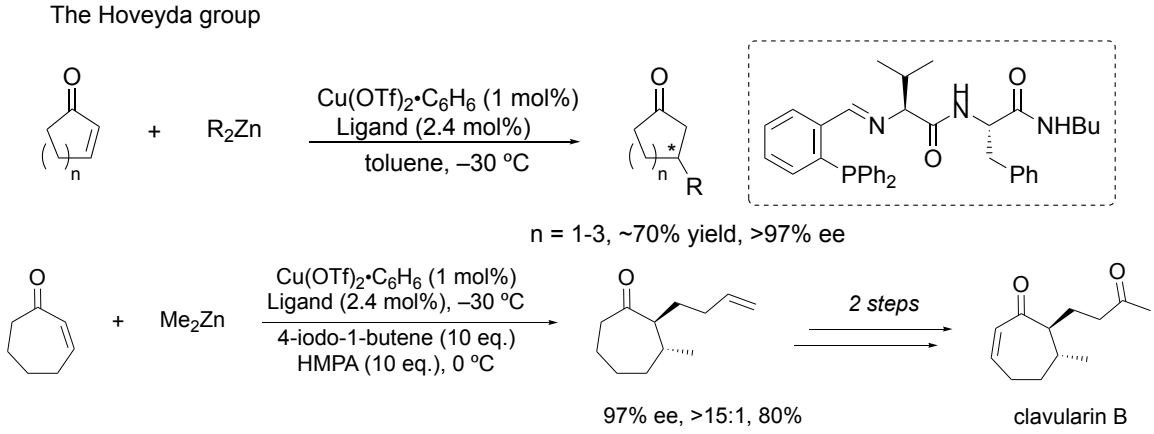
A negative non-linear effect was observed in the 1,4-addition, and they also proposed a catalytic cycle (Scheme 1-13) in which they suggested the zinc played two roles, transferring ethyl groups and activating the carbonyl oxygen.[29]



Scheme 1-14 Cu-catalyzed ACAs using organozincs

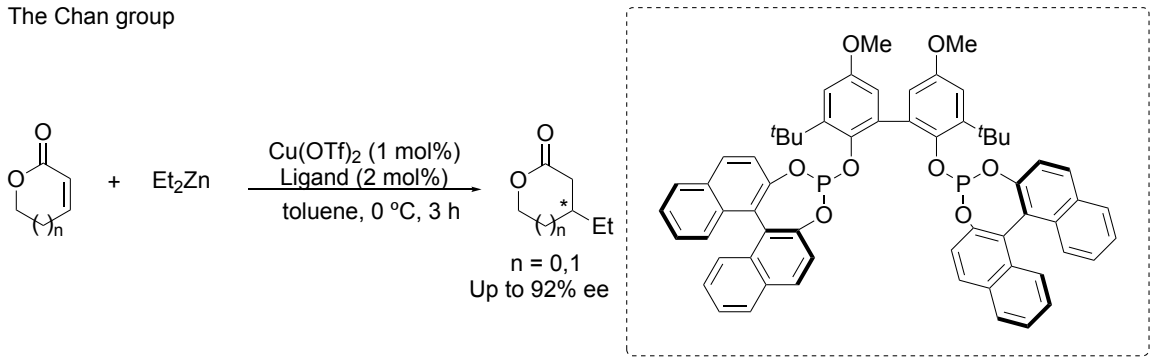
In 2002, the Alexakis group[30] turned to the development of new phosphoramidite ligands based on chiral amines and atropoisomerically flexible biphenols, inducing high enantioselectivities (ee's up to 99%) in the Cu-catalyzed ACAs of dialkylzinc reagents to a range of cyclic and acyclic Michael acceptors (Scheme1-14). For the product, 3-ethylcyclohexan-1-one, a yield over 99% with 96% ee was achieved using 2 mol% CuTC associating with 4 mol% ligand in Et_2O. They also found that their ACA could tolerate several different solvents, like toluene, DCM, THF, and EtOAc, affording excellent ee's. The wide solvent scope may solve the problem of the poor solubility of some substrates. This new approach replaced the traditional but expensive $Cu(OTf)_2$, popular in Cu-catalyzed ACAs, with cheaper copper carboxylates and showed that the Lewis acidity of the copper salt, an important factor in previous ACAs, was not a significant factor in their reactions.

Seminal work from Hoveyda also advanced this area (Scheme 1-15).[31] A phosphine-based catalyst was proposed, use of which in the Cu-catalyzed ACAs allowed efficient installations of alkyl groups to five-, six-, and seven-membered ring enones. The $Cu(OTf)_2 \bullet C_6H_6$ complex could be lowered to 1 mol% with only 2.4 mol% of phosphine, while the yield remained at around 70% with over 97% ee. Meanwhile, the Zn-enolate intermediate could be functionalized *in situ*, affording clavularin B after a four-step synthesis.



Scheme 1-15 Cu-catalyzed ACAs by Hoveyda

A highly enantioselective conjugate addition of diethylzincs to lactones was achieved by the Chan group (Scheme1-16).[32] The reaction was controlled by a diphosphate-copper complex, prepared *in situ*, and excellent enantioselectivities were obtained using this new diphosphate ligand. The ethyl group was introduced to 5,6-dihydro-2H-pyran-2-one with 92% ee.

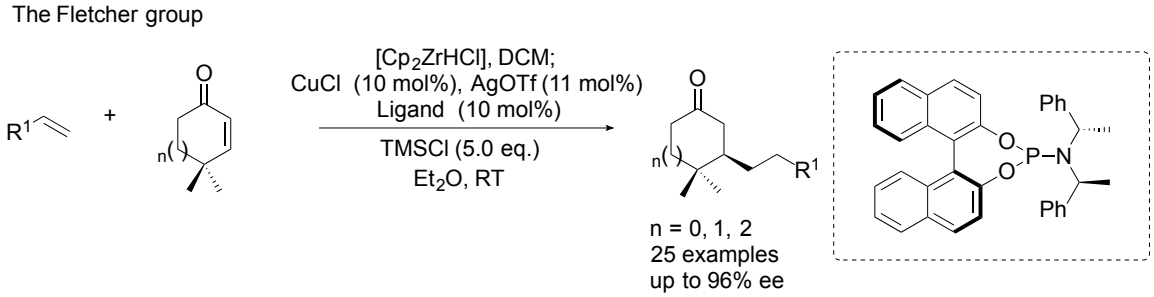


Scheme 1-16 Cu-catalyzed ACA to lactones

1.1.3 Cu-catalyzed asymmetric conjugate addition with alkylzirconium reagents

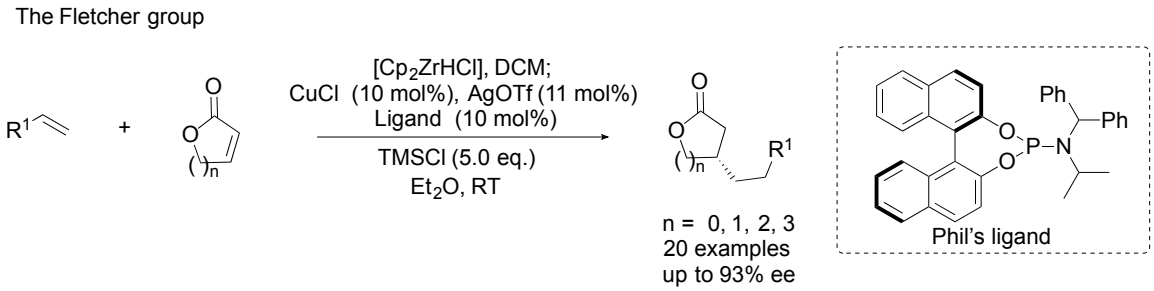
The Fletcher group reported the Cu-catalyzed ACA of alkylzirconium species, generated *in situ* from hydrozirconation of alkenes with the Schwartz's reagent, to cyclic enones. Based on thousands of readily available olefins, and the high functional group tolerance of zirconocene, the alkylzirconium species greatly

extend the scope of Michael donors in ACAs. Excellent results (25 examples, up to 96% ee) were achieved with catalytic amount of copper ligand complex, formed *in situ* from CuOTf and Leggy's ligand (Scheme 1-17).[20]



Scheme 1-17 Cu-catalyzed ACA of alkylzirconium species to cyclic enones

In 2014, the Fletcher group reported ACAs to lactones using alkylzirconium reagents and Cu-Phil's ligand complex affording up to 93% ee (Scheme1-18).[33] The new approach extensively broadened the scope of nucleophiles, and several important functional groups were also introduced without compromising on yield or ee.



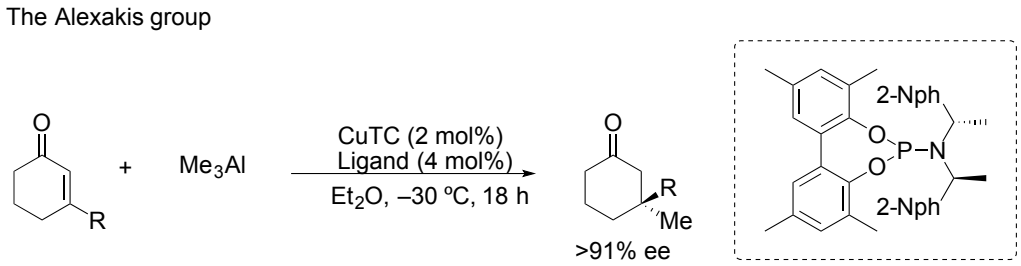
Scheme 1-18 Cu-catalyzed ACA to lactones of alkylzirconium reagents

1.1.4 Cu-catalyzed ACA for the construction of cyclic quaternary centres

The construction of quaternary centres with high levels of enantioselectivity is regarded as one of the most challenging tasks in asymmetric catalysis.[34] Hoveyda and Alexakis pioneered and developed robust Cu-catalyzed ACAs to

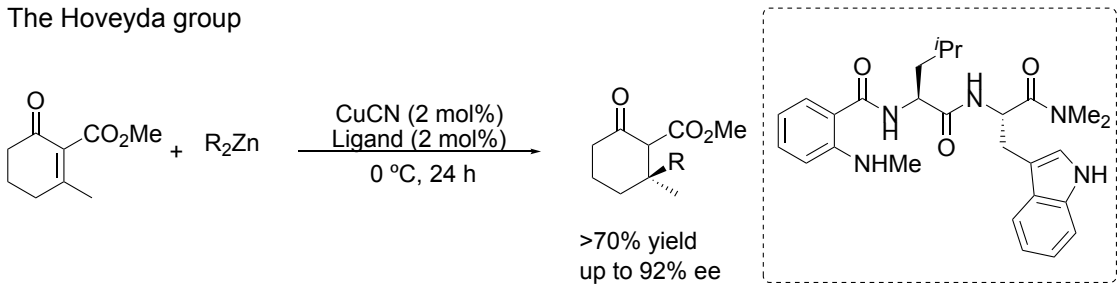
build quaternary centres from trisubstituted cyclic Michael acceptors after establishing reliable methods to form tertiary centres in cyclic enones.[35]

At the beginning of 2005, the Alexakis group reported the Cu-catalyzed ACA to trisubstituted cyclohexenones with trialkylaluminium reagents, which allowed straightforward construction of cyclic quaternary centres (Scheme 1-19).[36] Even though only ethyl and methyl groups could be introduced to a range of trisubstituted cyclohexenones, generally good yields and excellent ee's (>91%) were observed. Further studies on other substrates, e.g. *α*-substituted cyclohexenones, 1-cyclohexenylethan-2-one, gave good results, though the trialkylaluminium nucleophiles were limited to methyl or ethyl groups.[18]



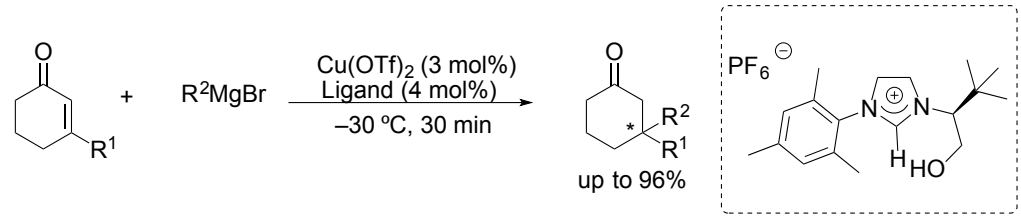
Scheme 1-19 First reported Cu-catalyzed ACA constructing cyclic quaternary centres

Later in the same year, Hoveyda disclosed the first Cu-catalyzed ACA of dialkyl- and diarylzinc reagents to *β*-substituted cyclic enones (Scheme1-20).[37] The copper catalyst complex was prepared from CuCN and amino acid-based ligands, and good results were obtained with only 2 mol% catalyst loading. The chiral product could be efficiently decarboxylated to a cyclic *β,β*-dialkyl ketone, which was not accessible by direct Cu-catalyzed addition. Also dialkylzinc reagents broadened the scope of nucleophiles compared with the previous trimethyl- and triethylaluminium species.



Scheme 1-20 Cu-catalyzed ACA constructing cyclic quaternary centres using organozincs

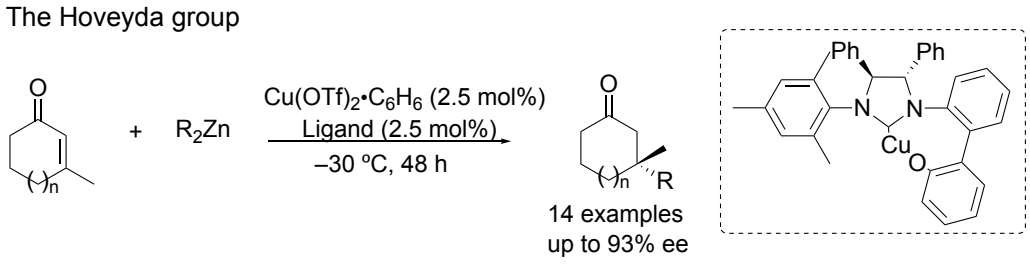
Alexakis *et al.* found another ACA, enantioselectively constructing cyclic quaternary centres enantioselectively with Grignard reagents (Scheme 1-21).[15] A catalytic amount of $Cu(OTf)_2$ associated with a chiral diaminocarbene ligand (NHC) afforded good to excellent yields while most ee's were below 90%. They also showed that there was no need to use specially activated enones, and the widely commercially available and easily prepared Grignard reagents greatly expanded the scope of nucleophiles. Later work from Alexakis[38] and Tomioka[39] continued developing NHC systems with Grignard reagents, but both of them failed to give excellent enantioselectivities when constructing quaternary centres.



Scheme 1-21 Cu-catalyzed ACA constructing cyclic quaternary centres of Grignard reagents

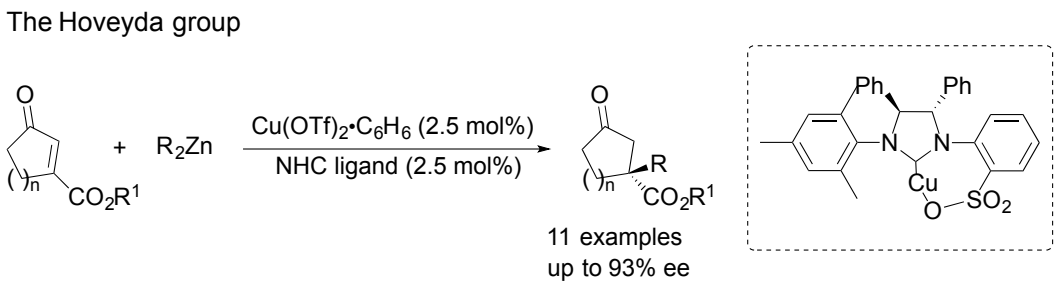
By applying NHC ligands in Cu-catalyzed ACAs, Hoveyda developed several approaches for the construction of quaternary centres with dialkylzincs and trialkylaluminium reagents.[40–42] They first combined dialkylzinc reagents with Cu-NHC systems. Easily prepared organozinc species were smoothly introduced with good results, especially for trisubstituted cyclohexenones, generally

achieving over 90% ee in most cases. In other substrates, results were only moderate (ca. 80% ee, Scheme 1-22).[40]



Scheme 1-22 Cu-NHC ACAs of dialkylzinc reagents

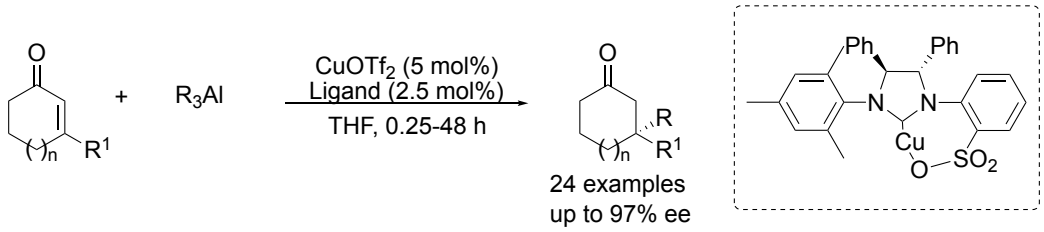
They next explored the reaction of cyclic *γ*-keto esters with dialkylzinc reagents catalyzed by another Cu-NHC complex.[41] Various cyclic ketones bearing carboxylic ester-substituted quaternary stereocenters were synthesized effectively with high yield and enantiomeric purity. The new chiral NHC ligand has distinct steric and electronic attributes and enhances the reactivity and selectivity (Scheme 1-23).



Scheme 1-23 Cu-NHC ACAs of dialkylzinc reagents

They also studied Cu-NHC ACAs with alkyl- and aryl- aluminium reagents.[42] 24 different chiral ketone products bearing a cyclic quaternary centre were prepared efficiently with a low catalyst loading (5 mol%). What is more important is that this new system also gave good results on cyclopentenones, which are normally hard to access in other systems (Scheme 1-24).[9, 13]

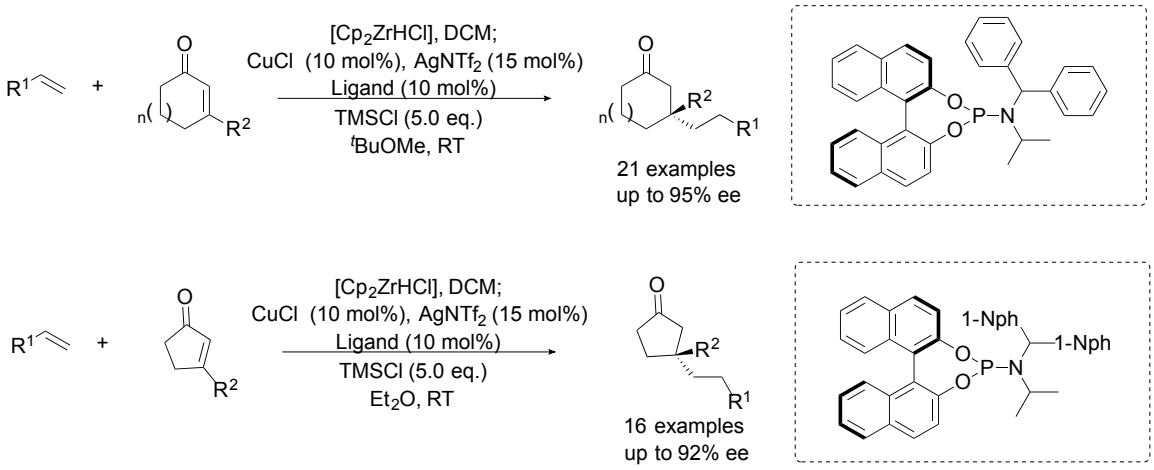
The Hoveyda group



Scheme 1-24 Cu-NHC ACAs of trialkylaluminium reagents

The Fletcher group explored ACAs constructing cyclic quaternary centres with alkylzirconium species, tolerating several important functional groups.[43,44] A combination of novel phosphoramidite ligands and $CuNTf_2$, generated *in situ*, played an important role in their systems. 37 examples bearing quaternary stereocenters were obtained with good yield and ee. Recently, a detailed study on trisubstituted cyclopentenones was conducted and a new ligand was disclosed which overcame the difficult problem of constructing quaternary centres in five-membered ring enones (Scheme1-25).[41]

The Fletcher group



Scheme 1-25 ACAs of alkylzirconium species to trisubstituted cyclic enones

1.2 Copper catalyzed asymmetric 1,4-addition to noncyclic systems

Compared with numerous studies on 1,4-addition to cyclic systems, research on noncyclic systems is scarce. This is partly because the controlled asymmetric addtion to linear enones is inherently more difficult than that of the corresponding cyclic enones. There is an *s-cis* and *s-trans* conformational interconversion in the system, which might interfere with enantiocontrol during the course of the reaction (Figure 1-1).[9] In terms of cyclic enones, this problem is avoided.

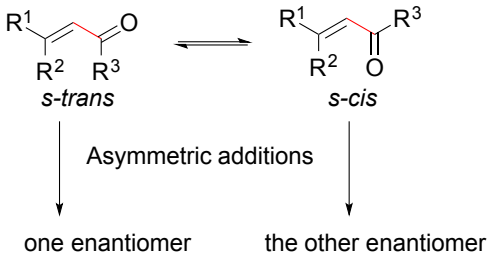
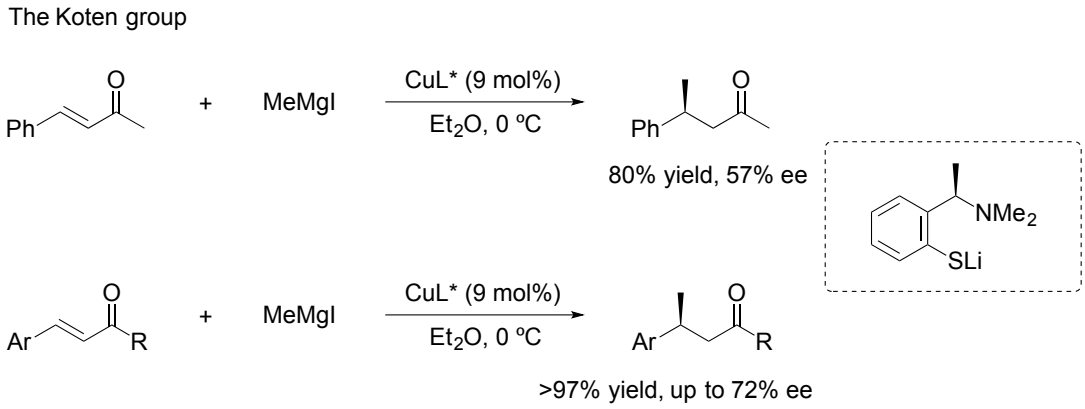


Figure 1-1 Interconversion between *s-cis* and *s-trans* conformers

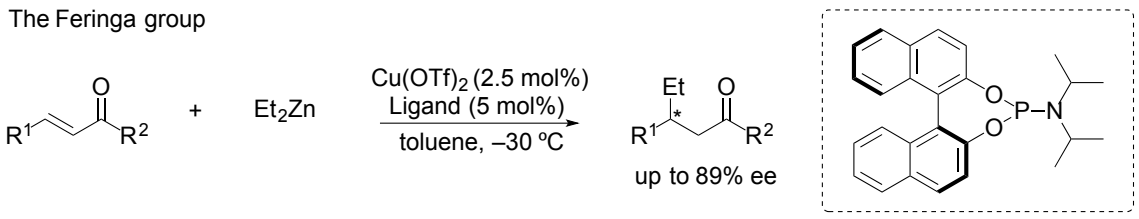
The Cu-catalyzed asymmetric conjugate addition to acyclic systems was initiated by the Koten group (Scheme 1-25).[45,46] They discovered a new arenethiolatocopper(I) complex (9 mol%), which affords good yields and enantioselectivities to a range of linear Michael acceptors. Further advancement was achieved in two aspects, the employment of complicated nucleophiles instead of simple methyl groups, and the improvement of ee from moderate to excellent results.



Scheme 1-26 First Cu-catalyzed asymmetric 1,4 addition to linear enones

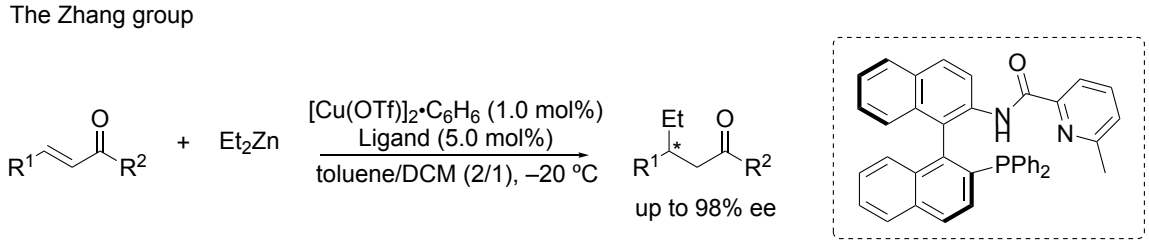
1.2.1 Cu-catalyzed ACA of dialkylzinc reagents to linear substrates

The development of Cu-catalyzed 1,4-addition to acyclic substrates proceeded slowly until the Feringa group discovered a new series of chiral phosphoramidite ligands.[28, 29] With only a catalytic amount of Cu(II) triflate (2.5 mol%) and nonracemic phosphorous ligand (5 mol%) in the system, ethyl groups from dialkylzinc reagents could be introduced to a range of linear enones bearing aryl groups (R^1 and R^2), affording good yields (~80%) and ee's of up to 89%. Compared with Koten's system, Feringa's systems showed an outstanding advantage (72% ee vs 89% ee). Since then, most research groups in this area focused on Cu-catalyzed ACA to linear substrates with dialkylzinc reagents and relied on chiral phosphorous ligands to control stereochemistry.

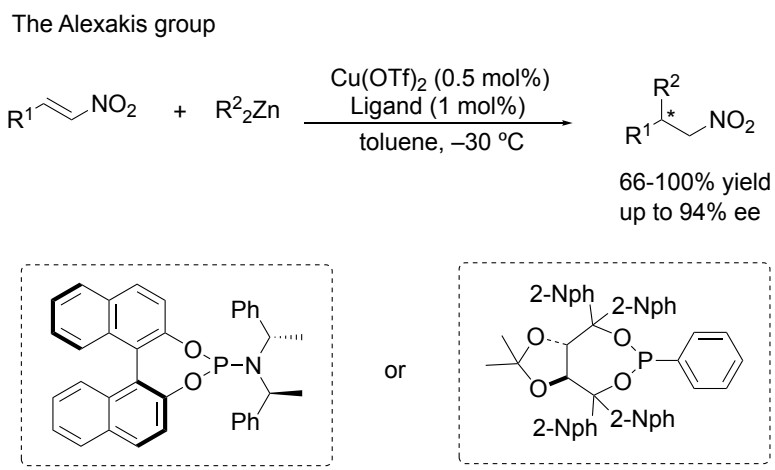


Scheme 1-27 Cu-catalyzed asymmetric 1,4 addition with organozincs

Meanwhile, the Zhang group reported another Cu-catalyzed ACA to acyclic enones with a novel chiral *P*,*N*-ligand (Scheme 1-28).[47] This new catalytic system could afford good results. In most cases, they obtained over 70% yield with 90% ee. They also varied R^1 and R^2 groups from alkyl group ^{i}Pr to different substituted arenes, and demonstrated that their reactions were capable of tolerating a range of linear enones without obvious loss on enantioselectivity or yield.



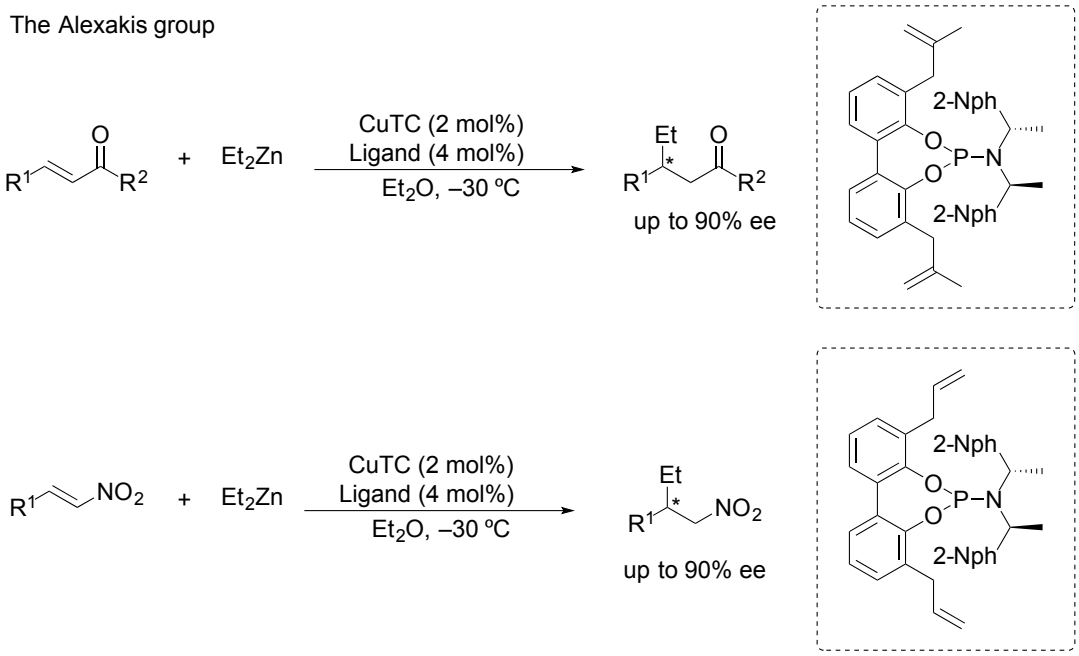
Scheme 1-28 Cu-catalyzed ACA of organozincs to linear enones



Scheme 1-29 ACAs to linear nitroolefins

The Alexakis group also made contributions to the area of ACAs to linear Michael acceptors through the discovery of a new class of ligands.[9,30] They developed a series of TADDOL-based phosphorous ligands, which were then used in ACAs of linear nitroolefins and showed comparable or even better results than those from Leggy's ligand (Scheme 1-28).[48] Alkyl and aryl group substituted nitroolefins were all suitable in their system with only 0.5% catalyst loading (66-100% yield with up to 94% ee). A range of biphenol-based phosphorous ligands,

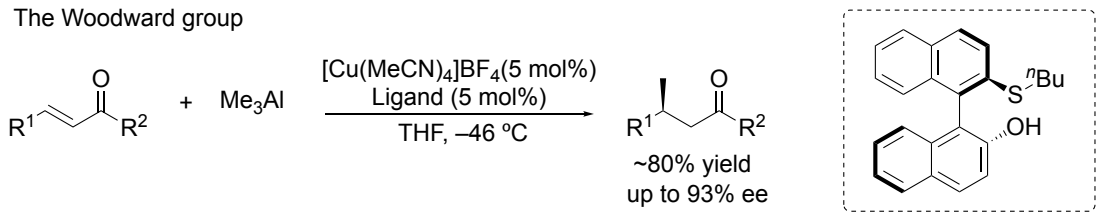
combined with copper(I)-thiophene-2-carboxylate (CuTC) form an asymmetric catalyst, which could construct chiral centres in various linear enones and nitroolefins with up to 90% ee (Scheme 1-30).[49]



Scheme1-30 ACAs to liner enones and nitroolefins

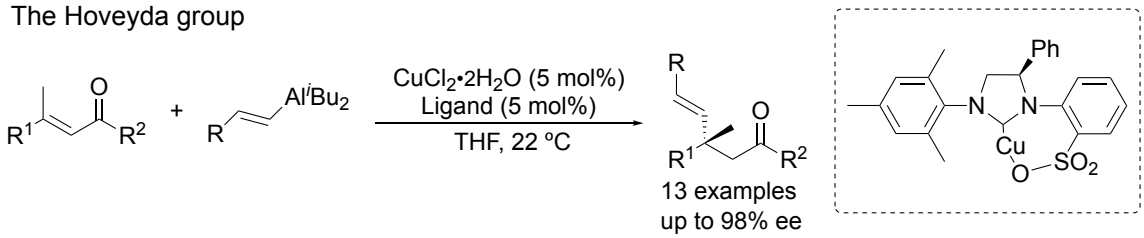
1.2.2 Cu-catalyzed ACA of trialkylaluminium reagents to linear enones

Seminal work from Woodward[50] and Hoveyda[51] applied trialkylaluminium reagents in ACAs to linear enones constructing teriary or quaternary centres. In Woodward's research, they applied trimethylaluminium reagents as nucleophiles in the addition (Scheme 1-30). Methyl groups were introduced to several linear enones using THF as solvent at –40 ºC. The ligand, 2-hydroxy-2'-alkylthio-1, 1'-binaphthyl (5 mol%) was used as a catalytic promoter to afford 80-93% ee in most cases. In terms of yield, most reactions gave around 80% isolated yield.



Scheme 1-31 ACAs of trimethylaluminium to linear enones

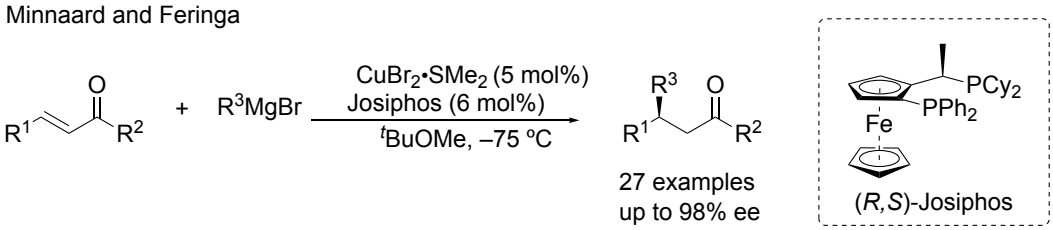
In 2014 the Hoveyda group[51] reported a method of constructing quaternary centres from trisubstituted enones using organoaluminium reagents (Scheme 1-32). They adopted one novel NHC ligand to induce the enantioselectivity in the system. With only 5 mol% catalyst loading, the nucleophiles were added efficiently at room temperature with very good yields and excellent ee's (up to 98%).



Scheme 1-32 ACAs of organoaluminium reagent to trisubstituted linear enones

1.2.3 Cu-catalyzed ACA with Grignard and alkylzirconium reagents

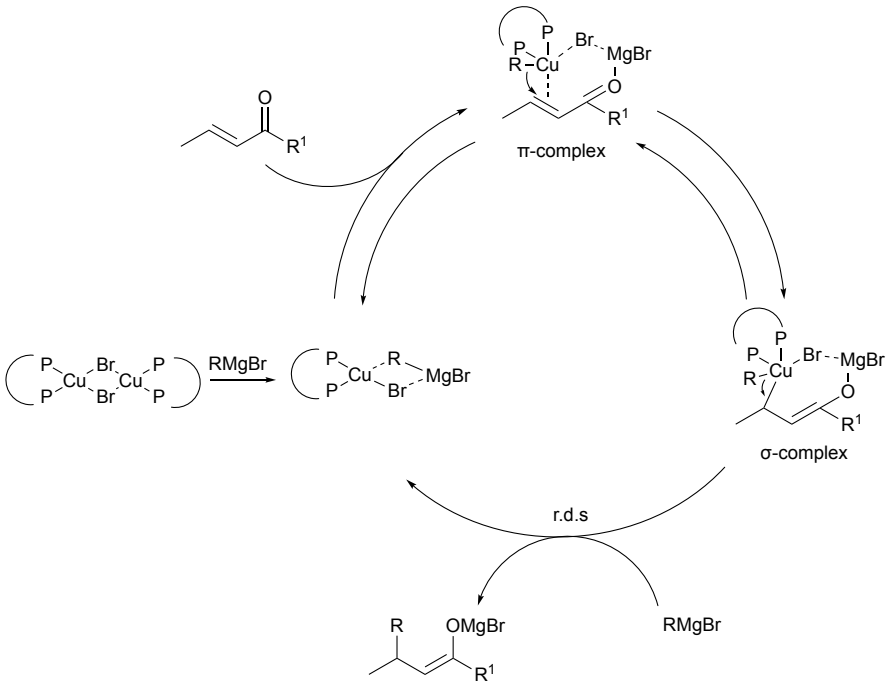
The most important advancement in forming chiral centres from linear enones was completed by Minnaard and Feringa. They discovered a (*R,S*)-Josiphos ligand, which was later found suitable in 1,4-additions to linear *α,β*-unsaturated enones,[52] *α,β*-unsaturated esters,[53] *α,β*-unsaturated thioesters[11,54] with Grignard reagents.



Scheme 1-33 ACAs of Grignard reagents

By simply mixing a catalytic amount of $CuBr_2 \cdot SMe_2$ (5 mol%) and (*R,S*)-Josiphos ligand (6 mol%) in ^{t}BuOMe, they obtained a catalytic complex, with which 27 chiral ketones were obtained in moderate to good yields (52% to 91%) and excellent ee's (>90% in most cases, Scheme 1-33).

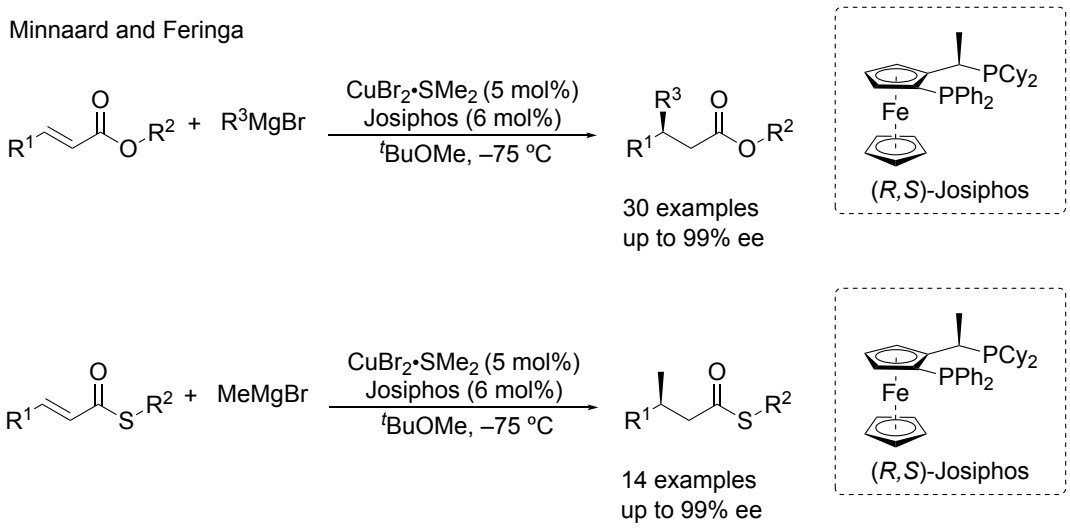
They next explored the mechanism of Cu-catalyzed enantioselective 1,4-addition of Grignard reagents to *α,β*-unsaturated carbonyl compounds (Scheme 1-34).[55] The pathway is initiated by transmetalation with Grignard reagent forming a Cu-Mg complex (left side in the cycle). The Cu-Mg complex works like organocuprates with chiral diphosphine ligand. It accelerates the ACA by stabilizing the intermediate π-complex, and overcomes back-ground 1,4- and 1, 2-additions during the course. Then the π-complex undergoes formation of a magnesium enolate through a Cu(III) σ-complex. In the last step, the σ-complex undergoes a reductive elimination, affording the desired 1,4-adduct and reusable Cu-ligand complex.



Scheme 1-34 Proposed catalytic cycle of 1,4 additions to linear enones

After the study of 1,4-addition to linear enones with Grignard reagents, Minnaard and Feringa moved to investigate *α,β*-unsaturated carboxylic acid derivatives, esters,[53] and thioesters,[11] which could be easily transformed to chiral aldehydes and other linear chiral intermediates or products, and remarkably extend the application of asymmetric 1,4-addition in total synthesis.

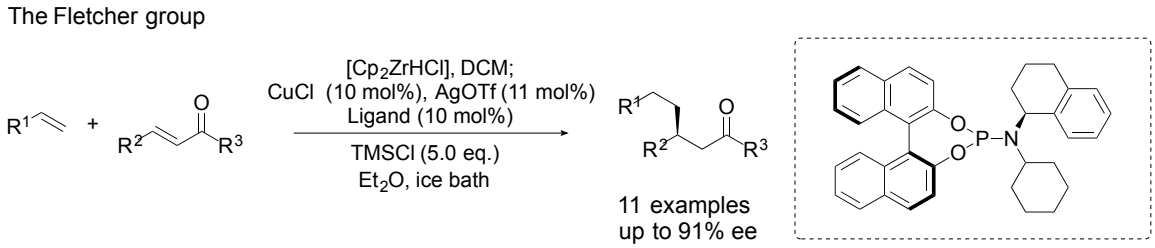
Based on the conditions of asymmetric 1,4-addition to noncyclic enones, they further explored a methodology on *α,β*-unsaturated esters (Scheme 1-35 top).[52] 30 chiral esters were prepared efficiently from alkyl and aryl groups substituted unsaturated esters with a range of Grignard reagents affording up to 99% ee. However, less reactive MeMgBr behaved poorly when introduced to unsaturated esters, even after broad optimisations.



Scheme 1-35 ACAs of *α,β*-unsaturated esters and thioesters

To address the issue, they turned to more active substrates, *α,β*-unsaturated thioesters.[11] Without further optimisations, the methyl group from MeMgBr is transferred effectively to a range of unsaturated thioesters (14 examples, up to 99% ee, Scheme 1-35 bottom). 1,3-Dimethyl arrays and deoxypropionate chains are also easily prepared by iterative synthesis using this method. They then synthesized a natural product, (–)-lardolure via their iterative synthesis (26% overall yield). A Cu-catalyzed conjugate addition of Grignard reagents to an unsaturated thioester was followed by a Fukuyama reduction, Horner-Wadsworth-Emmons reaction, and another ACA.

All the nucleophiles attacking Michael acceptors in the Cu-catalyzed ACAs mentioned above are nonfunctionalized nucleophiles, and the above methods barely have any tolerance for functional groups. To solve this drawback, the Fletcher group disclosed another ACA using alkylzirconium reagents to linear enones (Scheme 1-35).[56] Several important functional groups were introduced using alkylzirconium reagents combining a catalytic amount of catalyst (10 mol%) with up to 91% ee and excellent yields (>80%).



Scheme 1-36 ACA of alkylzirconium reagents to linear enones

Cu-catalyzed ACA approaches forming quaternary centres in linear systems are rare. Only three methods, discussed later in detail in chapter 2 were reported, and the quaternary centres were constructed from nitroolefins,[57,58] Meldrum's acid derivatives,[59]and limited trisubstituted enones.[60]

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Chapter 2

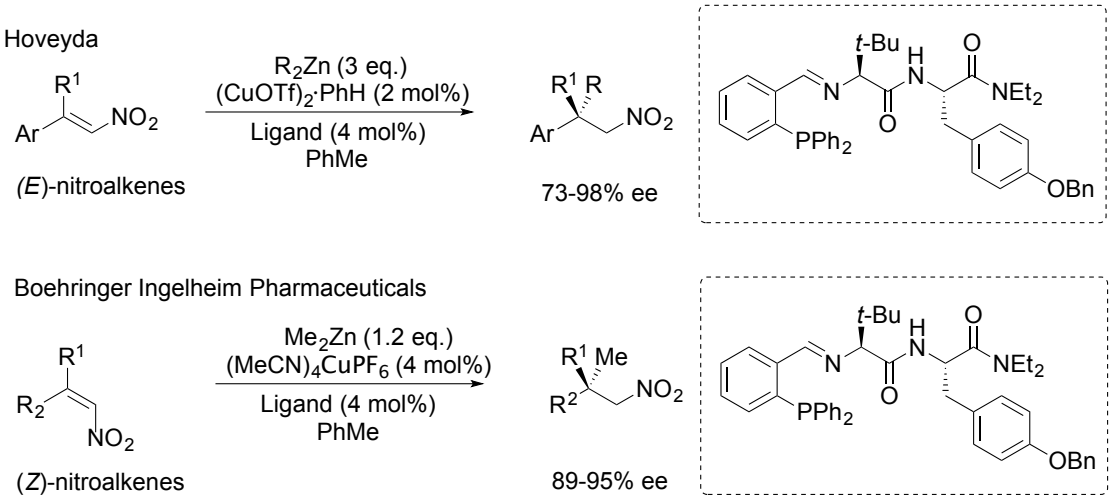
Construction of acyclic quaternary centres

Synthetic methods for the stereoselective formation of quaternary centres in acyclic systems are rare. In this chapter, a highly enantioselective Cu-catalyzed asymmetric conjugate addition (ACA) of alkylzirconium species to various acyclic trisubstituted enones is reported. A variety of sp^3-hybridized nucleophiles generated by *in situ* hydrozirconation of alkenes with Schwartz's reagent can be introduced efficiently, affording linear products bearing quaternary centres with up to 98% ee. Over 27 examples are achieved efficiently, and several important functional groups, e.g. halogens, unsaturated C-C bonds, silanes, protected alcohols *et al*, are tolerated. This approach applies a new chiral nonracemic phosphoramidite ligand in a complex with copper(I) triflate as the catalyst, which enantiomerically forms linear quaternary stereocenters to obtain a variety of valuable structures. This chapter consists of an introduction, followed by subsequent discussion of substrate preparation, method optimization, the scope of the reaction and preparative scale reactions. This work was published in *Chemical Science* in 2017.[1]

2.1 Introduction

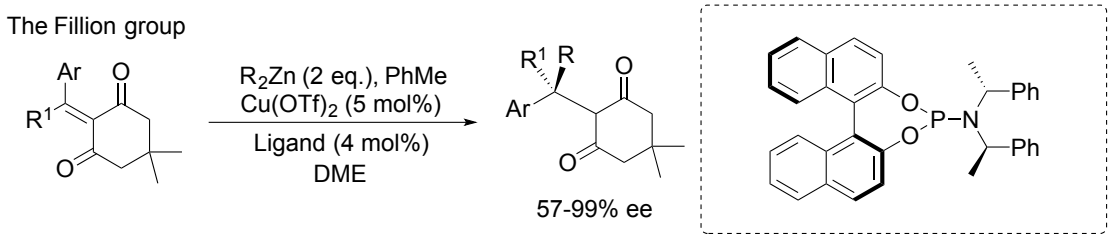
Tremendous attention has been drawn to stereoselective formation of quaternary centres, which is widely appreciated as a challenging transformation in synthetic chemistry.[2] While a wide variety of methods have been developed,[2–8] synthesis of quaternary centres, especially in acyclic substrates, remains difficult. In linear systems, both steric repulsion and conformational control need to be overcome by the chiral catalysts in order to guarantee high stereoselectivity.[9, 10]

Over the past ten years, Cu-catalyzed asymmetric conjugate addition (ACA) of alkyl nucleophiles to α,β-unsaturated enones and related substrates has been gradually developed as an robust route to construct quaternary stereocenters.[11,12] However, most work focused on cyclic systems. To the best of our knowledge, there are only three high enantioselective methods for the addition of non-stabilized alkyl nucleophiles to form quaternary centres in acyclic systems (Scheme 2-1-2-3). The Hoveyda group[13] developed asymmetric additions of dialkyl zinc reagents to (*E*)-nitroalkenes. This was further expanded to (*Z*)-nitroalkenes using the same chiral ligand by replacing $(CuOTf)_2 \cdot PhH$ with $(MeCN)_4CuPF_6$ as developed by Boehringer Ingelheim. A range of nitroalkanes bearing quaternary centres were obtained with excellent enantioselectivities and good yields from both (*E*) and (*Z*) substrates.[14]



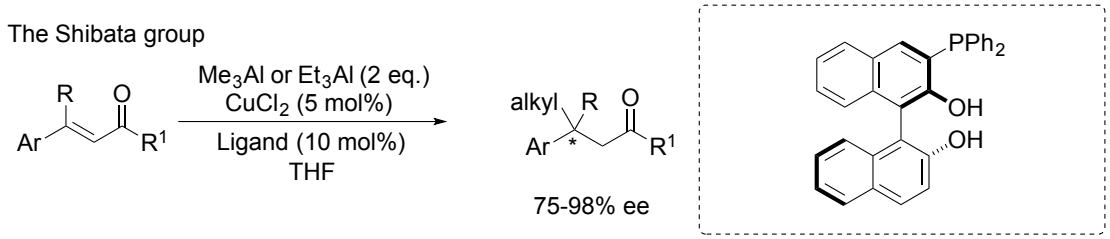
Scheme 2-1 Examples of Constructing linear quaternary centres

The Fillion group[15] reported efficient methodology to construct quaternary centres from highly activated electrophiles, Meldrum's acid derivatives, as Michael acceptors. Using this method, they formed quaternary centres with up to 99% ee using Leggy's ligand (Scheme 2-2).



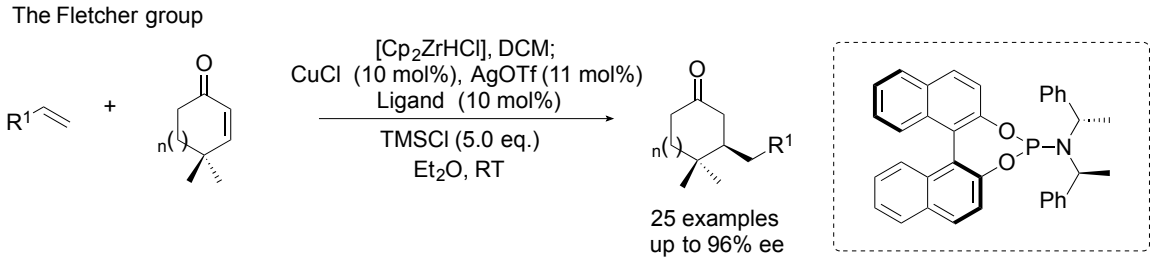
Scheme 2-2 Examples of Constructing linear quaternary centres

The third approach, reported by the Shibata group,[16] used linear trisubstituted enones, which are normally activated substrates, in combining with aluminium reagents. Though the results were good, this method was limited to addition of very simple alkyl groups such as methyl and ethyl groups.



Scheme 2-3 Examples of Constructing linear quaternary centres

In 2012, our group reported Cu-catalyzed ACAs using alkenes as the equivalents of alkyl nucleophiles (Scheme 2-4).[17] By reacting an alkene with Schwartz's reagent (Cp_2ZrHCl), organozirconium species are formed *in situ* and can undergo Cu-catalysed ACA using phosphoramidite ligands. This approach has no need for cryogenic conditions and tolerates a much wider range of functional groups than methods relying on premade organometallic nucleophiles. It can also be easily scaled up to grams without further fine-tuning.



Scheme 2-4 Hydrometalation/asymmetric conjugate addition of alkenes

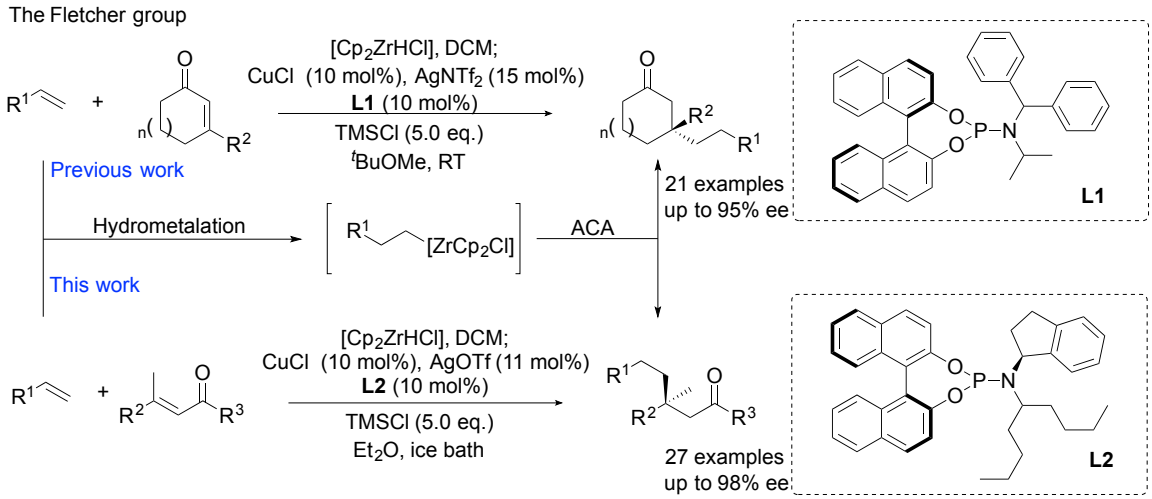
Later, Sidera *et al.*[18] developed a new approach to construct quaternary centres in cyclic systems by Cu-catalyzed asymmetric additions of alkylzirconium reagent (Scheme 2-5 top). Compared with cyclic systems, building quaternary centres in acyclic substrates is more difficult, presumably due to interconversions between *s-cis* and *s-trans* conformers. (Figure 2-1)



Figure 2-1 Interconversion between linear substrate conformers

Here, we report a novel approach to construct acyclic quaternary centres by Cu-catalyzed asymmetric addition of alkylzirconium species (Scheme 2-5 bottom)[1]. Up to 98% ee and 27 examples have been achieved using a new chiral nonracemic phosphoramidite ligand in a complex with copper(I) triflate after an overnight reaction in ice bath. This work expands the scope of linear α,β-

unsaturated enones that can be used to form acyclic quaternary centres. These reactions extend the traditional simple alkyl nucleophiles such as dialkyl zincs and Grignard reagents that are normally used and allow additions of zirconium species bearing several important functional groups, protected alcohols, halogens, silane, unsaturated C-C bonds, aromatic rings. Developing reactions capable of using functionalized coupling partners in asymmetric C-C bond forming reactions is a vital step toward being able to use the method in natural product synthesis and drug discovery. Overall, this method significantly broadens the range of acyclic products bearing quaternary centres that can be accessed.

