DEVELOPMENT OF NOVEL THREONINE DERIVED CHIRAL PHOSPHINES AND THEIR APPLICATIONS IN MORITA–BAYLIS–HILLMAN REACTION AND ENANTIOSELECTIVE [3+2] CYCLOADDITIONS

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NATIONAL UNIVERSITY OF SINGAPORE

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Summary

The phosphine-triggered organic transformations have become a practical and powerful tool in organic chemistry. The unique reactivity of organophosphines, compared to their amine counterparts, has led to the discovery of a variety of novel reactions. This thesis describes the development of novel threonine-derived phosphine organocatalysts and their applications in Morita–Baylis–Hillman reaction and enantioselective [3+2] cycloadditions.

Chapter 1 presented a brief introduction of nucleophilic phosphine catalysis and a series of phosphine-promoted enantioselective organic reactions. Selected examples illustrating recent advances in this research field were also presented.

In Chapter 2, a highly enantioselective Morita–Baylis–Hillman (MBH) reaction of acrylates with aromatic aldehydes using L-threonine-derived bifunctional phosphine–thiourea catalysts was described. The mechanistic aspects of the reaction were also discussed.

In Chapter 3, the development of a new family of dipeptide-based chiral phosphines was presented. Such catalysts were applied to the asymmetric [3+2] cycloaddition of allenoates to α-substituted acrylates, yielding functionalized cyclopentenes with quaternary stereogenic centers in high yields and with excellent enantioselectivities.

In Chapter 4, acrylamides derived from 3,5-dimethyl-1*H*-pyrazole were utilized in the asymmetric [3+2] cycloaddition with the allenoate catalyzed by dipeptide-derived phosphines.

In Chapter 5, a highly enantioselective [3+2] annulation of aliphatic or aromatic imines with allenoates was realized by employing threonine-based dipeptidic

phosphines as catalysts. Highly enantioselective 2-alkyl/aryl-substituted 3-pyrrolines could be generated in short reaction times and with low catalyst loadings. Moreover, synthetic value of this method was demonstrated by using imine–allene annulation as a key step in a concise formal synthesis of (+)-trachelanthamidine.

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List of Schemes

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List of Abbreviations

Ac	Acetyl
Aq	Aqueous
Ar	Aromatic
Atm	Atmosphere
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bz	Benzoyl
Bu	Butyl
CAN	Ceric ammonium nitrate
Cat.	Catalysts
Conc.	Concentrated
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethylene
DIAD	Diisopropylazodicarboxylate
DMAP	4-Dimethylaminopyridine
DME	Dimethyl ether
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DIPA	Diisopropylamine
Dpp	Diphenyphosphinyl
d.r.	Diastereomeric ratio
E^+	Electrophile

EDA	Ethyl diazoacetate
EDC•HCl	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	Enantiomeric excess
Et	Ethyl
EWG	Electron-withdrawing group
H	Hour
HOBt	Hydroxybenzotriazole
HPLC	High performance liquid chromatography
IPA	*iso*-Propanol
LA	Lewis acid
LDA	Lithium diisopropylamine
Me	Methyl
Mes	1,3,5-trimethyl benzene
Ms	