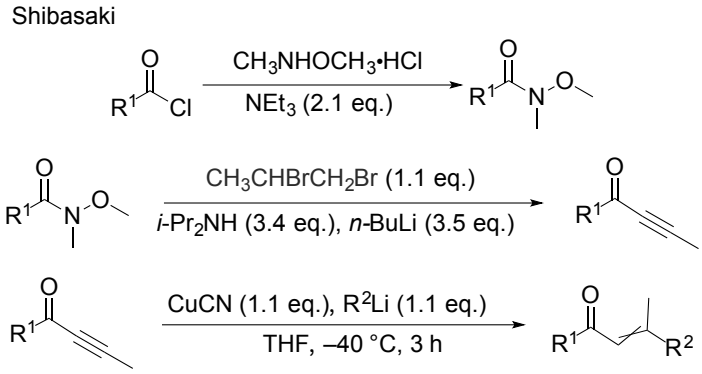


Scheme 2-5 Construction of acyclic quaternary centres

2.2 Synthesis of trisubstituted enones

The struggle of building linear quaternary centres starts with the stereocontrolled synthesis of trisubstituted enones. One robust synthetic pathway was published by Shibasaki (Scheme 2-6).[19] This approach is a three-step method, namely, (a) reaction of an acyl chloride with N, O-dimethylhydroxylamine to form a Weinreb-Nahm amide, (b) nucleophilic acyl substitution to introduce C-C triple bond, and finally (c) Cu-catalyzed addition of organolithium reagent to

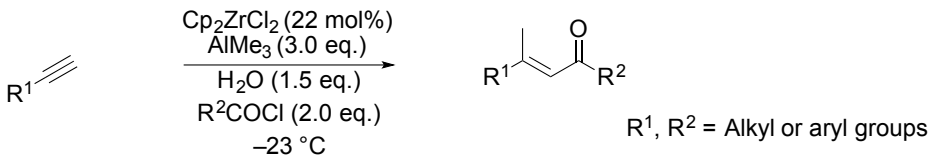
obtain enones. Using this method, various R^1 and R^2 groups are accessible, and plenty of trisubstituted enones are easily prepared. However, one drawback of the method is that the enone product is always a mixture of *(E)*- and *(Z)*-enones, and in some cases, the mixture of enones are laborious to separate. As the stereochemistry of the starting enone can affect the final stereochemistry obtained in the asymmetric transformation, as demonstrated later in the thesis, to obtain the highest level of ee in the products we need to use pure (*E*)- or *(Z)*-enones.



Scheme 2-6 Synthesis of trisubstituted enones from Shibasaki group

A method from the Hoveyda group[20] (Scheme 2-7) was later adopted to prepare various trisubstituted enones, since the reaction is stereospecific for producing only the (*E*)-enone and no (*Z*)-enone is obtained in NMR spectra, which means that *E*:*Z* is over than 20:1. This approach involves a Zr-catalyzed carbometalation, in which numerous (*E*) enones can be obtained by simply choosing alkynes and acyl chlorides with different R^1 and R^2 groups. Various alkyl and aryl groups are well tolerated for R^1 and R^2 without further optimizations. 14 (*E*)-enones were prepared using Hoveyda's method, most products were obtained in yield ~60% with > *20:1 E*:*Z* ratio (Figure 2-2).

The Hoveyda group



Scheme 2-7 Synthesis of trisubstituted (*E*)-enones

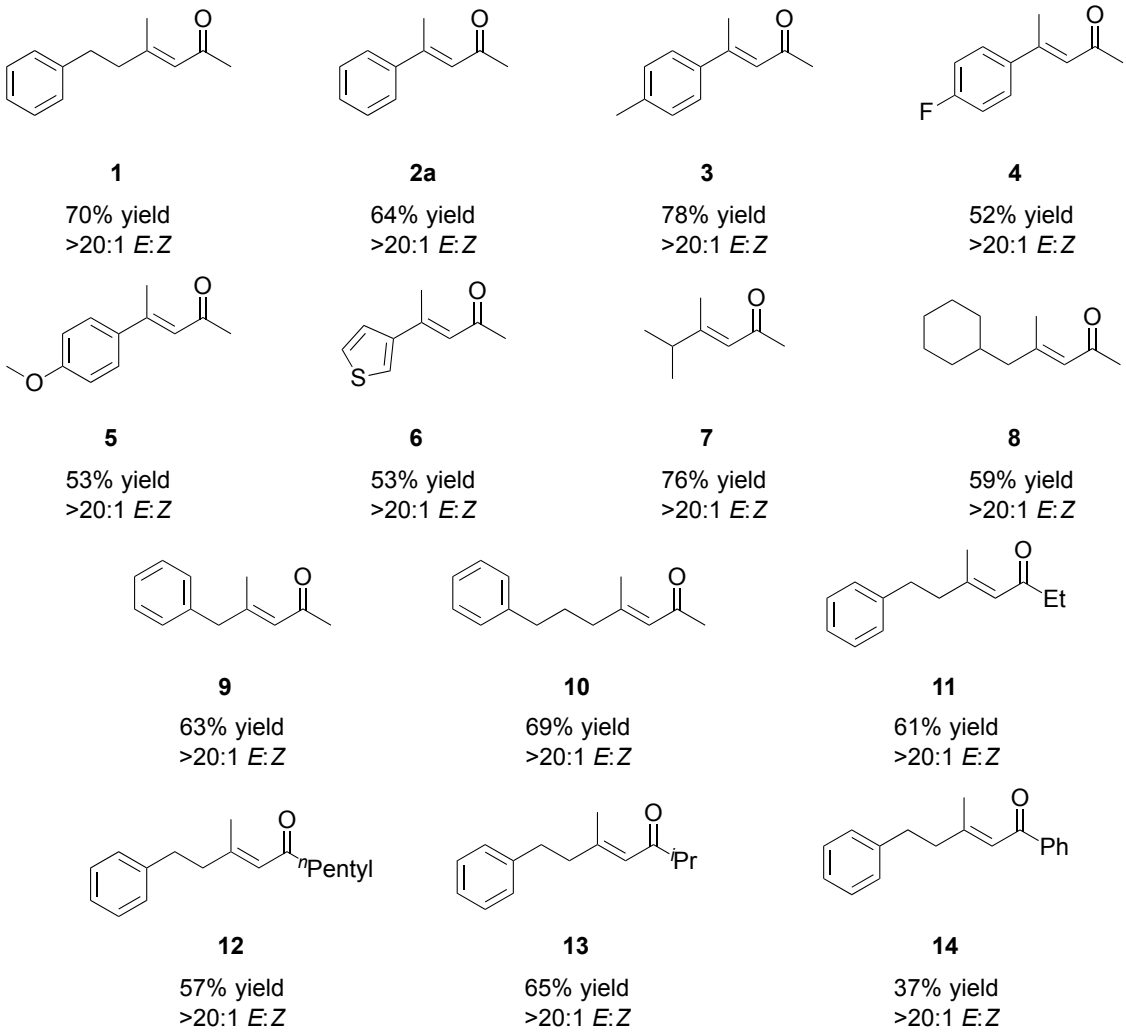
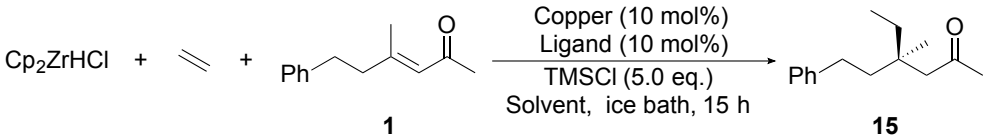


Figure 2-2 (*Z*)-trisubstituted enones synthesized by Hoveyda's method

2.3 Screening conditions



Scheme 2-8 Optimisation of ACAs to build acyclic quaternary centres

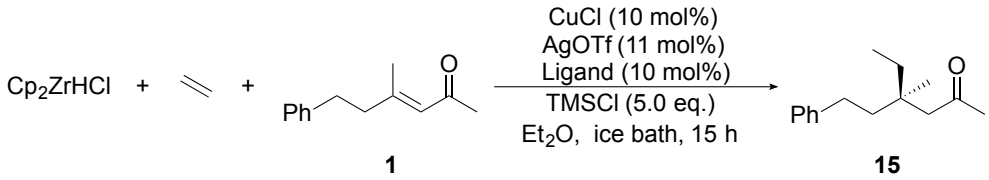
We examined the ACA of ethylene, which reacted with Schwartz's reagent *in situ* and formed organozirconium species, and (*E*)-4-methyl-6-phenylhex-3-en-2-one (**1**) under reaction conditions previously applied in the formation of cyclic quaternary centres[18] and acyclic tertiary centres.[21]

Chiral high-performance liquid chromatography (HPLC) is widely used to separate chiral analytes and determine their ee's. The HPLC separation of nonracemic ketone **15** was difficult to obtain. We first screened a range of chiral HPLC columns using hexane/isopropanol (99/1), and only Chiralpak® ID column was able to give a non-baseline separation. We then varied the ratio of hexane/isopropanol and flow rate, but still could not find a better separation. We also attempted other solvent systems, e.g. hexane/ Et_2O, hexane/chloroform, and hexane/methanol, but none of them could afford better results. In the end, we combined two Chiralpak® ID columns in series, decreased the flow rate, and finally obtained a baseline separation to determine the ee of **15**.

We explored conditions using different copper salts (10%), ligands (10%), solvents and reaction temperatures. We first explored different ligands (Figure 2-2). Reaction using **L1** gave **15** with 45% ee. We then compared both diastereomers of Leggy's ligand (**L3**, and **L4**), and found that the ligand with matched stereochemistry (**L3**, SSS) afforded a better enantioselectivity. We next varied backbones of the phosphoramidite ligand (**L5**-**L8**), but did not find a better

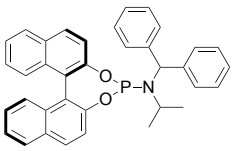
result than **L4**'s. We then kept the backbone as BINOL and varied the amine motif.

Phosphoramidite ligands containing amine moieties without chiral centres (**L9**-**L16**), which significantly reduce cost and difficulty of ligand preparation, were then examined. The best result was achieved using ligands **L15** and **L16**, both affording 50% ee. We then examined ligands with chiral centres in the amine moieties (**L17**-**L22**). After replacing isopropyl group in **L17** with cyclohexane ring ligand, **L18**, the ee went up from 56% to 77%. We also found that indane ligand **L20** behaved better than tetralin ligand **L17**, and the matched ligands (**L18** and **L20)** gave better performances than mismatched ones (**L19 and L21**). After a series of optimizations, we discovered **L22**, which could afford an over 84% ee. We then retained ligand **L22** and optimized other reaction variables.

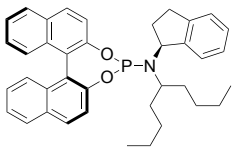


Scheme 2-9 Ligand optimizations

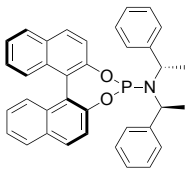
Figure 2-3 Ligand pool



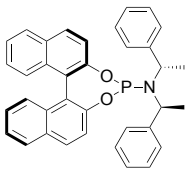
L1
45% ee



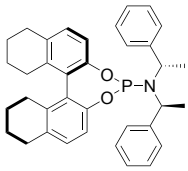
L2
91% ee



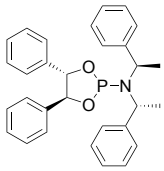
L3
46% ee



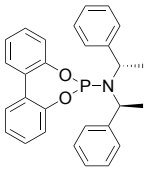
L4
25% ee



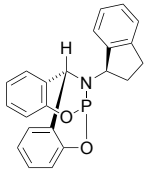
L5
38% ee



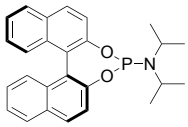
L6
no product



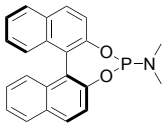
L7
8% ee



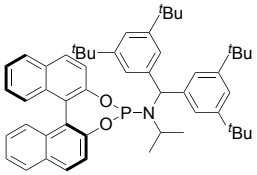
L8
no product



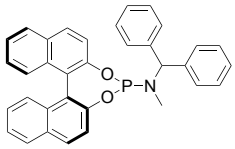
L9
7% ee



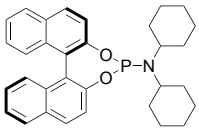
L10
32% ee



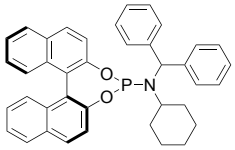
L11
20% ee



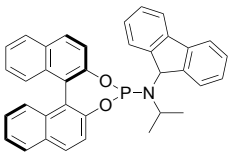
L12
8% ee



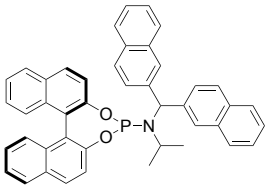
L13
36% ee



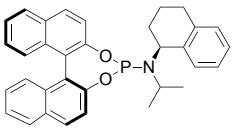
L14
24% ee



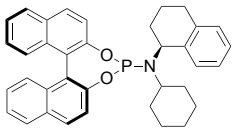
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50% ee



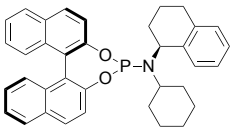
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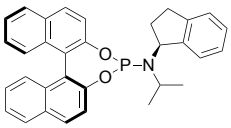
L17
56% ee



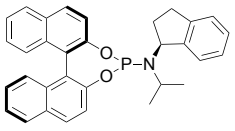
L18
77% ee



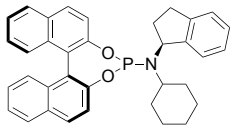
L19
52% ee



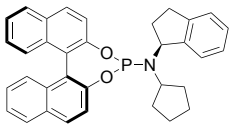
L20
64% ee



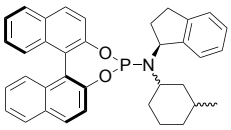
L21
52% ee



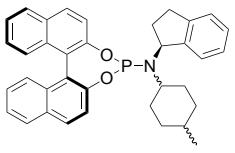
L22
84% ee



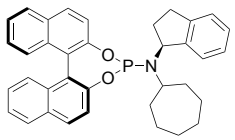
L23
71% ee



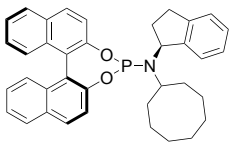
L24
85% ee



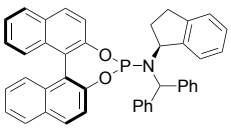
L25
85% ee



L26
86% ee

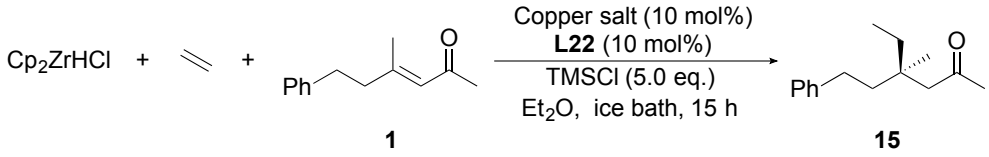


L27
86% ee



L28
88% ee

Table 2-1 Optimisation of copper source

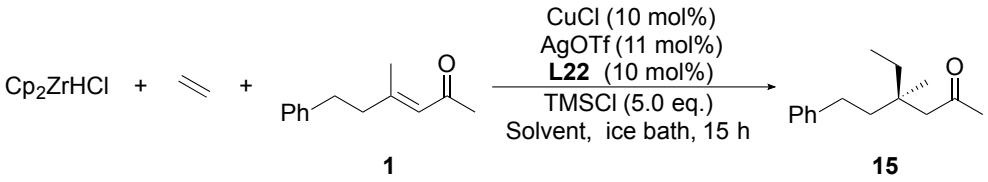


Entry	Copper source	Yield [%][a]	ee [%][b]
1	CuI	0	-
2	CuCl	0	-
3	CuCl + $AgBF_4$	0	-
4	CuCl + $AgPF_6$	0	-
5	CuCl + AgO_3SCH_3	0	-
6	CuCl + AgOTs	0	-
7	CuCl + $AgClO_4$	4	2
8	CuCl + $AgSbF_6$	13	20
9	CuCl + $AgNTf_2$	20	56
10	CuCl + AgOTf	80	84
11	$Cu(OTf)_2$	40	69

Reaction conditions: alkene (2.5 eq.), [Cp_2ZrHCl] (2 eq.), enone (1 eq.), copper salt (10 mol%), ligand (10 mol%), silver salt (11 mol%), TMSCl (5 eq.) [a] Yield of isolated product. [b] ee was determined by HPLC. The (S) enantiomer was obtained, and silver chloride precipitate filtered before use.

We explored the effects of counterions. We tried different copper halides and found no reaction (Table 2-1, entries 1 and 2). Other Cu-salts, generated *in situ* (entries 3-10) were then examined, because the silver salts are commercially available and the isolated Cu-salts are difficult to prepare. We noted that copper salts featuring non-coordinating anions gave very poor results (entries 3, 4, 7, and 8). We found that electron withdrawing counterions performed well, with $CuNTf_2$ and CuOTf providing the best ee's (56% and 84% respectively, entry 9 and 10). The use of Cu(II) triflate ($Cu(OTf)_2$) allowed asymmetric additions (entry 11, 40% yield, 69% ee), but the result was inferior to using Cu(I) triflate directly (entry 10, 80% yield, 84% ee).

Table 2-2 Solvent screening

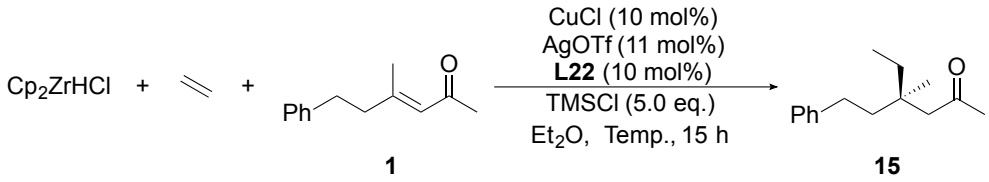


Entry	Solvent	Yield [%][a]	ee [%][b]
1	THF	41	75
2	2-Me-THF	26	70
3	^{t}BuOMe	41	77
4	$^{i}Pr_2O$	62	52
5	DCM	7	8
6	Toluene	4	30
7	Et_2O	80	84

Reaction conditions: alkene (2.5 eq.), [Cp_2ZrHCl] (2 eq.), enone (1 eq.), copper chloride (10 mol%), ligand (10 mol%), silver triflate (11 mol%), TMSCl (5 eq.) [a] Yield of isolated product. [b] ee was determined by HPLC.

We next studied the effect of solvents using **L22** and copper (I) triflate. We found the reaction performed well in various ethers (Table 2-2, entries 1, 2, 3, 7), among which Et_2O afforded the best result (entry 7, 80% yield, 84% ee). For chlorinated solvent, DCM and aromatic hydrocarbon solvent, toluene, they both gave poor results (entries 5 and 6).

Table 2-3 Other optimizations



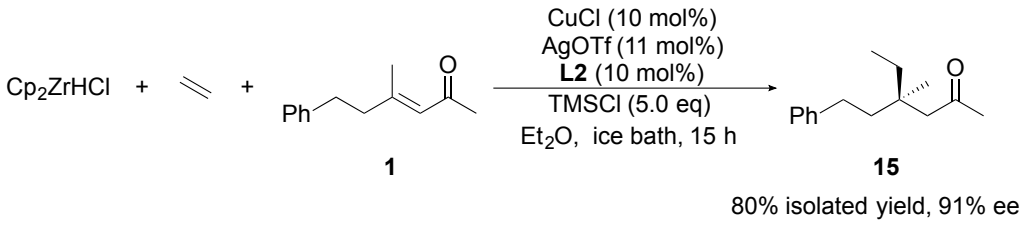
Entry	Cu/ligand [%]	Temp.	Additive[a]	Yield [%][b]	ee [%][c]
1	10:10	0 °C	TMSCl	80	84
2	10:5	0 °C	TMSCl	80	81
3	10:15	0 °C	TMSCl	82	82
4	10:10	20 °C	TMSCl	84	80
5	10:10	-10 °C	TMSCl	6	72
6	10:10	0 °C	None	9	58

Reaction conditions: alkene (2.5 eq.), [Cp_2ZrHCl] (2 eq.), enone (1 eq.), copper chloride (10 mol%), ligand (10 mol%), silver triflate (11 mol%), TMSCl (5 eq.) [a] 5 eq., when used. [b] Yield of isolated product. [c] ee was determined by HPLC.

We also investigated the ratio of copper to ligand, and found that when we varied the Cu/Ligand ratio from 2/1 to 2/3, no obvious differences in the result were observed (Table 2-3, entries 1-3). Raising the reaction temperature slightly increased the yield, but decreased the enantioselectivity (entry 4, 84% and 80% ee). When the temperature was lowered to –10 ºC, the yield and ee dropped to 6% and 72% respectively (entry 5). TMSCl has long been recognized to play an important role in copper catalysed conjugate addition[22–28] either by accelerating addition by activating the enone oxygen, or interacting with copper species themselves. The role of TMSCl in our reaction is not clear, but it is essential as the yield and ee both drop significantly when TMSCl is omitted (entry 6, 9% yield with 58% ee).

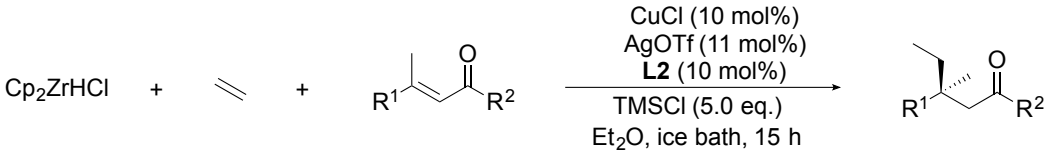
In order to further improve enantioselectivity, we designed and examined and some additional novel ligands (Figure 2-2, **L23**-**L28**, **L2**). These new ligands have different branched aliphatic groups attached to the amine moiety of the

phosphoramidite, and for reasons that are not yet clear, bulky aliphatic groups enhance the enantioselectivity. Ligand **L2** bearing two alkyl chains gives the best enantioselectivity and is capable of forming acyclic quaternary centres with 80% isolated yield and 91% ee (Scheme 2-10).



Scheme 2-10 Optimised conditions

2.4 Scope of the enone

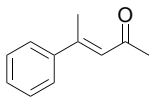
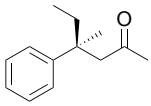
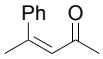
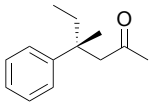
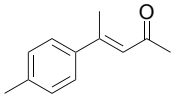
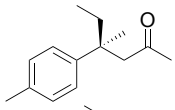
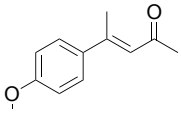
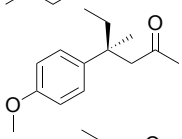
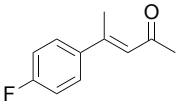
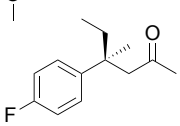
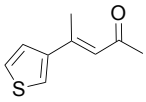
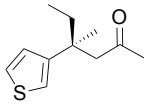
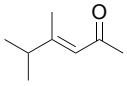
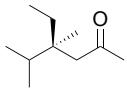
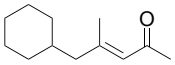
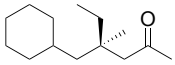
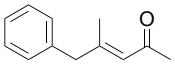
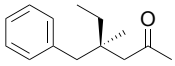
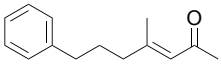
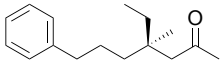
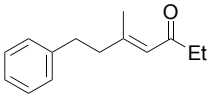
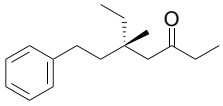
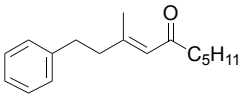
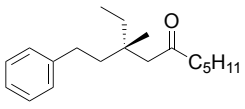
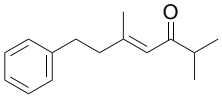
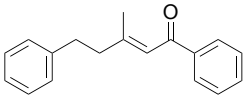


Scheme 2-11 Scope of enones

Using the conditions optimized above, we next studied using different electrophiles and examined ACA with a variety of (*E*)-substituted acyclic trisubstituted enones, where moieties adjacent to the olefin and carbonyl groups were varied (Scheme 2-11, and Table 2-4).

Generally, the reaction works very well, especially when enones are tri-*n*-alkyl substituted ones, which give both excellent yield and ee. We first studied if the stereochemistry of the starting enone would make a difference to our method, by comparing of **16** and ***ent*-16** (Table 2-4, entries 1 and 2).

Table 2-4 Scope of enones

Entry	Substrate		Product		Yield [%][a]	ee [%][b]
1		**2a**		**16**	50	90
2		**2b**		***ent*-16**	32	71
3		**3**		**17**	34	89
4		**4**		**18**	39	73
5		**5**		**19**	46	91
6		**6**		**20**	41	85
7[c]		**7**		**21**	48	92
8		**8**		**22**	71	98
9		**9**		**23**	61	93
10		**10**		**24**	80	93
11[d]		**11**		**25**	80	96
12[d]		**12**		**26**	54	96
13		**13**	-		0	-
14		**14**	-		0	-

Reaction conditions: alkene (2.5 eq.), [Cp_2ZrHCl] (2 eq.), enone (1 eq.), copper chloride (10 mol%), ligand (10 mol%), silver triflate (11 mol%), TMSCl (5 eq.) [a] Yield of isolated product. [b] ee was determined by HPLC. [c] ee was determined by GC. [d] The enantiomer of ligand of **L2** was used in these examples because the order of elution of the enantiomers aided ee determination.

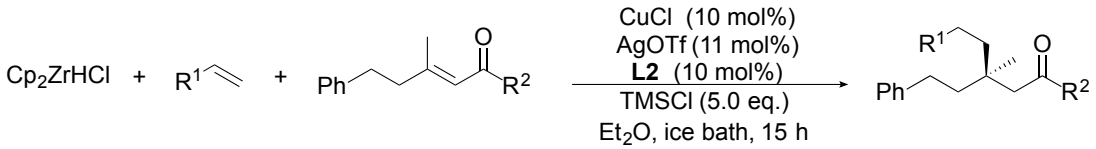
The *cis*-(*Z*)-enone **2b** afforded a poor result (32% yield, 71% ee), while the *trans*-(*E*)-enone **2a** gave a much better result (50% yield, 90% ee). This selectivity difference appears to arise from partial *cis*- to *trans*- isomerization during the course of the reaction; when we quenched a reaction with *cis*-(*Z*)-enone **2b** after one hour, ***ent*-16** was obtained in 26% yield with 86% ee. Also recovery of starting substrate showed that the enone was now present as a mixture of *cis*- and *trans*-enones, in 1:5 *trans* to *cis* ratio.

We next examined other aryl-substituted enones (entries 3-6). These performed similarly to **2a** except electron rich enone **4** (39% yield, 73% ee). We were pleased to find that challenging thiophene substrate **6** could afford 41% yield and 85% ee. *β*-Alkyl substituted enones **1**, **7**-**10**, (entries 7-10) all gave excellent yields and ee's.

We also investigated the influence of the group attached to the carbonyl. We were surprised to find that when we increased the length of carbon chain from methyl to ethyl or even to pentyl group, we observed much better enantioselectivities (both 96% ee, entries 11 and 12). We noted that the enantiomer of **L2** (***ent*-L2**) was used to make **25** and **26**, because it aided the ee determination on HPLC.

When we examined isopropyl (**13**) and phenyl (**14**) substituted enones (entries 13 and 14), no desired ketone was obtained. In these cases, a secondary carbon or an aromatic ring is next to the carbonyl, and evidently the catalytic reaction does not tolerate the additional substitution at this position, which might restrict the conformational freedom of the enones and inhibit the mechanistic pathway.

2.5 Scope of the alkene

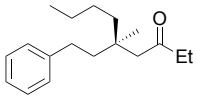
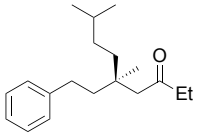
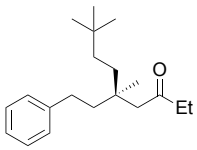
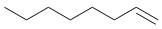
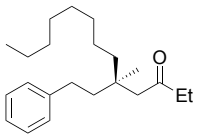
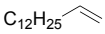
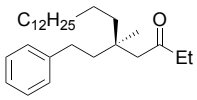
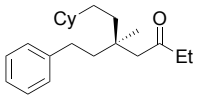


Scheme 2-12 Additions of complicated alkenes

We then examined more complicated nucleophiles in our additions. We replaced ethylene with several other non-functionalized alkenes (Scheme 2-12, and Table 2-5, entries 1-6), and found that ee's were uniformly high, even for the bulky *t*-Bu-substituted alkene (entry 3, 85% ee).

We also introduced more elaborated nucleophiles bearing functional groups (Table 2-6). The formation of acyclic quaternary centres tolerates halogens (entries 1 and 2), unsaturated C-C bonds (entries 3 and 4), a silane (entry 5), protected alcohols (entries 6 and 7), and aromatic rings (entries 3, 6, 8 and 9).

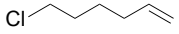
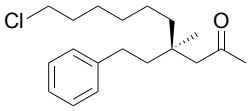
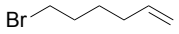
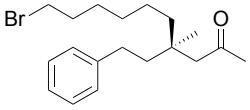
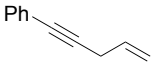
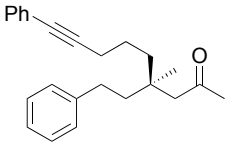
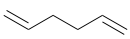
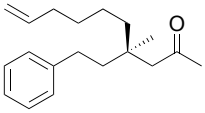
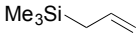
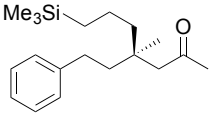
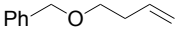
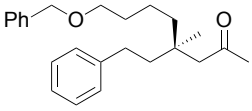
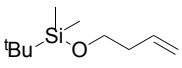
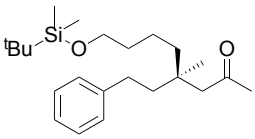
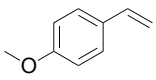
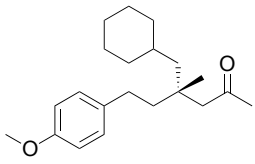
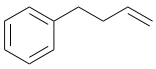
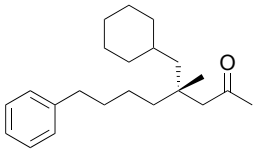
Table 2-5 Addition of non-functional alkenes

Entry	Substrate	Product		Yield [%][a]	ee [%][b]
1			**27**	53	93
2			**28**	70	90
3			**29**	69	85
4			**30**	56	92
5			**31**	59	90
6			**32**	64	90

Reaction conditions: alkene (2.5 eq.), [Cp_2ZrHCl] (2 eq.), enone (1 eq.), copper chloride (10 mol%), ligand (10 mol%), silver triflate (11 mol%), TMSCl (5 eq.) [a] Yield of isolated product. [b] ee was determined by HPLC.

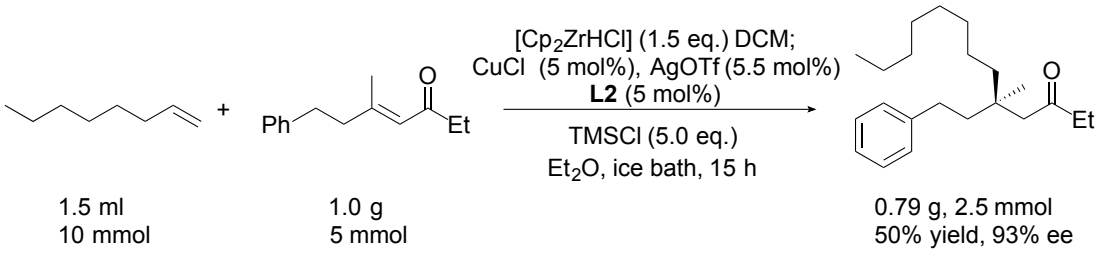
We attempted to introduce styrene derivatives in combination with electrophile **8** instead of **1**, which makes it easier to determine the ee of the product. We found that the styrene derivatives behaved poorly under our systems except 4-MeO-styrene, which gave 24% yield, and 88% ee. For ketone **41**, the ee was good, 92%, while the yield was only 35%. The low yield is due to the unreacted enones. We studied if we could improve these results by extending reaction times to 48 h (from 15 h), but we did not receive obvious improvements (35% yield, 91% ee).

Table 2-6 Addition of functionalized alkenes

Entry	Substrate	Product		Yield [%][a]	ee [%][b]
1			**33**	51	84
2			**34**	46	87
3			**35**	52	78
4			**36**	55	74
5			**37**	42	88
6			**38**	54	82
7			**39**	71	91
8[c]			**40**	24	88
9[c]			**41**	35	92

Reaction conditions: alkene (2.5 eq.), [Cp_2ZrHCl] (2 eq.), enone (1 eq.), copper triflate (10 mol%), ligand (10 mol%), silver triflate (11 mol%), TMSCl (5 eq.) [a] Yield of isolated product. [b] ee was determined by HPLC [c] Substrate **8** was used instead of **1**.

2.6 Absolute configuration of ketones and large-scale reactions



Scheme 2-13 Gram-scale catalytic acyclic ACA using 5% catalyst

The absolute configuration of **16**, **18**, and **23** were obtained by comparison of optical rotation data with the literature.[29]All other stereochemical assignments in this chapter are made by analogy to **16**, **18**, and **23**.

We carried out a preparative scale experiment to investigate if our approach was suitable for scale-up (Scheme 2-13). We chose 1-octene and enone **11** as reactants, and decreased the catalyst loading to 5 mol%, and the amount of Schwartz's reagent to 1.5 eq. We got good results (0.79 g, 50% yield, 93% ee), which are nearly the same compared as our general small scale reactions (56% yield, 92% ee).

2.7 Conclusions and future work

We have developed a Cu-catalyzed asymmetric conjugate addition to generate acyclic quaternary centres. The transformation gives high levels of enantioselectivity using novel phosphoramidite **L2,** which has been patented and commercialized via Fluorochem and Strem Chemicals. A wide range of trisubstituted acyclic enones can be used, and the best results (highest yields and ee's) are obtained when constructing tetra-*n*-alkyl substituted ketones. A variety of non-functionalized and functionalized nucleophiles are introduced, which significantly expands the range of nucleophiles that can be used to form

quaternary centres. These nucleophiles are generated by *in situ* hydrozirconation of relevant alkenes with Schwartz's reagent. Up to 98% ee and 27 working examples are achieved using (*E*)-enones. On a preparative scale, the catalyst could be lowered to a half (5 mol%) without compromising on enantioselectivity.

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Chapter 3

Asymmetric conjugate addition to carboxylic acid derivatives

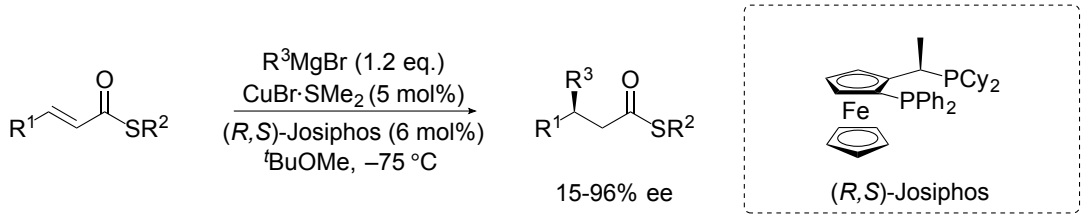
In this chapter, we investigated the Cu-catalyzed asymmetric conjugate addition of alkylzirconium species to α,β-unsaturated carboxylic acid derivatives. A variety of functionalized alkyl nucleophiles were introduced to different α,β-unsaturated thioesters with yields around 70% and ee's over 90%. We also applied this method to synthesize the commercially important chiral fragrances phenoxanol and hydroxycitronellal with ee's over 97%. Furthermore, we are capable of synthesizing functionalized acyclic arrays bearing several chiral centres by iteratively applying the method, where the stereochemistry of each stereogenic centre is entirely determined by our chiral catalysts. This work was published in *Chemical Communications* in 2017.[1]

3.1 Introduction

After developing methods to construct tertiary[2] and quaternary[3] stereocenters by asymmetric conjugate additions to noncyclic enones, we found it difficult to

differentiate the two CH_2 groups α- to the carbonyl group in our chiral ketone products. The strategy of using intermediate Zr-enolates produced in the 1,4-addition, as also observed by the Sebesta group,[4] proved difficult to advance. Fully differentiating the α-CH_2 in enones is the key to opening the door to synthesizing more complicated chiral molecules. One solution to this problem would be to develop robust asymmetric additions to α,β-unsaturated carboxylic acid derivatives, where there is only one CH_2-group present. While many asymmetric conjugate addition procedures have been developed and used in total synthesis only a few catalytic enantioselective approaches focus on addition to carboxylic acid derivatives.

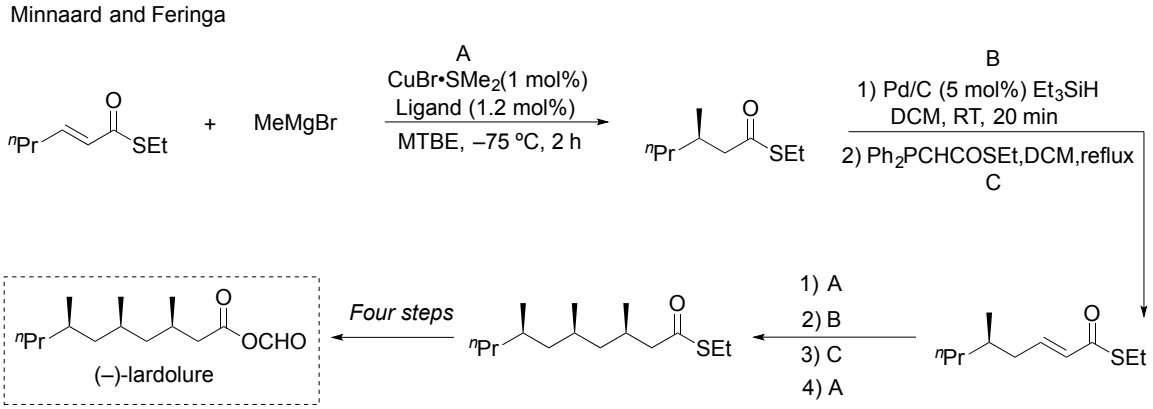
In 2005 Minnaard and Feringa[5] reported the first copper catalyzed asymmetric additions to α,β-unsaturated thioesters (Scheme 3-1). They adopted Grignard reagents as nucleophiles and (*R,S*)-Josiphos ligand was used to control the stereoselectivity giving up to 96% ee.



Scheme 3-1 ACA to α,β-unsaturated thioesters

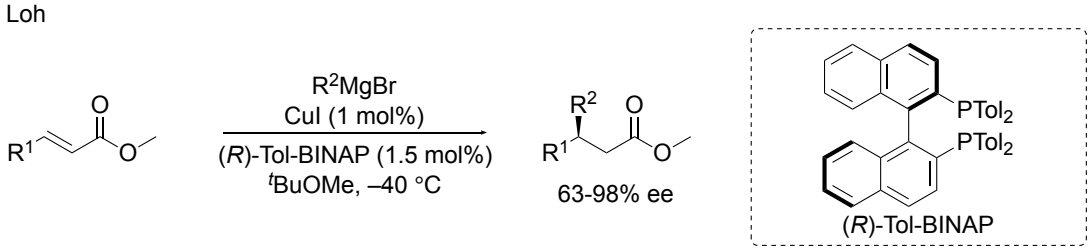
They also established an iterative catalytic route to enantiopure deoxypropionate subunits and successfully synthesized (–)-lardolure in 12 steps with 26% overall yield (Scheme 3-2). A Cu-catalyzed conjugate addition of Grignard reagents to an unsaturated thioester was followed by a Fukuyama reduction, Horner-Wadsworth-Emmons, and another 1,4-addition. By carrying out three ACAs, they achieved a linear thioester intermediate bearing three chiral

centres. The intermediate was then transformed to (–)-lardolure, a multimethyl-branched insect pheromone, after a four-step reaction (26% overall yield, 98:2 dr).



Scheme 3-2 Synthesis of (–)-lardolure via a 12-step procedure

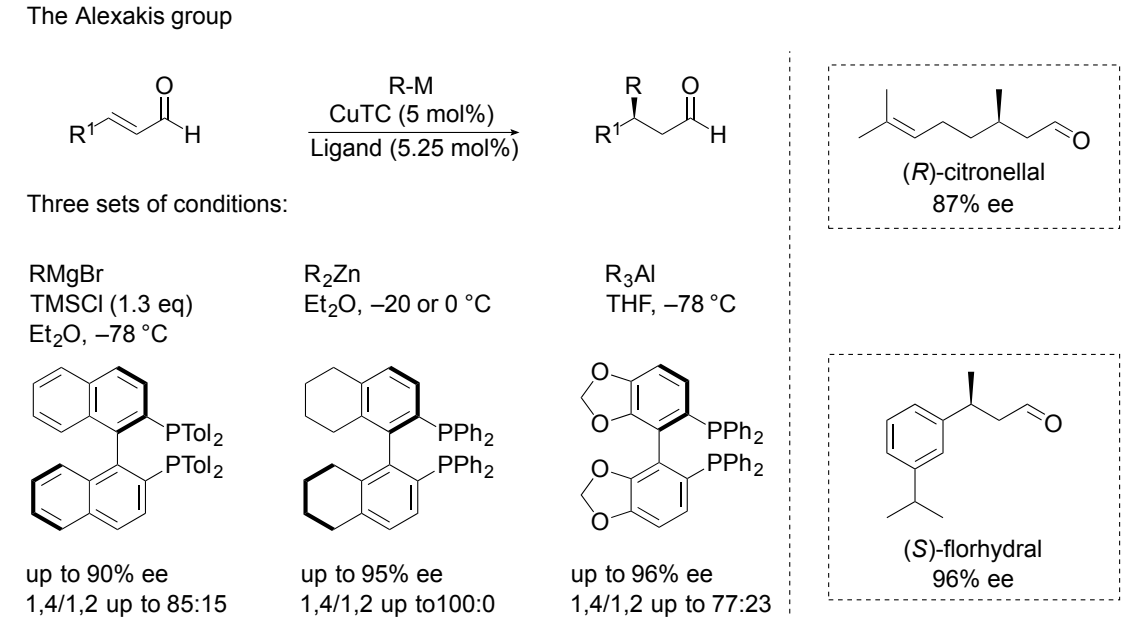
Later the Loh group[6] advanced enantioselective Cu(I)-Tol-BINAP-catalyzed asymmetric addition to α,β-unsaturated esters with 63%-98% ee (Scheme 3-3). In this work, they could introduce a variety of alky groups to a range of α,β-unsaturated esters (63-98% ee). Meanwhile, their method could also be applied to synthesize deoxypropionate units with good efficiency.



Scheme 3-3 ACAs on α,β-unsaturated esters

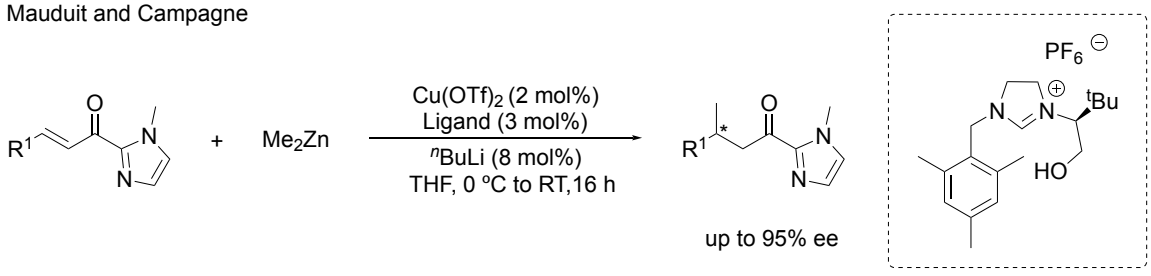
A catalytic asymmetric addition to α,β- unsaturated aldehydes was developed in 2016 by the Alexakis group[7] (Scheme 3-4, left). They studied asymmetric addition of various organometallic reagents and used the method to access (*R*)-citronellal and (*S*)-florhydral with satisfying enantioselectivities (87% and 96%, Scheme 3-4, right). (*R*)-Tol-BINAP, (*R*)-H_8-BINAP, and (*R*)-SEGPHOS were

three best ligands for reactions using Grignard reagents, organic zincs, and aluminium reagents respectively.



Scheme 3-4 ACAs to α,β-unsaturated aldehyde

Seminal work[8,9] from Mauduit and Campagne *et al.* involved efficient Cu-catalyzed enantioselective conjugate addition of dimethylzinc to α,β-unsaturated acyl-N-methylimidazoles using a chiral bidentate hydroxylalkyl-NHC ligand. A range of chiral N-methylimidazoles with excellent enantiomeric excesses (87-95% ee) were obtained, which could be easily transformed to the corresponding aldehydes, esters and ketones (Scheme 3-5).



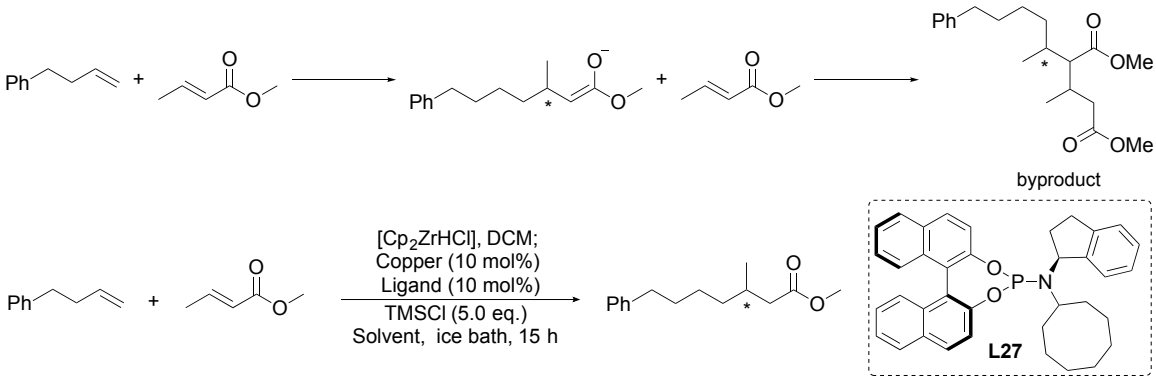
Scheme 3-5 ACAs to α,β-unsaturated acyl-N-methylimidazoles

All of these methods are limited to additions of simple alkyl nucleophiles in these methods, such as methyl or ethyl groups, and additions of more complex nucleophiles need to be developed. Also these approaches adopted diphosphine and NHC ligands, while approaches applying readily available monophos ligands, which are widely used in ACA to enones, have not been developed for carboxylic acid derivatives.[10] To overcome these limitations, we started research on asymmetric additions to α,β-unsaturated carboxylic acid derivatives using alkylzirconocenes species with monophos ligands. we studied α,β-unsaturated esters, α,β-unsaturated aldehydes, α,β-unsaturated imidazoles, and α,β-unsaturated thioesters and finally obtained excellent results with thioesters.

3.2 Study on α,β-unsaturated esters

We first studied α,β-unsaturated esters (Table 3-1), using methyl crotonate (Table 3-1 top) as our starting substrate due to its commercial availability. Based on our conditions in building β-to-carbonyl chiral centres from enones, we selected the combination of 10% copper catalyst and ice bath to start. We began with **L20**, which was later replaced by **L27**. These ligands were previously reported and behaved well in forming quaternary centres from trisubstituted enones.

Table 3-1 Optimisations of ACAs to α,β-unsaturated esters



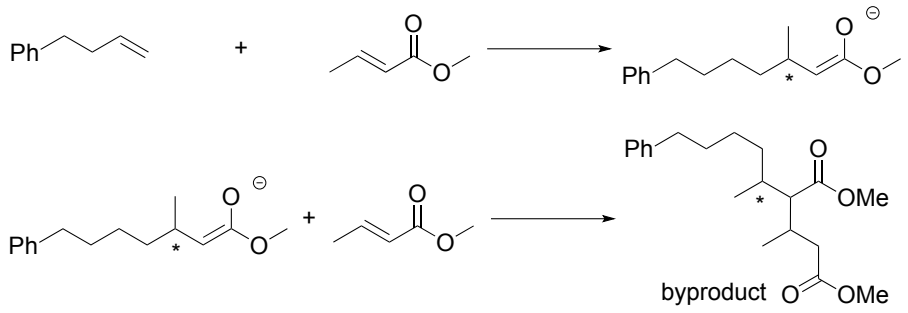
Entry	Copper source	Solvent	Additive[a]	Yield [%][b]	ee [%][c]
1[d]	CuCl + AgOTf	Et_2O	-	0	-
2[d]	CuCl + AgOTf	Et_2O	TMSCl	0	-
3[d]	CuCl + $AgNTf_2$	Et_2O	-	11	64
4[d]	CuCl + $AgNTf_2$	Et_2O	TMSCl	11	58
5[d]	CuCl + $AgPF_6$	Et_2O	-	0	-
6[d]	CuCl	Et_2O	-	0	-
7	CuCl + $AgNTf_2$	Et_2O	-	22	94
8	CuCl + $AgNTf_2$	^{t}BuOMe	-	17	92
9	CuCl + $AgNTf_2$	THF	-	15	94
10	CuCl + $AgNTf_2$	Et_2O/DCM	-	37	96
11[e]	CuCl + $AgNTf_2$	Et_2O/DCM	-	43	85

Reaction conditions: alkene (2.5 eq.), [Cp_2ZrHCl] (2 eq.), ester (1 eq.), copper salt (10 mol%), ligand (10 mol%), silver salt (15 mol%), TMSCl (5 eq.) [a] 5 eq., additive was used. [b] Yield of isolated product. [a] ee was determined by HPLC. [c] ee was determined by GC. [d] **L20** was used instead of **L27.** [e] RT instead of ice bath.

We first screened different counter anions, triflate and triflimide with and without added TMSCl (Table 3-1, entries 1-4), hexafluorophosphate (entry 5), and chloride (entry 6) in combination with **L20** in Et_2O. We found that only using the triflimide anion conditions could we obtain the desired products. The best result was achieved with triflimide without TMSCl (64% ee, entry 3). We then found a better result simply by replacing **L20** with **L27** (94% ee, entry 7). We next

explored different ether solvents, which normally behaved well under our systems, but did not find a better result[11] (entries 8-9). To our surprise a 1:1 mixture of Et_2O/DCM afforded a better result (37% yield, 96% ee, entry 10). We later raised the reaction temperature to room temperature (entry 11), the yield rose to 43% with a drop in ee to 85%.

In order to improve the yield, we isolated, characterized and determined the major byproduct by NMR, IR, and HRMS. We then proposed reactions accessing the byproduct (Scheme 3-6). The low yield resulted from the intermediate enolate undergoing subsequent reactions with the starting unsaturated esters and forming the byproduct. We tried to prevent this side reaction by optimizing solvents, copper salts, ligands, and additives, but no condition could give better yield.

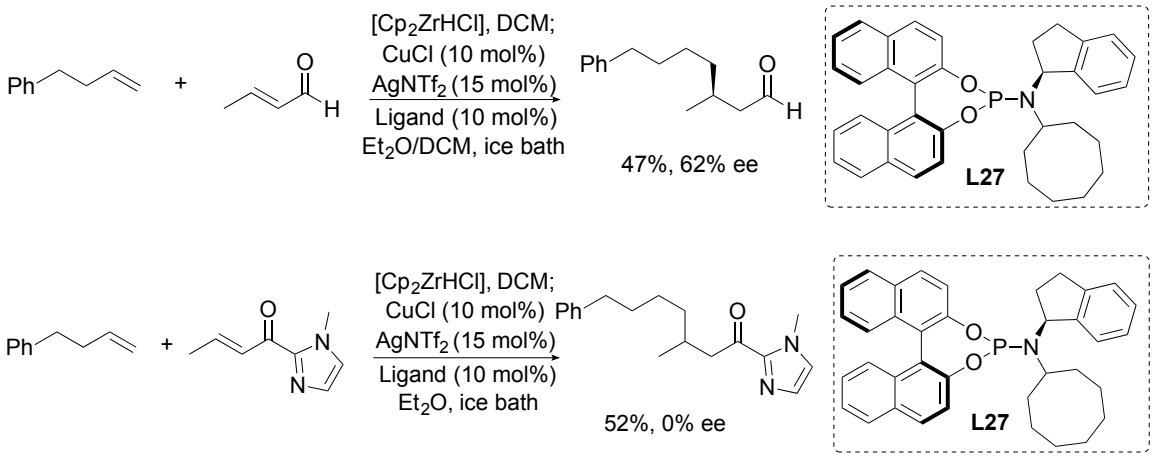


Scheme 3-6 A proposed side reaction during the ACA

3.3 Study on *α,β*-unsaturated aldehydes and *α,β*-unsaturated imidazoles

We next focused on *α,β*-unsaturated aldehydes and *α,β*-unsaturated imidazoles. For both starting substrate, we kept **L27** and trailed various solvents and counterions. The best results are as follows (Scheme 3-7).

The electron withdrawing counterion, triflimide is still the best anion for both systems. Mixed solvents Et_2O/DCM and Et_2O are the best solvents for aldehyde and imidazole respectively. For aldehyde substrate, we improved the yield to 47% with the ee dropping to 62% compared with ester product. As for imidazole substrates, we did not find any enantiocontrol using our nonracemic monophos ligands even though we obtained a good yield of 52%. We then explored ACAs to α,β-unsaturated thioesters by using alkylzirconium species.

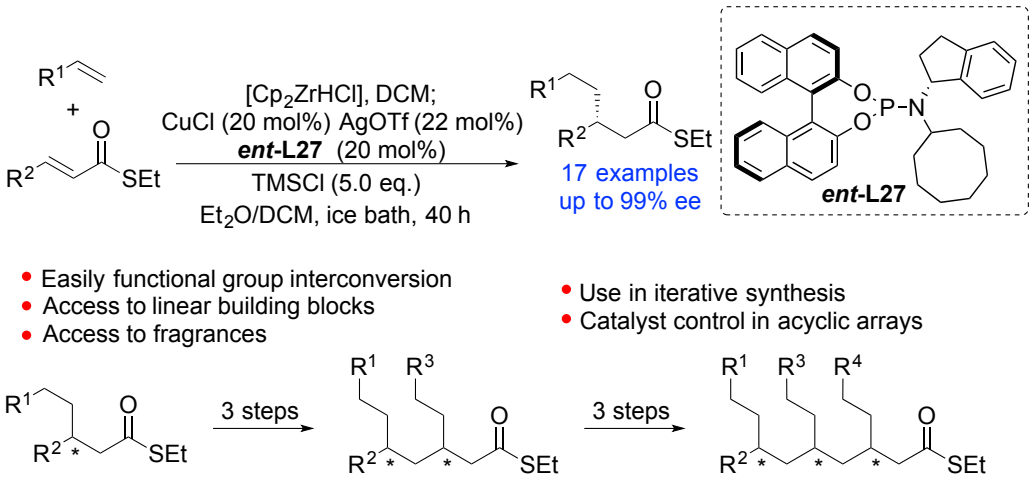


Scheme 3-7 ACAs on α,β-unsaturated aldehydes and imidazoles

3.4 Investigations on α,β-unsaturated thioesters

After attempts on α,β-unsaturated esters, aldehydes and imidazoles, we then investigated α,β-unsaturated thioesters. We were pleased to be able to develop a novel Cu-catalyzed asymmetric conjugate addition of alkylzirconium species to α,β-unsaturated thioesters with phosphoramidite ligands **L27** and ***ent*-L27**. A range of functionalized alkyl nucleophiles were first time introduced with very good yields and excellent ee's. We also applied this approach to the syntheses of chiral commercial fragrances, phenoxanol (97% ee), and hydroxycitronellal (98% ee). We next developed an iterative synthesis, where in our new iterative route a

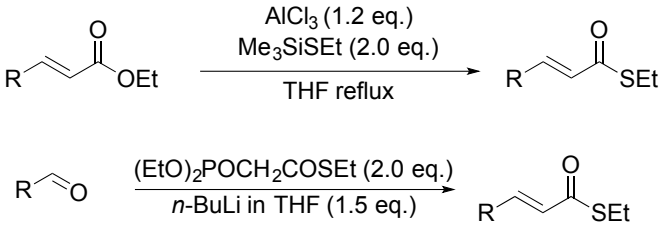
variety of functionalized acyclic arrays can be effectively prepared. Each of the newly formed linear chiral centres is demonstrated to be completely under catalyst control during its formations. These reactions are robust so that the nucleophiles can bear different functional groups (Scheme 3-8).



Scheme 3-8 ACA to α,β unsaturated thioesters and iterative synthesis routes

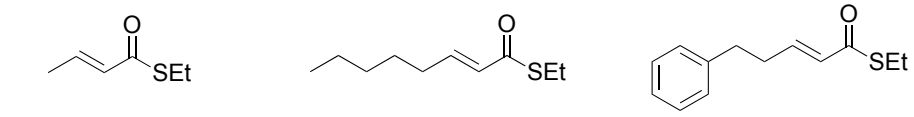
3.4.1 Preparation of α,β-unsaturated thioesters

Since most α,β-unsaturated thioesters are not commercially available, we initiated the research by preparing of various α,β-unsaturated thioesters. We found two reliable methods to prepare substrates from a range of literature approaches. The first approach simply mixes α,β-unsaturated esters with silanes, and the ester group is transformed to the thioester groups directly with the activation of $AlCl_3$ (Scheme 3-9 top).[12] For most commercially available α,β-unsaturated esters, they can be easily transformed to α,β-unsaturated thioesters with very good yields by using this method. Substrates **43**, **44**, **46**, **47** (Figure 3-1) were prepared by this method with no observation of (*Z*)-α,β-unsaturated thioesters in crude NMR spectra. We supposed that *E*:*Z* ratios should be over 20:1.



Scheme 3-9 Preparation of α,β-unsaturated thioesters

Another approach[13] combines aldehydes and Horner reagents[14](Scheme 3-9 bottom), which are easily made by reacting diethylphosphonoacetic acid with relevant thiols. This method also has an excellent selectivity on (*E*)-α,β-unsaturated thioesters. Substrates **45a** and **45b** were prepared at one time using the Horner approach with an overall 86% yield and 27:1 *E*:*Z* ratio. Six different substrates were synthesized using this method, and high yields are generally observed for aromatic ring substituted α,β- unsaturated thioesters (**46** and **47**).



43

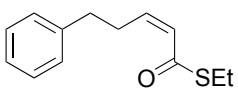
87% yield
> 20:1 *E*:*Z*

44

78% yield
> 20:1 *E*:*Z*

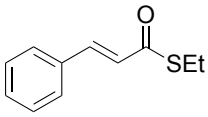
45a

83% yield
27:1 *E*:*Z*



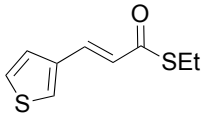
45b

3% yield
27:1 *E*:*Z*



46

96% yield
> 20:1 *E*:*Z*



47

85% yield
> 20:1 *E*:*Z*

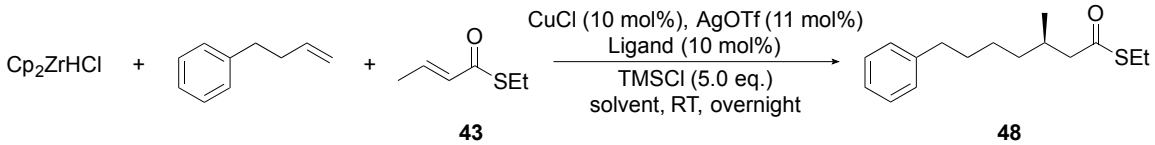
Figure 3-1 α,β-unsaturated thioesters in this study

3.4.2 Screening conditions

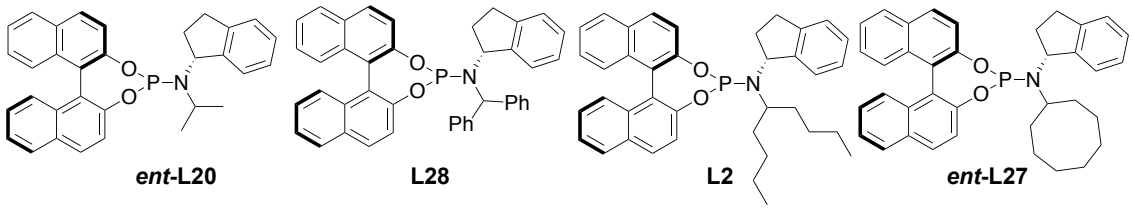
With various α,β-unsaturated thioesters at hand, we selected a general substrate **43** to optimize conditions. We found that the combination of Cu(I)

triflate and ***ent*-L20** in the presence of TMSCl afforded **48** with 46% conversion and 91% ee (Table 3-2, entry 1). After attempting reactions with several similar ligands **L28**, **L2**, and ***ent*-L27** (entries 2-4), we improved the result to 53% conversion with 92% ee. We next compared different solvents, and found better results by adding DCM, with the mixed solvent Et_2O/DCM (1/1) giving the best result (78% conversion, 97% ee, entry 6). We found the results can be further optimised by cooling the reaction to 0 ºC, doubling the catalyst to 20 mol% and extending reaction time to 40 hours (entries 7-11). By optimising all the conditions, we observed 98% conversion (85% isolated yield) and 97% ee. The addition of 20% catalyst is not necessary in our system, since it only improves the yield and ee slightly (entries 6, 8 and 12). The reason we used high catalyst loading was that we wanted to speed up the reactions and wait for less time. In case of low catalyst loading reaction, 5% loading gave over 66% conversion and 91% ee (entry 12). In preparative scale reactions (~ 1 g), we can easily minimize the catalyst loading to 10 mol% without any compromise on yield or ee after a reaction time of 40 hours (Scheme 3-13).

Table 3-2 Reaction conditions for ACAs to α,β-unsaturated thioester **43**



43 **48**



***ent*-L20** **L28** **L2** ***ent*-L27**

Entry	Solvent	Ligand	Conversion [%][a]	ee [%][b]
1	Et_2O	***ent*-L20**	46	91
2	Et_2O	**L28**	<10	83
3	Et_2O	**L2**	45	92
4	Et_2O	***ent*-L27**	53	92
5	DCM	***ent*-L27**	61	96
6	Et_2O/DCM	***ent*-L27**	78	97
7[c]	Et_2O/DCM	***ent*-L27**	77	98
8[d]	Et_2O/DCM	***ent*-L27**	86	97
9[d,e]	Et_2O/DCM	***ent*-L27**	98	97
10[c,d]	Et_2O/DCM	***ent*-L27**	93	98
11[c,d,e]	Et_2O/DCM	***ent*-L27**	98	98
12[c,e,f]	Et_2O/DCM	***ent*-L27**	66	91

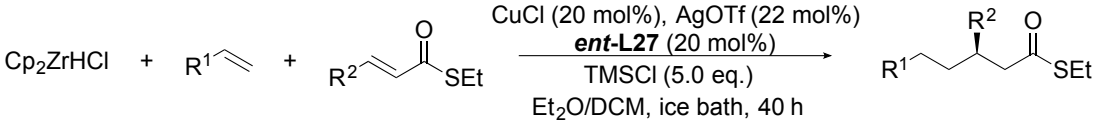
Reaction conditions: Hydrozirconation is performed on alkene before ACA. alkene (2.5 eq.), [Cp_2ZrHCl] (2 eq.), thioester (1 eq.), copper chloride (10 mol%), ligand (10 mol%), silver triflate (11 mol%), TMSCl (5 eq.), room temperature 15 h. [a] Calculated by HPLC or NMR. [b] Enantiomeric excess was determined by HPLC [c] ice bath. [d] 20 mol% catalyst. [e] 40 h reaction. [f] 1 mmol scale reaction using 5 mol% catalyst

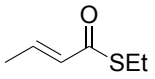
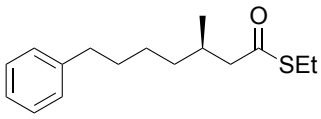
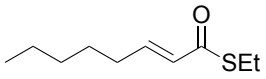
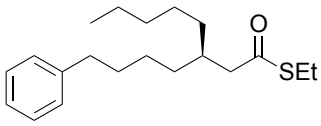
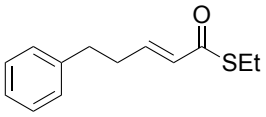
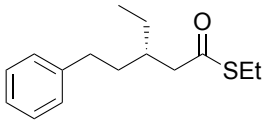
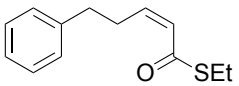
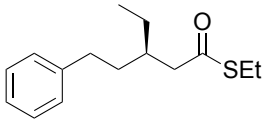
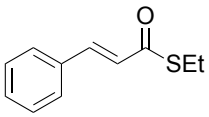
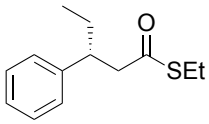
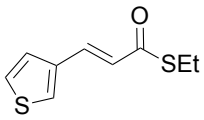
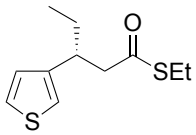
3.4.3 Scope of the reaction

We examined a range of β-substituted α,β-unsaturated thioesters. *n*-Pentyl substituted substrate **44** behaved as well as the model substrate **43**, affording 73% yield and 97% ee (Table 3-3 entries 2). To have a better HPLC separation on β-chiral centres, we replaced but-3-en-1-ylbenzene with ethylene in the following

study. We found that (*E*)-α,β-unsaturated thioesters performed much better than (*Z*)-α,β-unsaturated thioesters by comparing **45a** with **45b** (entries 3 and 4). Under the same conditions, (*E*)-substrate afforded 80% yield with 97% ee, while the (*Z*)-substrate only gave 47% yield and 73% ee. It may be due to double bond isomerization during the ACAs, since when we quenched the (*Z*)-thioester reaction after 15 hours (instead of 40 hours), we obtained ***ent*-50** with 25% yield, 78% ee and recovered some unsaturated thioesters with a *trans/cis* ratio of 1:19. We next examined (hetero)aromatic ring β-substituted unsaturated thioesters, which only afforded moderate yield with a substantial drop in ee (entries 5 and 6). The absolute configuration of **51** was obtained by comparision of optical rotation data with the literature.[5] All other stereochemical assignments in this chapter are made analogy to **51**.

Table 3-3 Scope of acyclic α,β-unsaturated thioesters

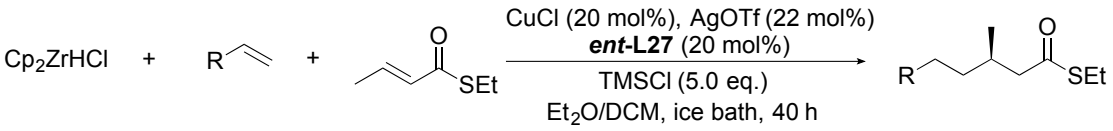


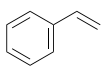
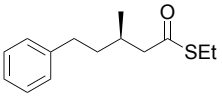
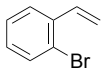
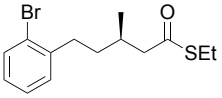
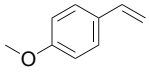
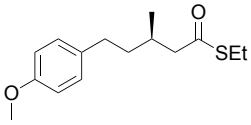
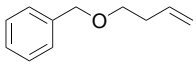
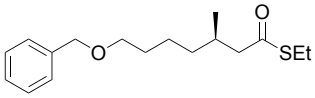
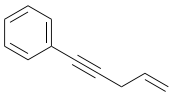
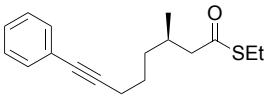
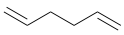
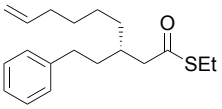
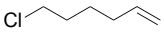
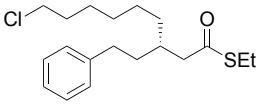
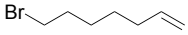
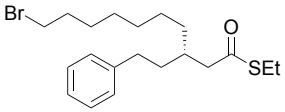
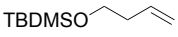
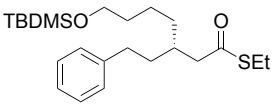
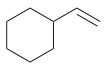
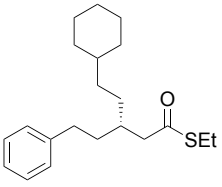
Entry	Substrate		Product		Yield [%][a]	ee[%][b]
1[c]		**43**		**48**	85	98
2[c]		**44**		**49**	73	97
3[d]		**45a**		**50**	80	97
4[d]		**45b**		***ent*-50**	47	73
5[d]		**46**		**51**	63	71
6[d]		**47**		**52**	60	66

Reaction conditions: alkene (2.5 eq.), [Cp_2ZrHCl] (2 eq.), thioester (1 eq.), copper chloride (20 mol%), ligand (20 mol%), silver triflate (22 mol%), TMSCl (5 eq.) [a] Yield of isolated product. [b] ee was determined by HPLC. [c] But-3-en-1-ylbenzene was used. [d] Ethylene was used.

We then did a wide scope of alkenes to demonstrate that our method was reliable for more complex olefins as well using substrates **43** and **45a** (Table 3-4). Styrene and its derivatives are generally very difficult alkenes in alkyl zirconocene asymmetric additions and often lead to various side reactions. We were pleased to find that styrene and its derivatives performed well in our ACAs. Styrene, 2-bromo styrene and 4-methoxyl styrene all afforded ~70% yields with over 97% ee's (Table 3-4, entries 1-3

Table 3-4 Scope of alkenes



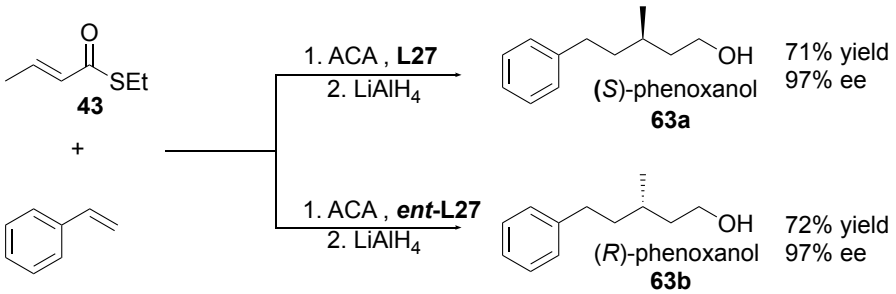
Entry	Substrate	Product		Yield [%][a]	ee[%][b]
1			**53**	75	97
2			**54**	70	99
3			**55**	64	97
4			**56**	75	98
5			**57**	73	93
6[c]			**58**	64	92
7[c]			**59**	62	97
8[c]			**60**	74	97
9[c]			**61**	74	96
10[c]			**62**	83	97

Reaction conditions: alkene (2.5 eq.), [Cp_2ZrHCl] (2 eq.), thioester (1 eq.), copper chloride (20 mol%), ligand (20 mol%), silver triflate (22 mol%), TMSCl (5 eq.) [a] Yield of isolated product. [b] ee was determined by HPLC. [c] α,β-unsaturated thioester **45a** was used instead of **43**.

We also introduced alkenes bearing benzyl ethers and alkynes to **43** without compromising on yields or ee's (entries 4-5). Unsaturated C-C double bonds (entry 6), halogens (entries 7-8), silyl ethers (entry 9) and bulky vinylcyclohexane (entry 10) were all efficiently added to **45a**, and in most cases, the ee was 97% with over 70% yield. This excellent enantioselectivity in copper catalyzed reactions is rare. To further test our method, we applied it to syntheses of several chiral commercial fragrances.

3.4.4 Applications of the ACA

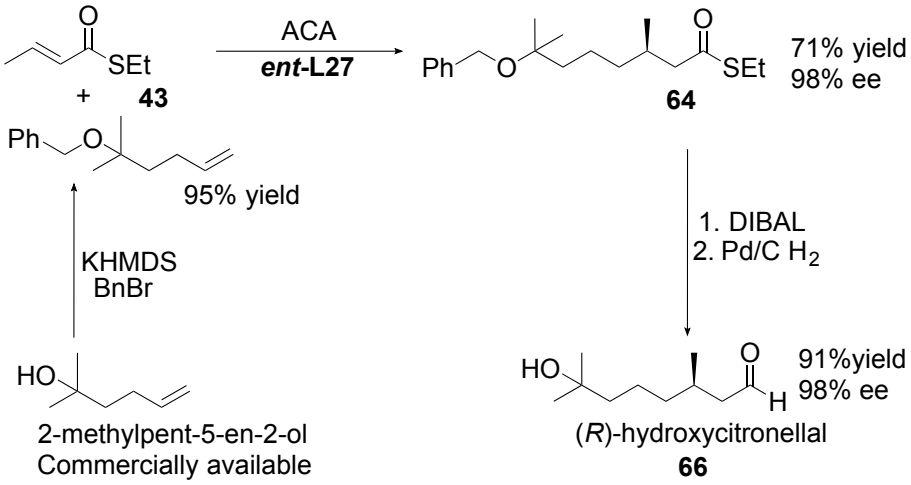
First, we made some chiral phenoxanols, which are rosy smell fragrances, and extensively used in various cosmetics.[15] The (*S*)-and (*R*)-enantiomer are determined merely by the chiral monophos ligand used. **L27** affords (*S*)-enantiomer, while its enantiomer gives (*R*)-product. Through a two-step sequence of asymmetric conjugate addition and $LiAlH_4$ reduction, both enantiomers were achieved with over 70% yield and 97% ee (Scheme 3-10). The absolute configurations were further confirmed by comparison with optical rotations in previous literatures.[16]



Scheme 3-10 Synthesis of chiral phenoxanol

We next applied our ACA to synthesize (*R*)-hydroxycitronellal using ***ent*-L27**, which serves as a perfume ingredient and has a much higher price than its (*S*)-enantiomer. The absolute configuration was further affirmed by comparing with

reported optical rotations in the literature.[17] Just in Lush cosmetics, we found over 20 products containing hydroxycitronellal. Our synthetic pathway started from a commercially available alkene, 2-methylpent-5-en-2-ol. It underwent benzyl protection, ACA, DIBAL reduction, deprotection and gave the desired product with an overall yield of 62% with 98% ee (Scheme 3-11).



Scheme 3-11 Synthesis (*R*)-hydroxycitronellal

Propionates and deoxypropionates are important units in polyketides, and their structures are shown in Figure 3-2.[18] A broad range of biological activities are associated with these structures, and a variety of synthetic methods have been developed to construct deoxypropionates, such as (–)-borrelidin,[19] (–)-lardolure,[5] mycocerosic acid,[20] (–)-doliculide,[21] and phthioceranic acid (Figure 3-3). [22, 23] While many strategies to obtain deoxypropionate fragments have been developed, among approaches based on the 1,4-addition of non-stabilized nucleophiles, Minnaard and Feringa pioneered this area.

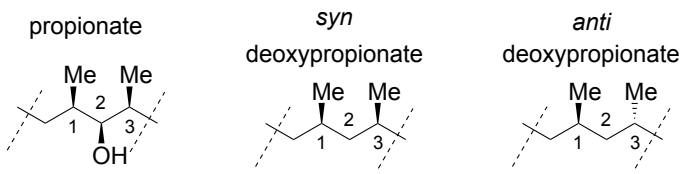


Figure 3-2 Structures of propionate and deoxypropionate

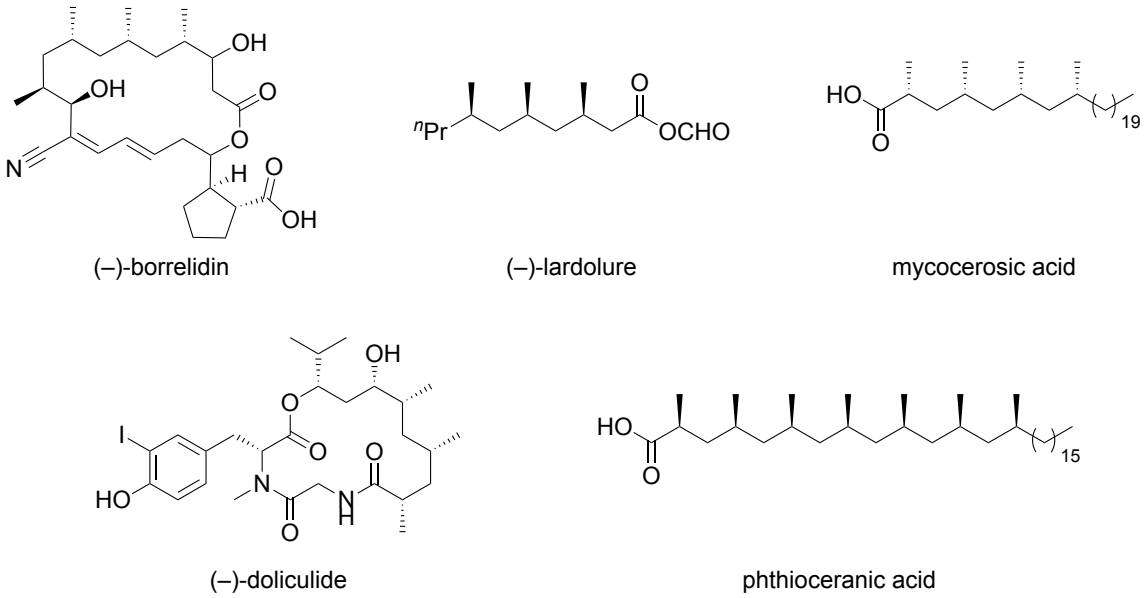
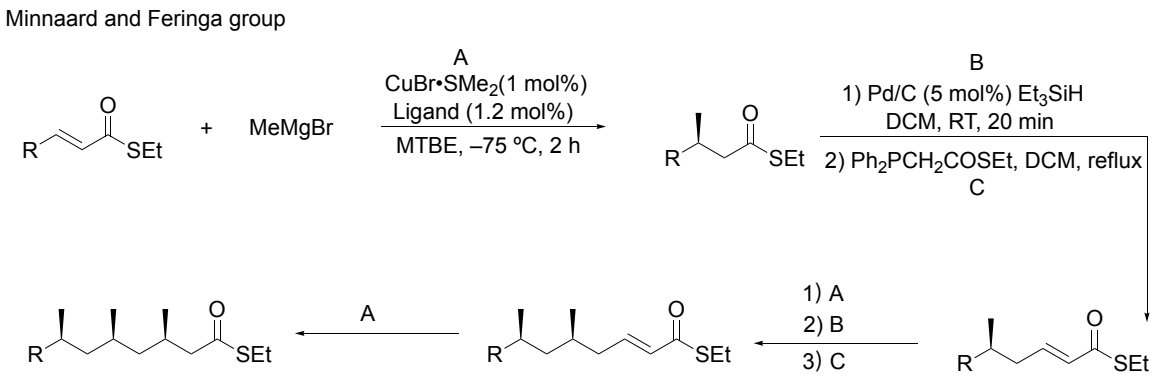


Figure 3-3 Examples of naturally occurring deoxypropionates

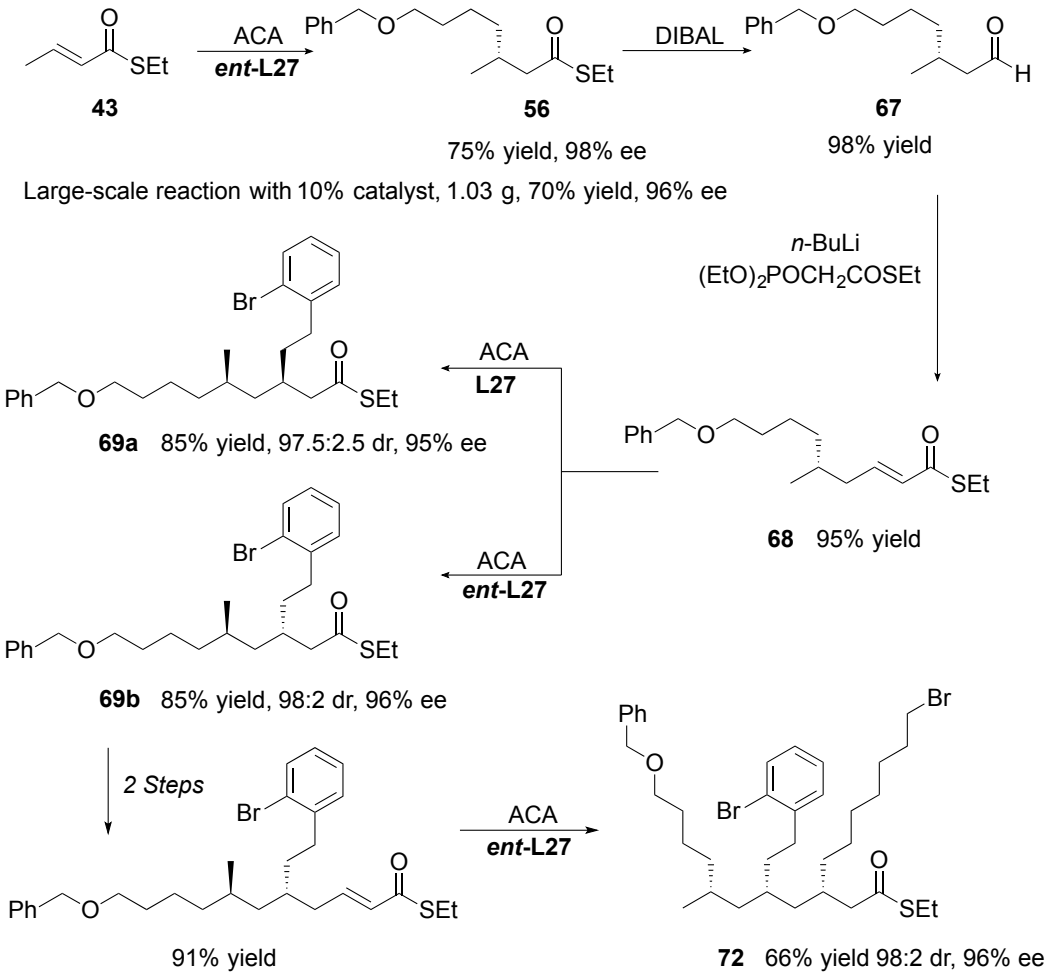
Minnaard and Feringa reported an 1,4-conjugated addition of MeMgBr to α,β-unsaturated thioesters using (*R,S*) Josiphos ligand. The 1,4-addition was followed by a Fukuyama reduction, Horner-Wadsworth-Emmons reaction, and another ACA and then a 1,3-dimethyl subunit was obtained. By simply repeating steps, various deoxypropionates were accessed (Scheme 3-12).[24]



Scheme 3-12 Access to deoxypropionates by Grignard reagents

We used alkylzirconium species in ACAs, expanding the scope and complexity of nucleophiles. By combination of Feringa's iterative synthesis and our ACAs of alkylzirconium species to α,β-unsaturated thioesters, we could prepare linear stereochemical arrays tolerating various functionalized nucleophiles. They are

similar to deoxypropionates, except that they have more complex branches, which are simple methyl groups in deoxypropionates.



Scheme 3-13 Synthesis of highly functionalized '''deoxypropionate''

We first did a preparative scale reaction synthesizing **56** with a half of the normal catalyst loading. No evident decline on yield or ee was observed compared to the normal scale reaction (0.2 mmol). The thioester **56** was subjected to DIBAL reduction to give aldehyde **67**, and Horner-Wadsworth-Emmons reaction (HWE) to give another unsaturated thioester **68**. A second ACA was then used to form a second stereocenter. By simply repeating the sequence mentioned above, we obtained product **72** featuring three acyclic chiral centres. In the formation of each stereocenter a different functional groups; a protected alcohol, an aromatic ring, and halogens can be effectively introduced with an

excellent diastereometric ratio of 98:2, and enantiomeric excess of 96%. During the formation of second chiral centre, we were pleased to find that the stereochemistry of the existing chiral centres in the unsaturated thioesters did not interfere with the yield and ee of forming a new stereocenter, since similar yields and dr's of **69a** and **69b** were achieved (Scheme 3-13).

3.5 Conclusions and future work

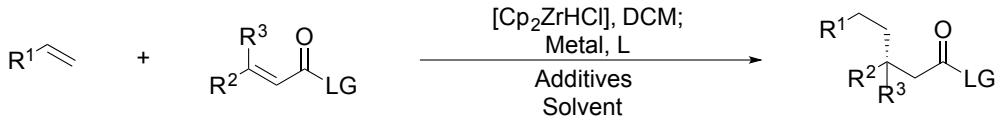
Here, we explored a new Cu-catalyzed ACA to enantioselectively generate new tertiary stereogentic centres in acyclic carboxylic acid derivatives. We investigated α,β-unsaturated esters, aldehydes, imidazoles and thioesters, and achieved best result in thioesters. A variety of α,β-unsaturated thioester can be used in our asymmetric approach giving excellent results.

Overall the best results are achieved when forming tri-*n*-alkyl substituted thioesters. Our method tolerates halides, arenes, unsaturated C-C bonds, benzyl and silyl ethers as functional groups on the alkene without significant loss of enantioselectivity.

We could adopt our approach to preparing the commercially used fragrances phenoxanol (both enantiomers, 97% ee) and (*R*)-hydroxycitronellal (98% ee). We have scaled up to 1.0 g with only 10% catalyst loading without any compromise on yield and ee. Our method also enables a catalytic asymmetric iterative synthesis of stereochemical arrays, in which the formation of each new stereogenic centre is fully under ligand control.

In the future we may be able to extend our method to form quaternary centres to tri-substituted unsaturated carboxylic acid derivatives (Scheme 3-14). We tried some asymmetric additions to tri-substituted unsaturated thioesters using our

established methods. However, we did not find any product, and recovered all of the starting material. As far as I know, this area has not been studied yet, more optimization and development need to be done to enrich the asymmetric catalysis arsenal.



Scheme 3-14 The formation of quaternary centres from α,β-unsaturated carboxylic acid derivatives is currently unknown.

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Chapter 4

Construction of β- to carbonyl chiral centres to dienones, dienthioates, ynenones, and ynethioates

In this chapter, we first attempted Cu-catalyzed ACAs of alkenyl zirconium species to enones, but failed to find asymmetric conditions. We then explored a novel Cu-catalyzed asymmetric 1,4-addition of alkylzirconium reagents to linear *α,β,γ,δ*-unsaturated substrates including dienones, dienthioates, ynenones, and ynethioates (~70% yield and >90% ee). We were also pleased to find that the method was able to tolerate a variety of alkyl zirconium species featuring different functional groups. Finally, we decreased the catalyst loading to 1.2-2.5% without losing enantiocontrol. This work was published on *Chemical Communications* this year.[1]

4.1 Introduction

In our previous work, we developed ACAs of alkylzirconium species to cyclic enones,[2,3] noncyclic enones,[4,5] *α,β*-unsaturated lactones,[6] and thioesters[7]. However, we were never able to access molecules with vinyl or alkynl groups adjacent to the stereogenic centre (Figure 4-1).

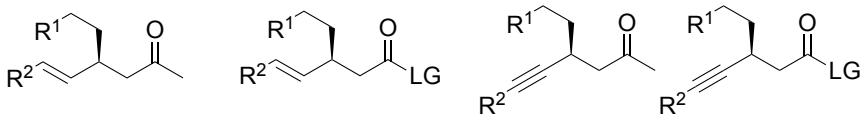


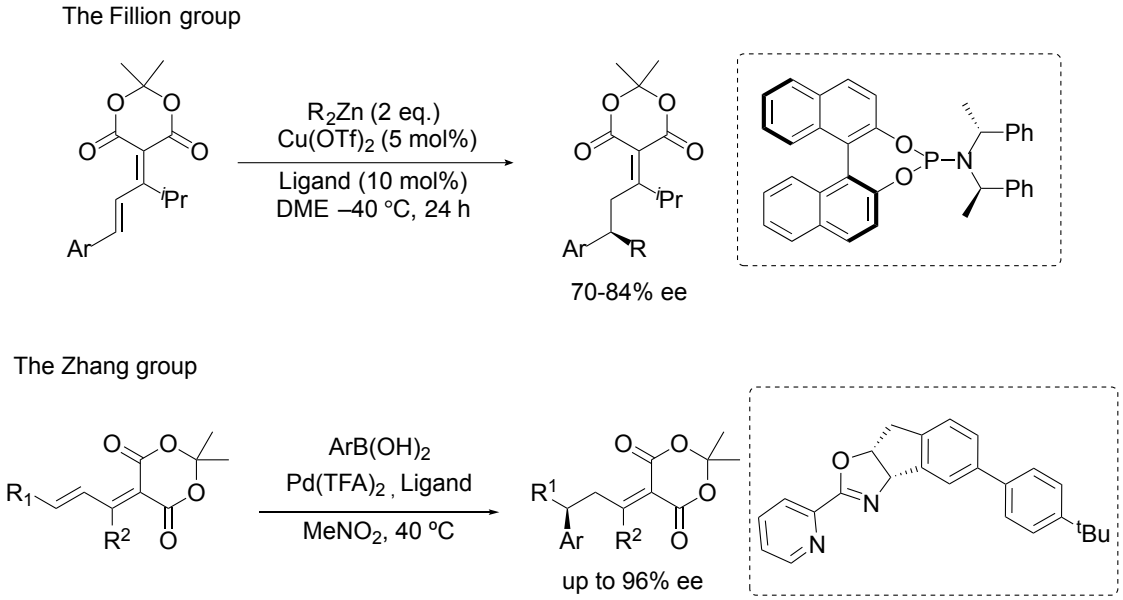
Figure 4-1 Targeted molecules

To obtain these unsaturated molecules, and expand the range of products that can be accessed using our methods, we examined two approaches, 1) we attempted Cu-catalyzed ACA of alkenylzirconocenes to construct C_{sp^2}-C_{sp^3} bonds to enones, and 2) we developed Cu-catalyzed ACA of alkylzirconocenes to construct *β*-to carbonyl stereogenic centres to polyunsaturated substrates.

In comparison with previous *α,β*-unsaturated substrates we had examined, study on polyunsaturated substrates is more challenging since more side reactions are possible. Good regioselectivity also needs to be achieved to obtain high yield of a desired product. Among research on polyunsaturated substrates, *α,β,γ,δ*-unsaturated substrates have received most attention, in which 1, 2-, 1,4-, and 1,6-additions all might happen during the course of the reaction. Asymmetric additions to *δ*-positions affording 1,6-adducts have been much more developed than enantioselective 1,4-additions to *α,β,γ,δ*-unsaturated substrates, and a variety of methods have now been developed to give different 1,6-adducts.[8]

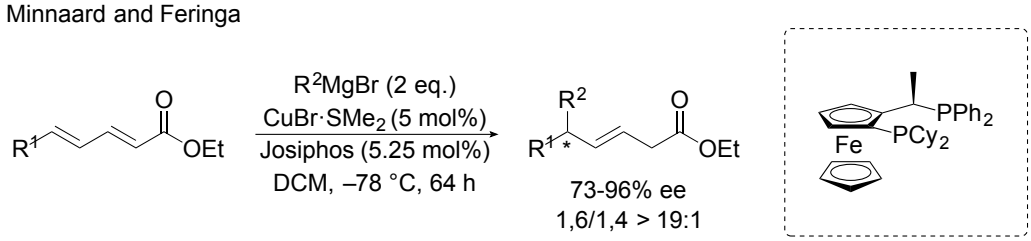
In 2006, the Fillion group[9] developed a Cu-catalyzed approach forming new *δ*-to carbonyl stereogenic centres from Meldrum's acid derivatives using 10 mol% Leggy's ligand combining with 5 mol% $Cu(OTf)_2$ (Scheme 4-1, top) with moderate

enantioselectivity (70-84% ee). Recently, the Zhang group[10] further developed related Pd-catalyzed reactions using novel Pyrox ligands, obtaining moderate to good yields and excellent ee's (28-89% yield, >90% ee in most cases, Scheme 4-1, bottom).



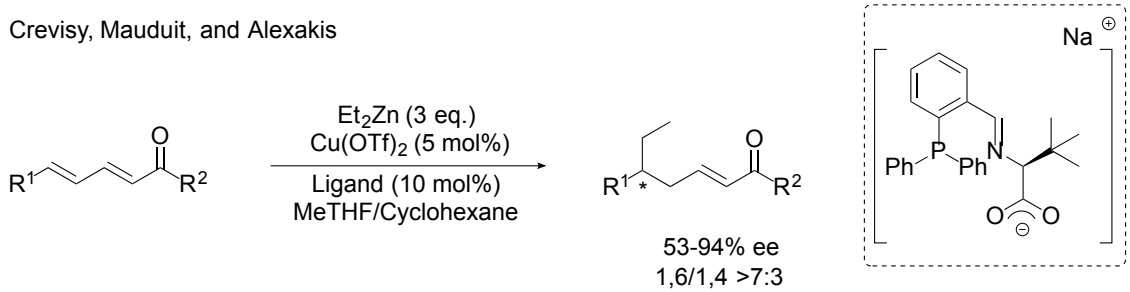
Scheme 4-1 ACAs to Meldrum's acid derivatives

Minnaard and Feringa [11] established another catalytic enantioselective 1,6-conjugate addition of Grignard reagents to linear dienoates using Josiphos as ligand (Scheme 4-2). Methyl and ethyl groups were introduced with excellent regioselectivity, yield and enantiocontrol (1,6-/1,4- > 19:1, 54-88% yield, 73-96% ee).



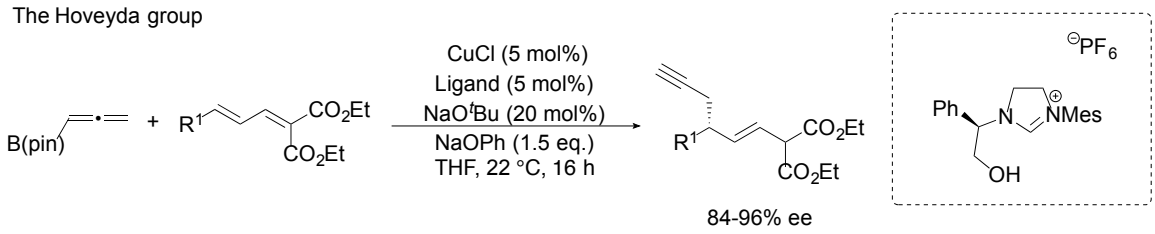
Scheme 4-2 ACAs of Grignard reagents to linear dienoates

Crévisy, Mauduit and Alexakis[12] later successfully developed enantioselective 1,6-conjugate addition of dialkylzinc reagents to linear dienones and dienoates catalyzed by Cu-DiPPAM complex (5 mol%, Scheme 4-3). Good to moderate results were obtained using a new “small peptide ligand”.



Scheme 4-3 ACAs of dialkylzinc reagents to linear dienones and dienoates

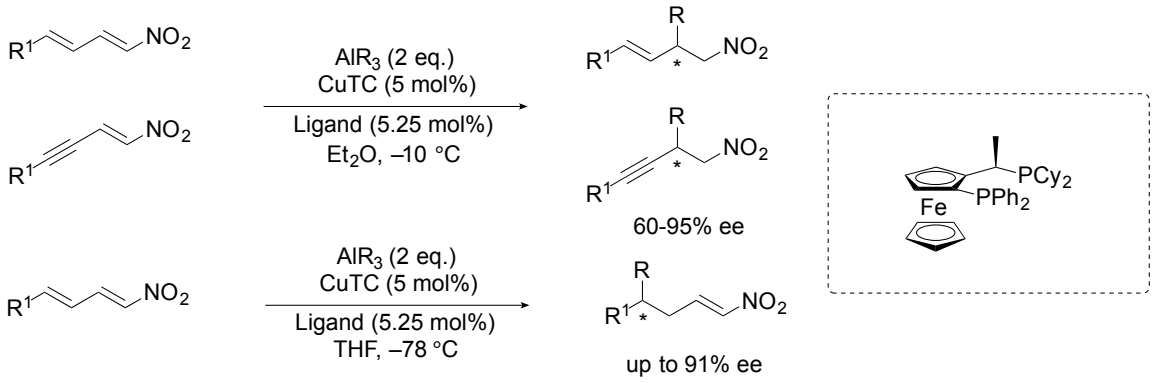
Hoveyda[13] also advanced enantioselective 1,6-conjugate addition of propargyl and allyl groups to the *δ*-position of dienoates using allenyl-boron compound with (NHC)-Cu complex affording excellent results (84-96% ee, Scheme 4-4). Meanwhile, they proposed a mechanism for the reaction based on DFT calculations.



Scheme 4-4 Enantioselective 1,6-conjugate additions of propargyl and allyl groups

Most research on *α,β,γ,δ*-unsaturated substrates focused on additions to the *δ*-position and only few groups have reported 1,4-asymmetric additions to *α,β,γ,δ*- unsaturated substrates. The Alexakis group[14, 15] developed Cu catalyzed ACAs to polyconjugated nitroolefins both at the *β*- and *δ*- to carbonyl positions using alkylaluminium reagents combined with ferrocene based phosphine ligands (eg. Josiphos ligand, Scheme 4-5).

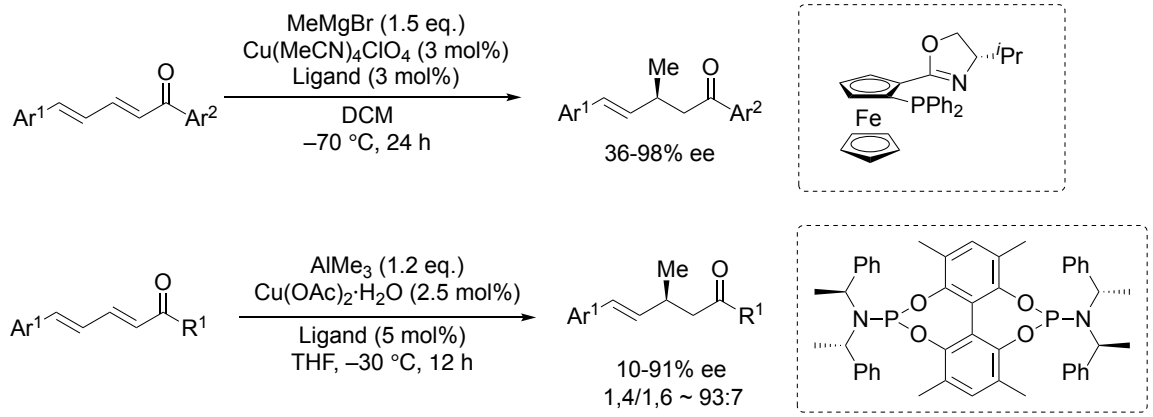
The Alexakis group



Scheme 4-5 ACAs to polyconjugated nitroolefins

The Zhang group[16, 17] explored several 1,4-ACAs to dienones. They found good conditions for Cu-catalysed ACAs of Grignard reagents and alkylaluminium reagents, presenting over 90% ee's for most products using a new chiral metallocene-based phosphinooxazoline ligand and a 1, 2-disubstituted planar phosphoramidite ligand respectively (Scheme 4-6).

The Zhang group



Scheme 4-6 1,4-ACAs to dienones

Based on previous ACAs to *α,β,γ,δ*-unsaturated substrates, there are good reasons for us to advance the study of 1,4-asymmetric additions to acyclic *α,β,γ,δ*-unsaturated substrates. First, few methods could access the 1,4-linear adducts to *α,β,γ,δ*-unsaturated substrates with excellent results. Additionally, these established approaches could only introduce very simple nucleophiles such

as methyl or ethyl groups to the substrates. Furthermore, reaction temperatures necessary are generally very low, which limits their applications. At last, each method is only applicable to a very limited number of substrates, which reduces the method utility in synthesis. To cope with the obstacles mentioned above, we decided to study Cu-catalyzed ACAs of alkenylzirconium or alkylzirconium species to enones or *α,β,γ,δ*- unsaturated substrates respectively to synthesize the desired products.

4.2 Attempted Cu-catalyzed ACA of alkenylzirconocenes to the enone

We first tried to construct C_{sp}^2-C_{sp}^3 directly using Cu-catalyzed ACAs of alkenylzirconium species to enones, which is a direct way to access our desired products. As far as we know, few reports[18–20] are on ACAs of vinyl or alkynl organometallic species to acyclic enones though there are quite a few to cyclic enones.[21–24]

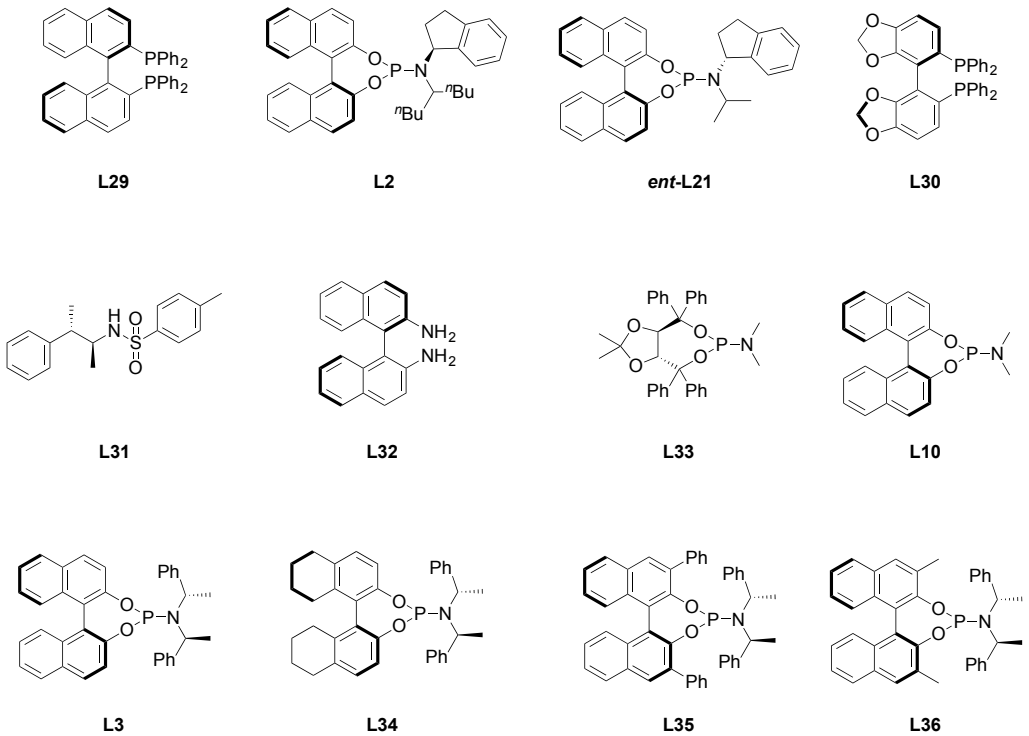
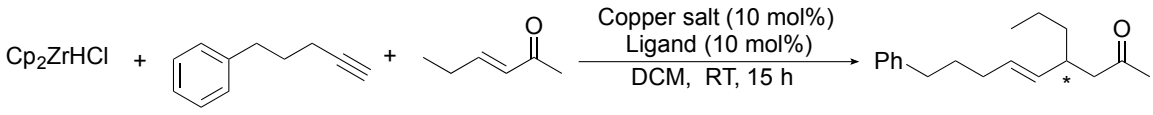


Figure 4-2 Chiral ligands used

Table 4-1 Attempted Cu-catalyzed ACA of alkenylzirconocenes to enones



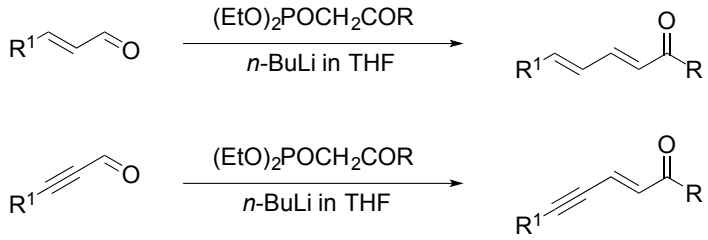
Entry	Copper source	Ligand	Yield [%][a]	ee[%][b]
1	CuI	**L29**	0	-
2	CuI	**L2**	70	0
3	CuI	***ent*-L21**	68	-
4	CuI	**L30**	0	-
5	CuI	**L31**	0	-
6	CuI	**L32**	61	0
7	CuI	**L33**	57	0
8	CuI	**L10**	63	0
9	CuI	**L3**	60	0
10	CuI	**L34**	65	0
11	CuI	**L35**	42	0
12	CuI	**L36**	44	0
13	CuCl	**L2**	0	-
14	CuTc	**L2**	0	-
15	CuCl + $AgNTf_2$	**L2**	<5	0
16	CuCl + AgOTf	**L2**	0	-
17[c]	CuCl + $AgNTf_2$	**L2**	26	0
18[c]	CuCl + AgOTf	**L2**	0	-

Reaction conditions: alkene (2.5 eq.), [Cp_2ZrHCl] (2 eq.), enone (1 eq.), copper salt (10 mol%), ligand (10 mol%), silver salt (11 mol%), TMSCl (5 eq.) [a] Yield of isolated product. [b] ee was determined by HPLC. [c] 5 eq., TMSCl was added.

We then combined alkenylzirconium species with enones. We picked CuI as our copper salt, and two commercially available substrates, (*E*)-hex-3-en-2-one and pent-4-yn-1-ylbenzene as our starting material. We then varied different phosphorus and nitrogen based chiral ligands (Figure 4-1, Table 4-1, entries 1-12). However, the best result obtained was racemic product with 70% yield (Table 4-1, entry 2). We also tried other copper salts, but none of them afforded enantioselectivity (entries 14-19).

Since we could not find suitable conditions for enantioselective additions of alkenylzirconocenes to enones, we moved to examine the addition of alkylzirconium species to *α,β,γ,δ*- unsaturated substrates. Based on conditions developed, constructing the *β*- to carbonyl chiral centres to acyclic enones,[4,5] we found good conditions for 1,4-addition of alkylzirconium species to *α,β,γ,δ*-unsaturated substrates after some subtle variation and optimization. We selected **71** as our model substrate, and after some ligand screening, we found that ligand **L2** could give high enantio- and regio-selectivity in polyunsaturated systems.

4.3 Preparation of polyunsaturated substrates



Scheme 4-7 Preparation of polyunsaturated substrates

We decided to use Horner-Wadsworth-Emmons (HWE) reaction to prepare a range of polyunsaturated starting substrates. We found a method[25] in which ^{n}BuLi was used as the base in the reaction and using this approach we synthesized

several dienones, dienthioates, ynenones, and ynethioates with moderate to good yields (Figure 4-3). The syntheses of alkyl group substituted dienones (**72**, and **73**) proceeded with good yields. For aryl group substituted dienones (**71**, **76**, **77**, and **78**), the syntheses are more challenging. Only phenyl group substituted dienone **71** afforded good yield. We also prepared dienthioate (**80**), ynenone (**97**), and ynethioate (**98**), all of which performed well in the HWE reactions. *E*:*Z* ratios are generally over 20: 1 for most alkene products, except for **76**, **77**, **78** dropping down to ~ 9:1.

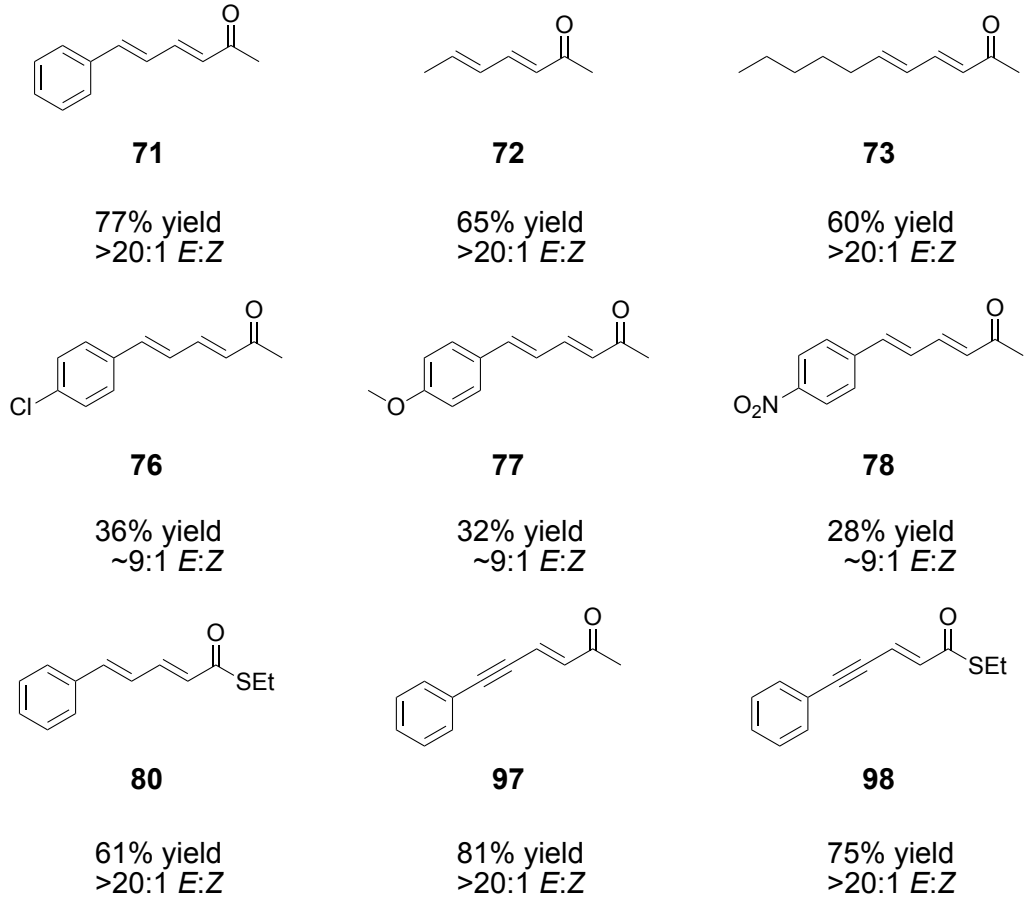


Figure 4-3 Examples of polyconjugated substrates

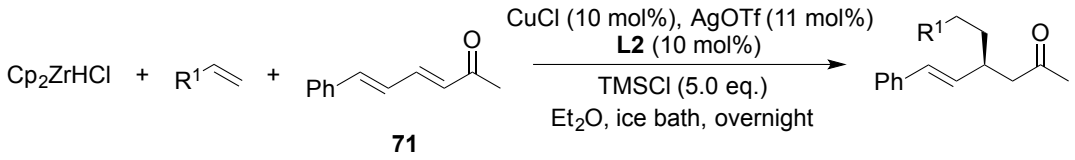
4.4 Scope of the alkene

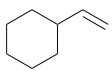
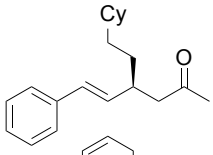
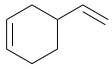
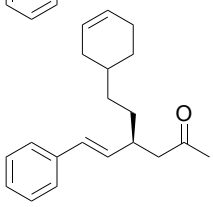
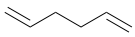
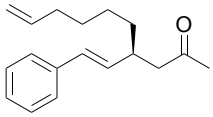
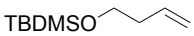
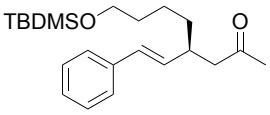
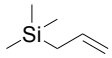
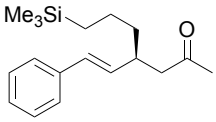
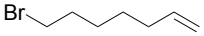
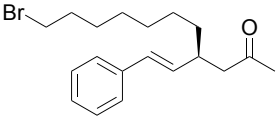
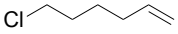
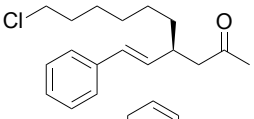
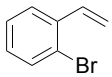
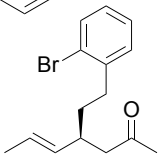
With various dienones and best conditions at hand, we started examining the scope of the reaction using a range of alkenes and substrates **71** and **72** (Table

4-2). The combination of copper(I) triflate (generated *in situ*) and chiral ligand **L2** in the presence of TMSCl at 0 °C afforded the 1,4-adduct as major products. We introduced bulky cyclohexane ring to the **71** with 70% yield and 90% ee (Table 4-2, entry 1). Without TMSCl, 35% yield was observed with 79% ee.

We also found that when we decreased the amount of Schwartz's reagent to 1.0 eq., the yield of **81** dropped to 60%, even though the ee rose to 95%. The reason for this phenomenon is not clear, but mechanistic studies on related systems are underway. Meanwhile, no 1,6-adduct was observed under these conditions. The scope of alkenes was carried out mainly with functionalized alkylzirconium species (generated by treating alkenes with Schwartz's reagent). Alkenes tolerating unsaturated C-C bonds (entries 2, 3), silyl ethers (entry 4), silanes (entry 5), and halogens (entries 6,7) all performed well (>70% yield and 90% ee) except for hexa-1,5-diene, which only gave moderate results (78% yield, 63% ee, entry 3). We were also pleased to see we could introduce halogen substituted aromatic rings (1-bromo-2-vinylbenzene) into **72** with 60% yield and 90% ee (entry 8), though we found some 1,6-adduct (1,4- to 1,6- ratio ~ 20:1). We think this might be because that a terminal aromatic ring on the polyene would promote competing 1,4-instead of 1,6-additions. While the terminal methyl group on the polyene weakens the favour of 1,4-adducts and gives tiny amount of 1,6-adducts as well. We assumed that the steric repulsion from the polyene would affect the preference of 1,4- or 1,6- adducts.

Table 4-2 Scope of alkenes



Entry	Substrate	Product		1,6:1,4	Yield [%][a]	ee [%][b]
1			**81**	<1:20	70	90
2			**82**	<1:20	70	92
3			**83**	<1:20	78	63
4			**84**	<1:20	79	92
5			**85**	<1:20	78	86
6			**86**	<1:20	78	92
7			**87**	<1:20	85	90
8[c]			**88**	<1:20	60	90

Reaction conditions: alkene (2.5 eq.), [Cp_2ZrHCl] (2 eq.), dienone (1 eq.), copper chloride (10 mol%), ligand (10 mol%), silver triflate (11 mol%), TMSCl (5 eq.) [a] Yield of isolated product. [b] ee was determined by HPLC. [c] Substrate **72** was used instead of **71.**

4.5 Scope of the dienone

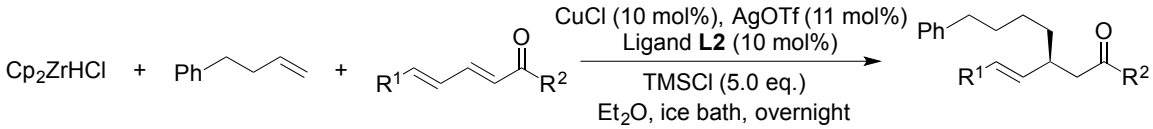
We next examined different dienones (Figure 4-3) with but-3-en-1-yl-benzene (Table 4-3). Alkyl substituted dienones **72** and **73** both gave over 60% yield and 96% ee of 1,4-products, though we also observed small amounts of 1,6-adducts (1,4- to 1,6- ratio~20:1). We then studied dimethyl substituted dienone **74**, which did not provide any 1,6-adduct and gave 87% yield of 1,4-product. Nucleophiles are more difficult to access *δ*- to carbonyl positions of **71** and **74** than **72** and **73** due to stronger steric hindrance, leading to far less 1,6-adducts observed with **72** and **73** than with **71** or **74**.

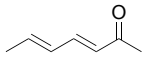
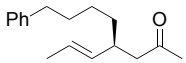
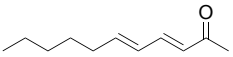
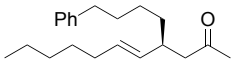
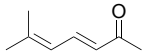
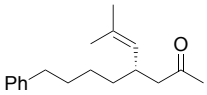
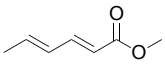
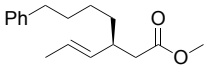
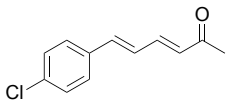
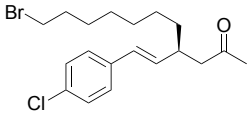
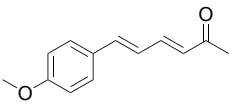
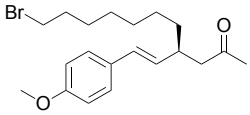
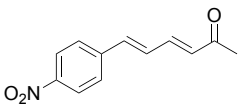
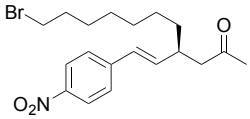
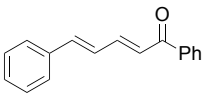
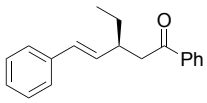
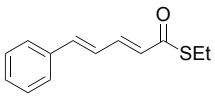
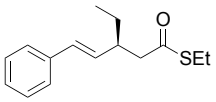
Dienoates **75** gave no product after an overnight reaction, and the unreacted substrate was nearly totally recovered (entry 4). We also tried several aryl group substituted dienones (entries 5-7), which gave moderate to good yield but a great loss of enantioselectivity for dienones bearing electron donating groups (**76** and **77**). For electron withdrawing groups, nitro-substituted dienone **78** worked very well (63% yield with 86% ee). With substrate **79**, where a phenyl group replaces the carbonyl methyl group, only 51% yield and 54% ee were achieved (entry 8).

However, for dienthioate **80**, the reaction proceeded well with 77% yield and 95% ee (entry 9), when using 20 mol% catalyst and 40 hours' reaction time. In principle, the thioester group could be further transformed into a range of carbonyl derivatives by simple functional group interconversions, which opens a door to total synthesis of complicated chiral linear molecules.

The absolute configuration of **95** was determined by comparison of optical rotation data with the literature.[16] All other stereochemical assignments were made by analogy to **95**.

Table 4-3 Scope of dienones



Entry	Substrate		Product		1,6:1,4	Yield [%][a]	ee [%][b]
1		**72**		**89**	<1:20	61	97
2		**73**		**90**	<1:20	65	96
3		**74**		**91**	<1:20	87	92
4		**75**		**75b**	-	0	-
5[c]		**76**		**92**	<1:20	53	47
6[c]		**77**		**93**	<1:20	70	43
7[c]		**78**		**94**	<1:20	63	86
8[d]		**79**		**95**	<1:20	51	54
9[d],[e]		**80**		**96**	<1:20	77	95

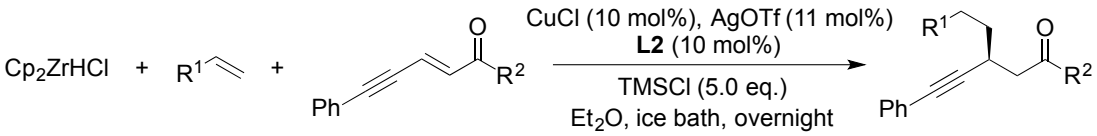
Reaction conditions: alkene (2.5 eq.), [Cp_2ZrHCl] (2 eq.), dienone or dienthioate (1 eq.), copper chloride (10 mol%), ligand (10 mol%), silver triflate (11 mol%), TMSCl (5 eq.) [a] Yield of isolated product. [b] ee was determined by HPLC. [c] 6-bromohex-1-ene was used instead of but-3-en-1-ylbenzene. [d] ethylene was used instead of but-3-en-1-ylbenzene. [e] 20% catalyst loading was applied with 40 hours' reaction time.

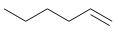
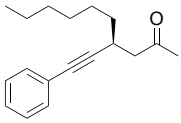
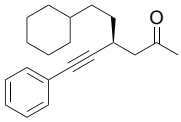
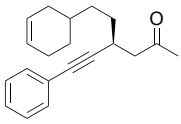
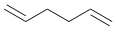
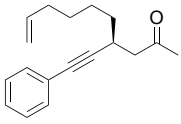
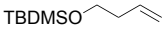
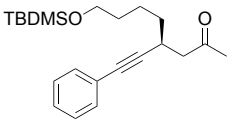
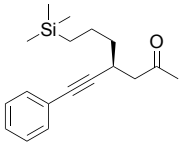
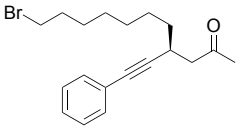
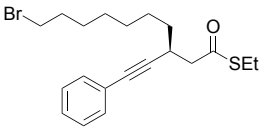
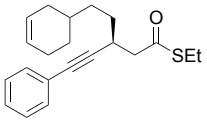
4.6 Additions to ynenones and ynethioates

We then explored ynenones and ynethioates to test the generality of our approach (Table 4-4). 1,6 adduct was not observed in the crude NMR spectra, and we estimated that the ratio of 1,6:1,4 should be lower than 1:20. Without further optimising conditions from those developed for dienones, we obtained **99** with 70% yield and 94% ee (entry 1). We examined more complex olefins with **97** as well. Bulky cyclohexane rings (entry 2), unsaturated C=C bonds (entries 3,4), protected alcohols (entry 5), silanes (entry 6), halogens (entry 7) were all well tolerated in additions to **97** (~70% yield with >92% ee).

We applied our system to ynethioate **98**. In our previous study of *α,β* unsaturated thioesters[7] we found that they are much less reactive than similar enones, and so reactions are normally performed with double catalyst loading (20 mol%) and longer reaction times. Here, we also doubled the catalyst loading from 10% to 20%, extended the reaction time to 40 hours and replaced solvent with a mixture of DCM/Et_2O (1:1). These conditions allowed alkenes bearing halogens and C=C bond to be introduced in around 70% yield with over 96% ee (entries 8, and 9).

Table 4-4 Scope of ynenones and ynethioates



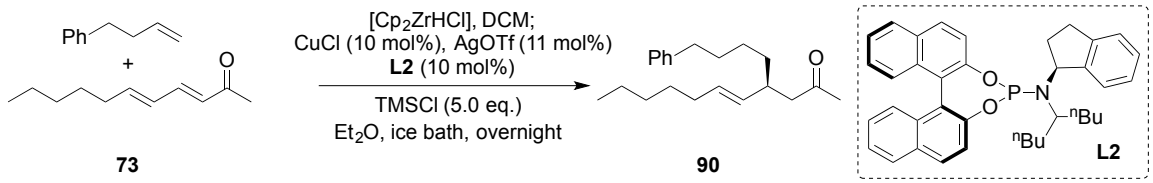
Entry	Substrate	Product		1,6:1,4	Yield [%][a]	ee [%][b]
1			**99**	<1:20	70	94
2			**100**	<1:20	87	95
3			**101**	<1:20	84	96
4			**102**	<1:20	69	92
5			**103**	<1:20	66	94
6			**104**	<1:20	75	94
7			**105**	<1:20	76	96
8[c]			**106**	<1:20	66	97
9[c]			**107**	<1:20	75	96

Reaction conditions: alkene (2.5 eq.), [Cp_2ZrHCl] (2 eq.), ynenone or ynenthioate (1 eq.), copper chloride (10 mol%), ligand (10 mol%), silver triflate (11 mol%), TMSCl (5 eq.) [a] Yield of isolated product. [b] ee was determined by HPLC. [c] Substrate **98** was used instead of **97**.

4.7 Study of catalyst loading

Low catalyst loading is attractive in asymmetric catalysis and we studied the catalyst loading to see if we could reduce it on a scale of 0.2 mmol of substrate. We first tested the combination of but-3-en-1-ylbenzene with substrate **73** and decreased catalyst loading from 10 mol% to 0.5 mol% (Table 4-5, entries 1-5). When the loading is lower than 5 mol%, the accurate weight of which is not able to access. We obtained the precise amount of catalyst by transferring corresponding volume of premixed catalyst solutions to another flask. For example, to access 1.2 mol% catalyst loading on a scale of 0.2 mmol, we first dissolved accurately weighted catalyst (0.02 mmol) in 1 mL Et_2O, followed by one hour stirring at room temperature; we then transferred 0.12 mL mixture from the catalyst solution to an argon protected empty flask, and filled the flask with 0.88 mL dry Et_2O. In this way, 1.2 mol% catalyst solution on a scale of 0.2 mmol was accurately obtained. Here, the yield remained around 60%, while ee started to drop at 1.2% catalyst loading. The lowest catalyst loading possible without any compromise on the yield or ee was 2.5%. When we applied 0.5% catalyst loading, the ee fell to 6%.

Table 4-5 Catalyst loading study with dienone **73**



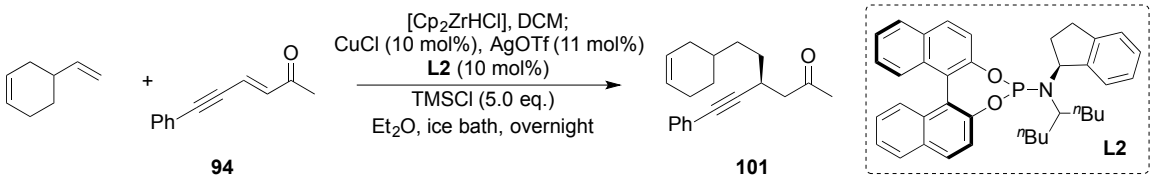
73 90

Entry	Catalyst loading [%]	Yield [%][a]	ee [b]
1	10.0	65	96
2	5.0	63	96
3	2.5	64	96
4	1.2	60	84
5	0.5	63	6

Reaction conditions: alkene (2.5 eq.), [Cp_2ZrHCl] (2 eq.), dienone (1 eq.), copper chloride (10 mol%), ligand (10 mol%), silver triflate (11 mol%), TMSCl (5 eq.) [a] Yield of isolated product. [b] ee was determined by HPLC.

Meanwhile, we also explored ynenone **94** with 4-vinylcyclohex-1-ene (Table 4-6). Here we found that we could further reduce the catalyst loading to 1.2 mol% without losing any yield and ee (Table 4-6, entries 1-4). In this case when only applying 0.5% loading, we can still obtain some enantiocontrol (36% ee, entry 5).

Table 4-6 Catalyst loading study on ynenone



94 101

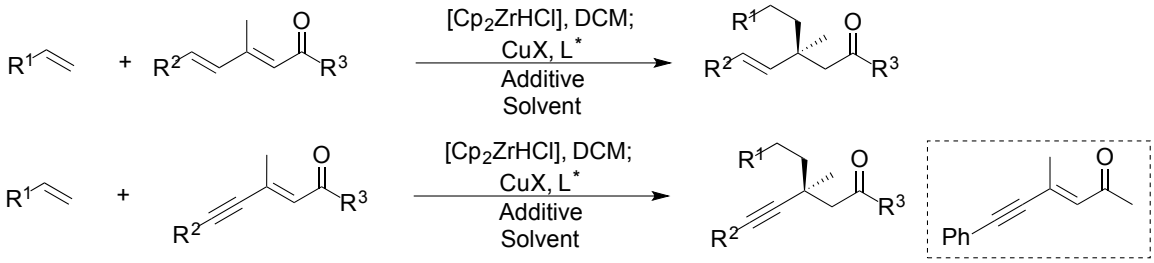
Entry	Catalyst loading [%]	Yield [%][a]	ee [b]
1	10.0	75	96
2	5.0	80	95
3	2.5	75	95
4	1.2	79	92
5	0.5	71	36

Reaction conditions: alkene (2.5 eq.), [Cp_2ZrHCl] (2 eq.), ynenone (1 eq.), copper chloride (10 mol%), ligand (10 mol%), silver triflate (11 mol%), TMSCl (5 eq.) [a] Yield of isolated product. [b] ee was determined by HPLC.

4.8 Conclusions and future work

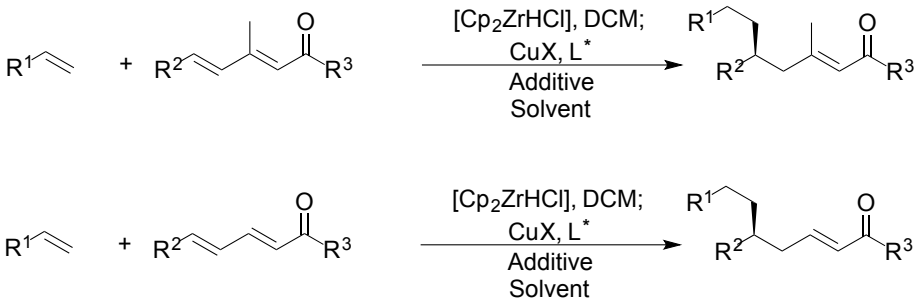
We have established a robust approach forming β- to carbonyl chiral centres from linear dienones, dienthioates, ynenones, and ynethioates using Cu-catalyzed asymmetric 1,4-additions with alkylzirconium species. By applying this new strategy, we successfully synthesized various β- to carbonyl chiral products featuring $C_{sp}{}^2$-$C_{sp}{}^3$, or C_{sp}-$C_{sp}{}^2$ bonds, which were not accessible by directly using alkenyl zirconium reagents. These products contain at least three useful functional groups, which we believe could be useful for the asymmetric synthesis of important molecules. Excellent yields, ee's and regioselectivity were simultaneously observed. Meanwhile, this method could introduce several important functional groups, e.g. halides, silyl ethers, arenes, silanes, and unsaturated C-C bonds without compromising on regio- and enantioselectivity. We also studied the effects of catalyst loading in our systems, and we found that the amount can be decreased to 2.5% for dienones and 1.2% for ynenones without any loss of yield or ee. We believe our method broadens the methods synthesizing linear chiral products.

In principle we could further develop methods to construct β- to carbonyl quaternary centres to dienones and ynenones (Scheme 4-8). We tried to introduce ethylzirconium species to (*E*)-4-methyl-6-phenylhex-3-en-5-yn-2-one （scheme 4-8, bottom right） using **L2**, obtaining 1,4-adduct only with 60% yield and 61% ee. Both yield and ee dropped in comparison with **97**. A further exploration of ligands, solvents, counterions, and temperature would be essential in order to improve yield and enantioselectivity.



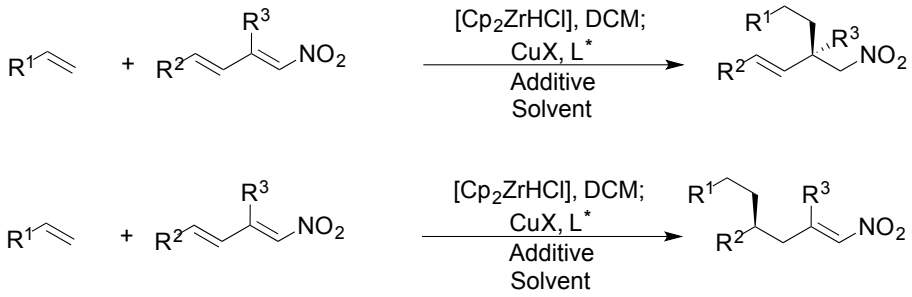
Scheme 4-8 Construction of quaternary centres to dienones and ynenones

It may also be possible to develop methods to form *δ*- to carbonyl chiral centres from dienones. We only found good regioselectivity to 1,4-adduct in the study above, so new conditions leading to 1,6-adduct would need to be developed. Trisubstituted dienones (Scheme 4-9, top) more favor 1,6-adduct than disubstituted dienones (Scheme 4-9, bottom), because of stronger steric hindrance at *β*-to carbonyl positions.



Scheme 4-9 Construction of *δ*- to carbonyl chiral centres to dienones

It may also be useful to advance 1,4-ACAs and 1,6-ACAs to polyunsaturated nitroalkenes to form new chiral tertiary and quaternary centres (Scheme 4-10). We have attempted some additions to nitroalkenes of alkylzirconium species using phosphoramidite ligands. However, we are still not able to find asymmetric conditions even after optimisations of copper salts and solvents.



Scheme 4-10 Construction of chiral centres to nitroolefins

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Chapter 5

Experimental

5.1 General information

Reactions were all carried out in flame-dried flasks with anhydrous solvents under argon protection. Analytical thin-layer chromatography was conducted on precoated glass-backed plates (Silica Gel 60 F_{254}, Merck). Visualization was performed by UV light (254 nm), aqueous ceric ammonium molybdate (CAM), p-Anisaldehyde Stain, aqueous basic potassium permanganate stains ($KMnO_4$) and vanillin solution. Flash column chromatography was carried out using Apollo Scientific silica gel 60 (0.040 – 0.063 nm), VWR (40-63 μm) silica gel, and Sigma Aldrich silica gel.

Reaction temperatures below 0 °C were obtained using a Julabo FT902 immersion cooler. 0 °C was achieved using an ice-water bath. Light sensitive reactions were processed under aluminium foil protection.

All NMR spectra were recorded at room temperature; ^{1}H and ^{13}C nuclear magnetic resonance experiments were carried out using Bruker DPX-200 (200/50 MHz), AVG-400 (400/100 MHz), AVH-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). Assignments were made with the assistance of COSY, DEPT-135, HSQC and NOESY NMR spectra.

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 Aldrich); all eluent systems were isocratic.

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

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

Optical rotations were recorded using a Perkin-Elmer 241 Polarimeter;

In those cases, where silver salts were used the resulting solutions were filtered using syringe filters PTFE (0.2 μm, 13 mm diameter) from Camlab.

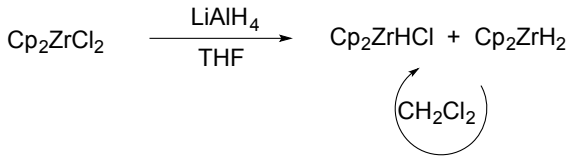
5.2 Chemicals

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 petroleum boiling in the range 40-60 °C. Deuterated solvents were purchased from Sigma-Aldrich ($CDCl_3$). Schwartz reagent was prepared

according to the literature procedure from Cp_2ZrCl_2 provided by Alfa Aesar. CuCl which purity is 98% is purchased from Strem Chemicals, the 99.99% purity CuCl is from Sigma-Aldrich, and all of them were directly used without any further purification. All the trimethylsilyl chloride (TMSCl) was distilled fresh and stored in Schlenk flasks under an argon atmosphere. All phosphoramidite ligands were synthesized by the Fletcher group.

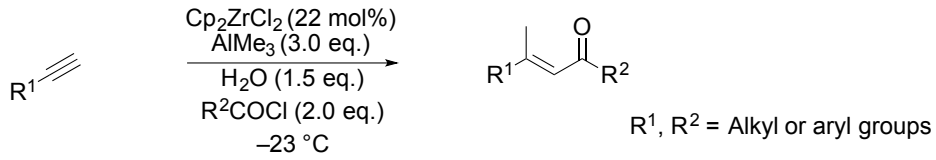
5.3 General Methods

A: Preparation of Schwartz reagent[1]



Zirconocene dichloride (30.0 g, 0.103 mol) was added to a flame-dry 250 mL Schlenk flask wrapped with aluminium foil under argon. Dry THF (120 mL) was added and the suspension was stirred at 35 °C for 30 minutes. $LiAlH_4$ in Et_2O (1 M, 28.2 mmol) was added dropwise to the mixture over about 30 minutes. The resulting suspension was stirred at room temperature for 2 h. The mixture was then Schlenk-filtered under argon and washed with tetrahydrofuran (200 mL), methylene chloride (200 mL), and diethyl ether (200 mL). The precipitate was dried under high vacuum for 2 h to give a white powder (20.3 g, 75%), which was stored under argon in a small flame-dried Schlenk flask while being protected from light.

B: Preparation of trisubstituted enones[2]



R^1, R^2 = Alkyl or aryl groups

Cp_2ZrCl_2 (643 mg, 2.2 mmol, 0.22 eq.) and dry DCM (50 mL) were added to flame-dried round bottom flask fitted with a magnetic stir bar under an argon atmosphere. Me_3Al (15 mL, 30 mmol, 3.0 eq.), was added dropwise by syringe over about 5 minutes. The resulting mixture was cooled to –23 °C and then distilled H_2O (0.27 mL, 15 mmol, 1.5 eq.), was added dropwise (over about 5 min) to the flask via syringe, after stirring for 15 min, the alkyne (10 mmol, 1.0 eq.) was added in one portion via syringe. Then, after 15 additional min, acetyl chloride (1.42 mL, 20 mmol, 2.0 eq.) was introduced in one portion. The reaction mixture was allowed to continue stirring at –23 °C for 15 min, and then allowed to warm to room temperature while stirring was continued for an additional 15 min. The reaction was quenched by slowly adding sat. aq. K_2CO_3 using a vent needle until gas evolution stopped (~ 30 mL). The water and organic layers were partitioned, and the aqueous phase was extracted with Et_2O. The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. After flash column chromatography (petroleum ether/ Et_2O; 80/20; silica), the enone product was obtained as yellow solid (~ 70% yield).

C: Preparation of amines



R, R^1, R^2 = Alkyl or H

General procedure **a**

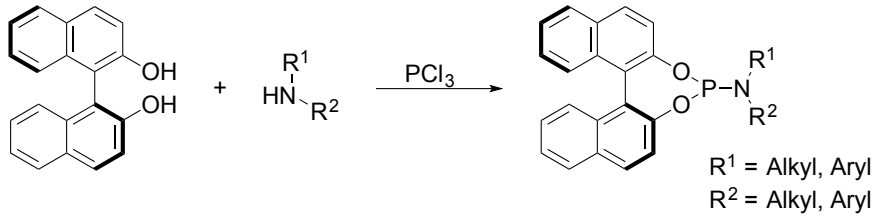
According to a modified procedure from Davies and co-workers[3], ketone (2.0 eq.) was added to a stirring solution of amine in THF at room temperature. After 5 minutes, $Na(OAc)_3H$ (2.0 eq.) was added into the mixture. The reaction was kept under room temperature for 48 hours, and the resulting suspension was added to a 1:1 mixture of Et_2O and $NaHCO_3$ (aq. sat.) and stirred for another half an hour. The mixture was partitioned between the aqueous and Et_2O layers and the aqueous phase extracted with Et_2O three times. The combined organic phase was concentrated in vacuo. Then HCl (aq. 2.0 M) was added dropwise (pH = 1). The mixture was partitioned between the aqueous and organic phases, and the organic phase was extracted with HCl (aq. 2.0 M). Then DCM was added to the combined aqueous phases and NaOH (4 M) was added till the mixture became basic (pH>14). The mixture was partitioned between aqueous and organic phases. DCM was used to extract residual product from the aqueous layer (three extracts). The combined organic layers were concentrated, dried ($MgSO_4$), filtered and concentrated to give the, desired product.

General procedure **b**[4]

$TiCl_4$ (1.1 eq., 1 M solution in DCM) was added slowly to an ice-cooled solution of ketone (1.0 eq.) in DCM. The solution was stirred for 10 minutes at room temperature and then a 2 M solution of amine (2.2 eq.) in THF was added dropwise to the reaction mixture. The reaction mixture was stirred for 3 hours before a 1 M solution of $NaB(CN)H_3$ (1.2 eq.) in THF, and then MeOH were added slowly to the reaction mixture and stirring at room temperature was continued for 48 hours. NaOH (2 M aq. solution) was added slowly and the mixture was stirred for 30 min before filtration over celite and washing with

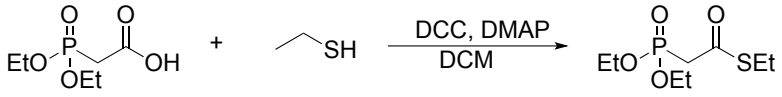
EtOAc. The mixture was partitioned between the aqueous and organic layers and the aqueous phase extracted with EtOAc (3 times). The combined organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo to afford yellow oil. Flash column chromatography of the residue (SiO_2) gave the desired amine.

D: Preparation of phosphoramidite ligands[5]



Triethylamine (5.0 eq.) was added dropwise to a stirred, ice-cooled solution of PCl_3 (1.0 eq.) in DCM. The ice bath was removed and the solution left to warm to room temperature before (*S*)-N-cyclohexyl-2, 3-dihydro-1H-inden-1-amine (1.0 eq.) was added to the stirred solution in one portion. After 5 hours, (*S*)-binaphthol (1.0 eq.) was tipped into the suspension and the reaction mixture was left to stir for another 15 hours. The mixture was then filtered over an ~ 2 cm pad of celite and silica gel, and DCM was used to rinse the pad. The filtrate was concentrated to give a yellow residue and after flash column chromatography (petroleum ether: DCM: Et_3N, 80:20:1; SiO_2) the ligand was obtained as a white crystalline solid.

E: Preparation of S-ethyl 2-(diethoxyphosphoryl)ethanethioate[6]

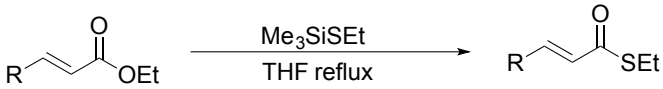


A solution of diethylphosphonoacetic acid (1.0 eq.), ethanethiol (1.0 eq.), and DMAP (0.1 eq.) in DCM was cooled to 0 °C. DCC (1.0 eq.) was added in portions. The reaction mixture was left to stir overnight under argon at room temperature.

The mixture was filtered through a Celite pad, and DCM was used to rinse the pad. The organic layer was washed with aqueous $NaHCO_3$, water and brine. The organic phase was dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The product was further purified by flash chromatography (ether: pentane) to colourless oil.

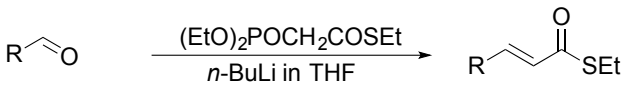
F: Preparation of unsaturated thioester

General procedure **a**[7] (from unsaturated ester)



Me_3SiSEt (2.0 eq.) and $AlCl_3$ (1.2 eq.) were added to a solution of *α,β*-unsaturated ester (1.0 eq.) in THF. The resulting mixture was stirred at reflux for 3 hours and the quenched at RT by addition of aqueous phosphate buffer solution (pH 7). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O three times. The combined organic materials were dried over $MgSO_4$, filtered, concentrated, and further purified by flash column chromatography (pentane: Et_2O; SiO_2) to afford the desired *α,β*-unsaturated thioester.

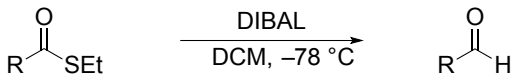
General procedure **b** HWE olefination (from aldehyde)[8]



n-BuLi (1.5 eq., solution in hexane) was added to a stirring solution of $(EtO)_2POCHCOSEt$ (1.5 eq.) in THF at 0 °C under argon. The mixture was stirred for another 20 min. A solution of aldehyde (1.0 eq.) in THF was added dropwise. The mixture was slowly warmed to room temperature and was continued overnight. The mixture was quenched with aqueous NH_4Cl (sat.). The reaction

mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O three times. The combined organic materials were dried ($MgSO_4$), filtered, concentrated, and further purified by flash column chromatography (pentane: Et_2O; 98:2; SiO_2) to afford the desired *α,β*-unsaturated thioester.

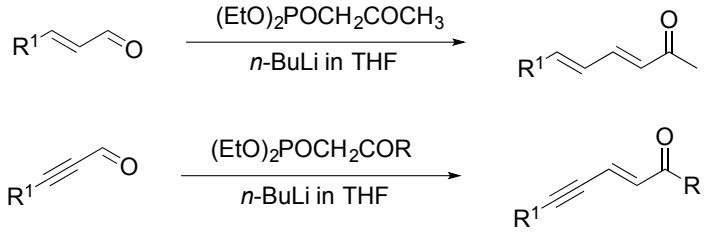
G: Reduction of thioesters to aldehydes



DIBAL (1.0 eq.) was added to a stirring mixture of thioester (1.0 eq.) in DCM at –78 °C under argon. The mixture was kept stirring until the reduction was completed (30-60 min). After that sat. Rochelle salt solution was added and Et_2O extracted the mixture three times. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product.

H: Preparation of linear *α,β,γ,δ*-unsaturated substrates

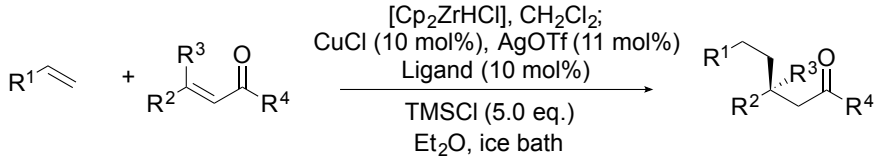
General procedure HWE olefination (from aldehyde)[8]



n-BuLi (1.5 eq., solution in hexane) was added to a stirring solution of Horner reagent (1.5 eq.) in THF at 0 °C under argon. The mixture was stirred for another 20 min. A solution of aldehyde (1.0 eq.) in THF was added dropwise. The mixture

was slowly warmed to room temperature and was continued overnight. The mixture was quenched with aqueous NH_4Cl (sat.). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O three times. The combined organic materials were dried ($MgSO_4$), filtered, concentrated, and further purified by flash column chromatography (pentane: Et_2O; 90:10; SiO_2) to afford the desired product.

I: Copper catalysed conjugate addition of alkylzirconium nucleophiles



Racemic product **a**

CuCl (0.1 eq.), and the racemic phosphoramidite ligands **L22** (0.05 eq.), and ***ent*-L22** (0.05 eq.) were added to a flame dried round bottom flask containing 1 mL Et_2O under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (0.11 eq.) was added and the mixture was stirred for an additional 15 min.

To a second, flame dried, round bottom flask, containing a stirred solution of alkene (2.5 eq.) in DCM (0.2 mL), under an argon atmosphere was added Cp_2ZrHCl (2.0 eq.), and after stirring for 15 min, a clear yellow solution was obtained.

The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before unsaturated substrate and TMSCl were sequentially added dropwise over about 1 min for

each. Stirring at 0 °C was continued for 15 additional hours, before the reaction was quenched by the addition of NH_4Cl (sat. aq., 1.5 mL) and then Et_2O (1.5 mL). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O (1.5 mL). The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product.

Asymmetric product **b1**

CuCl (0.1 eq.), and the phosphoramidite ligand (0.1 eq.) were added to a flame dried round bottom flask containing 1 mL Et_2O under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (0.11 eq.) was added and the mixture was stirred for an additional 15 min. To a second, flame dried, round bottom flask, Cp_2ZrHCl (2.0 eq.) was added. A balloon filled with ethylene was used to purge the flask with ethylene for 5 min, and then DCM (0.2 mL) was added. After stirring for 15 min under an ethylene atmosphere (balloon), a clear yellow solution was obtained. After stirring for 15 min, the stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before the Michael acceptor (1.0 eq.) and then TMSCl (5.0 eq.) were each added dropwise. Stirring was continued for 15 h at 0 °C, before the reaction was quenched by the addition of NH_4Cl (sat. aq., 1.5 mL) and then Et_2O (1.5 mL). The mixture was partitioned between the aqueous and organic phases, and the aqueous layer was extracted with Et_2O (3 x 10mL). The combined organic materials were dried with Na_2SO_4, filtered,

concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product.

Asymmetric product **b2**

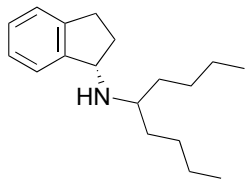
CuCl (0.1 eq.), and the phosphoramidite ligand (0.1 eq.) were added to a flame dried round bottom flask containing 1 mL Et_2O under argon and the resulting mixture was stirred at room temperature. After 1 hour, AgOTf (0.11 eq.) was added and the mixture was stirred for an additional 15 min.

To a second, flame dried, round bottom flask, containing a stirred solution of alkene (2.5 eq.) in DCM (0.2 mL), under an argon atmosphere was added Cp_2ZrHCl (2.0 eq.), and after stirring for 15 min, a clear yellow solution was obtained.

The stirred solution containing the copper and ligand was transferred, and filtered – using a syringe filter, to the solution containing the zirconocene species. The resulting black mixture was stirred for another 10 min before Michael acceptor and TMSCl were sequentially added dropwise over about 1 min for each. Stirring at 0 °C was continued for 15 additional hours, before the reaction was quenched by the addition of NH_4Cl (sat. aq., 1.5 mL) and then Et_2O (1.5 mL). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O (3 x 10mL). The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product.

5.4 Experimental procedures and data

(*S*)-*N*- (nonan-5-yl)-2,3-dihydro-1*H*-inden-1-amine **(A1)**



Prepared according to general procedure **Cb**, using $TiCl_4$ (3.9 mL (1 M solution in DCM), 1.1 eq., 3.9 mmol), 2-nonan-5-one (1.33 mL, 1.0 eq., 7.7 mmol), (*S*)-(+)-1-aminoindane (0.45 mL, 2.2 eq., 3.5 mmol) in THF, of $NaB(CN)H_3$ (9.24mL (1 M solution in THF), 1.2 eq., 9.24 mmol), and MeOH (10 mL). Flash column chromatography of the residue (96: 4 $CHCl_3$: MeOH, SiO_2) gave the desired amine (0.90 g, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.40-7.31 (m, 1H, Ar-*H*), 7.28 – 7.13 (m, 3H, Ar-*H*), 4.28 (t, *J* = 6.8 Hz, 1H, PhC*H*NH), 2.98 (ddd, *J* = 15.8 Hz, 8.5 Hz, 4.1 Hz, 1H, PhCH_2), 2.91 – 2.76 (m, 1H, PhCH_2), 2.76 – 2.68 (m, 1H, NHC*H*), 2.43 (dtd, *J* = 12.1 Hz, 7.5 Hz, 4.2 Hz, 1H, NHC*H*), 1.75 (dq, *J* = 12.4 Hz, 7.9 Hz, 1H, NHCHCH_2), 1.56 – 1.16 (m, 12H, 6 x CH_2), 0.8 (m, 6H, 2 x CH_3).

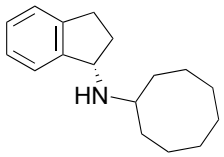
^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 146.5, 143.4, 127.2, 126.3, 124.7, 124.0, 60.8, 55.8, 35.1, 34.7, 34.1, 30.3, 28.3, 27.8, 23.2, 23.0, 14.2, 14.2,

IR (v_{max}/cm^{-1}, $CHCl_3$) 3022, 2955, 2858, 2389, 2285

MS (ESI) m/z calc. for $C_{18}H_{30}N$ $[M+H]^+$: 260.2373, found: 260.2371.

$[\alpha]^{20}_{589}$ = +28.0 (c 1.0, $CHCl_3$)

(*S*)-*N*-cyclooctyl-2,3-dihydro-1H-inden-1-amine **(A2)**



Prepared according to general procedure **Ca**, using cyclooctanone (1.47 g, 1.5 eq., 11.6 mmol), (*S*)-(+)-1-aminoindane (1.00 mL, 1.0 eq., 7.76 mmol.), $Na(OAc)_3H$ (2.50 g, 1.5 eq., 11.6 mmol) After 48 hours stirring at room temperature, acid-base work up gave the desired product (1.692 g, 90%) as a dark oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.4 – 7.3 (m, 1H, Ar-*H*), 7.2 (m, 3H, Ar-*H*), 4.3 (t, *J* = 6.8 Hz, 1H, PhC*H*NH), 3.1 – 2.9 (m, 2H, PhCH_2), 2.8 (dt, *J* = 15.8 Hz, 7.9 Hz, 1H, NHC*H*), 2.4 (dddd, *J* = 12.5 Hz, 8.1 Hz, 6.9 Hz, 4.3 Hz, 1H, $PhCH_2CH_2$), 2.0 – 1.8 (m, 1H, $PhCH_2CH_2$), 1.8 – 1.7 (m, 5H, CH_2), 1.7 – 1.4 (m, 7H, CH_2), 1.3-1.0 (m, 2H, CH_2).

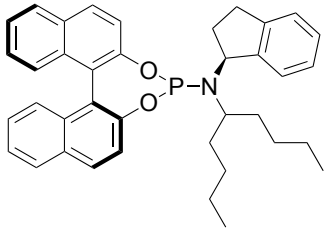
^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 146.4, 143.4, 127.2, 126.3, 124.7, 123.9, 60.5, 55.7, 34.8, 33.9, 32.2, 30.3, 27.5, 27.4, 25.8, 24.2, 24.1.

IR (v_{max}/cm_{-1}, $CHCl_3$) 3021, 2919, 2849, 1474, 1258

MS (ESI) m/z calc. for $C_{17}H_{26}N$ $[M+H]^+$: 244.2060, found: 244.2058.

$[\alpha]^{20}_{589}$ = +37.6 (c 2.0, $CHCl_3$)

(11b*S*)-*N*-((*S*)-2,3-dihydro-1*H*-inden-1-yl)-*N*-(nonan-5-yl)dinaphtho[2,1-*d*:1',2'-*f*][1,3, 2]dioxaphosphepin-4-amine **(L2)**



Prepared according to general procedure **D,** using triethylamine (8.46 mL, 5.0 eq., 63 mmol), PCl_3 (1.13 mL, 1.0 eq., 12.6 mmol) in DCM (60 mL), (*S*)-*N*-(nonan-5-yl)-2,3-dihydro-1H-inden-1-amine (3.28 g, 1.0 eq., 12.6 mmol), (*S*)-binaphthol (3.16 g, 1.0 eq., 12.6 mmol.) The flash column chromatography (petroleum ether: DCM: Et_3N, 80:20:1; SiO_2) afforded the title ligand as a white crystalline solid (2.35 g, 32%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm 7.95 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 7.90 (dd, *J* = 8.4 Hz, 2.2 Hz, 3H, Ar-*H*), 7.72 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 7.61 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 7.49 (d, *J* = 8.7 Hz, 1H, Ar-*H*), 7.44 – 7.37 (m, 3H, Ar-*H*), 7.34 (td, *J* = 7.2 Hz, 6.7 Hz, 2.0 Hz, 1H, Ar-*H*), 7.28 (tt, *J* = 3.9 Hz, 2.0 Hz, 2H, Ar-*H*), 7.27 – 7.19 (m, 3H, Ar-*H*), 4.76 (dt, *J* = 15.4 Hz, 7.8 Hz, 1H, PhC*H*NH), 3.11 – 2.86 (m, 2H, PhCH_2), 2.75 (dt, *J* = 16.1 Hz, 8.3 Hz, 1H, NHC*H*), 2.44 (d, *J* = 11.3 Hz, 1H, PhCH$_2$CH_2), 2.26 – 2.00 (m, 1H, PhCH$_2$CH_2), 1.78 (tt, *J* = 12.3 Hz, 4.4 Hz, 1H, CH_2), 1.72 – 1.61 (m, 1H, CH_2), 1.55 – 1.38 (m, 5H, CH_2), 1.39 – 0.97 (m, 5H, CH_2), 0.92 (t, *J* = 7.3 Hz, 3H, CH_3), 0.87 (t, *J* = 7.2 Hz, 3H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C/ppm 150.2 (d, *J* = 8.3Hz), 149.9, 144.5, 143.3, 132.8, 131.3, 130.4, 130.2, 129.5, 128.2, 128.1, 127.4, 127.1, 127.1, 126.4, 125.9, 125.8, 125.2, 124.8, 124.60, 124.3, 124.0 (d, *J* = 5.4 Hz), 122.3 (d, *J* = 2.0

Hz), 122.3, 121.8 (d, *J* = 2.4 Hz), 59.7 (d, *J* = 21.3 Hz), 55.15 (d, *J* = 4.3 Hz), 36.90 (d, *J* = 5.4 Hz), 34.70, 31.62, 30.4, 29.3, 28.7, 23.1, 22.8, 14.2, 14.1.

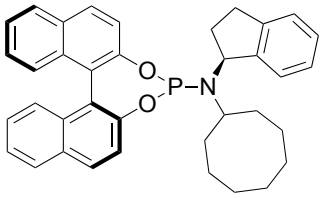
^{31}P NMR (162 MHz, $CDCl_3$) δ_p/ppm 149.9.

IR (v_{max}/cm^{-1}, $CHCl_3$) 2955, 2857, 1590, 1462, 1024, 947, 749, 697

MS (GCMS Ammonia Cl Spectrum) m/z calc. for $C_{38}H_{40}O_2NP$ $[M+H]^+$: 574.2875, found: 574.2876

$[\alpha]^{20}_{589}$ = +126.3 (c 1.0, $CHCl_3$)

(11b*S*)-*N*-cyclooctyl-*N*-((*S*)-2,3-dihydro-1*H*-inden-1-yl)dinaphtho[2, 1-*d*:1', 2'-*f*][1,3, 2]dioxaphosphepin-4-amine **(L27)**



Prepared according to general procedure **D,** using triethylamine (2.92 mL, 5.0 eq., 20.5 mmol), PCl_3 (0.38 mL, 1.0 eq., 4.1 mmol) in DCM, (*S*)-*N*-cyclohexyl-2, 3-dihydro-1H-inden-1-amine (0.94 mL, 1.0 eq., 4.1 mmol), (*S*)-binaphthol (1.12 g, 1.0 eq., 4.1 mmol The flash column chromatography (petroleum ether: DCM: Et_3N, 80:20:1; SiO_2) afforded the title ligand as a white crystalline solid (1.17 g, 51%).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm 7.97 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 7.92 (dd, *J* = 8.3 Hz, 1.2 Hz, 1H, Ar-*H*), 7.90 – 7.83 (m, 2H, Ar-*H*), 7.64 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 7.61 (s, 1H, Ar-*H*), 7.52 (d, *J* = 8.7 Hz, 1H, Ar-*H*), 7.44 – 7.37 (m, 3H, Ar-*H*), 7.37 – 7.29 (m, 2H, Ar-*H*), 7.30 – 7.18 (m, 4H, Ar-*H*), 4.76 (dt, *J* = 13.4 Hz, 8.1 Hz, 1H, PhC*H*NH), 3.11 (d, J = 10.6 Hz, 1H, PhCH_2CH$_2$), 3.02 – 2.90 (m, 1H, PhCH_2CH$_2$), 2.70 (p, *J* = 8.3 Hz, 1H, NHC*H*), 2.44 (d, *J* = 11.4 Hz, 1H,

$PhCH_2CH_2$), 2.16 (p, *J* = 9.9 Hz, 1H, $PhCH_2CH_2$), 2.09 – 1.79 (m, 3H, CH_2), 1.72 – 1.57 (m, 2H, CH_2), 1.43 – 1.05 (m, 8H, CH_2), 0.99 – 0.75 (m, 1H, CH_2).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C/ppm 150.2 (d, *J* = 8.0 Hz), 150.1, 144.6, 143.14, 132.8 (d, *J* = 2.2 Hz), 132.8, 131.3, 130.6, 130.2, 129.7, 128.3, 128.1, 127.3, 127.1, 127.1, 126.4, 125.9, 125.9, 124.7 (d, *J* = 5.1 Hz), 124.6, 124.3, 124.0 (d, *J* = 5.3 Hz), 122.4, 122.4, 122.3, 121.7 (d, *J* = 2.4 Hz), 60.7 (d, *J* = 16.3 Hz), 54.8 (d, *J* = 7.7 Hz), 36.5 (d, *J* = 131.2), 31.6, 30.2, 26.3, 25.8, 25.6, 24.5, 22.7, 14.2.

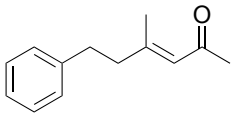
^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm 151.7.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2929, 2854, 2361, 1590, 1462

MS (GCMS Ammonia Cl Spectrum) m/z calc. for $C_{37}H_{36}O_2NP$ $[M+H]^+$: 557.2484, found: 558.2558

$[\alpha]^{20}_{589}$ = +117.1 (c 1.0, $CHCl_3$)

(*E*)-4-methyl-6-phenylhex-3-en-2-one **(1)**



Prepared according to general procedure **B**, using Cp_2ZrCl_2 (643 mg, 2.2 mmol, 0.22 eq.), Me_3Al (15 mL, 30 mmol, 3.0 eq.), H_2O (0.27 mL, 15 mmol, 1.5 eq.), 4-Phenyl-1-pentyne (1.41 mL, 10 mmol, 1.0 eq.), and acetyl chloride (1.42 mL, 20 mmol, 2.0 eq.). The flash column chromatography (petroleum ether/ Et_2O; 90/10; silica) afforded **1** (1.31 g, 70%) in > 20:1 *E*:*Z* ratio as a yellow oil.

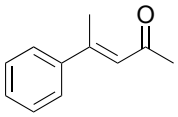
^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm 7.29 (d, *J* = 7.6 Hz, 2H, Ar-*H*), 7.24 – 7.13 (m, 3H, Ar-*H*), 6.04 (d, *J* = 1.3 Hz, 1H, C*H*CO), 2.79 (m, 2H, PhCH_2), 2.42 (m, 2H, CH_2), 2.17 (d, *J* = 1.3 Hz, 3H, CH_3), 2.15 (s, 3H, COCH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C/ppm 198.9, 157.3, 141.1, 128.5, 128.4, 126.2, 124.1, 43.1, 34.1, 31.9, 19.5.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3027, 2928, 1687, 1616, 1496.

HRMS (ESI) m/z calc. for $C_{13}H_{17}O$ $[M+H]^+$: 189.1274, found: 189.1275.

(*E*)-4-Phenylpent-3-en-2-one **(2a)**



Prepared according to general procedure **B**, using Cp_2ZrCl_2 (643 mg, 2.2 mmol, 0.22 eq.), Me_3Al (15 mL, 30 mmol, 3.0 eq.), H_2O (0.27 mL, 15 mmol, 1.5 eq.), phenylacetylene (1.1 mL, 10 mmol, 1.0 eq.), and acetyl chloride (1.42 mL, 20 mmol, 2.0 eq.). Purified by flash column chromatography (petroleum ether/ Et_2O; 80/20; silica) to give **2a** (1.02 g, 64%) in > 20:1 *E*:*Z* ratio as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm 7.62 – 7.40 (m, 2H, Ar-*H*), 7.40 – 7.31 (m, 3H, Ar-*H*), 6.47 (q, *J* = 1.3 Hz, 1H, C*H*COMe), 2.50 (d, *J* = 1.3 Hz, 3H, CH_3), 2.26 (s, 3H, COCH_3).

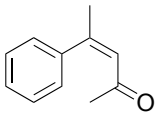
^{13}C NMR (126 MHz, $CDCl_3$) δ_C/ppm 199.0, 153.9, 142.5, 129.1, 128.5, 126.5, 124.5, 32.3, 18.4.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3058, 2360, 1679, 1598, 1574.

MS (ESI) m/z $[M+H]^+$: 161.1 (100)

This data was concordant with literature values.[9]

(*Z*)-4-phenylpent-3-en-2-one **(2b)**



2b was prepared through photocatalysis reactions from literature[10]. (*Z*)-4-phenylpent-3-en-2-one (0.32 g, 2.0 mmol, 1.0 eq.), anthracene (20 mg, 0.1 mmol, 0.05 eq.) and 30 mL dry MeCN was added in a flame-dried round bottom flask fitted with a magnetic stir bar under an argon atmosphere. After 24 h of UV-light (405 nm) irradiation and stirring, the stir bar was removed and the solution was evaporated to dryness by rotavap. After flash column chromatography (petroleum ether/ Et_2O; 90/10; silica), the enone product was obtained as yellow oil. (0.26 g, 81%)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.44 – 7.28 (m, 3H, Ar-*H*), 7.22 – 7.15 (m, 2H, Ar-*H*), 6.15-6.08(m, 1H, C*H*COMe), 2.18 (d, *J* = 1.3 Hz, 3H, CH_3), 1.79 (s, 3H, COCH_3).

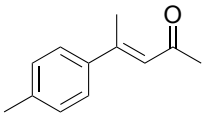
^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 200.3, 153.0, 140.9, 128.5, 128.4, 128.3, 127.2, 30.2, 27.4.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2976, 1665, 1619, 1433, 1354.

MS (ESI) m/z $[M+H]^+$: 161.1 (100)

This data was concordant with literature values.[11]

(*E*)-4-(*p*-tolyl) pent-3-en-2-one **(3)**



Prepared according to general procedure **B**, using Cp_2ZrCl_2 (428 mg, 1.46 mmol, 0.22 eq.), Me_3Al (10 mL, 20 mmol, 3.0 eq.), H_2O (0.18 mL, 10 mmol, 1.5 eq.), 4-ethynyl toluene (0.842 mL, 6.67 mmol, 1.0 eq.), and acetyl chloride (0.94 mL, 13.2 mmol, 2.0 eq.). Purified by flash column chromatography (petroleum ether/ Et_2O; 90/10; silica), to give **3** (0.90 g, 78%) in > 20:1 *E*:*Z* ratio as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.46 – 7.34 (m, 2H, Ar-*H*), 7.22 – 7.15 (m, 2H, Ar-*H*), 6.51 (q, *J* = 1.3 Hz, 1H, C*H*), 2.53 (d, *J* = 1.3 Hz, 3H, CH_3C=CH), 2.37 (s, 3H, CH_3), 2.28 (s, 3H, COCH_3).

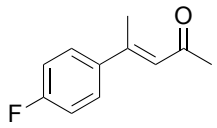
^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 198.9, 153.8, 139.5, 139.3, 129.3, 126.4, 123.7, 32.3, 32.2, 21.2, 18.2, 18.2.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2920, 1679, 1594, 1355, 1178, 961, 809, 611.

MS (ESI) m/z $[M+H]^+$: 175.1 (100)

This data was concordant with literature values.[12]

(*E*)-4-(4-fluorophenyl) pent-3-en-2-one **(4)**



Prepared according to general procedure **B**, using Cp_2ZrCl_2 (428 mg, 1.46 mmol, 0.22 eq.), Me_3Al (10 mL, 20 mmol, 3.0 eq.), H_2O (0.18 mL, 10 mmol, 1.5 eq.), 1-ethynyl-4 fluorobenzene (0.80 g, 6.67 mmol, 1.0 eq.), and acetyl chloride (0.94 mL, 13.2 mmol, 2.0 eq.). Purified by flash column chromatography (petroleum ether/ Et_2O; 90/10; silica) to give **4** (0.61 g, 52%) in > 20:1 *E*:*Z* ratio as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.57 – 7.30 (m, 2H, Ar-*H*), 7.16 – 6.86 (m, 2H, Ar-*H*), 6.46 (d, *J* = 1.6 Hz, 1H, C*H*COMe), 2.50 (d, *J* = 1.2 Hz, 3H, CH_3C=CH), 2.27 (s, 3H, COCH_3).

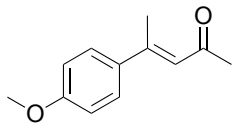
^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 198.7, 163.3 (d, *J* = 249 Hz), 152.6, 138.4 (d, *J* = 3.3 Hz), 128.3 (d, *J* = 8.3 Hz), 124.3 (d, *J* = 1.3 Hz), 115.5 (d, *J* = 21.6 Hz), 32.2, 18.3.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2980, 1681, 1599, 1507, 1376, 1179, 825.

MS (ESI) m/z $[M+H]^+$: 179.1 (100)

This data was concordant with literature values.[13]

(*E*)-4-(4-methoxyphenyl) pent-3-en-2-one **(5)**



Prepared according to general procedure **B**, using Cp_2ZrCl_2 (428 mg, 1.46 mmol, 0.22 eq.), Me_3Al (10 mL, 20 mmol, 3.0 eq.), H_2O (0.18 mL, 10 mmol, 1.5 eq.), 4-ethynylanisole (0.878 g, 6.67 mmol, 1.0 eq.), and acetyl chloride (0.94 mL, 13.2 mmol, 2.0 eq.). Purified by flash column chromatography (petroleum ether/ Et_2O; 90/10; silica) to give **5** (0.67 g, 53%) in > 20:1 *E*:*Z* ratio as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.55 – 7.25 (m, 2H, Ar-*H*), 6.96 – 6.68 (m, 2H, Ar-*H*), 6.42 (d, *J* = 1.4 Hz, C*H*COMe 1H), 3.74 (s, 3H, OCH_3), 2.44 (d, *J* = 1.2 Hz, 3H, CH_3C=CH), 2.19 (s, 3H, COCH_3).

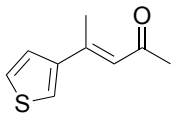
^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 198.8, 160.6, 153.3, 134.5, 127.9, 122.8, 113.9, 55.4, 32.3, 18.0.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3017, 2838, 1675, 1588, 1250, 1176, 1030, 825.

MS (ESI) m/z $[M+Na]^+$: 213.1 (100)

This data was concordant with literature values.[9]

(*E*)-4-(thiophen-3-yl) pent-3-en-2-one **(6)**



Prepared according to general procedure **B**, using Cp_2ZrCl_2 (428 mg, 1.46 mmol, 0.22 eq.), Me_3Al (10 mL, 20 mmol, 3.0 eq.), H_2O (0.18 mL, 10 mmol, 1.5 eq.), 3-ethynylthiophene (0.718 g, 6.67 mmol, 1.0 eq.), and acetyl chloride (0.94 mL, 13.2 mmol, 2.0 eq.). Purified by flash column chromatography (petroleum ether/ Et_2O; 90/10; silica) to give **6** (0.58 g, 53%) in > 20:1 *E*:*Z* ratio as a yellow oil.

^1H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.39 (t, *J* = 2.2Hz, 1H, Ar-*H*), 7.27 – 7.13 (m, 2H, Ar-*H*), 6.47 (d, *J* = 1.4 Hz, 1H, C*H*COH_3), 2.39 (d, *J* = 1.1Hz, 3H, C*H*$_3$C=CH), 2.15 (s, 3HCOC*H*$_3$).

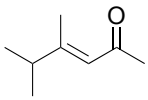
^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.1, 147.2, 143.6, 126.3, 125.2, 125.0, 122.6, 32.4, 17.7.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3105, 2980, 1677, 1589, 1507, 1174, 745.

MS (ESI) m/z $[M+H]^+$: 167.1 (100)

This data was concordant with literature values.[9]

(*E*)-4,5-dimethylhex-3-en-2-one **(7)**



Prepared according to general procedure **B**, using Cp_2ZrCl_2 (428 mg, 1.46 mmol, 0.22 eq.), Me_3Al (10 mL, 20 mmol, 3.0 eq.), H_2O (0.18 mL, 10 mmol, 1.5 eq.), 3-methyl butyne (0.68 mL, 6.67 mmol, 1.0 eq.), and acetyl chloride (0.94 mL, 13.2 mmol, 2.0 eq.). Purified by flash column chromatography (petroleum ether/ Et_2O; 90/10; silica) to give the **7** (0.64 g, 97%) in > 20:1 *E*:*Z* ratio as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 6.05 (t, *J* = 1.3 Hz, 1H, C*H*COH$_3$), 2.43 – 2.23 (m, 1H, C*H*), 2.15(s, 3H, COC*H*$_3$), 2.07 (d, *J* = 1.2 Hz, 3H, C*H*$_3$C=CH), 1.04 (d, *J* = 6.8 Hz, 6H, C*H*$_3$).

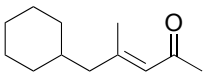
^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.3, 164.0, 121.4, 38.2, 31.9, 20.9, 16.8.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2966, 2875, 1687, 1615, 1317, 963, 744.

MS (ESI) m/z $[M+H]^+$: 127.1 (100)

This data was concordant with literature values.[13]

(*E*)-5-cyclohexyl-4-methylpent-3-en-2-one **(8)**



Prepared according to general procedure **B**, using Cp_2ZrCl_2 (214 mg, 0.73 mmol, 0.22 eq.), Me_3Al (5 mL, 10 mmol, 3.0 eq.), H_2O (0.09 mL, 5 mmol, 1.5 eq.), 3-cyclohexyl-1-propyne (0.47 mL, 3.3 mmol, 1.0 eq.), and acetyl chloride (0.47 mL, 6.64 mmol, 2.0 eq.). Purified by flash column chromatography (petroleum ether/ Et_2O; 90/10; silica) to give **8** (0.35 g, 59%) in > 20:1 *E*:*Z* ratio as a yellow oil.

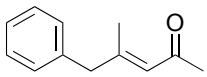
^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 6.13 – 5.83 (m, 1H, C*H*COCH$_3$), 2.15 (s, 3H, C*H*$_3$), 2.09 (d, *J* = 1.2 Hz, 3H, C*H*$_3$C=CH), 2.01 – 1.92 (m, 2H, C*H*$_2$C=CH), 1.76 – 1.57 (m, 6H, C*H*, C*H*$_2$), 1.30 – 1.02 (m, 3H, C*H*$_2$), 0.96 – 0.77 (m, 2H, C*H*$_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 198.6, 157.6, 124.8, 49.4, 35.8, 33.3, 31.8, 26.4, 26.2, 19.3.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2922, 2850, 1688, 1613, 1448, 1215, 960.

HRMS (ESI) m/z calc. for $C_{12}H_{21}O$ $[M+H]^+$: 181.1587, found: 181.1588.

(*E*)-4-methyl-5-phenylpent-3-en-2-one **(9)**



Prepared according to general procedure **B**, using Cp_2ZrCl_2 (214 mg, 0.73 mmol, 0.22 eq.), Me_3Al (5 mL, 10 mmol, 3.0 eq.), H_2O (0.09 mL, 5 mmol, 1.5 eq.), 3-phenyl-1-propyne (0.41 mL, 3.3 mmol, 1.0 eq.), and acetyl chloride (0.47 mL, 6.64 mmol, 2.0 eq.). Purified by flash column chromatography (petroleum ether/ Et_2O; 90/10; silica) to give **9** (0.37 g, 63%) in > 20:1 *E*:*Z* ratio as a yellow oil.

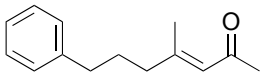
^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.37 – 7.30 (m, 2H, Ar-*H*), 7.30 – 7.23 (m, 1H, Ar-*H*), 7.22 – 7.16 (m, 2H, Ar-*H*), 6.09 (q, *J* = 1.3 Hz, 1H, C*H*$COCH_3$), 3.44 (s, 2H, CH_2C=CH), 2.20 (s, 3H, CH_3), 2.12 (d, *J* = 1.2 Hz, 3H, CH_3C=CH).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 198.9, 156.7, 137.8, 129.2, 128.6, 126.7, 125.0, 47.2, 31.9, 19.2.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3028, 1687, 1687, 1616, 1216, 773, 770.

HRMS (ESI) m/z calc. for $C_{12}H_{15}O$ $[M+H]^+$: 175.1117, found: 175.1118.

(*E*)-4-Methyl-7-phenylhept-3-en-2-one **(10)**



Prepared according to general procedure **B**, using Cp_2ZrCl_2 (643 mg, 2.2 mmol, 0.22 eq.), Me_3Al (15 mL, 30 mmol, 3.0 eq.), H_2O (0.27 mL, 15 mmol, 1.5 eq.), phenyl-1-pentyne (1.52 mL, 10 mmol, 1.0 eq.), and acetyl chloride (1.42 mL, 20 mmol, 2.0 eq.) Purified by flash column chromatography (petroleum ether/ Et_2O; 90/10; silica), to give **10** (1.41 g, 69%) in > 20:1 *E*:*Z* ratio as a yellow oil.

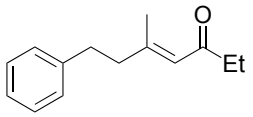
^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm 7.29 – 7.21 (m, 2H, Ar-*H*), 7.20 – 7.13 (m, 3H, Ar-*H*), 6.04 (q, *J* = 1.3 Hz, 1H, C*H*COMe), 2.63 – 2.55 (m, 2H, PhCH_2), 2.14 (s, 3H, COCH_3), 2.14 – 2.11 (m, 2H, $PhCH_2CH_2CH_2$), 2.10 (d, *J* = 1.3 Hz, 3H, $CH_3CCHCOCH_3$), 1.84 – 1.74 (m, 2H, $PhCH_2CH_2$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C/ppm 198.9, 158.4, 141.9, 128.5 (4C), 126.1, 123.8, 40.7, 35.55, 31.9, 29.3, 19.4.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3062, 2363, 1687, 1616, 1496, 1453.

HRMS (ESI) m/z calc. for $C_{14}H_{19}O$ $[M+H]^+$: 203.1430, found: 203.1431.

(*E*)-5-methyl-7-phenylhept-4-en-3-one **(11)**



Prepared according to general procedure **B**, using Cp_2ZrCl_2 (428 mg, 1.46 mmol, 0.22 eq.), Me_3Al (10 mL, 20 mmol, 3.0 eq.), H_2O (0.18 mL, 10 mmol, 1.5 eq.), 4-phenyl-1-pentyne (0.94 mL, 6.67 mmol, 1.0 eq.), and propionyl chloride (1.16 mL, 13.2 mmol, 2.0 eq.). Purified by flash column chromatography (petroleum ether/ Et_2O; 90/10; silica) to give **11** (0.83 g, 61% yield) in > 20:1 *E*:*Z* ratio as a yellow oil.

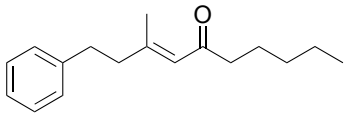
^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.21 – 7.08 (m, 2H, Ar-*H*), 7.08 – 6.97 (m, 3H, Ar-*H*), 5.86 (q, *J* = 1.2 Hz, 1H, C*H*COEt), 3.09 – 2.47 (m, 2H, PhCH_2), 2.35 – 2.18 (m, 4H, COCH_2, CH_2C=CH), 2.03 (d, *J* = 1.2 Hz, 3H, CH_3C=CH), 0.89 (t, *J* = 7.3 Hz, 3H, CH_3CH$_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 202.2, 157.2, 141.5, 128.8 (4C), 126.5, 123.8, 43.4, 37.9, 34.4, 19.8, 8.5.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3659, 2980, 2889, 1685, 1619, 1379, 1153, 699.

HRMS (ESI) m/z calc. for $C_{14}H_{18}O$ $[M+H]^+$: 203.1436, found: 203.1432.

(*E*)-3-methyl-1-phenyldec-3-en-5-one **(12)**



Prepared according to general procedure **B**, using Cp_2ZrCl_2 (428 mg, 1.46 mmol, 0.22 eq.), Me_3Al (10 mL, 20 mmol, 3.0 eq.), H_2O (0.18 mL, 10 mmol, 1.5 eq.), 4-phenyl-1-pentyne (0.94 mL, 6.67 mmol, 1.0 eq.), and hexanoyl chloride (1.86 mL, 13.2 mmol, 2.0 eq.). Purified by flash column chromatography (petroleum ether/ Et_2O; 95/5; silica) to give **12** (0.93 g, 57% yield) in > 20:1 *E*:*Z* ratio as yellow oil.

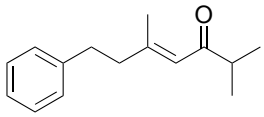
^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.35 – 7.27 (m, 2H, Ar-*H*), 7.26 – 7.17 (m, 3H, Ar-*H*), 6.04 (q, *J* = 1.3 Hz, 1H, C*H*CO), 2.92 – 2.73 (m, 2H, PhCH_2), 2.50 – 2.33 (m, 4H, COCH_2, CH_2C=CH), 2.21 (d, *J* = 1.2 Hz, 3H, CH_3CCH), 1.58 (p, *J* = 7.5 Hz, 2H, CH_2), 1.32 (dddd, *J* = 16.5Hz, 15.0 Hz, 8.8 Hz, 3.4 Hz, 4H, CH_2), 0.92 (t, *J* = 7.0 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 201.6, 156.9, 141.2, 128.5, 128.4, 126.2, 123.7, 44.5, 43.1, 34.1, 31.6, 24.1, 22.6, 19.5, 14.1.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3659, 2980, 2930, 1686, 1618, 1381, 1131, 698.

HRMS (ESI) m/z calc. for $C_{17}H_{24}O$ $[M+H]^+$: 245.1905, found: 245.1901.

(*E*)-2,5-Dimethyl-7-phenylhept-4-en-3-one **(13)**



Prepared according to general procedure **B**, using Cp_2ZrCl_2 (643 mg, 2.2 mmol, 0.22 eq.), Me_3Al (15 mL, 30 mmol, 3.0 eq.), H_2O (0.27 mL, 15 mmol, 1.5 eq.), 4-phenyl-1-pentyne (1.41 mL, 10 mmol, 1.0 eq.), and isobutyl chloride (2.10 mL, 20 mmol, 2.0 eq.). Purified by flash column chromatography (petroleum ether/ Et_2O; 95/5; silica) to give **13** (1.40 g, 65%) in > 20:1 *E*:*Z* ratio as a yellow oil.

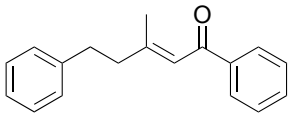
^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm 7.33 – 7.25 (m, 2H, Ar-*H*), 7.23 – 7.13 (m, 3H, Ar-*H*), 6.13 – 5.97 (m, 1H, C=C*H*), 2.85 – 2.76 (m, 2H, PhH_2), 2.54 (hept, *J* = 6.9 Hz, 1H, C*H*$(CH_3)_2$), 2.45 (ddd, *J* = 9.0 Hz, 6.2 Hz, 1.1 Hz, 2H, CH_2), 2.18 (d, *J* = 1.4 Hz, 3H, CH_3C=CH), 1.04 (d, *J* = 6.9 Hz, 6H, 2 × CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C/ppm 204.9, 157.5, 141.0, 128.4, 128.3, 126.1, 122.5, 43.1, 41.6, 34.0, 19.4, 18.3.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3648, 2932, 1714, 1603, 1497.

MS (ESI) m/z calc. for $C_{15}H_{21}O$ $[M+H]^+$: 217.1587, found: 217.1588.

(*E*)-3-Methyl-1, 5-diphenylpent-2-en-1-one **(14)**



Prepared according to general procedure **B**, using Cp_2ZrCl_2 (643 mg, 2.2 mmol, 0.22 eq.), Me_3Al (15 mL, 30 mmol, 3.0 eq.), H_2O (0.27 mL, 15 mmol, 1.5 eq.), 4-phenyl-1-pentyne (1.41 mL, 10 mmol, 1.0 eq.), and benzoyl chloride (1.85 mL, 16 mmol, 1.6 eq.). Purified by flash column chromatography (petroleum ether/ Et_2O; 95/5; silica) to give **14** (0.93 g, 36% yield) in > 20:1 *E*:*Z* ratio as a yellow oil.

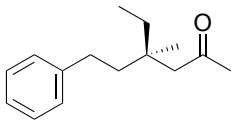
^{1}H NMR (500 MHz, $CDCl_3$) δ_H/ppm 7.81 – 7.69 (m, 2H, Ar-*H*), 7.55 – 7.47 (m, 1H, Ar-*H*), 7.45 – 7.38 (m, 2H, Ar-*H*), 7.32 (dd, *J* = 8.0 Hz, 6.7 Hz, 2H, Ar-*H*), 7.27 – 7.18 (m, 3H, Ar-*H*), 6.62 (q, *J* = 1.2 Hz, 1H, C*H*), 2.89 (t, *J* = 8.8 Hz, 6.8 Hz, 2H, PhCH_2), 2.57 (td, *J* = 7.6 Hz, 1.1 Hz, 2H, CH_2C=CH), 2.23 (d, *J* = 1.3 Hz, 3H, CH_3)

^{13}C NMR (126 MHz, $CDCl_3$) δ_C/ppm 192.0, 158.1, 141.1, 139.2, 132.4, 128.6, 128.5, 128.5, 128.3, 126.2, 121.7, 43.1, 34.1, 19.8.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3061, 2858, 1661, 1579, 1495, 1448.

MS (ESI) m/z calc. for $C_{18}H_{19}O$ $[M+H]^+$: 251.1430, found: 251.1432.

(*R*)-4-ethyl-4-methyl-6-phenylhexan-2-one **(15)**



Synthesized according to general procedure **Ib1,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol, 0.1 eq.), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), a balloon filled with ethylene, (*E*)-4-methyl-6-phenylhex-3-en-2-one **(1)** (38.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.) Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **15** (35 mg, 80% yield, 91% *ee*).

HPLC analysis indicated an enantiomeric excess of 91% [two Chiralpak® ID in series; flow: 0.8 mL/min; hexane/*i*-PrOH: 99:1; λ = 210 nm; major enantiomer tR = 14.58 min; minor enantiomer, tR = 15.65 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.23 – 7.16 (m, 2H, Ar-*H*), 7.14 – 7.06 (m, 3H, Ar-*H*), 2.51 – 2.39 (m, 2H, PhC*H*$_2$), 2.32 (s, 2H, C*H*$_2$COCH$_3$), 2.07 (s, 3H, COC*H*$_3$), 1.62 – 1.50 (m, 2H, PhCH$_2$C*H*$_2$), 1.38 (m, 2H, C*H*$_2$CH$_3$), 0.96 (s, 3H, C*H*$_3$), 0.79 (t, *J* = 7.5 Hz, 3H, CH$_2$C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.9, 143.0, 128.4 (4C), 125.7, 51.2, 41.1, 36.3, 32.7, 31.7, 30.4, 24.6, 8.1.

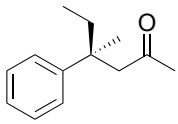
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3063, 2879, 1714, 1603, 1496, 1153, 699.

MS (ESI) m/z calc. for $C_{15}H_{22}O^{23}Na$ $[M+Na]^+$: 241.1563, found: 241.1563.

$[\alpha]^{20}_{589}$ = +4.1 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*S*)-4-methyl-4-phenylhexan-2-one **(16)**



Synthesized according to general procedure **Ib1,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol, 0.1 eq.), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), a balloon filled with ethylene, (*E*)-4-Phenylpent-3-en-2-one **(2a)** (32.0 mg, 0.2 mmol, 1.0 eq.), and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **16** (19 mg, 50% yield, 90% *ee*).

HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® IB; flow: 0.8 mL/min; hexane/*i*-PrOH: 99:1; λ = 210 nm; major enantiomer tR = 7.33 min; minor enantiomer, tR = 7.68 min]. For *cis*-enone product, ***ent*-16**, an enantiomeric excess of 71% was obtained with the same separation condition.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.50 – 7.21 (m, 4H, Ar-*H*), 7.23 – 7.02 (m, 1H, Ar-*H*), 2.83 (d, *J* = 14.1 Hz, 1H, C*H*$_2$CO), 2.54 (d, *J* = 14.2 Hz, 1H, C*H*$_2$CO), 1.80 (dt, *J* = 14.8 Hz, 7.3 Hz, 1H, C*H*$_2$CH$_3$), 1.71 (s, 3H, COC*H*$_3$), 1.69 – 1.55 (m, 1H, C*H*$_2$CH$_3$), 1.36 (s, 3H, C*H*$_3$), 0.63 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.3, 146.3, 128.5, 128.2, 126.2, 125.9, 56.1, 40.7, 35.5, 32.0, 23.2, 8.5.

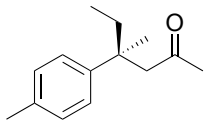
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3025, 2855, 1703, 1357, 760, 662.

MS (ESI) m/z = $[M+Na]^+$: 213.2 (100)

$[\alpha]^{20}_{589}$ = +44.7 (c 0.8, $CHCl_3$)

Absolute configuration was assigned by comparison to literature optical rotation values.[9]

(*S*)-4-methyl-4- (*p*-tolyl) hexan-2-one **(17)**



Synthesized according to general procedure **Ib1,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol, 0.1 eq.), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), a balloon filled with ethylene, (*E*)-4-(*p*-tolyl) pent-3-en-2-one **(3)** (35.0 mg, 0.2 mmol, 1.0 eq.), and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **17** (20 mg, 34% yield, 89% *ee*).

HPLC analysis indicated an enantiomeric excess of 89% [Chiralpak® IC; flow: 1.0 mL/min; hexane/*i*-PrOH: 99:1; λ = 210 nm; major enantiomer tR = 9.76 min; minor enantiomer, tR = 10.28 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.23 – 7.17 (m, 2H, Ar-*H*), 7.16 – 7.09 (m, 2H, Ar-*H*), 2.86 (d, *J* = 14.1 Hz, 1H, C*H*$_2$CO), 2.63 – 2.5 (m, 1H, C*H*$_2$CO), 2.32 (s, 3H, Ar-C*H*$_3$), 1.85 (dt, *J* = 13.7 Hz, 7.4 Hz, 1H, C*H*$_2$CH$_3$), 1.77 (s, 3H, COC*H*$_3$), 1.72 – 1.53 (m, 1H, C*H*$_2$CH$_3$), 1.39 (s, 3H, C*H*$_3$), 0.68 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.5, 143.2, 135.3, 129.0, 126.1, 56.1, 40.4, 35.5, 32.1, 23.3, 20.9, 8.5.

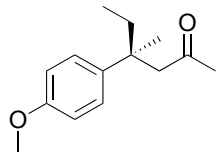
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2980, 2886, 1704, 1381, 1153, 955, 815.

MS (ESI) m/z calc. for $C_{14}H_{20}O^{23}Na$ $[M+Na]^+$: 227.1406, found: 227.1406.

$[\alpha]^{20}_{589}$ = +41.0 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*S*)-4-(4-methoxyphenyl)-4-methylhexan-2-one **(18)**



Synthesized according to general procedure **Ib1,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol, 0.1 eq.), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.),a balloon filled with ethylene, (*E*)-4-(4-methoxyphenyl) pent-3-en-2-one **(5)** (38.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **18**, (15 mg, 39% yield, 73% *ee*).

HPLC analysis indicated an enantiomeric excess of 73% [Chiralpak® ID; flow: 1.0 mL/min; hexane/*i*-PrOH: 95:5; λ = 225 nm; major enantiomer tR = 7.91 min; minor enantiomer, tR = 8.84 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.30 – 7.02 (m, 2H, Ar-*H*), 6.91 – 6.60 (m, 2H, Ar-*H*), 3.73 (s, 3H, OCH_3), 2.77 (d, *J* = 14.0 Hz, 1H, CH_2CO), 2.49 (d, *J* = 14.0 Hz, 1H, CH_2CO), 1.76 (dq, *J* = 14.7 Hz, 7.5 Hz, 1H, CH_2CH$_3$), 1.69 (s, 3H, COCH_3), 1.64 – 1.47 (m, 1H, CH_2CH$_3$), 1.31 (s, 3H, CH_3), 0.61 (t, *J* = 7.4 Hz, 3H, CH_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.6, 157.6, 138.2, 127.2, 113.5, 56.3, 55.2, 40.2 35.6, 32.1, 23.3, 8.4.

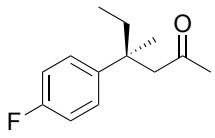
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3659, 2981, 2888, 1514, 1382, 1153, 955, 829.

MS (ESI) m/z $[M+Na]^+$: 243.1(100)

$[\alpha]^{20}_{589}$ = +35.5 (c 1.0, $CHCl_3$)

Absolute configuration assigned by comparison with literature.[9]

(*S*)-4-(4-fluorophenyl)-4-methylhexan-2-one **(19)**



Synthesized according to general procedure **Ib1,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol, 0.1 eq.), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq, Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), a balloon filled with ethylene, (*E*)-4-(4-fluorophenyl) pent-3-en-2-one **(4)** (36.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **19** (23 mg, 46% yield, 91% *ee*).

HPLC analysis indicated an enantiomeric excess of 91% [two Chiralpak® IC in series; flow: 1.0 mL/min; hexane/*i*-PrOH: 99:1; λ = 210 nm; major enantiomer tR = 17.95 min; minor enantiomer, tR = 18.48 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.31 – 7.16 (m, 2H, Ar-*H*), 7.04 – 6.91 (m, 2H, Ar-*H*), 2.83 (d, *J* = 14.6 Hz, 1H, C*H*$_2$CO), 2.64 – 2.51 (m, 1H, C*H*$_2$CO), 1.85 – 1.71 (m, 4H, COC*H*$_3$, C*H*$_2$CH$_3$), 1.63 (dq, *J* = 13.7 Hz, 7.4 Hz, 1H, C*H*$_2$CH$_3$), 1.37 (s, 3H, C*H*$_3$), 0.64 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$),

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 207.9, 161.0 (d, *J* = 244.1 Hz), 142.0 (d, *J* = 3.2 Hz), 127.7 (d, *J* = 8.0 Hz), 114.9 (d, *J* = 20.8 Hz), 56.0, 40.3, 35.7, 32.0, 23.4, 8.4.

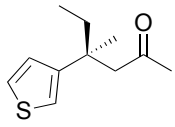
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3659, 2981, 2885, 1510, 1381, 1165, 956, 741.

MS (ESI) m/z $[M+Na]^+$: 231.1(100)

$[\alpha]^{20}_{589}$ = +30.0 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*S*)-4-methyl-4-(thiophen-3-yl) hexan-2-one **(20)**



Synthesized according to general procedure **Ib1,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol, 0.1 eq.), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq, Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), a balloon filled with ethylene, (*E*)-4-(thiophen-3-yl) pent-3-en-2-one **(6)** (34.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **20** (16 mg, 41% yield, 85% *ee*).

HPLC analysis indicated an enantiomeric excess of 85% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99:1; λ = 210 nm; major enantiomer tR = 6.65 min; minor enantiomer, tR = 7.15 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.26 – 7.08 (1H, m, Ar-*H*), 6.92 (1H, dd, *J* = 5.0 Hz, 1.4 Hz, Ar-*H*), 6.83 (1H, dd, *J* = 2.9 Hz, 1.4 Hz, Ar-*H*), 2.66 (1H, d, *J* = 13.6 Hz, C*H*$_2$CO), 2.45 (1H, d, *J* = 13.7 Hz, C*H*$_2$CO), 1.67 (3H, s, CO C*H*$_3$), 1.65 – 1.39 (2H, m, C*H*$_2$), 1.26 (3H, s, C*H*$_3$), 0.60 (3H, t, *J* = 7.4 Hz, CH_2 C*H*$_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.2, 148.3, 126.0, 125.4, 119.7, 55.3, 39.4, 35.0, 31.7, 23.8, 8.4

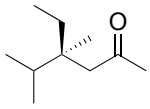
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3659, 2981, 2888, 1703, 1461, 1153, 955.

MS (ESI) m/z $[M+Na]^+$: 219.1 (100)

$[\alpha]^{20}_{589}$ = +45.8 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*S*)-4-ethyl-4,5-dimethylhexan-2-one **(21)**



Synthesized according to general procedure **Ib1,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol, 0.1 eq.), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq, Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), a balloon filled with ethylene, (*E*)-4,5-dimethylhex-3-en-2-one **(7)** (26.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **21** (15 mg, 48% yield, 95% *ee*).

GC analysis indicated an enantiomeric excess of 92% Macherey-Nagel Chiral GC Columns ® HYDRODEX β-3P; flow, major enantiomer tR = 43.14 min; minor enantiomer, tR = 44.00 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 2.30 (d, *J* = 1.5 Hz, 2H, C*H*$_2$COCH$_3$), 2.09 (s, 3H, COC*H*$_3$), 1.71 (p, *J* = 6.9 Hz, 1H, C*H*), 1.39 (qd, *J* = 7.5 Hz, 1.2 Hz, 2H, C*H*$_2$), 0.85 (s, 3H, C*H*$_3$), 0.82 – 0.69 (m, 9H, CHC*H*$_3$, CH$_2$C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 209.8, 48.7, 38.6, 33.3, 32.7, 29.1, 21.0, 17.3, 17.0, 8.1.

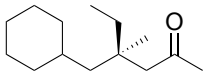
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3659, 2981, 2889, 1510, 1382, 1251, 1152, 1073, 954, 816.

MS (ESI) m/z $[M+Na]^+$, found: 179.1 (100)

$[\alpha]^{20}_{589}$ = –1.0 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*R*)-4-(cyclohexylmethyl)-4-methylhexan-2-one **(22)**



Synthesized according to general procedure **Ib1,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol, 0.1 eq.), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq, Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), a balloon filled with ethylene, (*E*)-5-cyclohexyl-4-methylpent-3-en-2-one **(8)** (36.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **22** (30 mg, 71% yield, 98% *ee*).

HPLC analysis indicated an enantiomeric excess of 98% [Chiralpak® IA; flow: 1.0 mL/min; hexane/*i*-PrOH: 99:1; λ = 222 nm; major enantiomer tR = 5.49 min; minor enantiomer, tR = 6.42 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 2.32 (s, 2H, COCH_2), 2.11 (s, 3H, COCH_3), 1.74 – 1.5- (m, 5H, CH_2, CH), 1.49 – 1.29 (m, 2H, CH_2), 1.32 – 1.01 (m, 6H, CH_2 C), 0.94 (m, 5H, CH_2, CH_3), 0.79 (t, *J* = 7.5 Hz, 3H, CH_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 209.2, 51.8, 46.6, 36.9, 35.9, 33.4, 32.6, 32.0, 26.7, 26.3, 24.9, 8.4.

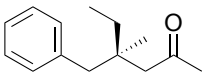
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3659, 2981, 2889, 1715, 1381, 1152, 1072, 954.

MS (ESI) m/z calc. for $C_{14}H_{27}O$ $[M+H]^+$: 211.2056, found: 211.2059.

$[\alpha]^{20}_{589}$ = +2.2 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*R*)-4-benzyl-4-methylhexan-2-one **(23)**



Synthesized according to general procedure **Ib1,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol, 0.1 eq.), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq, Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), a balloon filled with ethylene, (*E*)-4-methyl-5-phenylpent-3-en-2-one **(9)** (35.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the desired product **23** (25 mg, 61% yield, 93%*ee*).

HPLC analysis indicated an enantiomeric excess of 93% [Chiralpak® ID; flow: 0.8 mL/min; hexane/*i*-PrOH: 99:1; λ = 210 nm; major enantiomer tR = 7.60 min; minor enantiomer, tR = 8.25 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.28 – 7.14 (m, 3H, Ar-*H*), 7.12 – 7.04 (m, 2H, Ar-*H*), 2.74 (d, *J* = 13.1 Hz, 1H, PhC*H*$_2$), 2.63 (d, *J* = 13.1 Hz, 1H, PhC*H*$_2$), 2.23 (d, *J* = 1.9 Hz, 2H, C*H*$_2$CO), 2.08 (s, 3H COC*H*$_3$), 1.52 – 1.27 (m, 2H, C*H*$_2$CH$_3$), 0.92 (s, 3H, C*H*$_3$), 0.86 (t, *J* = 7.5 Hz, 3H, CH$_2$C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 209.0, 138.8, 130.6, 127.8, 126.0, 50.1, 44.7, 37.2, 32.4, 31.5, 24.3, 8.4.

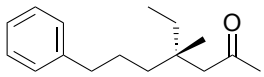
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3661, 2970, 1714, 1360, 1153, 703.

MS (ESI) m/z calc. for $C_{14}H_{20}O^{23}Na$ $[M+H]^+$: 227.1406, found: 227.1407.

$[\alpha]^{20}_{589}$ = –7.3 (c 1.0, $CHCl_3$)

Absolute configuration assigned by comparison with literature.[9]

(*S*)-4-ethyl-4-methyl-7-phenylheptan-2-one **(24)**



Synthesized according to general procedure **Ib1,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol, 0.1 eq.), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq, Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), a balloon filled with ethylene, (*E*)-4-Methyl-7-phenylhept-3-en-2-one **(10)** (40.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.) Purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the desired product **24** (33 mg, 71% yield, 93% *ee*).

HPLC analysis indicated an enantiomeric excess of 93% [two Chiralpak® ID in series; flow: 0.8 mL/min; hexane/*i*-PrOH: 99:1; λ = 210 nm; minor enantiomer tR = 14.17 min; major enantiomer, tR = 14.74 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.30 – 7.15 (m, 2H, Ar-*H*), 7.15 – 7.06 (m, 3H, Ar-*H*), 2.56 – 2.45 (m, 2H, PhCH_2), 2.23 (s, 2H, CH_2COCH$_3$), 2.03 (s, 3H, COCH_3), 1.52 – 1.37 (m, 2H, CH_2), 1.36 – 1.21 (m, 4H, CH_2), 0.86 (s, 3H, CH_3), 0.70 (t, *J* = 7.5 Hz, 3H, CH_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 209.2, 142.7, 128.4, 128.3, 125.7, 51.4, 38.6, 36.7, 36.1, 32.6, 31.7, 25.9, 24.6, 8.1.

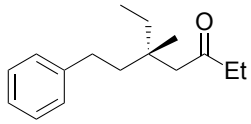
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3659, 2980, 2889, 1714, 1381, 1152, 955, 699.

MS (ESI) m/z calc. for $C_{16}H_{24}O^{23}Na$ $[M+H]^+$ 255.1719, found: 255.1719.

$[\alpha]^{20}_{589}$ = –3.1 (c 1.3, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*S*)-5-ethyl-5-methyl-7-phenylheptan-3-one **(25)**



Synthesized according to general procedure **Ib1,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), ***ent*-L2** (11.5 mg, 0.02 mmol, 0.1 eq.), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq, Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), a balloon filled with ethylene, (*E*)-5-methyl-7-phenylhept-4-en-3-one **(11)** (41.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the desired product **25** (37 mg, 80% yield, 96% *ee*).

HPLC analysis indicated an enantiomeric excess of 96% [Chiralpak® AYH; flow: 0.4 mL/min; hexane/*i*-PrOH: 99.2:0.8; λ = 210 nm; minor enantiomer tR = 15.66 min; major enantiomer, tR = 16.39 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.20 (dd, *J* = 7.9 Hz, 6.8 Hz, 2H, Ar-*H*), 7.16 – 7.06 (m, 3H, Ar-*H*), 2.61 – 2.39 (m, 2H, PhCH_2), 2.34 (q, *J* = 7.3 Hz, 2H, COCH_2CH$_3$), 2.29 (s, 2H, COCH_2), 1.65 – 1.50 (m, 2H, PhCH$_2$ CH_2), 1.44 – 1.30 (m, 2H, CH_2CH$_3$), 1.02 – 0.86 (m, 6H, CH_3), 0.78 (t, *J* = 7.5 Hz, 3H, CH$_2$CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 211.4, 143.1, 128.4, 128.4, 125.6, 50.0, 41.2, 38.4, 36.4, 31.7, 30.4, 24.7, 8.2, 7.8.

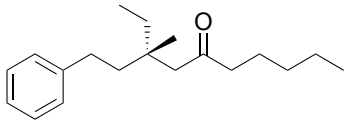
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3026, 2937, 1711, 1455, 1107, 1030, 698.

MS (ESI) m/z calc. for $C_{16}H_{24}O^{23}Na$ $[M+H]^+$: 255.1719, found: 255.1719.

$[\alpha]^{20}_{589}$ = –7.9 (c 1.4, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*S*)-3-ethyl-3-methyl-1-phenyldecan-5-one **(26)**



Synthesized according to general procedure **Ib2,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), ***ent*-L2** (11.5 mg, 0.02 mmol, 0.1 eq.), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq, Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), a balloon filled with ethylene, (*E*)-3-methyl-1-phenyldec-3-en-5-one **(12)** (50.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the desired product **26** (30 mg, 54% yield, 96% *ee*).

HPLC analysis indicated an enantiomeric excess of 91% [two Chiralpak® IA in series; flow: 0.8 mL/min; hexane/*i*-PrOH: 99.4:0.6; λ = 210 nm; minor enantiomer, tR = 12.72 min, major enantiomer tR = 13.33 min;].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.20 (td, *J* = 7.3 Hz, 1.7, 2H, Ar-*H*), 7.11 (dt, *J* = 8.1 Hz, 1.9, 3H, Ar-*H*), 2.51 – 2.39 (m, 2H,), 2.32 (d, *J* = 7.3 Hz, 2H, PhCH_2), 2.29 (s, 2H, CH_2CO), 1.61 – 1.53 (m, 2H, $PhCH_2CH_2$), 1.49 (dd, *J* = 12.9 Hz, 5.5 Hz, 2H, CH_2), 1.44 – 1.33 (m, 2H, CH_2), 1.21 (dddd, *J* = 15.8 Hz, 14.1 Hz, 7.3 Hz, 4.2 Hz, 4H, CH_2), 0.94 (s, 3H, CH_3), 0.80 (dt, *J* = 13.2 Hz, 7.2 Hz, 6H, CH_2CH_3, $CH_2CH_2CH_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 211.2, 143.1, 128.4, 128.3, 125.6, 50.3, 45.3, 41.2, 36.4, 31.7, 31.4, 30.4, 24.7, 23.5, 22.5, 14.0, 8.1.

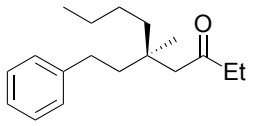
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3063, 2931, 1711, 1456, 1031, 699.

MS (ESI) m/z calc. for $C_{19}H_{30}O^{23}Na$ $[M+Na]^+$: 297.2189, found: 297.2188.

$[\alpha]^{20}_{589}$ = –5.9 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*R*)-5-methyl-5-phenethylnonan-3-one **(27)**



Synthesized according to general procedure **Ib1,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol, 0.1 eq.), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq, Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), a balloon filled with 1-butene, (*E*)-5-methyl-7-phenylhept-4-en-3-one **(11)** (40.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the desired product **27** (25 mg, 53% yield, 93% *ee*).

HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® IA; flow: 1.0 mL/min; hexane/*i*-PrOH: 99.7:0.3; λ = 210 nm; major enantiomer tR = 5.56 min; minor enantiomer, tR = 5.79 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.31 – 7.22 (m, 2H, Ar-*H*), 7.16 (dt, *J* = 8.1 Hz, 1.9 Hz, 3H, Ar-*H*), 2.56 – 2.47 (m, 2H, PhCH_2), 2.39 (q, *J* = 7.3 Hz, 2H, COCH_2CH$_3$), 2.36 (s, 2H, COCH_2), 1.69 – 1.58 (m, 2H, PhCH$_2$CH_2), 1.44 – 1.34 (m, 2H, CH_2), 1.34 – 1.12 (m, 4H, CH_2), 1.08 – 0.95 (m, 6H, CH_3), 0.90 (t, *J* = 7.1 Hz, 3H, CH$_2$CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 211.4, 143.1, 128.4, 128.3, 125.6, 50.5, 41.7, 39.3, 38.4, 36.3, 30.4, 26.0, 25.2, 23.5, 14.2, 7.8.

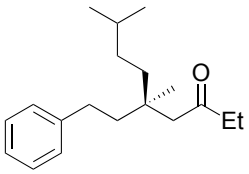
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2980, 2888, 1382, 1252, 1152, 1073, 954.

MS (ESI) m/z calc. for $C_{18}H_{29}O$ $[M+H]^+$: 261.2213, found: 261.2215.

$[\alpha]^{20}_{589}$ = +3.8 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*R*)-5,8-dimethyl-5-phenethylnonan-3-one **(28)**



Synthesized according to general procedure **Ib1,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol, 0.1 eq.), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq, Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), a balloon filled with 3 methyl-1 butene, (*E*)-5-methyl-7-phenylhept-4-en-3-one **(11)** (40.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the desired product **28** (40 mg, 70% yield, 90% *ee*).

HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® AYH; flow: 1.0 mL/min; hexane/*i*-PrOH: 99.5:0.5; λ = 210 nm; major enantiomer tR = 4.26 min; minor enantiomer, tR = 4.45 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.20 (dd, *J* = 8.1 Hz, 6.9 Hz, 2H, Ar-*H*), 7.11 (dt, *J* = 8.0 Hz, 1.8 Hz, 3H, Ar-*H*), 2.51 – 2.39 (m, 2H, PhCH_2), 2.33 (q, *J* = 7.3 Hz, 2H, COCH_2CH$_3$), 2.29 (s, 2H, COCH_2), 1.64 – 1.49 (m, 2H, PhCH$_2$CH_2), 1.47 – 1.35 (m, 1H, C*H*), 1.35 – 1.28 (m, 2H, CH_2), 1.15 – 1.01 (m, 2H, CH_2), 1.01 – 0.89 (m, 6H), 0.82 (d, *J* = 6.6 Hz, 6H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 211.3, 143.1, 128.4, 128.3, 125.6, 50.5, 41.6, 38.4, 37.1, 36.2, 32.8, 30.4, 28.7, 25.2, 22.8, 7.8.

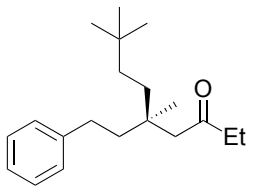
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3659, 2981, 2885, 1510, 1381, 1165, 956, 741.

MS (ESI) m/z calc. for $C_{19}H_{31}O$ $[M+H]^+$: 275.2369, found: 275.2372.

$[\alpha]^{20}_{589}$ = +4.3 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*S*)-5,8,8-trimethyl-5-phenethylnonan-3-one **(29)**



Synthesized according to general procedure **Ib2**, using CuCl (1.9 mg, 0.02 mmol, 0.10 eq.), and phosphoramidite **L2** (11.5 mg, 0.02 mmol, 0.10 eq.), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq, Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), 3,3-dimethyl-1-butene (0.15 mL, 0.5 mmol, 2.5 eq.) in DCM (0.4 mL), (*E*)-5-methyl-7-phenylhept-4-en-3-one **(11)** (40 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the desired product **29** (39 mg, 69% yield, 85% *ee*).

HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® IA; flow: 1.0 mL/min; hexane/*i*-PrOH: 99.5:0.5; λ = 210 nm; major enantiomer tR = 4.34 min; minor enantiomer, tR = 4.54 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.37 – 7.26 (m, 2H, Ar-*H*), 7.26 – 7.16 (m, 3H, Ar-*H*), 2.61 – 2.51 (m, 2H, PhC*H*$_2$), 2.45 (q, *J* = 7.3 Hz, 2H, COC*H*$_2$CH$_3$), 2.40 (s, 2H, COC*H*$_2$), 1.67 (ddt, *J* = 10.9 Hz, 7.4 Hz, 1.7 Hz, 2H, PhCH$_2$C*H*), 1.46 – 1.30 (m, 2H, C*H*$_2$), 1.23 – 1.11 (m, 2H, C*H*$_2$), 1.11 – 1.01 (m, 6H, CH$_2$C*H*$_3$), 0.92 (s, 9H, C (C*H*$_3$)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 211.3, 143.1, 128.4 (4C), 125.6, 50.5, 41.5, 38.4, 37.4, 36.0, 33.7, 30.4, 30.2, 29.4, 25.2, 7.8.

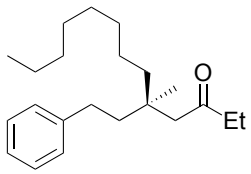
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2980, 2888, 1382, 1251, 1152, 955.

MS (ESI) m/z calc. for $C_{20}H_{33}O$ $[M+H]^+$: 289.2526, found: 289.2528.

$[\alpha]^{20}_{589}$ = +2.1 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*R*)-5-methyl-5-phenethyltridecan-3-one **(30)**



Synthesized according to general procedure **Ib2**, using CuCl (1.9 mg, 0.02 mmol, 0.10 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol, 0.10 eq.), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq, Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), 1-Octene (0.1 mL, 0.5 mmol, 2.5 eq.), (*E*)-5-methyl-7-phenylhept-4-en-3-one **(11)** (40 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the desired product **30** (35 mg, 56% yield, 92% *ee*).

HPLC analysis indicated an enantiomeric excess of 92% [Chiralpak® IA; flow: 0.8 mL/min; hexane/*i*-PrOH: 99.8:0.2; λ = 210 nm; major enantiomer tR = 8.01 min; minor enantiomer, tR = 8.62 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.38 – 7.25 (m, 2H, Ar-*H*), 7.21 (dt, *J* = 8.0 Hz, 1.9 Hz, 3H, Ar-*H*), 2.61 – 2.51 (m, 2H, PhCH_2), 2.49 – 2.41 (m, 2H, COCH_2CH$_3$), 2.40 (s, 2H, CH_2CO), 1.79 – 1.56 (m, 2H, CH_2), 1.41 (t, *J* = 7.4 Hz, 2H, CH_2), 1.38-1.18 (m, 12H, CH_2, CH_3), 1.13 – 1.01 (m, 6H, CH_2), 0.92 (t, *J* = 6.8 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 211.4, 143.1, 128.4, 128.3, 125.6, 50.5, 41.7, 39.6, 38.4, 36.3, 31.9, 30.5, 29.7, 29.4, 25.2, 23.7, 22.7, 14.1, 7.8.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3659, 2980, 2889, 1382, 1252, 1153, 1073, 954.

MS (ESI) m/z calc. for $C_{22}H_{37}O$ $[M+H]^+$: 317.2839, found: 317.2841.

$[\alpha]^{20}_{589}$ = +4.7 (c 1.0, $CHCl_3$)

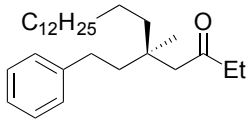
Absolute configuration assigned by analogy to compound **16**.

Large Scale

Synthesized according to general procedure **Ib2**, using CuCl (25 mg, 0.25 mmol, 0.05 eq.), phosphoramidite **L2** (145 mg, 0.25 mmol, 0.05 eq.), AgOTf (70 mg, 0.275 mmol, 0.055 eq.), 1-octene (2.0 mL, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (1.93 g, 0.4 mmol, 1.5 eq.), (*E*)-5-methyl-7-phenylhept-4-en-3-one **(11)** (1.0 g, 5 mmol, 1.0 eq.) and TMSCl (3.2 mL, 25 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the desired product **30** (0.793 g, 50% yield, 93% *ee*).

HPLC analysis indicated an enantiomeric excess of 93% [Chiralpak® IA; flow: 0.8 mL/min; hexane/*i*-PrOH: 99.8:0.2; λ = 210 nm; major enantiomer tR = 8.01 min; minor enantiomer, tR = 8.62 min].

(*R*)-5-methyl-5-phenethylnonadecan-3-one **(31)**



Synthesized according to general procedure **Ib2**, using CuCl (1.9 mg, 0.02 mmol, 0.10 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol, 0.10 eq.), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq.), 1-tetradecene (0.15 mL, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-5-methyl-7-phenylhept-4-en-3-one **(11)** (40 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the desired product **31** (45 mg, 59% yield, 90% *ee*).

HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® IA; flow: 1.0 mL/min; hexane/*i*-PrOH: 99.8:0.2; λ = 210 nm; major enantiomer tR = 6.28 min; minor enantiomer, tR = 6.89 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.35 – 7.25 (m, 2H, Ar-*H*), 7.21 (dt, *J* = 8.0 Hz, 1.8 Hz, 3H, Ar-*H*), 2.62 – 2.50 (m, 2H, PhCH_2), 2.44 (q, *J* = 7.3 Hz, 2H, COCH_2CH$_3$), 2.40 (s, 2H, COCH_2), 1.75 – 1.58 (m, 2H, PhCH$_2$CH_2), 1.49 – 1.36 (m, 2H, CH_2), 1.29 (s, 24H, CH_2), 1.15 – 0.98 (m, 6H, CH_3, COCH$_2$CH_3), 0.99 – 0.80 (m, 3H, CH$_2$CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 211.4, 143.1, 128.4, 128.3, 125.6, 50.5, 41.7, 39.6, 38.4, 36.3, 31.9, 30.5, 29.7 (8C), 29.4, 25.2, 23.7, 22.7, 14.1, 7.8.

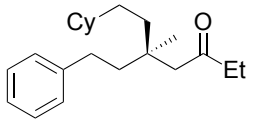
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2980, 2880, 1473, 1382, 1252, 1152, 1072, 954.

MS (ESI) m/z calc. for $C_{28}H_{48}O^{23}Na$ $[M+Na]^+$: 423.3597, found: 423.3596.

$[\alpha]^{20}_{589}$ = +2.9 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*R*)-7-cyclohexyl-5-methyl-5-phenethylheptan-3-one **(32)**



Synthesized according to general procedure **Ib2**, using CuCl (1.9 mg, 0.02 mmol, 0.10 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol, 0.10 eq.), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq.), vinylcyclohexane (0.08 mL, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-5-methyl-7-phenylhept-4-en-3-one **(11)** (40 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the desired product **32** (40 mg, 64% yield, 90% *ee*).

HPLC analysis indicated an enantiomeric excess of 90% [Chiralpak® IA; flow: 1.0 mL/min; hexane/*i*-PrOH: 99.5:0.5; λ = 210 nm; major enantiomer tR = 5.02 min; minor enantiomer, tR = 5.22 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.30 – 7.19 (m, 2H, Ar-*H*), 7.19 – 7.08 (m, 3H, Ar-*H*), 2.54 – 2.45 (m, 2H, PhCH_2), 2.38 (q, *J* = 7.3 Hz, 2H COCH_2CH$_3$), 2.33 (s, 2H, COCH_2), 1.74 – 1.53 (m, 6H, PhCH$_2$CH_2, C*H*, CH_2), 1.44 – 1.31 (m, 2H, CH_2), 1.27 – 1.03 (m, 6H, CH_2), 1.03 – 0.97(m, 6H, CH_2), 0.85 (ddd, *J* = 23.7 Hz, 12.0 Hz, 6.2, 3H, CH$_2$CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 211.4, 143.1, 128.4, 128.3, 125.6, 50.5, 41.6, 38.4, 36.6, 36.2, 33.6, 31.3, 30.4, 26.7, 26.5, 25.2, 7.8.

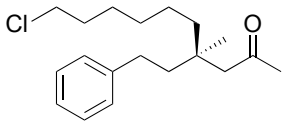
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2980, 2889, 1382, 1252, 1152, 1073, 955.

MS (ESI) m/z calc. for $C_{22}H_{35}O$ $[M+H]^+$: 315.2682, found: 315.2685.

$[\alpha]^{20}_{589}$ = +3.5 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*R*)-10-chloro-4-methyl-4-phenethyldecan-2-one **(33)**



Synthesized according to general procedure **Ib2**, using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq.), 6-chlorohex-1-ene (0.08 mL, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-4-methyl-6-phenylhex-3-en-2-one **(1)** (38 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 80:20; SiO_2) to give the desired product **33** (31 mg, 51% yield, 84% *ee*).

HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® IA; flow: 0.8 mL/min; hexane/*i*-PrOH: 98.5:1.5; λ = 210 nm; major enantiomer tR = 6.70 min; minor enantiomer, tR = 7.27 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.23 – 7.12 (m, 2H, Ar-*H*), 7.11 – 7.02 (m, 3H, Ar-*H*), 3.43 (t, *J* = 6.7 Hz, 2H, CH_2Cl), 2.42 (t, *J* = 8.7 Hz, 2H, PhCH_2), 2.30 (s, 2H, CH_2COCH_3), 2.03 (s, 3H, $COCH_3$), 1.78 – 1.57 (m, 3H, CH_2), 1.57 – 1.45 (m, 2H, CH_2), 1.41 – 1.23 (m, 3H, CH_2), 1.28 – 1.07 (m, 4H, CH_2), 0.94 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.7, 142.9, 128.4, 128.3, 125.7, 51.6, 45.1, 41.6, 39.3, 36.2, 32.6, 30.4, 29.7, 26.9, 25.1, 23.6.

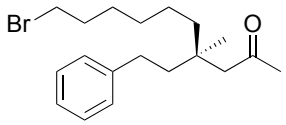
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2981, 2889, 1382, 1252, 1153, 955.

MS (ESI) m/z calc. for $C_{19}H_{30}O^{35}Cl$ $[M+H]^+$: 309.1979, found: 309.1981.

$[\alpha]^{20}_{589}$ = +1.0 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*R*)-10-bromo-4-methyl-4-phenethylnonan-2-one **(34)**



Synthesized according to general procedure **Ib2**, using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq.), 5-bromo-1 pentene (0.06 mL, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-4-methyl-6-phenylhex-3-en-2-one **(1)** (38 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the desired product **34** (37 mg, 55% yield, 87% *ee*).

HPLC analysis indicated an enantiomeric excess of 87% [Chiralpak® IA; flow: 1.0 mL/min; hexane/*i*-PrOH: 99:1; λ = 210 nm; major enantiomer tR = 6.22 min; minor enantiomer, tR = 6.73 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.25 – 7.16 (m, 2H, Ar-*H*), 7.15 – 7.06 (m, 3H, Ar-*H*), 3.34 (t, *J* = 6.8 Hz, 2H, C*H*$_2$Br), 2.62 – 2.40 (m, 2H, PhC*H*$_2$), 2.33 (s, 2H, C*H*$_2$COCH$_3$), 2.07 (s, 3H, COC*H*$_3$), 1.80 (dq, *J* = 8.9 Hz, 6.9 Hz, 2H, C*H*$_2$), 1.57 (m, 2H, C*H*$_2$), 1.48 – 1.29 (m, 4H, C*H*$_2$), 1.29 – 1.10 (m, 2H, C*H*$_2$), 0.97 (s, 3H, C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.7, 142.8, 128.4, 128.3, 125.7, 51.6, 41.6, 39.2, 36.2, 33.9, 32.7, 32.7, 30.4, 28.9, 25.1, 22.9.

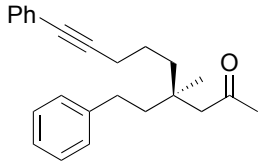
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3659, 2981, 2885, 1510, 1381, 1165, 956, 741.

MS (ESI) m/z calc. for $C_{19}H_{30}O^{79}Br$ $[M+Na]^+$: 353.1475, found: 353.1473.

$[\alpha]^{20}_{589}$ = –1.2 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*R*)-4-methyl-4-phenethyl-9-phenylnon-8-yn-2-one **(35)**



Synthesized according to general procedure **Ib2,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq.), pent-4-en-1-yn-1-ylbenzene (0.08 mL, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-4-methyl-6-phenylhex-3-en-2-one **(1)** (38 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **35** (34 mg, 52% yield, 78%*ee*).

HPLC analysis indicated an enantiomeric excess of 78% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 98:2; λ = 210 nm; major enantiomer tR = 19.18 min; minor enantiomer, tR = 20.44 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.51 – 7.36 (m, 2H, Ar-*H*), 7.35 – 7.26 (m, 5H, Ar-*H*), 7.22 (dt, *J* = 7.8 Hz, 1.9 Hz, 3H, Ar-*H*), 2.70 – 2.52 (m, 2H, PhCH_2), 2.52 – 2.39 (m, 4H, CH_2), 2.18 (s, 3H, COCH_3), 1.75 – 1.67 (m, 2H, CH_2), 1.67 – 1.56 (m, 4H, CH_2), 1.12 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.5, 142.8, 131.6, 128.5, 128.4, 128.2, 127.6, 125.7, 123.9, 90.1, 80.9, 51.6, 41.6, 38.6, 36.1, 32.6, 30.4, 25.1, 23.4, 20.1.

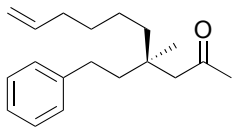
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2981, 2388, 1712, 1380, 1154, 755, 667.

MS (ESI) m/z calc. for $C_{24}H_{29}O$ $[M+H]^+$ 333.2213, found: 333.2216.

$[\alpha]^{20}_{589}$ = –1.1 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*R*)-4-methyl-4-phenethyldec-9-en-2-one **(36)**



Synthesized according to general procedure **Ib2,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq.), 1,5-hexadiene (0.25 mL, 2.0 mmol, 10 eq.) in DCM (0.4 mL), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-4-methyl-6-phenylhex-3-en-2-one **(1)** (38 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the desired product **36** (30 mg, 55% yield, 74% *ee*).

HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® IA; flow: 1.0 mL/min; hexane/*i*-PrOH: 99:1; λ = 210 nm; major enantiomer tR = 4.62 min; minor enantiomer, tR = 4.82 min].

^{1}H NMR (400 MHz, $CDCl_3$) δH/ppm 7.23 – 7.16 (m, 2H, Ar-*H*), 7.14 – 7.06 (m, 3H, Ar-*H*), 5.74 (ddt, *J* = 16.9 Hz, 10.2 Hz, 6.7 Hz, 1H, C*H*=CH_2), 5.13 – 4.54 (m, 2H, CH=CH_2), 2.56 – 2.38 (m, 2H, PhCH_2), 2.33 (s, 2H, CH_2COCH$_3$), 2.06 (s, 3H, COCH_3), 2.05 – 1.95 (m, 2H, PhCH$_2$CH_2), 1.61 – 1.52 (m, 2H, CH_2), 1.38 – 1.25 (m, 4H, CH_2), 1.21 (m, 2H, CH_2), 0.97 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δC/ppm 208.8, 142.9, 139.0, 128.4 (4C), 125.7, 114.4, 51.7, 41.6, 39.2, 36.3, 33.7, 32.6, 30.4, 29.6, 25.1, 23.1.

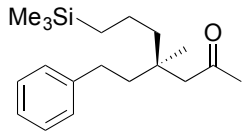
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2980, 2888, 1382, 1252, 1152, 955.

MS (ESI) m/z calc. for $C_{19}H_{29}O$ $[M+H]^+$: 273.2213, found: 273.2215.

$[\alpha]^{20}_{589}$ = +0.7 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*S*)-4-methyl-4-phenethyl-7-(trimethylsilyl)heptan-2-one **(37)**



Synthesized according to general procedure **Ib2,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq.), allyltrimethylsilane (0.07 mL, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-4-methyl-6-phenylhex-3-en-2-one **(1)** (38 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 95:15; SiO_2) to give the desired product **37** (25 mg, 42% yield, 88% *ee*).

HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® AYH; flow: 1.0 mL/min; hexane/*i*-PrOH: 99.5:0.5; λ = 210 nm; major enantiomer tR = 5.73 min; minor enantiomer, tR = 6.39 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.33 – 7.24 (m, 2H, Ar-*H*), 7.23 – 7.14 (m, 3H, Ar-*H*), 2.63 – 2.46 (m, 2H, PhC*H*$_2$), 2.41 (s, 2H, C*H*$_2$COCH$_3$), 2.15 (s, 3H, COC*H*$_3$), 1.74 – 1.55 (m, 2H, PhCH$_2$C*H*$_2$), 1.54 – 1.37 (m, 2H, C*H*$_2$), 1.35 – 1.14 (m, 2H, C*H*$_2$), 1.05 (s, 3H, C*H*$_3$), 0.67 – 0.23 (m, 2H, C*H*$_2$ Si), 0.0 (s, 9H, SiC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 210.4, 144.5, 129.9, 129.9, 127.2, 53.3, 45.4, 43.2, 38.0, 34.2, 32.0, 26.6, 19.5, 19.0, 0.0.

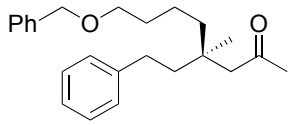
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2980, 2886, 1382, 1153, 1073, 956.

MS (ESI) m/z calc. for $C_{19}H_{33}O^{28}Si$ $[M+H]^+$: 305.2295, found: 305.2296.

$[\alpha]^{20}_{589}$ = +0.8 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*R*)-8-(benzyloxy)-4-methyl-4-phenethyloctan-2-one **(38)**



Synthesized according to general procedure **Ib2,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq.), 4-benzyloxy-1-butene (0.08 mL, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-4-methyl-6-phenylhex-3-en-2-one **(1)** (38 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.) Purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the desired product **38** (38 mg, 54% yield, 82% *ee*).

HPLC analysis indicated an enantiomeric excess of 82%% [Chiralpak® IA; flow: 1.0 mL/min; hexane/*i*-PrOH: 99:1; λ = 210 nm; major enantiomer tR = 7.57 min; minor enantiomer, tR = 8.36 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.31 – 7.23 (m, 4H, Ar-*H*), 7.23 – 7.15 (m, 3H, Ar-*H*), 7.09 (ddt, *J* = 7.0 Hz, 3.6 Hz, 1.4 Hz, 3H, Ar-*H*), 4.43 (s, 2H, OCH_2Ph), 3.41 (t, *J* = 6.5 Hz, 2H, OCH_2), 2.59 – 2.38 (m, 2H, PhCH_2), 2.33 (s, 2H CH_2COCH$_3$), 2.05 (s, 3H, CH$_2$COCH_3), 1.67 – 1.43 (m, 4H, CH_2), 1.45 – 1.15 (m, 4H, CH_2), 0.97(s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.8, 142.9, 138.6, 128.4 (4C), 127.7 (3C), 127.5, 125.7, 72.9, 70.2, 51.6, 41.6, 39.2, 36.2, 32.6, 30.4, 25.1, 20.4.

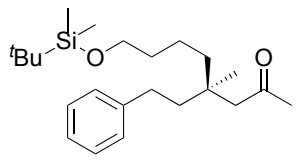
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3659, 2981, 2885, 1510, 1381, 1165, 956, 741.

MS (ESI) m/z calc. for $C_{24}H_{33}O_2$ $[M+H]^+$: 353.2475, found: 353.2476.

$[\alpha]^{20}_{589}$ = +1.0 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*R*)-8-((*tert*-butyldimethylsilyl)oxy)-4-methyl-4-phenethyloctan-2-one **(39)**



Synthesized according to general procedure **Ib2,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq.), 4-[(tert-butyldimethylsilyl)oxy]-1-butene (0.11 mL, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-4-methyl-6-phenylhex-3-en-2-one **(1)** (38 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the desired product **39** (50 mg, 71% yield, 91% *ee*).

HPLC analysis indicated an enantiomeric excess of 91% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99.95:0.05; λ = 210 nm; minor enantiomer tR = 16.30 min; major enantiomer, tR = 16.65 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.26 – 7.16 (m, 2H, Ar-*H*), 7.16 – 7.07 (m, 3H, Ar-*H*), 3.57 (t, *J* = 6.4 Hz, 2H, C*H*$_2$O), 2.54 – 2.40 (m, 2H, PhC*H*$_2$), 2.35 (s, 2H, C*H*$_2$COCH$_3$), 2.08 (s, 3H, COC*H*$_3$), 1.68 – 1.52 (m, 2H, PhCH$_2$C*H*$_2$), 1.50 – 1.41 (m, 2H, C*H*$_2$), 1.41 – 1.32 (m, 2H, C*H*$_2$), 1.31 – 1.19 (m, 2H, C*H*$_2$), 0.99 (s, 3H, C*H*$_3$), 0.84 (s, 9H, C (C*H*$_3$)$_3$), 0.0 (s, 6H, SiC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.7, 142.9, 128.4(4C), 125.7, 63.1, 51.6, 41.6, 39.2, 36.3, 33.6, 32.6, 30.4, 26.0, 25.1, 20.0, 18.4, -5.2(3C).

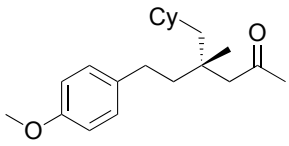
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2980, 2888, 1383, 1252, 1073, 955.

MS (ESI) m/z calc. for $C_{23}H_{41}O_2{}^{28}Si$ $[M+H]^+$: 377.2870, found: 377.2877.

$[\alpha]^{20}_{589}$ = +1.0 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*R*)-4-(cyclohexylmethyl)-6-(4-methoxyphenyl)-4-methylhexan-2-one **(40)**



Synthesized according to general procedure **Ib2,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq.), 1-methoxy-4-vinylbenzene (0.07 mL, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-4-(4-methoxyphenyl) pent-3-en-2-one **(5)** (36 mg, 0.2 mol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the title product **40** (15 mg, 24% yield, 88% *ee*).

HPLC analysis indicated an enantiomeric excess of 88% [Chiralpak® IA; flow: 1.0 mL/min; hexane/*i*-PrOH: 99.5:0.5; λ = 210 nm; minor enantiomer tR = 11.27 min; major enantiomer, tR = 11.73 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.18 – 7.04 (m, 2H, Ar-*H*), 6.90 – 6.69 (m, 2H, Ar-*H*), 3.78 (s, 3H, OC*H*$_3$), 2.48 (td, *J* = 9.2 Hz, 2.3Hz, 2H, PhC*H*$_2$), 2.42 (s, 2H, C*H*$_2$COCH$_3$), 2.13 (s, 3H, COC*H*$_3$), 1.80 – 1.51 (m, 6H, C*H,* C*H*$_2$), 1.37 – 1.27 (m, 3H, C*H*$_2$), 1.27 – 1.09 (m, 3H, C*H*$_2$), 1.09-0.91 (m, 6H, C*H*$_2$, C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.8, 157.7, 135.0, 129.2, 113.8, 55.3, 52.1, 47.1, 42.2, 36.9, 36.0, 33.5, 32.7, 29.6, 26.6, 26.2, 25.5.

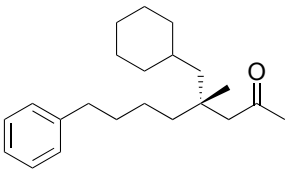
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2980, 2889, 1383, 1251, 1152, 1073, 955, 819.

MS (ESI) m/z calc. for $C_{21}H_{33}O_2$ $[M+H]^+$: 317.2475, found: 317.2477.

$[\alpha]^{20}_{589}$ = –1.7 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

(*R*)-4-(cyclohexylmethyl)-4-methyl-8-phenyloctan-2-one **(41)**



Synthesized according to general procedure **Ib2,** using CuCl (1.9 mg, 0.02 mmol, 0.1 eq.), phosphoramidite **L2** (11.5 mg, 0.02 mmol), AgOTf (5.6 mg, 0.022 mmol, 0.11 eq.), 4-phenyl-1-butene (0.08 mL, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-5-cyclohexyl-4-methylpent-3-en-2-one **(8)** (36 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1.0 mmol, 5.0 eq.) Purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the desired product **41** (23 mg, 35% yield, 92% *ee*).

HPLC analysis indicated an enantiomeric excess of 92% [Chiralpak® IE; flow: 0.8 mL/min; hexane/*i*-PrOH: 99.5:0.5; λ = 210 nm; major enantiomer tR = 9.96 min; minor enantiomer, tR = 10.97 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.26 – 7.14 (m, 2H, Ar-*H*), 7.14 – 7.05 (m, 3H, Ar-*H*), 2.67 – 2.45 (m, 2H, PhCH_2), 2.25 (s, 2H, CH_2COCH_3), 2.02 (s, 3H, COCH_3), 1.73 – 1.44 (m, 8H, C*H*, CH_2), 1.37 – 1.26 (m, 2H, CH_2), 1.25 – 1.00 (m, 7H, CH_2), 0.89 (s, 3H, CH_3), 0.88 – 0.80 (m, 2H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 209.1, 142.7, 128.4, 128.2, 125.6, 52.2, 47.1, 39.6, 36.8, 35.9, 35.9, 33.4, 32.6, 32.2, 26.6, 26.3, 25.5, 23.6.

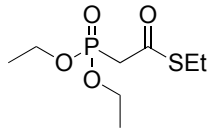
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2981, 1715, 1451, 1381, 1152, 954, 698.

MS (ESI) m/z calc. for $C_{22}H_{34}O^{23}Na$ $[M+Na]^+$: 337.2502 found: 337.2502.

$[\alpha]^{20}_{589}$ = +0.6 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **16**.

S-ethyl 2-(diethoxyphosphoryl) ethanethioate **(42)**



Prepared according to general procedure **E**, using diethylphosphonoacetic acid (10.0 mL, 60.8 mmol, 1.0 eq.), ethanethiol (5.60 mL, 60.8 mmol, 1.0 eq.), DMAP (742 mg, 6.08 mmol, 0.1 eq.), DCC (12.6 g, 60.8 mg, 1.0 eq.). Purified by flash chromatography (ether: pentane; 30:70) to title product **42** (10.5 g, 44 mmol, 72%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 4.12 (dqd, *J* = 8.0 Hz, 7.0 Hz, 1.1 Hz, 4H, OC*H*$_2$CH$_3$), 3.16 (d, *J* = 21.3 Hz, 2H, C*H*$_2$COSEt), 2.88 (qd, *J* = 7.4 Hz, 0.6 Hz, 2H, COSC*H*$_2$CH$_3$), 1.29 (td, *J* = 7.1Hz, 0.6 Hz, 6H, OCH$_2$C*H*$_3$), 1.22 (t, *J* = 7.4 Hz, 3H, COSCH$_2$C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 190.2 (d, *J* = 6.9 Hz), 62.8, 62.7, 42.8(d, *J* = 131.1 Hz), 24.2, 16.3, 16.2, 14.4.

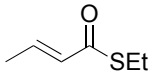
^{31}P NMR (162 MHz, $CDCl_3$) δ_P/ppm 18.2.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 2360, 1738, 1680, 1380, 1257, 1019, 966.

HRMS (ESI) m/z calc. for $C_8H_{18}O_4P^{32}S$, $[M+H]^+$: 241.0658, found: 241.0657.

This data was concordant with literature values.[6]

(*E*)-*S*-ethyl-but-2-enethioate **(43)**



Prepared according to general procedure **Fa,** using Me_3SiSEt (9.72 mL, 60 mmol, 2.0 eq.), $AlCl_3$ (4.80 g, 36 mmol, 1.2 eq.), and methyl (*E*)-but-2-enoate (3.18 mL, 30 mmol, 1.0 eq.) in 100 mL THF. Purified by flash column chromatography (pentane: Et_2O; 98:2; SiO_2) to afford desired product **43** (3.40 g, 26 mmol, 87%) in > 20:1 *E*:*Z* ratio as a yellow oil.

^1H NMR (400 MHz, $CDCl_3$) δ_H/ppm 6.89 (dq, *J* = 15.5 Hz, 6.9, 1H, C*H*COSEt), 6.12 (dq, *J* = 15.4 Hz, 1.7 Hz, 1H, C*H*CH_3), 2.93 (q, *J* = 7.4 Hz, 2H, SC*H*$_2CH_3$), 1.87 (dd, *J* = 6.9 Hz, 1.7 Hz, 3H, CHC*H*$_3$), 1.26 (t, *J* = 7.4 Hz, 3H, SCH_2CH_3).

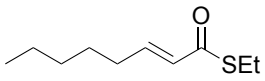
^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 190.0, 140.5, 130.3, 23.0, 17.9, 14.8.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2980, 1677, 1637, 1384, 1252, 1151, 1072.

HRMS (ESI) m/z calc. for $C_6H_{11}O^{32}S$ $[M+H]^+$: 131.0525, found: 131.0526.

This data was concordant with literature values.[14]

(*E*)-*S*-ethyl-oct-2-enethioate **(44)**



Prepared according to general procedure **Fa,** using Me_3SiSEt (3.30 mL, 20 mmol, 2.0 eq.), $AlCl_3$ (1.60 g, 12 mmol, 1.2 eq.), and ethyl (*E*)-oct-2-enoate (1.70 g, 10 mmol, 1.0 eq.) in 30 mL THF. Purified by flash column chromatography (pentane: Et_2O; 98:2; SiO_2) to afford the desired product **44** (1.46 g, 7.8 mmol, 78%) in > 20:1 *E*:*Z* ratio as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 6.88 (dt, *J* = 15.5 Hz, 6.9Hz, 1H, C*H*COSEt), 6.09 (dt, *J* = 15.5 Hz, 1.5 Hz, 1H, C*H*=CH), 2.92 (q, *J* = 7.4 Hz, 2H, SC*H*$_2$CH$_3$), 2.18 (qd, *J* = 7.2 Hz, 1.5 Hz, 2H, C*H*$_2$CH=CH), 1.46 (p, *J* = 7.3 Hz, 2H, C*H*$_2$), 1.31 – 1.09 (m, 7H, C*H*$_2$, CH$_2$C*H*$_3$), 0.89 (t, 3H, SCH$_2$C*H*$_3$).

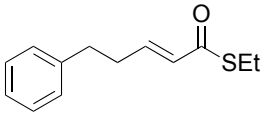
^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 190.2, 145.5, 128.7, 32.1, 31.3, 27.7, 23.0, 22.4, 14.9, 14.0.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3657, 2980, 1673, 1633, 1457, 1391, 1263, 1117, 941, 773.

HRMS (ESI) m/z calc. for $C_{10}H_{19}O^{32}S$ $[M+H]^+$: 187.1151, found: 187.1153.

This data was concordant with literature values.[14]

(*E*)-*S*-ethyl-5-phenylpent-2-enethioate **(45a)**



Prepared according to general procedure **Fb,** using 1.6 M *n*-BuLi in hexane (9.4 mL, 15 mmol, 1.5 eq.), $(EtO)_2POCH_2COSEt$ **42** (4.8 g, 20 mmol, 2.0 eq.), and 3-phenylpropanal (1.34 g, 10 mmol, 1.0 eq.). Purified by flash column chromatography (pentane: Et_2O; 98:2; SiO_2) to afford the desired product **45a** (1.83 g, 8.3 mmol, 83%) in > 27:1 *E*:*Z* ratio as a yellow oil.

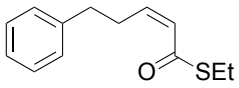
^1H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.40 – 7.27 (m, 2H, Ar-*H*), 7.27 – 7.15 (m, 3H, Ar-*H*), 6.95 (dt, *J* = 15.5 Hz, 6.8 Hz, 1H, C*H*COSEt), 6.32 – 5.95 (m, 1H, C*H*=CH), 2.97 (q, *J* = 7.4 Hz, 2H, SC$H_2$$CH_3$), 2.80 (dd, *J* = 8.8 Hz, 6.7 Hz, 2H, CH_2Ph), 2.54 (dtd, *J* = 8.7 Hz, 6.9 Hz, 1.5 Hz, 2H, CH_2CH=CH), 1.30 (t, *J* = 7.4 Hz, 3H, SCH_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 190.1, 144.0, 140.7, 129.2, 128.5, 128.4, 126.2, 34.4, 33.9, 23.1, 14.8.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3697, 2929, 1670, 1632, 1453, 1029, 937, 748, 699.

HRMS (ESI) m/z calc. for $C_{13}H_{17}O^{32}S$ $[M+H]^+$: 221.0995 found 221.0994.

(*Z*)-*S*-ethyl-5-phenylpent-2-enethioate **(45b)**



Prepared according to general procedure **Fb,** using 1.6 M *n*-BuLi in hexane (9.4 mL, 15 mmol, 1.5 eq.), $(EtO)_2POCH_2COSEt$ **42** (4.8 g, 20 mmol, 2.0 eq.), and 3-phenylpropanal (1.34 g, 10 mmol, 1.0 eq.). Purified by flash column chromatography (pentane: Et_2O; 98:2; SiO_2) to afford the desired product **45b** (76 mg, 0.3 mmol, 3%) in > 27:1 *E*:*Z* ratio as a yellow oil.

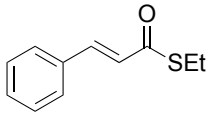
^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.34 – 7.25 (m, 2H, Ar-*H*), 7.25 – 7.17 (m, 3H, Ar-*H*), 6.24 – 5.86 (m, 2H, C*H*=C*H*), 3.07 – 2.87 (m, 4H, CH_2CH_2Ph), 2.78 (t, *J* = 7.7 Hz, 2H, SCH_2CH$_3$), 1.29 (t, *J* = 7.4 Hz, 3H, SCH$_2$CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 189.8, 145.4, 141.0, 128.5, 128.4, 126.8, 126.0, 35.1, 31.3, 23.3, 14.8.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3657, 2980, 1670, 1619, 1473, 1152, 1073, 953, 699.

HRMS (ESI) m/z calc. for $C_{13}H_{17}O^{32}S$ $[M+H]^+$: 221.0995 found 221.0994.

(*E*)-*S*-ethyl-3-phenylprop-2-enethioate **(46)**



Prepared according to general procedure **Fa**, using Me_3SiSEt (3.60 mL, 22 mmol, 2.0 eq.), $AlCl_3$ (1.80 g, 13.2 mmol, 1.2 eq.), and methyl cinnamate (1.78 g, 11 mmol, 1.0 eq.). Purified by flash column chromatography (pentane: Et_2O; 98:2; SiO_2) to afford the desired product **46** (2.03 g, 10.6 mmol, 96%) in in > 20:1 *E*:*Z* ratio as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.57 (d, *J* = 15.8 Hz, 1H, C*H*COSEt), 7.53 – 7.47 (m, 2H, Ar-*H*), 7.39 – 7.30 (m, 3H, Ar-*H*), 6.68 (d, *J* = 15.8 Hz, 1H, C*H*=CH), 2.98 (q, *J* = 7.4 Hz, 2H, CH_2CH$_3$), 1.29 (t, *J* = 7.4 Hz, 3H, CH$_2$CH_3).

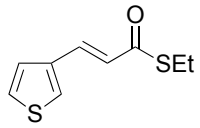
^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 190.0, 140.2, 134.2, 130.5, 129.0, 128.4, 125.1, 23.4, 14.9.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3028, 1655, 1615, 1449, 1138, 999, 753.

HRMS (ESI) m/z calc. for $C_{11}H_{13}O^{32}S$ $[M+H]^+$: 193.0682, found: 193.0684.

This data was concordant with literature values.[15]

(*E*)-*S*-ethyl-3-(thiophen-3-yl) prop-2-enethioate **(47)**



Synthesized according to general procedure **Fa**, using Me_3SiSEt (3.60 mL, 22 mmol, 2.0 eq.), $AlCl_3$ (1.80 g, 13.2 mmol, 1.2 eq.), ethyl (*E*)-3-(thiophen-3-yl) acrylate (2.0 g, 11 mmol, 1.0 eq.) Purified by flash column chromatography (pentane: Et_2O; 98:2; SiO_2) to afford the desired product **47** (1.85 g, 9.3 mmol, 85%) in > 20:1 *E*:*Z* ratio as a yellow oil.

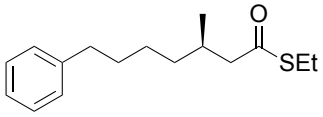
^1H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.47 (d, *J* = 15.7 Hz, 1H, C*H*COSEt), 7.43-7.40 (m, 1H, Ar-*H*), 7.26 – 7.12 (m, 2H, Ar-*H*), 6.42 (d, *J* = 15.7 Hz, 1H, C*H*=CH), 2.89 (q, *J* = 7.4 Hz, 2H, CH_2CH$_3$), 1.19 (t, *J* = 7.4 Hz, 3H, CH$_2$CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 190.1, 137.3, 133.7, 129.0, 127.1, 125.1, 124.9, 23.4, 14.9.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3097, 1656, 1604, 1245, 1131, 1024, 776.

HRMS (ESI) m/z calc. for $C_9H_{11}O^{32}S_2$ $[M+H]^+$: 199.0246, found: 199.0247.

(*R*)-*S*-ethyl-3-methyl-7-phenylheptanethioate **(48)**



Synthesized according to general procedure **Ib2**, using CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), phosphoramidite ***ent*-L27** (22.3 mg, 0.04 mmol 0.2 eq.), 1.6 mL DCM/Et_2O (1/1), AgOTf (11.2 mg, 0.44 mmol, 0.22 eq.), but-3-en-1-ylbenzene (66 mg, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-*S*-ethyl-but-2-enethioate **(43)** (26.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product **48** (45 mg, 0.17 mmol, 85%).

HPLC analysis indicated an enantiomeric excess of 98% [Chiralpak® IC; flow: 0.8 mL/min; hexane/*i*-PrOH: 99.7:0.3; λ = 210 nm; major enantiomer tR = 9.48 min; minor enantiomer, tR = 9.27 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.34 – 7.23 (m, 2H, Ar-*H*), 7.22 – 6.99 (m, 3H, Ar-*H*), 2.87 (q, *J* = 7.4 Hz, 2H, S*CH*$_2$CH$_3$), 2.60 (t, *J* = 7.8 Hz, 2H, *CH*$_2$Ph), 2.51 (dd, *J* = 14.4 Hz, 6.1 Hz, 1H, *CH*$_2$COSEt), 2.34 (dd, *J* = 14.4 Hz, 8.0 Hz, 1H, *CH*$_2$COSEt)), 2.12 – 1.89 (m, 1H, C*H*), 1.69 – 1.53 (m, 3H, *CH*$_2$), 1.41 – 1.28 (m, 2H, *CH*$_2$), 1.24 (t, *J* = 7.4 Hz, 4H, *CH*$_2$, SCH$_2$*CH*$_3$), 0.92 (d, *J* = 6.6 Hz, 3H CHC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.3, 142.7, 128.4, 128.3, 125.6, 51.4, 36.4, 35.9, 31.5, 31.0, 26.5, 23.3, 19.5, 14.8.

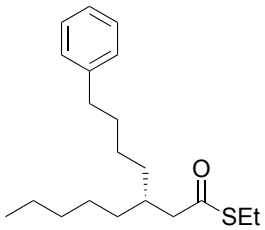
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2980, 1688, 1384, 1252, 1151, 1072, 966.

HRMS (ESI) m/z calc. for $C_{16}H_{24}O^{23}Na^{32}S$ $[M+Na]^+$: 287.1440, found: 287.1440.

$[\alpha]^{20}_{589}$ = +2.3 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **51**.

(*R*)-*S*-ethyl-3-(4-phenylbutyl) octanethioate **(49)**



Synthesized according to general procedure **Ib2**, using CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), phosphoramidite ***ent*-L27** (22.3 mg, 0.04 mmol 0.2 eq.), 1.6 mL DCM/Et_2O (1/1), AgOTf (11.2 mg, 0.44 mmol, 0.22 eq.), but-3-en-1-ylbenzene (66 mg, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-*S*-ethyl-oct-2-enethioate **44** (37.2 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product **49** (47 mg, 0.15 mmol, 73%).

HPLC analysis indicated an enantiomeric excess of 97% [Chiralpak® IB; flow: 1.0 mL/min; 100% hexane; λ = 210 nm; major enantiomer tR = 13.22 min; minor enantiomer, tR = 12.17 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.33 – 7.22 (m, 2H, Ar-*H*), 7.17 (ddt, *J* = 7.0 Hz, 3.8 Hz, 2.2 Hz, 3H, Ar-*H*), 2.86 (q, *J* = 7.4 Hz, 2H, SC*H*$_2$CH$_3$), 2.59 (dd, *J* = 8.7 Hz, 6.8 Hz, 2H, C*H*$_2$Ph), 2.46 (dd, *J* = 6.9 Hz, 0.9 Hz, 2H, C*H*$_2$COSEt), 2.04 – 1.83 (m, 1H, C*H*), 1.65-1.48 (m, 2H, C*H*$_2$), 1.39 – 1.19 (m, 15H, C*H*$_2$, SCH$_2$C*H*$_3$), 0.88 (td, *J* = 7.0 Hz, 2.5 Hz, 3H, CH$_2$C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.6, 142.7, 128.4, 128.3, 125.6, 48.9, 35.9, 35.7, 33.6, 33.5, 32.1, 31.7, 26.2, 23.3, 22.6, 22.4, 14.8, 14.1.

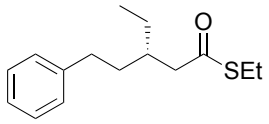
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3657, 2980, 1689, 1382, 1152, 955, 774.

HRMS (ESI) m/z calc. for $C_{20}H_{33}O^{32}S$ $[M+H]^+$: 321.2247 found 321.2247.

$[\alpha]^{20}_{589}$ = +3.6 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **51**.

(*S*)-*S*-ethyl-3-ethyl-5-phenylpentanethioate **(50)**



Synthesized according to general procedure **Ib1**, using CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), phosphoramidite ***ent*-L27** (22.3 mg, 0.04 mmol 0.2 eq.), 1.6 mL DCM/Et_2O (1/1), AgOTf (11.2 mg, 0.44 mmol, 0.22 eq.), a balloon filled with ethylene, Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-*S*-ethyl-5-phenylpent-2-enethioate **(45a)** (37.2 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product **50** (40 mg, 0.16 mmol, 80%).

HPLC analysis indicated an enantiomeric excess of 97% [Chiralpak® IB; flow: 1.0 mL/min; hexane:*i*-PrOH 99.6:0.4; λ = 210 nm; major enantiomer tR = 6.17 min; minor enantiomer, tR = 7.03 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.32 – 7.24 (m, 2H, Ar-*H*), 7.21 – 7.12 (m, 3H, Ar-*H*), 2.88 (q, *J* = 7.4 Hz, 2H, S*CH*$_2$CH$_3$), 2.60 (dd, *J* = 9.5 Hz, 7.1Hz, 2H, C*H*$_2$Ph), 2.54 (d, *J* = 6.9 Hz, 2H, C*H*$_2$COSEt), 1.96 (hept, *J* = 6.5 Hz, 1H, C*H*), 1.71 – 1.57 (m, 2H, C*H*$_2$CH$_2$Ph), 1.42 (dtd, *J* = 13.6Hz, 7.5 Hz, 6.2 Hz, 2H, C*H*$_2$CH$_3$), 1.25 (t, *J* = 7.4 Hz, 3H, SCH$_2$C*H*$_3$), 0.90 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.4, 142.5, 128.4, 128.3, 125.7, 48.2, 36.9, 35.1, 33.0, 26.1, 23.4, 14.8, 10.7.

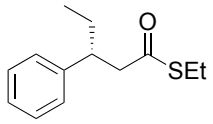
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3660, 2980, 1688, 1382, 1251, 1152, 954.

HRMS (ESI) m/z calc. for $C_{15}H_{23}O^{32}S$ $[M+H]^+$: 251.1464 found 251.1465.

$[\alpha]^{20}_{589}$ = +5.7 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **51**.

(*R*)-*S*-ethyl-3-phenylpentanethioate **(51)**[14]



Synthesized according to general procedure **Ib1**, using CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), phosphoramidite ***ent*-L27** (22.3 mg, 0.04 mmol 0.2 eq.), 1.6 mL DCM/Et_2O (1/1), AgOTf (11.2 mg, 0.44 mmol, 0.22 eq.), a balloon filled with ethylene, Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), a balloon filled with ethylene, *S*-ethyl (*E*)-3-phenylprop-2-enethioate **46** (38.4 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product **51** (28 mg, 0.13 mmol, 63%).

HPLC analysis indicated an enantiomeric excess of 71% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99.5:0.5; λ = 210 nm; major enantiomer tR = 5.70 min; minor enantiomer, tR = 8.24 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.34 – 7.25 (m, 2H, Ar-*H*), 7.24 – 7.12 (m, 3H, Ar-*H*), 3.07 (dtd, *J* = 9.4 Hz, 7.4 Hz, 5.2 Hz, 1H, C*H*), 2.93 – 2.72 (m, 4H, SCH_2CH$_3$, CH_2COSEt), 1.90 – 1.46 (m, 2H, CH_2CH$_3$), 1.17 (t, *J* = 7.4 Hz, 3H, SCH_2CH_3), 0.78 (t, *J* = 7.3 Hz, 3H, CH_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 198.5, 143.5, 128.4, 127.6, 126.4, 50.8, 44.4, 28.8, 23.3, 14.7, 11.9.

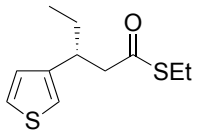
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3650, 2980, 1687, 1380, 1153, 966, 700.

HRMS (ESI) m/z calc. for $C_{13}H_{19}O^{32}S$ $[M+H]^+$: 223.1151 found 223.1153.

$[\alpha]^{20}_{589}$ = –25.1 (c 1.0, $CHCl_3$)

Absolute configuration was assigned by comparison to literature optical rotation values.[14]

(*R*)-*S*-ethyl-3-(thiophen-3-yl) pentanethioate **(52)**



Synthesized according to general procedure **Ib1**, using CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), phosphoramidite ***ent*-L27** (22.3 mg, 0.04 mmol 0.2 eq.), 1.6 mL DCM/Et_2O (1/1), AgOTf (11.2 mg, 0.44 mmol, 0.22 eq.), a balloon filled with ethylene, Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-*S*-ethyl-3-(thiophen-3-yl) prop-2-enethioate **47** (40.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1 mmol, 5.0 eq.) Purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (27 mg, 0.12 mmol, 60%).

HPLC analysis indicated an enantiomeric excess of 66% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99.5:0.5; λ = 210 nm; major enantiomer tR = 5.17 min; minor enantiomer, tR = 5.94 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.37 – 7.08 (m, 1H, Ar-*H*), 7.06 – 6.77 (m, 2H, Ar-*H*), 3.23 (dtd, *J* = 8.8 Hz, 7.4 Hz, 5.2 Hz, 1H, C*H*), 2.92 – 2.66 (m, 4H, SC*H*$_2$CH$_3$, C*H*$_2$COSEt), 1.91 – 1.38 (m, 2H, C*H*$_2$CH$_3$), 1.18 (t, *J* = 7.4 Hz, 3H, SCH$_2$C*H*$_3$), 0.81 (t, *J* = 7.3 Hz, 3H, CH$_2$C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 198.5, 144.3, 126.6, 125.5, 120.5, 50.5, 39.6, 28.70, 23.3, 14.7, 11.8.

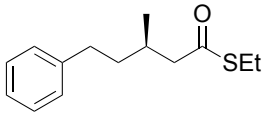
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3650, 2980, 1686, 1381, 1153, 955, 774.

HRMS (ESI) m/z calc. for $C_{11}H_{17}O^{32}S_2$ $[M+H]^+$: 229.0715 found 229.0716.

$[\alpha]^{20}_{589}$ = –29.2 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **51**.

(*R*)-*S*-ethyl-3-methyl-5-phenylpentanethioate **(53)**



Synthesized according to general procedure **Ib2**, using CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), phosphoramidite ***ent*-L27** (22.3 mg, 0.04 mmol 0.2 eq.), 1.6 mL DCM/Et_2O (1/1), AgOTf (11.2 mg, 0.44 mmol, 0.22 eq.), styrene (52 mg, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-*S*-ethyl-but-2-enethioate **(43)** (26.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product **53** (33 mg, 0.14 mmol, 70%).

HPLC analysis indicated an enantiomeric excess of 97% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99.8:0.2; λ = 210 nm; major enantiomer tR = 9.37 min; minor enantiomer, tR = 8.03 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.32 – 7.24 (m, 2H, Ar-*H*), 7.22-7.12 (m, 3H, Ar-*H*), 2.88 (q, *J* = 7.4 Hz, 2H, S*CH*$_2$CH$_3$), 2.70 – 2.59 (m, 2H, C*H*$_2$Ph), 2.56 (t, *J* = 6.5 Hz, 1H, C*H*$_2$COSEt), 2.41 (dd, *J* = 14.5 Hz, 8.0 Hz, 1H, C*H*$_2$COSEt), 2.20 – 1.96 (m, 1H, C*H*), 1.67 (ddt, *J* = 13.5 Hz, 10.5 Hz, 5.9 Hz, 1H, C*H*$_2$), 1.55 – 1.39 (m, 1H, C*H*$_2$), 1.25 (t, *J* = 7.4 Hz, 3H, SCH$_2$C*H*$_3$), 1.01 (d, *J* = 6.7 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.1, 142.3, 128.4, 128.3, 125.8, 51.2, 38.5, 33.3, 30.9, 23.3, 19.5, 14.8.

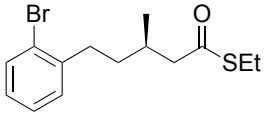
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3657, 2980, 1687, 1382, 1152, 954.

HRMS (ESI) m/z calc. for $C_{14}H_{21}O^{32}S$ $[M+H]^+$: 237.1308, found: 237.1309.

$[\alpha]^{20}_{589}$ = +9.1 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **51**.

(*R*)-*S*-ethyl-5-(2-bromophenyl)-3-methylpentanethioate **(54)**



Synthesized according to general procedure **Ib2**, using CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), phosphoramidite ***ent*-L27** (22.3 mg, 0.04 mmol 0.2 eq.), 1.6 mL DCM/Et_2O (1/1), AgOTf (11.2 mg, 0.44 mmol, 0.22 eq.), 1-bromo-2-vinylbenzene (91 mg, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-*S*-ethyl-but-2-enethioate **(43)** (26.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product **54** (44 mg, 0.14 mmol, 70%).

HPLC analysis indicated an enantiomeric excess of 99% [Chiralpak® AYH; flow: 1.0 mL/min; hexane/*i*-PrOH: 99.7:0.3; λ = 210 nm; major enantiomer tR = 10.10 min; minor enantiomer, tR = 8.92 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.63 – 7.44 (m, 1H, Ar-*H*), 7.24 – 7.16 (m, 2H, Ar-*H*), 7.04 (ddd, *J* = 7.9 Hz, 6.1 Hz, 2.9 Hz, 1H, Ar-*H*), 2.88 (q, *J* = 7.4 Hz, 2H, SCH_2CH$_3$), 2.81 – 2.65 (m, 2H, CH_2Ph), 2.62 (dd, *J* = 14.6 Hz, 6.0 Hz, 1H, CH_2COSEt), 2.43 (dd, *J* = 14.5 Hz, 8.1 Hz, 1H, CH_2COSEt), 2.13 (ddt, *J* = 14.1 Hz, 8.0 H, 6.4 Hz, 1H, C*H*), 1.64 (ddt, *J* = 13.4 Hz, 11.1 Hz, 5.6 Hz, 1H, CH_2), 1.49 (dddd, *J* = 13.2 Hz, 10.9 Hz, 7.6 Hz, 5.5 Hz, 1H, CH_2), 1.24 (t, *J* = 7.4 Hz, 3H, SCH$_2$CH_3), 1.04 (d, *J* = 6.7 Hz, 3H, CHCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.1, 141.6, 132.8, 130.2, 127.6, 127.5, 124.3, 51.1, 36.8, 33.7, 31.1, 23.4, 19.5, 14.8.

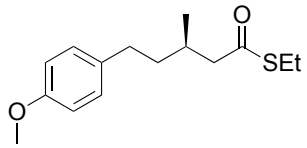
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3659, 2980, 1687, 1382, 1152, 954.

HRMS (ESI) m/z calc. for $C_{14}H_{20}O^{79}Br^{32}S$ $[M+H]^+$: 315.0413, 317.0392, found: 315.0415, 317.0393.

$[\alpha]^{20}_{589}$ = +9.4 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **51**.

(*R*)-*S*-ethyl-5-(4-methoxyphenyl)-3-methylpentanethioate **(55)**



Synthesized according to general procedure **Ib2**, using CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), phosphoramidite ***ent*-L27** (22.3 mg, 0.04 mmol 0.2 eq.), 1.6 mL DCM/Et_2O (1/1), AgOTf (11.2 mg, 0.44 mmol, 0.22 eq.), 1-methoxy-4-vinylbenzene (67 mg, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-*S*-ethyl-but-2-enethioate **(43)** (26.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product **55** (34 mg, 0.13 mmol, 64%).

HPLC analysis indicated an enantiomeric excess of 97% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99.3:0.7; λ = 210 nm; major enantiomer tR = 6.67 min; minor enantiomer, tR = 6.08 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.18 – 7.00 (m, 2H, Ar-*H*), 6.97 – 6.73 (m, 2H, Ar-*H*), 3.79 (s, 3H, OC*H*$_3$), 2.87 (q, *J* = 7.4 Hz, 2H, SC*H*$_2$CH$_3$), 2.68 – 2.46 (m, 3H, C*H*$_2$Ph, C*H*$_2$COSEt), 2.40 (dd, *J* = 14.4 Hz, 8.0 Hz, 1H, C*H*$_2$COSEt), 2.18 – 1.96 (m, 1H, C*H*), 1.80 – 1.57 (m, 1H, C*H*$_2$CH$_2$Ph), 1.47 (dddd, *J* = 13.5 Hz, 10.3Hz, 7.7 Hz, 5.8 Hz, 1H, C*H*$_2$CH$_2$Ph), 1.25 (t, *J* = 7.4 Hz, 3H, SCH$_2$C*H*$_3$), 1.00 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.1, 157.7, 134.4, 129.2, 113.8, 55.3, 51.2, 38.7, 32.3, 30.8, 23.3, 19.5, 14.8.

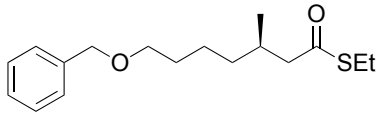
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3657, 2889, 1686, 1382, 1248, 1152, 954.

HRMS (ESI) m/z calc. for $C_{15}H_{22}O_2{}^{23}Na^{32}S$ $[M+Na]^+$: 289.1233 found: 289.1233.

$[\alpha]^{20}_{589}$ = +14.5 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **51**.

(*R*)-*S*-ethyl-7-(benzyloxy)-3-methylheptanethioate **(56)**



Synthesized according to general procedure **Ib2**, using CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), phosphoramidite ***ent*-L27** (22.3 mg, 0.04 mmol 0.2 eq.), 1.6 mL DCM/Et_2O (1/1), AgOTf (11.2 mg, 0.44 mmol, 0.22 eq.), ((but-3-en-1-yloxy) methyl) benzene (81 mg, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-*S*-ethyl-but-2-enethioate **(43)** (26.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product **56** (44 mg, 0.15 mmol, 75%).

HPLC analysis indicated an enantiomeric excess of 98% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99.0:1.0; λ = 210 nm; major enantiomer tR = 6.09 min; minor enantiomer, tR = 5.53 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.38 – 7.29 (m, 4H, Ar-*H*), 7.29 – 7.23 (m, 1H, Ar-*H*), 4.48 (s, 2H, OCH_2Ph), 3.44 (t, *J* = 6.5 Hz, 2H, CH_2OCH_2Ph), 2.85 (q, *J* = 7.4 Hz, 2H, SCH_2CH_3), 2.50 (dd, *J* = 14.4 Hz, 6.0 Hz, 1H, CH_2COSEt), 2.32 (dd, *J* = 14.4 Hz, 8.1 Hz, 1H, CH_2COSEt), 2.11 – 1.93 (m, 1H, C*H*), 1.72-1.53 (m, 3H, CH_2), 1.35 (ddtd, *J* = 19.1 Hz, 12.8 Hz, 10.4 Hz, 4.9 Hz, 3H, CH_2), 1.22 (t, *J* = 7.4 Hz, 3H, SCH_2CH_3), 0.91 (d, *J* = 6.6 Hz, 3H, CHCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.3, 138.6, 128.4, 127.6, 127.5, 72.9, 70.2, 51.4, 36.4, 31.1, 29.8, 23.5, 23.3, 19.5, 14.8.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3657, 2980, 1687, 1382, 1251, 1152, 954, 772.

HRMS (ESI) m/z calc. for $C_{17}H_{27}O_2{}^{32}S$ $[M+H]^+$: 295.1726, found: 295.1727.

$[\alpha]^{20}_{589}$ = +14.6 **(**c 1.0, $CHCl_3$)

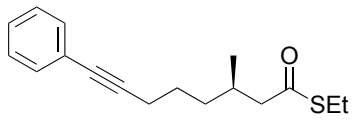
Absolute configuration assigned by analogy to compound **51**.

Large-scale reactions

Synthesized according to general procedure **Ib2**, using CuCl (50.0 mg, 0.5 mmol, 0.1 eq.), and phosphoramidite ***ent*-L27** (280 mg, 0.5 mmol 0.1 eq.), 20 mL DCM/Et_2O (1/1), AgOTf (140 mg, 0.55 mmol, 0.11 eq.), ((but-3-en-1-yloxy) methyl) benzene (2.02 g, 12.5 mmol, 2.5 eq.), Cp_2ZrHCl (2.58 g, 10 mmol, 2.0 eq.), (*E*)-*S*-ethyl-but-2-enethioate **(43)** (0.75 mL, 5.0 mmol, 1.0 eq.) and TMSCl (3.2 mL, 25 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (1.04 g, 3.5 mmol, 70%).

HPLC analysis indicated an enantiomeric excess of 96% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99.0:1.0; λ = 210 nm; major enantiomer tR = 6.11 min; minor enantiomer, tR = 5.54 min].

(*R*)-*S*-ethyl-3-methyl-8-phenyloct-7-ynethioate **(57)**



Synthesized according to general procedure **Ib2**, using CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), phosphoramidite ***ent*-L27** (22.3 mg, 0.04 mmol 0.2 eq.), 1.6 mL DCM/Et_2O (1/1), AgOTf (11.2 mg, 0.44 mmol, 0.22 eq.), pent-4-en-1-yn-1-ylbenzene (71 mg, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-*S*-ethyl-but-2-enethioate **(43)** (26.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (40 mg, 0.15 mmol, 73%).

HPLC analysis indicated an enantiomeric excess of 93% [Chiralpak® ID; flow: 1.2 mL/min; hexane/*i*-PrOH: 99.8:0.2; λ = 210 nm; major enantiomer tR = 10.12 min; minor enantiomer, tR = 12.12 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.55 – 7.47 (m, 2H, Ar-*H*), 7.44 – 7.36 (m, 3H, Ar-*H*), 2.99 (q, *J* = 7.5 Hz, 2H, SC*H*$_2$CH$_3$), 2.84 – 2.61 (m, 1H, C*H*$_2$COSEt), 2.61 – 2.44 (m, 3H, C*H*$_2$COSEt, C*H*$_2$CCPh), 2.31 – 2.09 (m, 1H, C*H*), 1.88 – 1.42 (m, 4H), 1.36 (t, 3H, SCH$_2$C*H*$_3$), 1.09 (d, *J* = 6.7 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.2, 131.5, 128.2, 127.5, 124.0, 100.0, 90.0, 80.8, 51.3, 35.8, 30.8, 26.2, 23.3, 19.5, 19.5, 14.8.

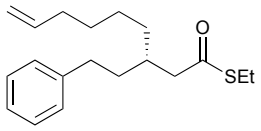
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3690, 2930, 1687, 1633, 1490, 1391, 1218, 1017, 941, 771.

HRMS (ESI) m/z calc. for $C_{17}H_{23}O^{32}S$ $[M+H]^+$: 275.1464, found: 275.1465.

$[\alpha]^{20}_{589}$ = +8.8 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **51**.

(*S*)-*S*-ethyl-3-phenethylnon-8-enethioate **(58)**



Synthesized according to general procedure **Ib2**, using CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and phosphoramidite ***ent*-L27** (22.3 mg, 0.04 mmol 0.2 eq.), 1.6 mL DCM/Et_2O (1/1), AgOTf (11.2 mg, 0.44 mmol, 0.22 eq.), hexa-1, 5-diene (41 mg, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-*S*-ethyl-5-phenylpent-2-enethioate **45a** (44.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product **58** (39 mg, 0.13 mmol, 64%).

HPLC analysis indicated an enantiomeric excess of 92% [Chiralpak® IB; flow: 1.0 mL/min; hexane:*i*-PrOH 99.5:0.5; λ = 210 nm; major enantiomer tR = 6.17 min; minor enantiomer, tR = 6.93 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.34 – 7.23 (m, 2H, Ar-*H*), 7.19 (tq, *J* = 4.4 Hz, 1.5 Hz, 3H, Ar-*H*), 5.81 (ddt, *J* = 16.9 Hz, 10.2 Hz, 6.7 Hz, 1H, C*H*=CH_2), 5.09 – 4.82 (m, 2H, CH=CH_2), 2.89 (q, *J* = 7.4 Hz, 2H, SC$H_2$$CH_3$), 2.65 – 2.58 (m, 2H, C$H_2$Ph), 2.57 – 2.53 (m, 2H, CH_2COSEt), 2.22 – 1.94 (m, 3H, CH_2CH=CH_2, C*H*), 1.72 – 1.58 (m, 2H, CH_2), 1.48 – 1.27 (m, 6H, CH_2), 1.26 (t, *J* = 7.4 Hz, 3H, SCH_2C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.3, 142.4, 138.9, 128.4, 128.3, 125.8, 114.4, 48.6, 35.6, 35.5, 33.5, 33.4, 33.0, 29.0, 25.9, 23.4, 14.8.

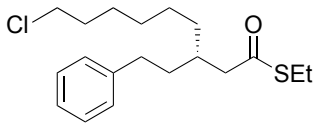
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3657, 2980, 1687, 1382, 1152, 1072, 955.

HRMS (ESI) m/z calc. for $C_{19}H_{28}O^{23}Na^{32}S$ $[M+Na]^+$: 327.1753 found 327.1752.

$[\alpha]^{20}_{589}$ = –2.9 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **51**.

(*S*)-*S*-ethyl-9-chloro-3-phenethylnonanethioate **(59)**



Synthesized according to general procedure **Ib2**, using CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and phosphoramidite ***ent*-L27** (22.3 mg, 0.04 mmol 0.2 eq.), 1.6 mL DCM/Et_2O (1/1), AgOTf (11.2 mg, 0.44 mmol, 0.22 eq.), 6-chlorohex-1-ene (59 mg, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-*S*-ethyl-5-phenylpent-2-enethioate **45a** (44.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product **59** (42 mg, 0.12 mmol, 62%).

HPLC analysis indicated an enantiomeric excess of 97% [Chiralpak® IB; flow: 1.0 mL/min; hexane:*i*-PrOH, 99.5:0.5; λ = 210 nm; major enantiomer tR = 8.56 min; minor enantiomer, tR = 9.73 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.32 – 7.23 (m, 2H, Ar-*H*), 7.22 – 7.12 (m, 3H, Ar-*H*), 3.53 (t, *J* = 6.7 Hz, 2H, C*H*$_2$Cl), 2.89 (q, *J* = 7.4 Hz, 2H, SC*H*$_2$CH$_3$), 2.61 (t, *J* = 8.2 Hz, 2H, C*H*$_2$Ph), 2.55 (dd, *J* = 6.8 Hz, 2.4 Hz, 2H, C*H*$_2$COSEt), 2.01 (p, *J* = 6.3 Hz, 1H, C*H*), 1.76 (dq, *J* = 7.9 Hz, 6.8 Hz, 2H, C*H*$_2$), 1.69 – 1.57 (m, 2H, C*H*$_2$), 1.48 – 1.28 (m, 8H, C*H*$_2$), 1.26 (t, *J* = 7.4 Hz, 3H, SCH$_2$C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.3, 142.4, 128.4, 128.3, 125.8, 48.6, 45.1, 35.6, 35.5, 33.5, 33.0, 32.6, 29.0, 26.8, 26.3, 23.4, 14.8.

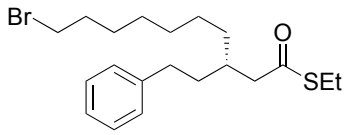
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2980, 1686, 1382, 1252, 1152, 1073, 954.

HRMS (ESI) m/z calc. for $C_{19}H_{29}O^{35}Cl^{23}Na^{32}S$ $[M+Na]^+$: 363.1520 found 363.1520.

$[\alpha]^{20}_{589}$ = –3.9 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **51**.

(*S*)-*S*-ethyl-10-bromo-3-phenethyldecanethioate **(60)**



Synthesized according to general procedure **Ib2**, using CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and phosphoramidite ***ent*-L27** (22.3 mg, 0.04 mmol 0.2 eq.), 1.6 mL DCM/Et_2O (1/1), AgOTf (11.2 mg, 0.44 mmol, 0.22 eq.), 7-bromohept-1-ene (88 mg, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-*S*-ethyl-5-phenylpent-2-enethioate **45a** (44.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product **60** (59 mg, 0.15 mmol, 74%).

HPLC analysis indicated an enantiomeric excess of 97% [Chiralpak® IB; flow: 1.0 mL/min; hexane:*i*-PrOH, 99.5:0.5; λ = 210 nm; major enantiomer tR = 8.45 min; minor enantiomer, tR = 9.38 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.35 – 7.23 (m, 2H, Ar-*H*), 7.18 (tq, *J* = 4.5 Hz, 1.6 Hz, 3H, Ar-*H*), 3.41 (t, *J* = 6.9 Hz, 2H, C*H*$_2$Br), 2.89 (q, *J* = 7.4 Hz, 2H, SC*H*$_2$CH$_3$), 2.65 – 2.57 (m, 2H, C*H*$_2$Ph), 2.55 (dd, *J* = 6.8 Hz, 1.3, 2H, C*H*$_2$COSEt), 2.07-1.94 (m, 1H, C*H*), 1.85 (dq, *J* = 8.7 Hz, 6.9 Hz, 2H, C*H*$_2$), 1.71 – 1.57 (m, 2H, C*H*$_2$), 1.48 – 1.28 (m, 8H, C*H*$_2$), 1.25 (t, *J* = 7.4 Hz, 5H, C*H*$_2$, SCH$_2$C*H*$_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.3, 142.4, 128.4, 128.3, 125.8, 48.6, 35.6, 35.5, 34.0, 33.5, 33.0, 32.8, 29.6, 28.7, 28.1, 26.3, 23.4, 14.8.

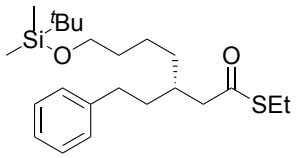
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3660, 2981, 1688, 1381, 1252, 1152, 1072, 953.

HRMS (ESI) m/z calc. for $C_{20}H_{31}O^{79}Br^{23}Na^{32}S$ $[M+Na]^+$: 421.1171, 423.1151 found 421.1170, 423.1148.

$[\alpha]^{20}_{589}$ = –15.0 **(**c 1.3, $CHCl_3$)

Absolute configuration assigned by analogy to compound **51**.

(*S*)-*S*-ethyl-7-((*tert*-butyldimethylsilyl) oxy)-3-phenethylheptanethioate **(61)**



Synthesized according to general procedure **Ib2**, using CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and phosphoramidite ***ent*-L27** (22.3 mg, 0.04 mmol 0.2 eq.), 1.6 mL DCM/Et_2O (1/1), AgOTf (11.2 mg, 0.44 mmol, 0.22 eq.), (but-3-en-1-yloxy) (tert-butyl) dimethylsilane (93 mg, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-*S*-ethyl-5-phenylpent-2-enethioate **45a** (44.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product **61** (60 mg, 0.15 mmol, 74%).

HPLC analysis indicated an enantiomeric excess of 96% [Chiralpak® IB; flow: 1.0 mL/min; hexane:*i*-PrOH, 99.5:0.5; λ = 210 nm; major enantiomer tR = 5.13 min; minor enantiomer, tR = 5.54 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.32 – 7.22 (m, 2H), 7.17 (ddd, *J* = 7.9 Hz, 3.5 Hz, 1.2 Hz, 3H, Ar-*H*), 3.59 (t, *J* = 6.4 Hz, 2H, O*C*H_2), 2.87 (q, *J* = 7.5 Hz, 2H, S*C*H_2CH$_3$), 2.63 – 2.56 (m, 2H, PhCH_2), 2.54 (d, *J* = 6.8 Hz, 2H,CH_2CO), 2.11 – 1.90 (m, 1H,C*H*), 1.62 (tdd, *J* = 7.6 Hz, 6.3 Hz, 3.1 Hz, 2H, CH_2), 1.54 – 1.43 (m, 2H, CH_2), 1.42 – 1.28 (m, 4H, CH_2), 1.24 (t, *J* = 7.4 Hz, 3H), 0.89 (s, 9H,C (CH_3)$_3$), 0.04 (s, 6H, SiCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.3, 142.4, 128.3 (4C), 125.7, 63.1, 48.6, 35.5, 33.4, 33.0, 32.9, 26.0 (3C), 23.4, 22.7, 18.4, 14.8, -5.23.

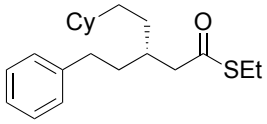
IR (v_{max}/cm^{-1}, $CHCl_3$) 3657, 2980, 1688, 1382, 1152, 1073, 954.

HRMS (ESI) m/z calc. for $C_{23}H_{40}O_2SSi$ $[M+H]^+$: 409.2588, found: 409.2588.

$[\alpha]^{20}_{589}$ = –2.1 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **51**.

(*S*)-*S*-ethyl-5-cyclohexyl-3-phenethylpentanethioate **(62)**



Synthesized according to general procedure **Ib2**, using CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), and phosphoramidite ***ent*-L27** (22.3 mg, 0.04 mmol 0.2 eq.), 1.6 mL DCM/Et_2O (1/1), AgOTf (11.2 mg, 0.44 mmol, 0.22 eq.), vinylcyclohexane (55 mg, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*E*)-*S*-ethyl-5-phenylpent-2-enethioate **45a** (44.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (55 mg, 0.17 mmol, 83%).

HPLC analysis indicated an enantiomeric excess of 97% [Chiralpak® IB; flow: 1.0 mL/min; hexane:*i*-PrOH, 99.5:0.5; λ = 210 nm; major enantiomer tR = 5.35 min; minor enantiomer, tR = 5.91 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.35 – 7.24 (m, 2H, Ar-*H*), 7.22-7.13 (m, 3H, Ar-*H*), 2.89 (q, *J* = 7.4 Hz, 2H, S*C*$H_2$$CH_3$), 2.61 (dd, *J* = 9.5 Hz, 7.1 Hz, 2H, CH_2Ph), 2.55 (d, *J* = 6.8 Hz, 2H, CH_2COSEt), 1.99 (p, *J* = 6.5 Hz, 1H, C*H*CH_2CH_2Cy), 1.84 – 1.58 (m, 8H, C*H,* CH_2), 1.50 – 1.31 (m, 2H, CH_2), 1.26 (t, *J* = 7.4 Hz, 3H, SCH_2CH_3), 1.23 – 1.08 (m, 5H, CH_2), 0.88 (q, *J* = 10.5 Hz, 9.8 Hz, 2H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.3, 142.5, 128.3 (4C), 125.7, 48.7, 37.9, 35.8, 35.6, 34.1, 33.4, 33.4, 33.0, 30.7, 26.7, 26.4, 23.4, 14.8.

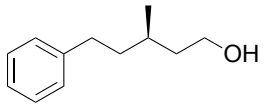
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3660, 2981, 1690, 1382, 1152, 1073, 954.

HRMS (ESI) m/z calc. for $C_{21}H_{33}O^{32}S$, $[M+H]^+$: 333.2247, found: 333.2249.

$[\alpha]^{20}_{589}$ = –2.8 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **51**.

(*R*)-3-methyl-5-phenylpentan-1-ol **(63a)**



(*R*)-*S*-ethyl-3-methyl-5-phenylpentanethioate was obtained from (*E*)-*S*-ethyl-but-2-enethioate and styrene by general procedure.

1 mol/L $LiAlH_4$ in Et_2O (1 mL, 1 mmol, 1.0 eq.) was added to a stirring mixture of (*R*)-*S*-ethyl-3-methyl-5-phenylpentanethioate (0.236 g, 1 mmol, 1.0 eq.) in DCM at 0 °C under argon. The mixture was kept stirring until the reduction was completed (ca.60 min). 5 mL sat. Rochelle salt solution was added to the solution and Et_2O extracted the mixture three times. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 60:40; SiO_2) to give the desired product (0.167 g, 0.94 mmol, 94% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.25 – 7.16 (m, 2H, Ar-*H*), 7.11 (d, *J* = 7.3 Hz, 3H, Ar-*H*), 3.60 (hept, *J* = 7.1 Hz, 6.2 Hz, 2H, C*H*$_2$OH), 2.71 – 2.28 (m, 2H, C*H*$_2$Ph), 1.67 – 1.50 (m, 3H, C*H,* C*H*$_2$), 1.46 – 1.30 (m, 1H, C*H*$_2$), 1.28 – 1.15 (m, 1H, C*H*$_2$), 0.90 (d, *J* = 6.4 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 142.8, 128.3 (4C), 125.7, 61.1, 39.8, 39.0, 33.4, 29.3, 19.6.

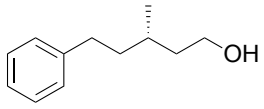
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3336, 2928, 1738, 1455, 1378, 1059, 1073, 698.

HRMS (ESI) m/z calc. for $C_{12}H_{18}O^{23}Na$, $[M+Na]^+$: 201.1250, found: 201.1249.

$[\alpha]^{20}_{589}$ = +10.7 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **53**.

(*S*)-3-methyl-5-phenylpentan-1-ol **(63b)**



(*S*)-S-ethyl-3-methyl-5-phenylpentanethioate was obtained from (*E*)-*S*-ethyl-but-2-enethioate, styrene and **L27** by general procedure.

1 mol/L $LiAlH_4$ in Et_2O (1 mL, 1 mmol, 1.0 eq.) was added to a stirring mixture of (*S*)-*S*-ethyl-3-methyl-5-phenylpentanethioate (0.236 g, 1 mmol, 1.0 eq.) in DCM at 0 °C under argon. The mixture was kept stirring until the reduction was completed (ca.60 min). 5 mL sat. Rochelle salt solution was added to the solution and the mixture was extracted by Et_2O three times. The combined organic materials were dried (Na_2SO_4), filtered, concentrated, and the resulting yellow residual purified by flash column chromatography (Petrol: Et_2O; 60:40; SiO_2) to give the desired product (0.170 g, 0.96 mmol, 96% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.25 – 7.16 (m, 2H, Ar-*H*), 7.11 (d, *J* = 7.3 Hz, 3H, Ar-*H*), 3.60 (hept, *J* = 7.1 Hz, 6.2 Hz, 2H, C*H*$_2$OH), 2.71 – 2.28 (m, 2H, C*H*$_2$Ph), 1.67 – 1.50 (m, 3H, C*H,* C*H*$_2$), 1.46 – 1.30 (m, 1H, C*H*$_2$), 1.28 – 1.15 (m, 1H, C*H*$_2$), 0.90 (d, *J* = 6.4 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 142.8, 128.3(4C), 125.7, 61.1, 39.8, 39.0, 33.4, 29.3, 19.6.

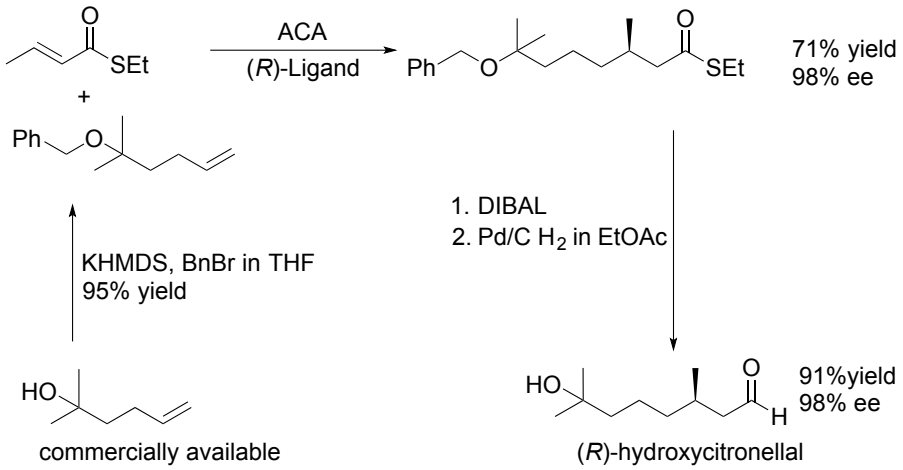
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3336, 2928, 1738, 1455, 1378, 1059, 1073, 698.

HRMS (ESI) m/z calc. for $C_{12}H_{18}O^{23}Na$, $[M+Na]^+$: 201.1250, found: 201.1249.

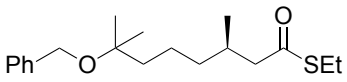
$[\alpha]^{20}_{589}$ = –10.3 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **53**.

Synthesis of (*R*)-hydroxycitronellal



(*R*)-*S*-ethyl-7-(benzyloxy)-3,7-dimethyloctanethioate **(64)**



Synthesized according to general procedure **Ib2**, using CuCl (10.0 mg, 0.1 mmol, 0.1 eq.), phosphoramidite ***ent*-L27** (56 mg, 0.1 mmol 0.1 eq.), 6.0 mL DCM/Et_2O (1/1), AgOTf (28.0 mg, 0.11 mmol, 0.11 eq.), (((2-methylpent-4-en-2-yl) oxy) methyl) benzene (480 mg, 2.5 mmol, 2.5 eq.), Cp_2ZrHCl (515 mg, 2.0 mmol, 2.0 eq.), (*E*)-*S*-ethyl-but-2-enethioate **43** (130 mg, 1.0 mmol, 1.0 eq.) and TMSCl (0.65 mL, 5 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the desired product **64** (230 mg, 0.71 mmol, 71%).

HPLC analysis indicated an enantiomeric excess of 98% [Chiralpak® IA; flow: 1.0 mL/min; hexane:*i*-PrOH 99.7:0.3; λ = 210 nm; major enantiomer tR = 7.54 min; minor enantiomer, tR = 10.36 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.36 – 7.26 (m, 4H, Ar-*H*), 7.26 – 7.17 (m, 1H, Ar-*H*), 4.39 (s, 2H, PhCH_2O), 2.86 (q, *J* = 7.4 Hz, 2H, SCH_2CH$_3$), 2.52 (dd, *J* = 14.4 Hz, 6.1 Hz, 1H, CH_2COSEt), 2.34 (dd, *J* = 14.4 Hz, 8.1 HZ, 1H, CH_2COSEt), 2.03 (dtdd, *J* = 14.4 Hz, 6.6 Hz, 5.5 Hz, 1.4 Hz, 1H, C*H*), 1.56 -1.47(m, 2H, CH_2),

1.47 – 1.27 (m, 3H, CH_2), 1.29 – 1.10 (m, 10H, CH_2, CH_3), 0.93 (d, *J* = 6.7 Hz, 3H, CHCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.3, 139.9, 128.3, 127.3, 127.1, 75.2, 63.7, 51.4, 40.5, 37.1, 31.1, 25.7, 23.3, 21.2, 19.5, 14.8.

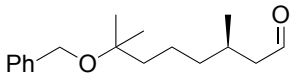
IR (v_{max}/cm^{-1}, $CHCl_3$) 2970, 1688, 1454, 1381, 1060, 734

HRMS (ESI) m/z calc. for $C_{19}H_{30}O_2{}^{23}Na^{32}S$, $[M+Na]^+$: 345.1859, found: 345.1855

$[\alpha]^{20}_{589}$ = +6.1 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **51**.

(*R*)-7-(benzyloxy)-3,7-dimethyloctanal **(65)**



Prepared according to general procedure **G**, using 0.65 mL DIBAL (1.0 M in DCM, 1.0 eq.), (*R*)-*S*-ethyl-7-(benzyloxy)-3,7-dimethyloctanethioate **64** (0.20 g, 0.65 mmol, 1.0 eq) Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **65** (0.165 g, 0.63 mmol, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 9.68 (dd, *J* = 2.6 Hz, 2.0 Hz, 1H, C*H*O), 7.29 – 7.22 (m, 4H, Ar-*H*), 7.22 – 7.13 (m, 1H, Ar-*H*), 4.34 (s, 2H, PhCH_2O), 2.33 (ddd, *J* = 16.1 Hz, 5.7 Hz, 2.1 Hz, 1H, CH_2CHO), 2.16 (ddd, *J* = 16.0 Hz, 7.9 Hz, 2.6 Hz, 1H, CH_2CHO), 2.01 (tdt, *J* = 7.7 Hz, 6.6 Hz, 5.6 Hz, 1H, C*H*), 1.60 – 1.19 (m, 5H, CH_2), 1.21 – 1.10 (m, 7H, CH_2, CH_3), 0.90 (d, *J* = 6.7 Hz, 3H, CHCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 203.1, 139.9, 128.3, 127.3, 127.1, 75.1, 63.7, 51.1, 40.6, 37.4, 28.2, 25.7, 21.3, 20.0.

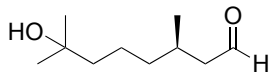
IR (v_{max}/cm^{-1}, $CHCl_3$) 3659, 2980, 1725, 1382, 1153, 1089, 954.

HRMS (ESI) m/z calc. for $C_{17}H_{27}O_2$, $[M+H]^+$: 263.2006, found: 263.2008.

$[\alpha]^{20}_{589}$ = +4.8 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **64**.

(*R*)-7-hydroxy-3, 7-dimethyloctanal **(66)**



A 10 mL round bottle flask charged 10% Pd-C (30 mg, 0.03 mmol, 0.15 eq.) was flushed with H_2 for 5 minutes. 1 mL EtOAc and (*R*)-7-(benzyloxy)-3,7-dimethyloctanal (53 mg, 0.2 mmol, 1.0 eq.) at room temperature under H_2. The mixture was kept stirring until the reduction was completed (90 min). The catalyst was filtered off through Celite and washed with the Et_2O. The filtrate was concentrated under reduced pressure and further purified by flash column chromatography (Et_2O/petane; 1:1; SiO_2) to give the pure (*R*)- hydroxycitronellal (32 mg, 0.19 mmol, 94%)

HPLC analysis indicated an enantiomeric excess of 98% [Chiralpak® IA; flow: 1.0 mL/min; hexane:*i*-PrOH, 95:5; λ = 275 nm; major enantiomer tR = 15.36 min; minor enantiomer, tR = 14.59 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 9.69 (t, *J* = 2.3 Hz, 1H, C*H*O), 7.20 (s, 1H, O*H*) 2.35 (ddd, *J* = 16.1 Hz, 5.8 Hz, 2.1 Hz, 1H, CH_2CHO), 2.18 (ddd, *J* = 16.1 Hz, 7.8 Hz, 2.6 Hz, 1H, CH_2CHO), 2.01 (tdt, *J* = 7.7 Hz, 6.6 Hz, 5.6 Hz, 1H, C*H*), 1.45 – 1.17 (m, 6H, CH_2), 1.15 (s, 6H, CH_3), 0.91 (d, *J* = 6.7 Hz, 3H, CHCH_3).

13C NMR (101 MHz, $CDCl_3$) δ_C/ppm 203.0, 70.9, 51.1, 43.9, 37.3, 29.4, 29.3, 28.1, 21.7, 20.0.

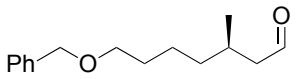
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2980, 1722, 1382, 1251, 1153, 954.

HRMS (ESI) m/z calc. for $C_{10}H_{20}O_2{}^{23}Na$, $[M+Na]^+$: 195.1356, found: 195.1356.

$[\alpha]^{20}_{589}$ = +8.5 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **64**.

(*R*)-7-(benzyloxy)-3-methylheptanal **(67)**



Prepared according to general procedure **G**, using 2.5 mL DIBAL (1.0 M in DCM, 1.0 eq.), (*R*)-*S*-methyl-7-(benzyloxy)-3-methylheptanethioate **64** (0.701 g, 2.5 mmol, 1.0 eq.) Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product (0.574 g, 2.45 mmol, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 9.75 (dd, *J* = 2.6 Hz, 2.0 Hz, 1H, C*H*O), 7.38 – 7.32 (m, 4H, Ar-*H*), 7.34 – 7.24 (m, 1H, Ar-*H*), 4.50 (s, 2H, PhCH_2O), 3.47 (t, *J* = 6.5 Hz, 2H, OCH_2), 2.39 (ddd, *J* = 16.0 Hz, 5.7 Hz, 2.0 Hz, 1H, CH_2CHO), 2.22 (ddd, *J* = 16.1 Hz, 7.8 Hz, 2.6 Hz, 1H, CH_2CHO), 2.13 – 1.98 (m, 1H, C*H*), 1.74 – 1.55 (m, 2H, CH_2), 1.52 – 1.15 (m, 4H, CH_2), 0.96 (d, *J* = 6.7 Hz, 3H, CHCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 203.1, 138.6, 128.4, 127.7, 127.5, 72.9, 70.2, 51.0, 36.7, 29.8, 28.1, 23.6, 20.0.

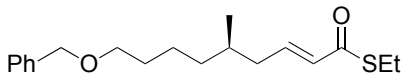
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3659, 2980, 1724, 1380, 1100, 1073, 954, 737.

HRMS (ESI) m/z calc. for $C_{15}H_{23}O_2$, $[M+H]^+$: 235.1693, found: 235.1691.

$[\alpha]^{20}_{589}$ = +5.1 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to compound **56**.

(*R*, *E*)-*S*-ethyl-9-(benzyloxy)-5-methylnon-2-enethioate **(68)**



Prepared according to general procedure **Fb**, using 2.54 mL *n*-BuLi (1.5 M solution in hexane, 4.05 mmol, 1.5 eq.), $(EtO)_2POCH_2COSEt$ **42** (0.97 g, 4.05 mmol, 1.5 eq.), (*R*)-7-(benzyloxy)-3-methylheptanal **67** (0.611 g, 2.6 mmol, 1.0 eq.) Purified by flash column chromatography (pentane: Et_2O; 90:10; SiO_2) to afford the desired product **68** (0.794 g, 2.47 mmol, 95%)

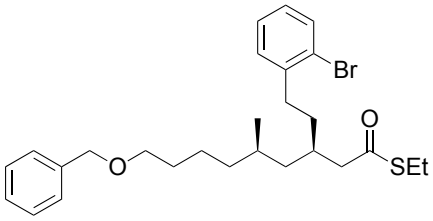
^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.37 – 7.30 (m, 4H, Ar-*H*), 7.30 – 7.23 (m, 1H, Ar-*H*), 6.85 (dt, *J* = 15.3 Hz, 7.5 Hz, 1H, C*H*CH_3), 6.08 (dt, *J* = 15.4 Hz, 1.5 Hz, 1H, CH=C*H*CH_2), 4.49 (s, 2H, PhC*H*$_2$O), 3.45 (t, *J* = 6.5 Hz, 2H, OC*H*$_2$), 2.93 (q, *J* = 7.4 Hz, 2H, SC*H*$_2$$CH_3$), 2.18 (dddd, *J* = 14.3 Hz, 7.2 Hz, 5.6 Hz, 1.5 Hz, 1H, C*H*$_2$CH=CH), 2.00 (dtd, *J* = 14.2 Hz, 7.6 Hz, 1.4 Hz, 1H, C*H*$_2$CH=CH), 1.70 – 1.51 (m, 4H, C*H*, C*H*$_2$), 1.45 – 1.30 (m, 2H, C*H*$_2$), 1.27 (t, *J* = 7.4 Hz, 3H, C*H*$_3$), 1.21 – 1.09 (m, 1H, C*H*$_2$), 0.88 (d, *J* = 6.7 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 190.1, 144.2, 138.6, 129.8, 128.4, 127.7, 127.5, 72.9, 70.3, 39.6, 36.5, 32.6, 29.9, 23.7, 23.1, 19.6, 14.8.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3658, 2981, 1669, 1632, 1381, 1154, 970, 735.

HRMS (ESI) m/z calc. for $C_{19}H_{29}O_2{}^{32}S$, $[M+H]^+$: 321.1883, found: 321.1886.

(3*R*, 5*R*)-*S*-ethyl-9-(benzyloxy)-3-(2-bromophenethyl)-5methylnonanethioate**(69a)**



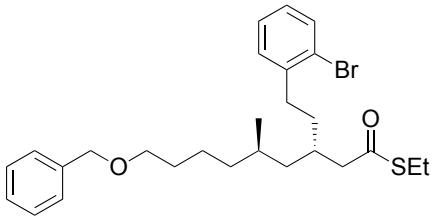
Prepared according to general procedure **Ib2**, using CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), phosphoramidite **L27** (22.3 mg, 0.04 mmol 0.2 eq.), 1.6 mL DCM/Et_2O (1/1), AgOTf (11.2 mg, 0.44 mmol, 0.22 eq.), 1-bromo-2-vinylbenzene (92 mg, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*R*, *E*)-*S*-ethyl-9-(benzyloxy)-5-methylnon-2-enethioate **68** (64.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (85 mg, 0.17 mmol, 85%).
HPLC analysis indicated a diastereomeric ratio of 97.5: 2.5 [Chiralpak® IB; flow: 1.0 mL/min; hexane/i-PrOH: 99.0:1.0; λ = 210 nm; major enantiomer tR = 7.21 min; minor enantiomer, tR = 7.63 min].
^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.48 – 7.37 (m, 1H, Ar-*H*), 7.27 (d, *J* = 4.4 Hz, 4H, Ar-*H*), 7.23 – 7.16 (m, 1H, Ar-*H*), 7.16 – 7.11 (m, 2H, Ar-*H*), 6.96 (ddd, *J* = 8.0 Hz, 5.5 Hz, 3.6 Hz, 1H, Ar-*H*), 4.43 (s, 2H, PhCH_2O), 3.39 (t, *J* = 6.6 Hz, 2H, OCH_2), 2.80 (q, *J* = 7.4 Hz, 2H, SCH_2CH$_3$), 2.73 – 2.56 (m, 2H, CH_2PhBr), 2.55 – 2.39 (m, 2H, CH_2CO), 2.20 – 1.90 (m, 1H, C*H*), 1.61 – 1.45 (m, 5H, C*H,* CH_2), 1.45 – 1.19 (m, 3H, CH_2), 1.19 – 1.13 (m, 4H, SCH$_2$CH_3, CH_2), 1.15 – 0.96 (m, 2H, CH_2), 0.80 (d, *J* = 6.5 Hz, 3H, CH_3).
^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.2, 141.7, 138.7, 132.8, 130.3, 128.4, 127.7, 127.5, 127.5, 127.4, 124.3, 72.9, 70.5, 48.7, 41.7, 36.9, 34.7, 33.4, 30.1, 30.0, 23.6, 23.4, 19.8, 14.9.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2930, 2858, 2360, 1687, 1455, 1101, 1023, 749

HRMS (ESI) m/z calc. for $C_{27}H_{37}O_2{}^{79}Br^{23}Na^{32}S$, $[M+Na]^+$: 527.1590, 529.1569, found: 527.1588, 529.1564

$[\alpha]^{20}_{589}$ = –6.5 **(**c 1.0, $CHCl_3$)

(3*S*, 5*R*)*S*-ethyl-9-(benzyloxy)-3-(2-bromophenethyl)-5-methylnonanethioate**(69b)**



Prepared according to general procedure **Ib2**, using CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), phosphoramidite ***ent*-L27** (22.3 mg, 0.04 mmol 0.2 eq.), 1.6 mL DCM/Et_2O (1/1), AgOTf (11.2 mg, 0.44 mmol, 0.22 eq.), 1-bromo-2-vinylbenzene (92 mg, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (*R*, *E*)-*S*-ethyl-9-(benzyloxy)-5-methylnon-2-enethioate **68** (64.0 mg, 0.2 mmol, 1.0 eq.) and TMSCl (0.127 mL, 1 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (85 mg, 0.17 mmol, 85%).

HPLC analysis indicated a diastereomeric ratio 98:2 [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99.0:1.0; λ = 210 nm; major enantiomer tR = 7.94 min; minor enantiomer, tR = 7.53 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.58 – 7.35 (m, 1H, Ar-*H*), 7.30 – 7.23 (m, 4H, Ar-*H*), 7.22 – 7.15 (m, 1H, Ar-*H*), 7.16 – 7.09 (m, 2H, Ar-*H*), 6.96 (ddd, *J* = 8.0 Hz, 5.7 Hz, 3.4 Hz, 1H, Ar-*H*), 4.42 (s, 2H, PhCH_2O), 3.39 (t, *J* = 6.6 Hz, 2H, OCH_2), 2.81 (qd, *J* = 7.4 Hz, 1.6 Hz, 2H, SCH_2CH$_3$), 2.70 – 2.50 (m, 3H, CH_2PhBr, CH_2CO), 2.43 (dd, *J* = 14.8 Hz, 7.1 Hz, 1H, CH_2CO), 2.14 – 1.99 (m, 1H, C*H*), 1.69 – 1.37 (m, 5H, C*H,* CH_2), 1.36 – 1.20 (m, 4H, CH_2), 1.18 (t, *J* = 7.4 Hz, 3H, SCH$_2$CH_3), 1.10 – 0.99 (m, 2H, CH_2), 0.78 (d, *J* = 6.5 Hz, 3H, C*H*CH_3).

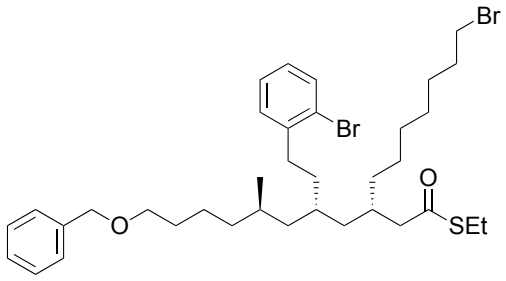
^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.2, 141.7, 138.7, 132.8, 130.3, 128.4, 127.7, 127.6, 127.5, 127.4, 124.3, 72.9, 70.5, 49.2, 41.5, 37.2, 33.8, 33.3, 33.1, 30.1, 23.6, 23.4, 19.6, 14.9.

IR (v_{max}/cm^{-1}, $CHCl_3$) 2930, 2859, 2360, 1686, 1455, 1101, 1023, 749

HRMS (ESI) m/z calc. for $C_{27}H_{37}O_2{}^{79}Br^{23}Na^{32}S$, $[M+Na]^+$: 527.1590, 529.1569, found: 527.1588, 529.1564

$[\alpha]^{20}_{589}$ = –7.8 **(**c 1.0, $CHCl_3$)

(3*S*, 5*S*, 7*R*)-*S*-ethyl-11-(benzyloxy)-3-(7-bromoheptyl)-5-(2-bromophenethyl)-7-methylundecanethioate **(70)**



Prepared according to general procedure **Ib2**, using CuCl (4.0 mg, 0.04 mmol, 0.2 eq.), phosphoramidite ***ent*-L27** (22.3 mg, 0.04 mmol 0.2 eq.), 1.6 mL DCM/Et_2O (1/1), AgOTf (11.2 mg, 0.44 mmol, 0.22 eq.), 7-bromohept-1-ene (88 mg, 0.5 mmol, 2.5 eq.), Cp_2ZrHCl (103 mg, 0.4 mmol, 2.0 eq.), (5*S*,7*R*,*E*)-*S*-ethyl-11-(benzyloxy)-5-(2-bromophenethyl)-7-methylundec-2-enethioate (106 mg, 0.2 mmol, 1.0 eq.), and TMSCl (0.127 mL, 1 mmol, 5.0 eq.). Purified by flash column chromatography (Petrol: Et_2O; 98:2; SiO_2) to give the desired product (104 mg, 0.15 mmol, 73%).

HPLC analysis indicated a diastereomeric ratio of 98: 2 [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99.0:1.0; λ = 210 nm; major enantiomer tR = 7.71 min; minor enantiomer, tR = 7.17 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.54 – 7.46 (m, 1H, Ar-*H*), 7.38 – 7.29 (m, 4H, Ar-*H*), 7.28 – 7.22 (m, 1H, Ar-*H*), 7.22 – 7.16 (m, 2H, Ar-*H*), 7.02 (m, 1H, Ar-*H*), 4.49 (s, 2H, PhCH_2O), 3.45 (t, *J* = 6.6 Hz, 2H, OCH_2), 3.38 (t, *J* = 6.9 Hz, 2H, CH_2Br), 2.86 (q, *J* = 7.2 Hz, 2H, SCH_2CH$_3$), 2.73 – 2.57 (m, 2H, CH_2PhBr), 2.52 – 2.38 (m, 2H, CH_2CO), 2.04 (d, *J* = 8.4 Hz, 1H, C*H*), 1.83 (p, *J* = 6.9 Hz, 2H, C*H,* C*H*), 1.66 – 1.30 (m, 12H, CH_2), 1.28 (m, 10H, CH_2), 1.23 (t, *J* = 7.4 Hz, 3H, CH_2), 1.18 – 0.99 (m, 2H, CH_2), 0.83 (d, *J* = 6.6 Hz, 3H, CHCH_3).

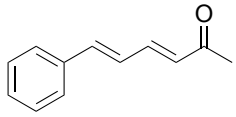
^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.4, 142.2, 138.7, 132.8, 130.3, 128.4, 127.6, 127.5, 127.4, 124.4, 72.9, 70.5, 49.2, 41.8, 39.3, 37.6, 34.1, 33.9, 33.8, 33.3, 32.9, 32.8, 32.3, 30.2, 29.7, 28.7, 28.1, 26.3, 23.7, 23.4, 19.8, 14.9.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2927, 2854, 1687, 1454, 1101, 1023, 748.

HRMS (ESI) m/z calc. for $C_{36}H_{55}O_2{}^{79}Br_2{}^{32}S$, $[M+H]^+$: 709.2284, 711.2264, 713.2243, 714.2277 found: 709.2285, 711.2261, 713.2240, 714.2274.

$[\alpha]^{20}_{589}$ = –16.7 (c 1.0, $CHCl_3$)

(3*E*, 5*E*)-6-phenylhexa-3, 5-dien-2-one **(71)**



Prepared according to general procedure **H**, using *n*-BuLi (9.6 mL, 1.5 eq., in hexane, 15 mmol), diethyl (2-oxopropyl) phosphonate (2.92 mL, 1.5 eq., 15 mmol) in 30 mL THF, cinnamaldehyde (1.25 mL, 1.0 eq., 10 mmol). Purified by flash column chromatography (pentane: Et_2O; 90:10; SiO_2) to afford the desired product **71** (1.32 g, 7.7 mmol, 77%) in >20:1 *E*:*Z* ratio.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.57 – 7.44 (m, 2H, Ar-*H*), 7.43 – 7.26 (m, 4H, Ar-*H,* C*H*), 7.07 – 6.80 (m, 2H, C*H*), 6.28 (d, *J* = 15.5 Hz, 1H, C*H*), 2.34 (s, 3H, CH_3).

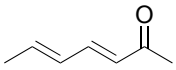
^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 198.4, 143.4, 141.3, 136.0, 130.5, 129.2, 128.9, 127.3, 126.7, 27.4.

IR (v_{max}/cm^{-1}, $CHCl_3$) 2981, 1668, 1652, 1586, 1258, 990.

HRMS (ESI) m/z calc. for $C_{12}H_{12}O^{35}Cl$ $[M+H]^+$: 173.0961, found: 173.0962.

This data was concordant with literature values.[16]

(3*E*, 5*E*)-hepta-3, 5-dien-2-one **(72)**



Prepared according to general procedure **H**, using *n*-BuLi (4.8 mL, 1.5 eq., in hexane, 7.5 mmol), diethyl (2-oxopropyl) phosphonate (1.46 mL, 1.5 eq., 7.5 mmol), (*E*)-but-2-enal (0.53 g, 1.0 eq., 5.0 mmol) Purified by flash column chromatography (pentane: Et_2O; 90:10; SiO_2) to afford the desired product **72** (0.35 g, 3.3 mmol, 65%) in >20:1 *E*:*Z* ratio.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.18 – 6.91 (m, 1H, C*H*), 6.24 – 6.15 (m, 2H, C*H*), 6.03 (d, *J* = 15.1 Hz, 1H, C*H*), 2.24 (s, 3H, COCH_3), 1.97 – 1.80 (m, 3H, CH_3).

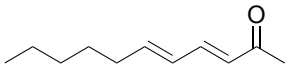
^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 198.8, 143.9, 140.3, 130.3, 128.6, 27.2, 18.8.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 2359, 1681, 1558, 1362, 1256, 981.

HRMS (ESI) m/z calc. for $C_7H_{11}O$ $[M+H]^+$: 111.0804, found: 111.0803.

This data was concordant with literature values.[17]

(3*E*, 5*E*)-undeca-3, 5-dien-2-one **(73)**



Prepared according to general procedure **H**, using *n*-BuLi (4.8 mL, 1.5 eq., in hexane, 7.5 mmol), diethyl (2-oxopropyl) phosphonate (1.46 mL, 1.5 eq., 7.5 mmol), (*E*)-oct-2-enal (0.63 g, 1.0 eq., 5.0 mmol) Purified by flash column chromatography (pentane: Et_2O; 90:10; SiO_2) to afford the desired product **73** (0.50 g, 3.0 mmol, 60%) in >20:1 *E*:*Z* ratio.

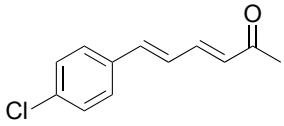
^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.19 – 6.90 (m, 1H, C*H*CO), 6.25 – 6.15 (m, 2H, C*H*), 6.05 (d, *J* = 15.6 Hz, 1H, C*H*), 2.26 (s, 3H, COCH_3), 2.18 (dtd, *J* = 7.6 Hz, 5.3 Hz, 2.6 Hz, 2H, CH_2CH), 1.51 – 1.36 (m, 2H, CH_2), 1.39 – 1.22 (m, 4H, CH_2), 1.02 – 0.80 (m, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 198.8, 145.9, 144.1, 128.8, 33.1, 31.4, 28.4, 27.2, 22.5, 14.0.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2958, 2929, 1668, 1632, 1253, 997.

HRMS (ESI) m/z calc. for $C_{11}H_{19}O$ $[M+H]^+$: 167.1430, found: 167.1431.

(3*E*, 5*E*)-6-(4-chlorophenyl) hexa-3, 5-dien-2-one **(76)**[18]



Prepared according to general procedure **H**, using *n*-BuLi (4.8 mL, 1.5 eq., in hexane, 7.5 mmol), diethyl (2-oxopropyl) phosphonate (1.45 mL, 1.5 eq., 7.5 mmol) in 20 mL, (*E*)-3-(4-chlorophenyl) acrylaldehyde (0.83 g, 1.0 eq., 5.0 mmol) Purified by flash column chromatography (pentane: Et_2O; 7:3; SiO_2) to afford the desired product **76** (0.37 g, 1.8 mmol, 36%) in ~9:1 *E*:*Z* ratio.

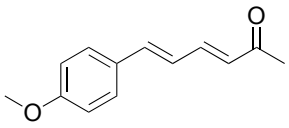
^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.43 – 7.34 (m, 2H, Ar-*H*), 7.34 – 7.26 (m, 2H, Ar-*H*), 7.23 (t, *J* = 7.7 Hz, 1H, C*H*), 6.94 – 6.76 (m, 2H, C*H*), 6.24 (d, *J* = 15.5 Hz, 1H, C*H*), 2.29 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 198.4, 143.0, 139.7, 135.0, 134.5, 130.9, 129.1, 128.4, 127.2, 27.5.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2980, 1650, 1616, 1588, 1360, 1251, 996

HRMS (ESI) m/z calc. for $C_{12}H_{12}O^{35}Cl$ $[M+H]^+$: 207.0571, found: 207.0572

(3*E*, 5*E*)-6-(4-methoxyphenyl) hexa-3, 5-dien-2-one **(77)**[18]



Prepared according to general procedure **H**, using *n*-BuLi (4.8 mL, 1.5 eq., in hexane, 7.5 mmol), diethyl (2-oxopropyl) phosphonate (1.45 mL, 1.5 eq., 7.5 mmol) in 20 mL THF, (*E*)-3-(4-methoxyphenyl) acrylaldehyde (0.81 g, 1.0 eq., 5.0 mmol). Purified by flash column chromatography (pentane: Et_2O; 1:1; SiO_2) to afford the desired product **77** (0.32 g, 1.6 mmol, 32%) in ~9:1 *E*:*Z* ratio.

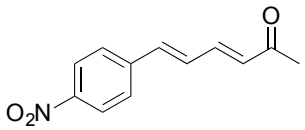
^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.46 – 7.29 (m, 2H, Ar-*H*), 7.33 – 7.06 (m, 1H, C*H*), 6.92 – 6.75 (m, 3H, C*H,* Ar-*H*), 6.70 (m, 1H, C*H*), 6.15 (d, *J* = 15.5 Hz, 1H, C*H*), 3.77 (s, 3H, OCH_3), 2.24 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 198.5, 160.6, 144.1, 141.1, 129.4 (3C), 128.8, 124.5, 114.3, 55.4, 27.3.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 1653, 1594, 1511, 1251, 990.

HRMS (ESI) m/z calc. for $C_{13}H_{15}O_2$ $[M+H]^+$: 203.1067 found: 203.1066.

(3*E*, 5*E*)-6-(4-nitrophenyl) hexa-3, 5-dien-2-one **(78)**



Prepared according to general procedure **H**, using *n*-BuLi (4.8 mL, 1.5 eq., in hexane, 7.5 mmol), diethyl (2-oxopropyl) phosphonate (1.45 ml, 1.5 eq., 7.5 mmol) in 20 mL THF, (*(E)-3-(*4-nitrophenyl) acrylaldehyde (0.89 g, 1.0 eq., 5.0 mmol) Purified by flash column chromatography (pentane: Et_2O; 60:40; SiO_2) to afford the desired product **78** (0.31 g, 1.4 mmol, 28%) in ~9:1 *E*:*Z* ratio.

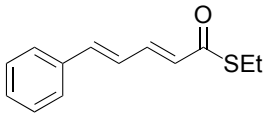
^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 8.32 – 8.03 (m, 2H, Ar-*H*), 7.70 – 7.40 (m, 2H, Ar-*H*), 7.38 – 7.17 (m, 1H, C*H*), 7.07 – 6.77 (m, 2H, C*H*), 6.33 (d, *J* = 15.5 Hz, 1H, C*H*), 2.31 (s, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 198.1, 147.7, 142.1, 141.7, 138.0, 132.6, 130.8, 127.7, 124.2, 27.7.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 1683, 1594, 1512, 1339, 997.

HRMS (ESI) m/z calc. for $C_{12}H_{12}O_3N$ $[M+H]^+$: 218.0812, found: 218.0812.

S-ethyl (2*E*, 4*E*)-5-phenylpenta-2,4-dienethioate **(80)**



Prepared according to general procedure **H**, using *n*-BuLi (4.8 mL, 1.0 eq., in hexane, 7.5 mmol), *S*-ethyl 2-(diethoxyphosphoryl) ethanethioate (1.8 ml, 1.0 eq., 7.5 mmol) in 20 mL, cinnamaldehyde (0.66 g, 1.0 eq., 5.0 mmol) Purified by flash column chromatography (pentane: Et_2O; 97:3; SiO_2) to afford the desired product **80** (0.67 g, 3.1 mmol, 61%) in >20:1 *E*:*Z* ratio.

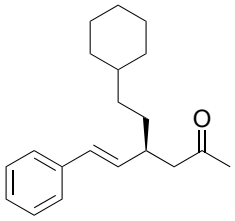
^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.53 – 7.43 (m, 2H, Ar-*H*), 7.43-7.30 (m, 4H, Ar-*H,* C*H*), 6.97 (d, J = 15.5 Hz, 1H, C*H*), 6.84 (ddd, *J* = 15.5 Hz, 10.8 Hz, 0.8 Hz, 1H, C*H*), 6.28 (dt, *J* = 15.2 Hz, 0.7 Hz, 1H, C*H*), 3.00 (q, *J* = 7.4 Hz, 2H, S$CH_2$$CH_3$), 1.31 (t, *J* = 7.4 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 189.9, 141.7, 140.3, 136.0, 129.2, 128.9, 128.3, 127.2, 126.1, 23.3, 14.9.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2976, 2361, 1653, 1594, 1022, 820.

HRMS (ESI) m/z calc. for $C_{13}H_{15}O^{32}S$ $[M+H]^+$: 219.0838, found: 218.0840.

(*S*, *E*)-4-(2-cyclohexylethyl)-6-phenylhex-5-en-2-one **(81)**



Synthesized according to general procedure **Ib2**, using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), phosphoramidite **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), vinylcyclohexane (55 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), (3*E*, 5*E*)-6-phenylhexa-3, 5-dien-2-one **(71)** (34 mg, 1.0 eq., 0.2 mmol) and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **81**(40 mg, 14 mmol, 70%).

HPLC analysis indicated an enantiomeric excess of 90% [Chiralpak® IA; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1.0; λ = 254 nm; major enantiomer tR = 6.90 min; minor enantiomer, tR = 7.40 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.28 – 7.17 (m, 4H, Ar-*H*), 7.16 – 7.08 (m, 1H, Ar-*H*), 6.30 (d, *J* = 15.8 Hz, 1H, C*H*), 5.92 (dd, *J* = 15.9 Hz, 8.7 Hz, 1H, C*H*), 2.68 – 2.49 (m, 1H, C*H*CH_2COCH_3), 2.44 (d, *J* = 6.9 Hz, 2H, CH_2COCH_3), 2.05 (s, 3H, COCH_3), 1.72 – 1.46 (m, 5H, C*H*, 2 x CH_2), 1.45 – 1.21 (m, 2H, CH_2), 1.21 – 0.98 (m, 6H, 3 x CH_2), 0.88 – 0.70 (m, 2H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.1, 137.4, 133.3, 130.2, 128.5, 127.1, 126.1, 49.6, 39.3, 37.8, 35.0, 33.5, 33.3, 32.4, 30.7, 26.7, 26.4, 26.4.

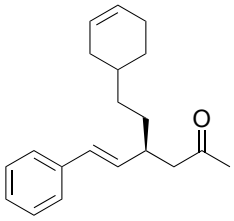
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 1716, 1382, 1154, 966.

HRMS (ESI) m/z calc. for $C_{20}H_{29}O$ $[M+H]^+$: 285.2213 found: 285.2211.

$[\alpha]^{20}_{589}$ = +10.0 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(4*S*, *E*)-4-(2-(cyclohex-3-en-1-yl) ethyl)-6-phenylhex-5-en-2-one **(82)**



Synthesized according to general procedure **Ib2***,* using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), phosphoramidite **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), 4-vinylcyclohex-1-ene (54 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), (3*E*, 5*E*)-6-phenylhexa-3, 5-dien-2-one **(71)** (34 mg, 1.0 eq., 0.2 mmol) and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **82** (39 mg, 14 mmol, 70%).

HPLC analysis indicated an enantiomeric excess of 92% [Chiralpak® IA; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1.0; λ = 254 nm; major enantiomer tR = 7.73 min; minor enantiomer, tR = 8.15 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.19 – 7.06 (m, 4H, Ar-*H*), 7.04 – 6.97 (m, 1H, Ar-*H*), 6.20 (d, *J* = 15.8 Hz, 1H, C*H*), 5.81 (dd, *J* = 15.8 Hz, 8.7 Hz, 1H, C*H*), 5.45 (d, *J* = 2.3, 2H, 2 x C*H*CH_2), 2.65 – 2.44 (m, 1H, C*H* CH_2COCH_3), 2.34 (d, *J* = 6.9 Hz, 2H, CH_2COCH_3), 1.94 (s, 3H, COCH_3), 1.90 – 1.76 (m, 2H, CH_2), 1.64 – 1.27 (m, 3H, C*H,* CH_2), 1.26 – 0.93 (m, 4H, 2 x CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.0, 137.4, 133.2, 130.3, 128.5, 127.2, 127.1, 126.5, 126.1, 49.5, 39.2, 34.2, 33.6, 32.4, 31.9, 30.7, 28.9, 25.3.

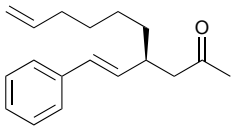
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 1716, 1382, 1154, 966.

HRMS (ESI) m/z calc. for $C_{20}H_{27}O$ $[M+H]^+$: 283.2056 found: 283.2057.

$[\alpha]^{20}_{589}$ = +4.7 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(*S*, *E*)-4-styryldec-9-en-2-one **(83)**



Synthesized according to general procedure **Ib2***,* using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), hexa-1,5-diene (41 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), (3*E*, 5*E*)-6-phenylhexa-3, 5-dien-2-one **(71)** (34 mg, 1.0 eq., 0.2 mmol) and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **83** (45 mg, 16 mmol, 78%).

HPLC analysis indicated an enantiomeric excess of 63% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 254 nm; major enantiomer tR = 7.01 min; minor enantiomer, tR = 8.10 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.39 – 7.23 (m, 4H, Ar-*H*), 7.25 – 7.17 (m, 1H, Ar-*H*), 6.39 (d, *J* = 15.8, 1H, C*H*), 6.00 (dd, *J* = 15.8 Hz, 8.7 Hz, 1H, C*H*), 5.79 (ddt, *J* = 16.9 Hz, 10.2 Hz, 6.7 Hz, 1H, C*H*), 5.17 – 4.80 (m, 2H, CH_2), 2.73 (q, *J* = 6.9 Hz, 1H, C*H*), 2.52 (d, *J* = 6.9 Hz, 2H, CH_2COCH$_3$), 2.13 (s, 3H, COCH_3), 2.04 (ddt, *J* = 9.3 Hz, 7.8 Hz, 4.0 Hz, 2H, CH_2CH=CH$_2$), 1.53 – 1.14 (m, 6H, 3 x CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.0, 138.9, 137.4, 133.1, 130.3, 128.5, 127.1, 126.1, 114.3, 49.5, 38.9, 34.9, 33.7, 30.7, 28.9, 26.7.

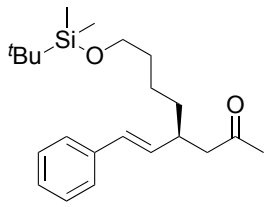
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2926, 2390, 2284, 1715, 1357, 966.

HRMS (ESI) m/z calc. for $C_{18}H_{25}O$ $[M+H]^+$: 257.1900 found: 257.1900.

$[\alpha]^{20}_{589}$ = +6.1 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(*S*, *E*)-8-((tert-butyldimethylsilyl) oxy)-4-styryloctan-2-one **(84)**



Synthesized according to general procedure **Ib2***,* using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), tert-butyldimethyl (pent-4-en-1-yloxy) silane (100 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), (3*E*, 5*E*)-6-phenylhexa-3, 5-dien-2-one **(71)** (34 mg, 1.0 eq., 0.2 mmol) and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **84** (57 mg, 16 mmol, 79%).

HPLC analysis indicated an enantiomeric excess of 92% [Chiralpak® IA; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1.0; λ = 254 nm; major enantiomer tR = 5.51 min; minor enantiomer, tR = 5.90 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.35 – 7.22 (m, 4H, Ar-*H*), 7.21 – 7.13 (m, 1H, Ar-*H*), 6.36 (d, *J* = 15.9 Hz, 1H, C*H*), 5.96 (dd, *J* = 15.8 Hz, 8.7 Hz, 1H, C*H*), 3.56 (t, *J* = 6.5 Hz, 2H, CH_2O), 2.69 (p, *J* = 7.5 Hz, 6.8 Hz, 1H, C*H*CH_2COCH_3), 2.50 (d, *J* = 6.9 Hz, 2H, CH_2COCH_3), 2.10 (s, 3H, COCH_3), 1.59 – 1.08 (m, 6H, 3 x CH_2), 0.84 (s, 9H, 3 x CH_3), -0.00 (s, 6H, SiCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.0, 137.3, 133.1, 130.4, 128.5, 127.1, 126.1, 63.1, 49.5, 39.0, 34.9, 32.8, 30.7, 26.0 (3C), 23.5, 18.4, -5.3.

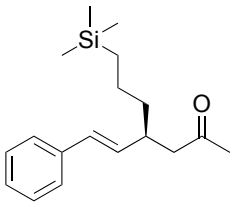
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 1717, 1386, 1155, 966.

HRMS (ESI) m/z calc. for $C_{22}H_{37}O_2{}^{28}Si$ $[M+H]^+$: 361.2557, 362.2590 found: 361.2558, 362.2585.

$[\alpha]^{20}_{589}$ = +4.4 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(*S*, *E*)-4-styryl-7- (trimethylsilyl) heptan-2-one **(85)**



Synthesized according to general procedure **Ib2**, using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), allyltrimethylsilane (57 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), (3*E*, 5*E*)-6-phenylhexa-3, 5-dien-2-one **(71)** (34 mg, 1.0 eq., 0.2 mmol) and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **85** (45 mg, 16 mmol, 78%).

HPLC analysis indicated an enantiomeric excess of 86% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1.0; λ = 252 nm; major enantiomer tR = 6.02 min; minor enantiomer, tR = 6.86 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.41 – 7.29 (m, 4H, Ar-*H*), 7.28 – 7.21 (m, 1H, Ar-*H*), 6.42 (d, *J* = 15.8 Hz, 1H, C*H*), 6.03 (dd, *J* = 15.9 Hz, 8.7 Hz, 1H, C*H*), 2.98 – 2.64 (m, 1H, C*H*CH_2COCH_3), 2.55 (d, *J* = 6.9 Hz, 2H, CH_2COCH_3), 2.17 (s, 3H, COCH_3), 1.54 – 1.19 (m, 4H, 2 x CH_2), 0.75 – 0.41 (m, 2H, CH_2Si), 0.00 (s, 9H, Si(CH_3)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_P/ppm 209.7, 139.0, 134.9, 131.8, 130.1, 128.7, 127.7, 51.1, 40.6, 40.3, 32.3, 23.1, 18.2, 0.0.

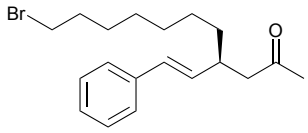
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 1716, 1382, 1155, 966.

HRMS (ESI) m/z calc. for $C_{18}H_{29}O^{28}Si$ $[M+H]^+$: 289.1982, found: 289.1982.

$[\alpha]^{20}_{589}$ = +0.8 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(*S*, *E*)-11-bromo-4-styrylundecan-2-one **(86)**



Synthesized according to general procedure **Ib2***,* using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), 7-bromohept-1-ene (89 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), (3*E*, 5*E*)-6-phenylhexa-3, 5-dien-2-one **(71)** (34 mg, 1.0 eq., 0.2 mmol) and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **86** (55 mg, 16 mmol, 78%).

HPLC analysis indicated an enantiomeric excess of 92% [Chiralpak® IA; flow: 1.0 mL/min; hexane/i-PrOH: 99: 1.0; λ = 254 nm; major enantiomer tR = 9.78 min; minor enantiomer, tR = 10.60 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.34 – 7.22 (m, 4H, Ar-*H*), 7.22 – 7.13 (m, 1H, Ar-*H*), 6.36 (d, *J* = 15.9 Hz, 1H, C*H*), 5.96 (dd, *J* = 15.8 Hz, 8.7 Hz, 1H, C*H*), 3.36 (t, *J* = 6.9 Hz, 2H, CH_2Br), 2.68 (m, 1H, C*H*CH_2COCH_3), 2.49 (d, *J* = 6.9 Hz, 2H, CH_2COCH_3), 2.10 (s, 3H, COCH_3), 1.92 – 1.69 (m, 2H, CH_2), 1.49 – 1.13 (m, 10H, 5 x CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.1, 137.3, 133.1, 130.3, 128.5, 127.2, 126.1, 49.5, 39.0, 35.0, 34.1, 32.8, 30.8, 29.4, 28.7, 28.1, 27.1.

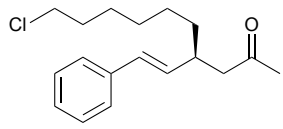
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 2929, 1715, 1381, 1157, 966.

HRMS (ESI) m/z calc. for $C_{19}H_{28}O^{79}Br$ $[M+H]^+$: 351.1318, 353 .1298 found: 351.1315, 353.1294.

$[\alpha]^{20}_{589}$ = +6.1 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(*S*, *E*)-10-chloro-4-styryldecan-2-one **(87)**



Synthesized according to general procedure **Ib2**, using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), 6-chlorohex-1-ene (59 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), (3*E*, 5*E*)-6-phenylhexa-3, 5-dien-2-one **(71)** (34 mg, 1.0 eq., 0.2 mmol) and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **87** (50 mg, 17 mmol, 85%).

HPLC analysis indicated an enantiomeric excess of 90% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1.0; λ = 254 nm; major enantiomer tR = 9.81 min; minor enantiomer, tR = 11.37 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.33 – 7.21 (m, 4H, Ar-*H*), 7.20 – 7.11 (m, 1H, Ar-*H*), 6.34 (d, *J* = 15.8 Hz, 1H, C*H*), 5.95 (dd, *J* = 15.8 Hz, 8.8 Hz, 1H, C*H*), 3.47 (t, *J* = 6.7 Hz, 2H, CH_2Cl), 2.77 – 2.61 (m, 1H, C*H*), 2.48 (d, *J* = 6.9 Hz, 2H, CH_2COCH$_3$), 2.09 (s, 3H, CH_3), 1.71 (dq, *J* = 8.1 Hz, 6.8 Hz, 2H, CH_2CH), 1.50 – 1.14 (m, 8H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 207.9, 137.3, 133.1, 130.4, 128.5, 127.2, 126.1, 49.5, 45.1, 38.9, 35.0, 32.6, 30.7, 28.8, 27.1, 26.8.

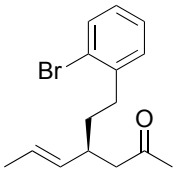
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 1715, 1382, 1158, 967.

HRMS (ESI) m/z calc. for $C_{18}H_{26}O^{35}Cl$ $[M+H]^+$: 293.1667, 295.1637, found: 293.1669, 295.1639.

$[\alpha]^{20}_{589}$ = +9.8 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(*S*, *E*)-4-(2-bromophenethyl) hept-5-en-2-one **(88)**



Synthesized according to general procedure **Ib2***,* using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), 1-bromo-2-vinylbenzene (91 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), (3E, 5E)-hepta-3, 5-dien-2-one (22 mg, 1.0 eq., 0.2 mmol) **(72)** (34 mg, 1.0 eq., 0.2 mmol) and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **88** (35 mg, 12 mmol, 60%).

HPLC analysis indicated an enantiomeric excess of 90% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1.0; λ = 210 nm; major enantiomer tR = 7.23 min; minor enantiomer, tR = 6.92 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.50 (dd, *J* = 7.8 Hz, 1.1, 1H, Ar-*H*), 7.30 – 7.10 (m, 2H, Ar-*H*), 7.03 (m, 1H, Ar-*H*), 5.62 – 5.44 (m, 1H, C*H*), 5.28 (m, 1H, C*H*), 2.75 (m, 1H, C*H*CH_2COCH_3), 2.61 (m, 2H, CH_2Ar), 2.50 – 2.37 (m, 2H, CH_2COCH_3), 2.10 (s, 3H, COCH_3), 1.68 (dd, *J* = 6.5 Hz, 1.6 Hz, 3H, CH_3), 1.66 – 1.61 (m, 1H, CH_2), 1.52 (m, 1H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.2, 141.7, 133.4, 132.8, 130.3, 127.5, 127.4, 126.3, 124.3, 49.6, 38.6, 35.3, 34.0, 30.6, 18.0.

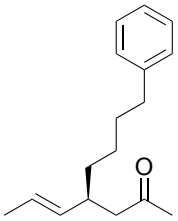
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 1716, 1382, 1153, 966.

HRMS (ESI) m/z calc. for $C_{15}H_{20}O^{79}Br$ $[M+H]^+$: 295.0692, 297.0672, found: 295.0695, 297.0674.

$[\alpha]^{20}_{589}$ = + 2.4 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(*S*, *E*)-8-phenyl-4-(prop-1-en-1-yl) octan-2-one **(89)**



Synthesized according to general procedure **Ib2**, using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), but-3-en-1-ylbenzene (0.08 mL, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), (3E, 5E)-hepta-3, 5-dien-2-one (22 mg, 1.0 eq., 0.2 mmol) **(72)** (34 mg, 1.0 eq., 0.2 mmol) and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **89** (30 mg, 12 mmol, 61%).

The enantiomeric excess of 97% was determined by SFC [Chiralpak® IG; 1500 psi, 30 °C; 1% to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ= 210 nm; minor enantiomer tR = 2.99 mins, major enantiomer tR = 2.58 mins]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.12 – 7.01 (m, 2H, Ar-*H*), 7.01 – 6.86 (m, 3H, Ar-*H*), 5.32 – 5.11 (m, 1H, C*H*), 5.08 – 4.87 (m, 1H, C*H*), 2.37 (td, *J* = 7.8 Hz, 3.2 Hz, 2H, CH_2Ph), 2.26 (td, *J* = 8.2 Hz, 4.8 Hz, 1H, C*H*CH_2COCH_3), 2.23 – 2.06 (m, 2H, CH_2CO), 1.88 (s, 3H, COCH_3), 1.41 (dd, *J* = 6.4 Hz, 1.6 Hz, 3H, CH_3), 1.42 – 1.25 (m, 3H, CH_2), 1.24 – 0.93 (m, 3H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.7, 142.7, 133.9, 128.4, 128.2, 125.6, 125.5, 49.8, 38.7, 35.9, 35.0, 31.4, 30.6, 26.8, 17.9.

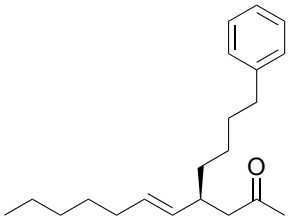
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 1716, 1382, 1153, 997.

HRMS (ESI) m/z calc. for $C_{17}H_{25}O$ $[M+H]^+$: 245.1900, found: 245.1901.

$[\alpha]^{20}_{589}$ = + 1.3 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(*S*, *E*)-4-(4-phenylbutyl) undec-5-en-2-one **(90)**



Synthesized according to general procedure **Ib2***,* using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), but-3-en-1-ylbenzene (0.08 mL, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), (3*E*, 5*E*)-undeca-3, 5-dien-2-one (33 mg, 1.0 eq., 0.2 mmol) **(73)** (34 mg, 1.0 eq., 0.2 mmol) and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **90** (39 mg, 13 mmol, 65%).

The enantiomeric excess of 96% was determined by SFC [Chiralpak® IG; 1500 psi, 30 °C; 1% to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ= 210 nm; minor enantiomer tR = 2.99 mins, major enantiomer tR = 2.57 mins]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.27 – 7.19 (m, 2H, Ar-*H*), 7.13 (td, m, 3H, Ar-*H*), 5.47 – 5.25 (m, 1H, C*H*), 5.10 (m, 1H, C*H*), 2.54 (tt, *J* = 8.9 Hz, 6.7 Hz, 2H, CH_2Ph), 2.48 – 2.39 (m, 1H, C*H*CH_2COCH_3), 2.37 – 2.26 (m, 2H, CH_2CO), 2.05 (s, 3H, COCH_3), 1.98 – 1.83 (m, 2H, CH_2CH=CH), 1.63 – 1.43 (m, 2H, CH_2), 1.39 – 1.08 (m, 10H, 5 x CH_2), 0.84 (t, *J* = 7.0 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.7, 142.7, 132.6, 131.4, 128.4, 128.2, 125.6, 49.9, 38.8, 35.9, 35.0, 32.5, 31.4, 31.4, 30.6, 29.2, 26.8, 22.5, 14.1.

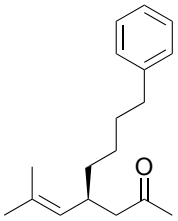
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 1715, 1382, 1153, 954.

HRMS (ESI) m/z calc. for $C_{21}H_{33}O$ $[M+H]^+$: 301.2526, found: 301.2524.

$[\alpha]^{20}_{589}$ = + 1.8 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(*S*)-4-(2-methylprop-1-en-1-yl)-8-phenyloctan-2-one **(91)**



Synthesized according to general procedure **Ib2**, using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), but-3-en-1-ylbenzene (0.08 mL, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), (*E*)-6-methylhepta-3,5-dien-2-one (25 mg, 1.0 eq., 0.2 mmol) **(74)** (25 mg, 1.0 eq., 0.2 mmol) and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **91** (45 mg, 17 mmol, 87%).

HPLC analysis indicated an enantiomeric excess of 92% [Chiralpak® AYH; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1.0; λ = 210 nm; major enantiomer tR = 7.24 min; minor enantiomer, tR = 6.97 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.16 – 6.99 (m, 2H, Ar-*H*), 7.00 – 6.87 (m, 3H, Ar-*H*), 4.59 (dp, *J* = 9.8 Hz, 1.4 Hz, 1H, C*H*), 2.63 – 2.43 (m, 1H, C*H*CH_2COCH_3), 2.43 – 2.28 (m, 2H, CH_2Ph), 2.11 (qd, *J* = 15.1 Hz, 7.0 Hz, 2H, CH_2CO), 1.86 (s, 3H, COCH_3), 1.42 (m, 7H, 2 x CH_3, CH_2), 1.40 – 1.26 (m, 1H, CH_2), 1.25 – 0.91 (m, 4H, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.8, 142.8, 132.2, 128.4, 128.2, 128.1, 125.6, 50.1, 35.9, 35.7, 34.4, 31.6, 30.6, 26.9, 25.8, 18.2.

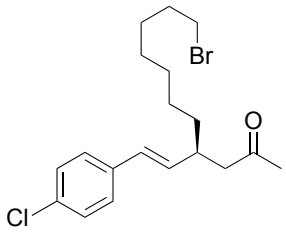
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 1716, 1382, 1153, 966.

HRMS (ESI) m/z calc. for $C_{18}H_{27}O$ $[M+H]^+$: 259.2056, found: 259.2058.

$[\alpha]^{20}_{589}$ = + 9.9 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(*S*, *E*)-11-bromo-4- (4-chlorostyryl) undecan-2-one **(92)**



Synthesized according to general procedure **Ib2***,* using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), 7-bromohept-1-ene (89 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), (3*E*, 5*E*)-6-(4-chlorophenyl) hexa-3, 5-dien-2-one (41 mg, 1.0 eq., 0.2 mmol) **(76)** (25 mg, 1.0 eq., 0.2 mmol) and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 70:30; SiO_2) to give the desired product **92** (41 mg, 11 mmol, 53%).

HPLC analysis indicated an enantiomeric excess of 47% [Chiralpak® IA; flow: 1.0 mL/min; hexane/i-PrOH: 95: 5.0; λ = 210 nm; major enantiomer tR = 7.68 min; minor enantiomer, tR = 8.08 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.23 (s, 4H, Ar-*H*), 6.31 (dd, *J* = 15.8 Hz, 0.9 Hz, 1H, C*H*), 5.95 (dd, *J* = 15.8 Hz, 8.7 Hz, 1H, C*H*), 3.37 (t, *J* = 6.8 Hz, 2H, CH_2Br), 2.81 – 2.58 (m, 1H, C*H* CH_2COCH_3), 2.58 – 2.42 (m, 2H, CH_2COCH_3), 2.11 (s, 3H, COCH_3), 2.00 – 1.71 (m, 2H, CH_2), 1.51 – 1.05 (m, 10H, 5 x CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 207.9, 135.8, 133.9, 132.7, 129.1, 128.6, 127.3, 49.4, 38.8, 34.9, 34.0, 32.8, 30.7, 29.4, 28.7, 28.1, 27.1.

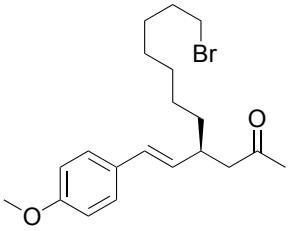
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 2929, 1716, 1490, 1091, 967.

HRMS (ESI) m/z calc. for $C_{19}H_{27}O^{79}Br^{35}Cl$ $[M+H]^+$: 385.0928, 387.0908, 389.0878, 390.0912 found: 385.0928, 387.0905, 389.0879, 390.0911.

$[\alpha]^{20}_{589}$ = +3.2 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(*E*)-11-bromo-4- (4-methoxystyryl) undecan-2-one **(93)**



Synthesized according to general procedure **Ib2**, using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), 7-bromohept-1-ene (89 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), (3*E*, 5*E*)-6-(4-methoxyphenyl) hexa-3, 5-dien-2-one (40 mg, 1.0 eq., 0.2 mmol) **(77)** and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 70:30; SiO_2) to give the desired product **93** (40 mg, 14 mmol, 70%).

HPLC analysis indicated an enantiomeric excess of 43% [Chiralpak® IA; flow: 1.0 mL/min; hexane/*i*-PrOH: 95: 5.0; λ = 254 nm; major enantiomer tR = 8.94 min; minor enantiomer, tR = 9.75 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.28 – 6.97 (m, 2H, Ar-*H*), 6.80 – 6.50 (m, 2H, Ar-*H*), 6.16 (d, *J* = 15.8 Hz, 1H, C*H*), 5.68 (dd, *J* = 15.8 Hz, 8.7 Hz, 1H, C*H*), 3.63 (s, 3H, OCH_3), 3.23 (t, *J* = 6.9 Hz, 2H, CH_2Br), 2.52 (t, *J* = 7.7 Hz, 1H, C*H*), 2.35 (d, *J* = 6.9 Hz, 2H, CH_2COCH$_3$), 1.97 (s, 3H, COCH_3), 1.78 – 1.53 (m, 2H, CH_2), 1.44 – 0.87 (m, 10H, 5 x CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.2, 158.9, 131.0, 130.2, 129.6, 127.2, 113.9, 55.3, 49.7, 39.0, 35.1, 34.0, 32.8, 30.7, 29.4, 28.7, 28.1, 27.1.

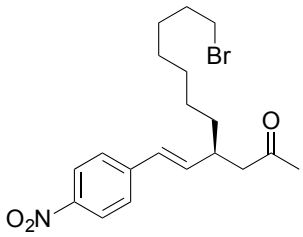
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2927, 2853, 1713, 1510, 1247, 968.

HRMS (ESI) m/z calc. for $C_{20}H_{30}O_2{}^{79}Br$ $[M+H]^+$: 381.1424, 383.1403 found: 381.1427, 383.1406.

$[\alpha]^{20}_{589}$ = +6.5 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(*S*, *E*)-11-bromo-4- (4-nitrostyryl) undecan-2-one **(94)**



Synthesized according to general procedure **Ib2***,* using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), 7-bromohept-1-ene (89 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), ((3*E*, 5*E*)-6-(4-nitrophenyl) hexa-3, 5-dien-2-one (43 mg, 1.0 eq., 0.2 mmol) **(78)** and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 70:30; SiO_2) to give the desired product **94** (49 mg, 12 mmol, 62%).

HPLC analysis indicated an enantiomeric excess of 86% [Chiralpak® IA; flow: 1.0 mL/min; hexane/*i*-PrOH: 96: 4.0; λ = 210 nm; major enantiomer tR = 19.55 min; minor enantiomer, tR = 21.13 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 8.32 – 7.98 (m, 2H, Ar-*H*), 7.56 – 7.38 (m, 2H, Ar-*H*), 6.45 (d, *J* = 15.9 Hz, 1H, C*H*), 6.20 (dd, *J* = 15.9 Hz, 8.7 Hz, 1H, C*H*), 3.39 (t, *J* = 6.8, 2H, CH_2Br), 2.97 – 2.69 (m, 1H, C*H*), 2.67 – 2.38 (m, 2H, CH_2COCH$_3$), 2.14 (s, 3H, COCH_3), 1.95 – 1.70 (m, 2H, CH_2), 1.64 – 0.96 (m, 10H, 5 x CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 207.3, 146.7, 143.8, 138.5, 128.6, 126.6, 124.0, 48.9, 38.8, 34.7, 34.0, 32.7, 30.7, 29.3, 28.6, 28.1, 27.1.

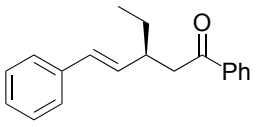
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 2930, 1716, 1515, 1341, 968.

HRMS (ESI) m/z calc. for $C_{19}H_{26}O_3{}^{79}Br^{23}Na$ $[M+Na]^+$: 418.0988, 420.0968 found: 418.0985, 420.0964.

$[\alpha]^{20}_{589}$ = +1.2 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(*S*, *E*)-3-ethyl-1,5-diphenylpent-4-en-1-one **(95)**[19]



Synthesized according to general procedure **Ib1**, using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), a balloon filled with ethylene, Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), (*2E,4E*)-1,5-diphenylpenta-2,4-dien-1-one (47 mg, 1.0 eq., 0.2 mmol) **(79)** and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 95:5; SiO_2) to give the desired product **95** (27 mg, 0.10 mmol, 51%).

The enantiomeric excess of 54% was determined by SFC [Chiralpak® IF; 1500 psi, 30 °C; 1% to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ= 243 nm; minor enantiomer tR = 3.12 mins, major enantiomer tR = 2.96 mins]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.90 – 7.75 (m, 2H, Ar-*H*), 7.50 – 7.40 (m, 1H, Ar-*H*), 7.39 – 7.31 (m, 2H, Ar-*H*), 7.25 – 7.14 (m, 4H, Ar-*H*), 7.13 – 7.03 (m, 1H, Ar-*H*), 6.29 (d, *J* = 15.8 Hz, 1H, C*H*), 5.97 (dd, *J* = 15.8 Hz, 8.6 Hz, 1H, C*H*), 3.10 – 2.82 (m, 2H, CH_2CO), 2.80 – 2.64 (m, 1H, C*H*CH_2CH_3), 1.69 – 1.27 (m, 2H, CH_2CH_3), 0.84 (t, *J* = 7.4 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 199.4, 137.5, 137.4, 133.3, 132.9, 130.4, 128.6, 128.5, 128.1, 127.0, 126.1, 44.0, 40.8, 27.9, 11.8.

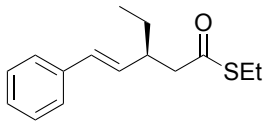
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2961, 2360, 1685, 1448, 748.

HRMS (ESI) m/z calc. for $C_{19}H_{21}O$ $[M+H]^+$: 265.1587 found: 265.1586.

$[\alpha]^{20}_{589}$ = +11.7 (c 0.6, $CHCl_3$)

Absolute configuration assigned by comparing optical rotations to literature.[19]

(*S*,*E*)-*S*-ethyl-3-ethyl-5-phenylpent-4-enethioate **(96)**



Synthesized according to general procedure **Ib1**, using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), a balloon filled with ethylene, Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), *S*-ethyl (2*E*,4*E*)-5-phenylpenta-2,4-dienethioate (43 mg, 1.0 eq., 0.2 mmol) **(80)** and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 97:3; SiO_2) to give the desired product **96** (38 mg, 0.15 mmol, 77%).

The enantiomeric excess of 95% was determined by SFC [Chiralpak® IG; 1500 psi, 30 °C; 1% to 30% MeOH in 5 mins; flow: 1.5 mL/min; λ= 243 nm; minor enantiomer tR = 2.25 mins, major enantiomer tR = 2.35 mins]

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.38 – 7.25 (m, 4H, Ar-*H*), 7.23 – 7.15 (m, 1H, Ar-*H*), 6.40 (d, *J* = 15.8 Hz, 1H, C*H*), 6.16 – 5.81 (m, 1H, C*H*), 2.85 (q, *J* = 7.4 Hz, 2H, SC*H*$_2$CH$_3$), 2.74 – 2.54 (m, 3H, C*H*$_2$CO, C*H*), 1.66 – 1.50 (m, 1H, C*H*$_2$CH$_3$), 1.46 – 1.33 (m, 1H, C*H*$_2$CH$_3$), 1.20 (t, *J* = 7.4 Hz, 3H, SCH$_2$C*H*$_3$), 0.91 (t, *J* = 7.4 Hz, 3H, C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 198.4, 137.4, 132.3, 130.8, 128.5, 127.1, 126.2, 49.4, 42.1, 27.6, 23.4, 14.8, 11.6.

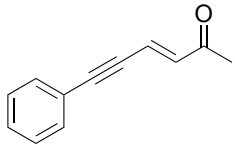
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2969, 2341, 1685, 1449, 1022, 748.

HRMS (ESI) m/z calc. for $C_{15}H_{21}O^{32}S$ $[M+H]^+$: 249.1308 found: 249.1308.

$[\alpha]^{20}_{589}$ = +72.6 (c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(*E*)-6-phenylhex-3-en-5-yn-2-one **(97)**



Prepared according to general procedure **H**, using *n*-BuLi (4.8 mL, 1.0 eq., in hexane, 7.5 mmol), diethyl (2-oxopropyl) phosphonate (1.45 mL, 1.0 eq., 7.5 mmol) in 20 mL THF, 3-phenylpropiolaldehyde (0.98 g, 1.0 eq., 7.5 mmol) Purified by flash column chromatography (pentane: Et_2O; 90:10; SiO_2) to afford the desired product **97** (1.03 g, 6.0 mmol, 81%) in >20:1 *E*:*Z* ratio.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.57 – 7.43 (m, 2H, Ar-*H*), 7.41 – 7.32 (m, 3H, Ar-*H*), 6.83 (d, *J* = 16.0 Hz, 1H, C*H*), 6.57 (d, *J* = 16.0 Hz, 1H, C*H*), 2.30 (s, 3H, CH_3).

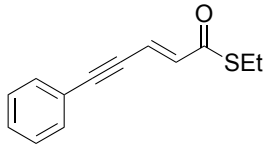
^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 197.0, 137.8, 132.0, 129.4, 128.5, 123.8, 122.2, 99.7, 86.7, 27.7.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2980, 2196, 1671, 1586, 1361, 1248, 957.

HRMS (ESI) m/z calc. for $C_{12}H_{11}O$ $[M+H]^+$: 171.0804, found: 171.0805.

This data was concordant with literature values.[20]

(*E*)-*S*-ethyl-5-phenylpent-2-en-4-ynethioate **(98)**



Prepared according to general procedure **H**, using *n*-BuLi (4.8 mL, 1.0 eq., in hexane, 7.5 mmol), *S*-ethyl 2-(diethoxyphosphoryl) ethanethioate (1.8 mL, 1.0 eq., 7.5 mmol) in 20 mL THF at 0 °C under argon. The mixture was stirred for another 20 min. A solution of 3-phenylpropiolaldehyde (0.98 g, 1.0 eq., 7.5 mmol) in THF was added dropwise. The mixture was slowly warmed to room temperature and was continued overnight. The mixture was quenched with aqueous NH_4Cl (sat.). The reaction mixture was partitioned between the aqueous and organic phases, and the aqueous layer extracted by Et_2O three times. The combined organic materials were dried ($MgSO_4$), filtered, concentrated, and further purified by flash column chromatography (pentane: Et_2O; 97:3; SiO_2) to afford the desired product **98** (1.23 g, 5.7 mmol, 75%) in >20:1 *E*:*Z* ratio.

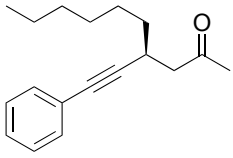
^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.47 – 7.35 (m, 2H, Ar-*H*), 7.34 – 7.21 (m, 3H, Ar-*H*), 6.82 (d, *J* = 15.6 Hz, 1H, C*H*), 6.48 (d, *J* = 15.5 Hz, 1H, C*H*), 2.92 (q, *J* = 7.4 Hz, 2H, SCH_2), 1.23 (t, *J* = 7.4 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 188.9, 136.1, 132.0, 129.4, 128.5, 122.2, 120.7, 98.7, 86.8, 23.5, 14.7.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 2975, 2190, 1658, 1589, 1054, 976, 756.

HRMS (ESI) m/z calc. for $C_{13}H_{13}O^{32}S$ $[M+H]^+$: 217.0682, found: 217.0682.

(*S*)-4-(phenylethynyl) decan-2-one **(99)**



Synthesized according to general procedure **Ib2***,* using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), hex-1-ene (42 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), 6-phenylhex-5-yn-2-one (34 mg, 1.0 eq., 0.2 mmol) **(97)** and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **99** (36 mg, 14 mmol, 70%).

HPLC analysis indicated an enantiomeric excess of 94% [Chiralpak® IB; flow: 0.8 mL/min; hexane/*i*-PrOH: 99: 1; λ = 210 nm; major enantiomer tR = 7.39 min; minor enantiomer, tR = 7.83 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.25 – 7.16 (m, 2H, Ar-*H*), 7.15 – 7.04 (m, 3H, Ar-*H*), 3.12 – 2.72 (m, 1H, C*H*), 2.58 (dd, *J* = 16.2 Hz, 7.6 Hz, 1H, CH_2COCH$_3$), 2.42 (dd, *J* = 16.2 Hz, 6.4 Hz, 1H, CH_2COCH$_3$), 2.04 (s, 3H, COCH_3), 1.47 – 1.05 (m, 10H, 5 x CH_2), 0.82 – 0.66 (m, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 207.0, 131.6, 128.2, 127.7, 123.6, 92.1, 81.9, 49.0, 34.9, 31.8, 30.6, 29.0, 27.8, 27.3, 22.7, 14.1.

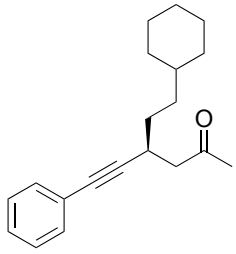
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2980, 2929, 1717, 1362, 1159, 757.

HRMS (ESI) m/z calc. for $C_{18}H_{25}O$ $[M+H]^+$: 257.1900 found: 257.1899.

$[\alpha]^{20}_{589}$ = –7.9 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **92.**

(*S*)-4-(2-cyclohexylethyl)-6-phenylhex-5-yn-2-one **(100)**



Synthesized according to general procedure **Ib2***,* using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), vinylcyclohexane (44 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), 6-phenylhex-5-yn-2-one (34 mg, 1.0 eq., 0.2 mmol) **(97)** and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **100** (49 mg, 17 mmol, 87%).

HPLC analysis indicated an enantiomeric excess of 95% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 242 nm; major enantiomer tR = 6.00 min; minor enantiomer, tR = 6.39 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.35 – 7.26 (m, 2H, Ar-*H*), 7.24 – 7.15 (m, 3H, Ar-*H*), 2.97 (m, 1H, C*H*), 2.68 (dd, *J* = 16.2 Hz, 7.6 Hz, 1H, CH_2COCH$_3$), 2.52 (dd, *J* = 16.2 Hz, 6.4 Hz, 1H, CH_2COCH$_3$)), 2.15 (s, 3H, COCH_3), 1.74 – 1.53 (m, 5H, C*H, 2 x* CH_2), 1.52 – 1.02 (m, 7H, CH_2), 0.96 – 0.68 (m, 3, CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 206.9, 131.6, 128.2, 127.7, 123.7, 92.1, 81.9, 49.0, 37.5, 35.0, 33.6, 33.2, 32.3, 30.6, 28.1, 26.7, 26.4.

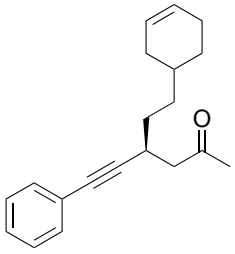
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 1462, 1383, 1153, 954.

HRMS (ESI) m/z calc. for $C_{20}H_{27}O$ $[M+H]^+$: 283.2056 found: 283.2057.

$[\alpha]^{20}_{589}$ = –5.8 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(4*S*)-4-(2-(cyclohex-3-en-1-yl) ethyl)-6-phenylhex-5-yn-2-one **(101)**



Synthesized according to general procedure **Ib2***,* using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), 4-vinylcyclohex-1-ene (43 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), 6-phenylhex-5-yn-2-one (34 mg, 1.0 eq., 0.2 mmol) **(97)** and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol).Purified by column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **101** (47 mg, 17 mmol, 84%).

HPLC analysis indicated an enantiomeric excess of 96% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 242 nm; major enantiomer tR = 6.49 min; minor enantiomer, tR = 7.01 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.23 – 7.15 (m, 2H, Ar-*H*), 7.11 – 7.01 (m, 3H, Ar-*H*), 5.63 – 5.32 (m, 2H, C*H*=C*H*), 3.04 – 2.79 (m, 1H C*H* CH_2COCH_3), 2.57 (dd, *J* = 16.3 Hz, 7.5 Hz, 1H, C$H_2$$COCH_3$), 2.41 (dd, *J* = 16.3 Hz, 6.5 Hz, 1H, C$H_2$$COCH_3$), 2.02 (s, 3H, COC$H_3$), 1.96 – 1.79 (m, 3H, CH=CHCH_2), 1.66 – 1.17 (m, 5H, CH=CHCH_2, 2 x CH_2), 1.13 – 0.95 (m, H, C*H*).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 206.8, 131.6, 128.2, 127.7, 127.1, 126.5, 123.6, 92.0, 82.0, 49.0, 34.2, 33.3, 32.3, 32.1, 30.6, 29.1, 28.0, 25.3.

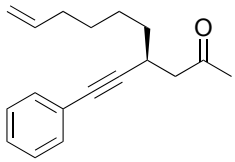
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 1716, 1461, 1382, 1154, 955.

HRMS (ESI) m/z calc. for $C_{20}H_{25}O$ $[M+H]^+$: 281.1900 found: 281.1901.

$[\alpha]^{20}_{589}$ = –11.1 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(*S*)-4-(phenylethynyl) dec-9-en-2-one **(102)**



Synthesized according to general procedure **Ib2***,* using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), hexa-1,5-diene (41 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), 6-phenylhex-5-yn-2-one (34 mg, 1.0 eq., 0.2 mmol) **(97)** and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **102** (40 mg, 16 mmol, 79%).

HPLC analysis indicated an enantiomeric excess of 92% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 210 nm; major enantiomer tR = 6.28 min; minor enantiomer, tR = 6.73 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.30 – 7.13 (m, 2H, Ar-*H*), 7.12 – 7.00 (m, 3H, Ar-*H*), 5.62 (m, 1H, C*H*=CH_2), 4.95 – 4.60 (m, 2H, CH=CH_2), 2.88 (m, 1H, C*H*), 2.56 (dd, *J* = 16.3 Hz, 7.5 Hz, 1H, CH_2COCH_3), 2.40 (dd, *J* = 16.3 Hz, 6.5 Hz, 1H, CH_2COCH_3), 2.02 (s, 3H, COCH_3), 1.88 (dtt, *J* = 8.0 Hz, 6.6 Hz, 1.3 Hz, 2H, CH_2CH=CH_2), 1.58 – 1.05 (m, 6H, 3 x CH_2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 206.8, 138.9, 131.6, 128.2, 127.7, 123.6, 114.4, 91.9, 82.0, 49.0, 34.7, 33.7, 30.6, 28.6, 27.8, 26.8.

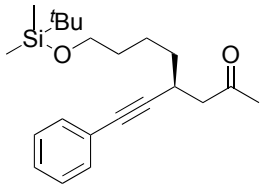
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 1717, 1462, 1383, 1154, 954.

HRMS (ESI) m/z calc. for $C_{18}H_{23}O$ $[M+H]^+$: 255.1743 found: 255.1744.

$[\alpha]^{20}_{589}$ = –6.0 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(*S*)-8-((tert-butyldimethylsilyl) oxy)-4-(phenylethynyl) octan-2-one **(103)**



Synthesized according to general procedure **Ib2**, using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), tert-butyldimethyl (pent-4-en-1-yloxy) silane (80 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), 6-phenylhex-5-yn-2-one (34 mg, 1.0 eq., 0.2 mmol) **(97)** and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **103** (47 mg, 13 mmol, 66%).

HPLC analysis indicated an enantiomeric excess of 94% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 210 nm; major enantiomer tR = 5.64 min; minor enantiomer, tR = 6.04 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.39 – 7.32 (m, 2H, Ar-*H*), 7.30 – 7.20 (m, 3H, Ar-*H*), 3.61 (t, *J* = 5.9 Hz, 2H, C*H*$_2$OSi), 3.18 – 2.96 (m, 1H, C*H*), 2.89 – 2.67 (m, 1H, C*H*$_2$COCH$_3$), 2.58 (m, 1H, C*H*$_2$COCH$_3$), 2.20 (s, 3H, COC*H*$_3$), 1.71-1.26 (m, 6H, 3 x C*H*$_2$), 0.87 (s, 9H, SiC(C*H*$_3$)$_3$), 0.03 (s, 6H, Si(C*H*$_3$)$_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 206.8, 131.6, 128.2, 127.7, 123.6, 91.8, 82.0, 63.0, 49.0, 34.7, 32.6, 30.6, 27.8, 26.0(3C), 23.7, 18.4, -5.3

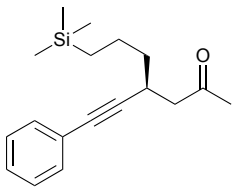
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 1462, 1383, 1153, 955.

HRMS (ESI) m/z calc. for $C_{22}H_{35}O_2{}^{28}Si$ $[M+H]^+$: 359.2401, 360.2434 found: 359.2405, 360.2437.

$[\alpha]^{20}_{589}$ = –6.9 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(*S*)-4-(phenylethynyl)-7-(trimethylsilyl) heptan-2-one **(104)**



Synthesized according to general procedure **Ib2***,* using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), allyltrimethylsilane (57 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), 6-phenylhex-5-yn-2-one (34 mg, 1.0 eq., 0.2 mmol) **(97)** and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol).Purified by column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **104** (42 mg, 15 mmol, 75%).

HPLC analysis indicated an enantiomeric excess of 94% [Chiralpak® IB; flow: 0.7 mL/min; hexane/*i*-PrOH: 99: 1; λ = 242 nm; major enantiomer tR = 7.57 min; minor enantiomer, tR = 7.96 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.42 – 7.33 (m, 2H, Ar-*H*), 7.31 – 7.24 (m, 3H, Ar-*H*), 3.10 (m, 1H, C*H*CH_2COCH_3), 2.75 (dd, *J* = 16.2 Hz, 7.7 Hz, 1H, C*H*$_2COCH_3$), 2.59 (dd, *J* = 16.2 Hz, 6.4 Hz, 1H, C*H*$_2COCH_3$), 2.22 (s, 3H, COC*H*$_3$), 1.70 – 1.23 (m, 4H, 2 x C*H*$_2$), 0.79 – 0.32 (m, 2H, C*H*$_2$Si), 0.00 (s, 9H, 3 x C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 208.5, 133.2, 129.8, 129.3, 125.3, 93.6, 83.6, 50.6, 40.2, 32.2, 29.2, 23.3, 17.9, 0.0.

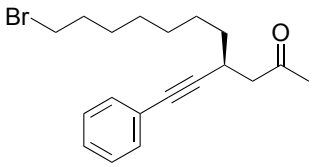
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 1461, 1383, 1251, 1153, 954.

HRMS (ESI) m/z calc. for $C_{18}H_{27}O^{28}Si$ $[M+H]^+$: 287.1826, 288.1859 found: 287.1825, 288.1861.

$[\alpha]^{20}_{589}$ = –23.5 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(*S*)-11-bromo-4-(phenylethynyl) undecan-2-one **(105)**



Synthesized according to general procedure **Ib2***,* using CuCl (1.9 mg, 0.1 eq., 0.02 mmol), **L2** (11.5 mg, 0.1 eq., 0.02 mmol), AgOTf (5.6 mg, 0.11 eq., 0.022 mmol), 7-bromohept-1-ene (89 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), 6-phenylhex-5-yn-2-one (34 mg, 1.0 eq., 0.2 mmol) **(97)** and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **105** (53 mg, 15 mmol, 76%).

HPLC analysis indicated an enantiomeric excess of 96% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 210 nm; major enantiomer tR = 7.96 min; minor enantiomer, tR = 9.12 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.22 – 7.14 (m, 2H, Ar-*H*), 7.11 – 7.03 (m, 3H, Ar-*H*), 3.20 (t, *J* = 6.9 Hz, 2H, C*H*$_2$Br), 3.01 – 2.75 (m, 1H, C*H*), 2.56 (dd, *J* = 16.3 Hz, 7.5 Hz, 1H, C*H*$_2$COCH$_3$), 2.40 (dd, *J* = 16.3 Hz, 6.5 Hz, 1H, C*H*$_2$COCH$_3$), 2.02 (s, 3H, COC*H*$_3$), 1.75 – 1.54 (m, 2H, C*H*$_2$), 1.46 – 0.97 (m, 10H, 5 x C*H*$_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 206.8, 131.6, 128.2, 127.7, 123.6, 91.9, 82.0, 49.0, 34.8, 34.0, 32.8, 30.6, 29.1, 28.6, 28.1, 27.8, 27.2.

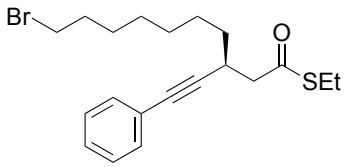
IR (ν_{max}/cm^{-1}, $CHCl_3$) 2981, 1717, 1462, 1154, 954.

HRMS (ESI) m/z calc. for $C_{19}H_{26}O^{79}Br$ $[M+H]^+$: 349.1162, 351.1141 found: 349.1162, 351.1141 .

$[\alpha]^{20}_{589}$ = –10.1 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95**.

(*S*)-*S*-ethyl-10-bromo-3- (phenylethynyl) decanethioate **(106)**



Synthesized according to general procedure **Ib2***,* using CuCl (3.8 mg, 0.2 eq., 0.04 mmol), **L2** (22.9 mg, 0.2 eq., 0.04 mmol), 1.6 mL Et_2O/DCM (1/1), AgOTf (12 mg, 0.22 eq., 0.044 mmol), 7-bromohept-1-ene (89 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), (*E*)-*S*-ethyl-5-phenylpent-2-en-4-ynethioate (**98**) (43 mg, 1.0 eq., 0.2 mmol) and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **106** (52 mg, 15 mmol, 66%).

HPLC analysis indicated an enantiomeric excess of 97% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 243 nm; major enantiomer tR = 5.44 min; minor enantiomer, tR = 6.44 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.18 (m, 2H, Ar-*H*), 7.06 (m, 3H, Ar-*H*), 3.20 (t, *J* = 6.8 Hz, 2H, C*H*$_2$Br), 2.91 (td, *J* = 7.5 Hz, 3.9 Hz, 1H, C*H*), 2.71 (q, *J* = 7.4 Hz, 2H, SC*H*$_2$CH$_3$), 2.63 (dd, *J* = 14.8 Hz, 7.4 Hz, 1H, C*H*$_2$COCH$_3$), 2.52 (dd, *J* = 14.8 Hz, 7.1 Hz, 1H, C*H*$_2$COCH$_3$), 1.65 (p, *J* = 7.0 Hz, 2H, C*H*$_2$), 1.45 – 1.10 (m, 10H, 5 x C*H*$_2$), 1.06 (t, *J* = 7.4 Hz, 3H, C*H*$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 197.6, 131.6, 128.2, 127.8, 123.6, 91.1, 82.5, 49.1, 34.4, 34.0, 32.8, 29.3, 29.1, 28.6, 28.1, 27.1, 23.5, 14.8.

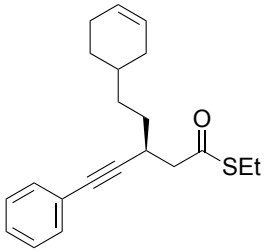
IR (ν_{max}/cm^{-1}, $CHCl_3$) 3026, 2842, 1687, 1429, 1305, 1016, 911

HRMS (ESI) m/z calc. for $C_{20}H_{28}O^{79}Br^{32}S$ $[M+H]^+$: 395.1039, 397.1018, 398.1052, 399.0976 found: 395.1037, 397.1015, 398.1047, 399.0976.

$[\alpha]^{20}_{589}$ = +5.2 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95.**

(3*S*)-*S*-ethyl-3-(2-(cyclohex-3-en-1-yl) ethyl)-5-phenylpent-4-ynethioate **(107)**



Synthesized according to general procedure **Ib2***,* using CuCl (3.8 mg, 0.2 eq., 0.04 mmol), **L2** (22.9 mg, 0.2 eq., 0.04 mmol), 1.6 mL Et_2O/DCM (1/1), AgOTf (12 mg, 0.22 eq., 0.044 mmol), 4-vinylcyclohex-1-ene (54 mg, 2.5 eq., 0.5 mmol), Cp_2ZrHCl (103 mg, 2.0 eq., 0.4 mmol), (*E*)-*S*-ethyl-5-phenylpent-2-en-4-ynethioate (**98**) (43 mg, 1.0 eq., 0.2 mmol) and TMSCl (0.127 mL, 5.0 eq., 1.0 mmol). Purified by flash column chromatography (Petrol: Et_2O; 90:10; SiO_2) to give the desired product **107** (49 mg, 15 mmol, 75%).

HPLC analysis indicated an enantiomeric excess of 96% [Chiralpak® IB; flow: 1.0 mL/min; hexane/*i*-PrOH: 99: 1; λ = 243 nm; major enantiomer tR = 4.76 min; minor enantiomer, tR = 5.16 min].

^{1}H NMR (400 MHz, $CDCl_3$) δ_H/ppm 7.23 – 7.13 (m, 2H, Ar-*H*), 7.13 – 6.97 (m, 3H, Ar-*H*), 5.45 (d, *J* = 2.3 Hz, 2H, 2 x C*H*), 3.07 – 2.80 (m, 1H, C*H*), 2.76 – 2.67 (m, 2H, SCH_2), 2.64 (dd, *J* = 14.7 Hz, 7.4 Hz, 1H, CH_2COCH$_3$), 2.53 (dd, *J* = 14.8 Hz, 7.1 Hz, 1H, CH_2COCH$_3$), 1.99 – 1.88 (m, 2H, CH_2CH=CH), 1.86 – 1.79 (m, 2H, CH_2CH=CH), 1.65 – 1.19 (m, 7H, C*H,* 3 x CH_2), 1.06 (t, *J* = 7.4 Hz, 3H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C/ppm 197.5, 131.6, 128.16, 127.7, 127.1, 126.5, 123.6 91.2, 82.5, 49.1, 34.1, 33.3, 31.9, 31.7, 29.6, 29.1, 25.3, 23.5, 14.8.

IR (ν_{max}/cm^{-1}, $CHCl_3$) 3024, 2839, 1687, 1432, 1305, 1025, 912.

HRMS (ESI) m/z calc. for $C_{21}H_{27}O^{32}S$ $[M+H]^+$: 327.1777, 328.1811 found: 327.1776, 328.1811.

$[\alpha]^{20}_{589}$ = +18.4 **(**c 1.0, $CHCl_3$)

Absolute configuration assigned by analogy to **95.**

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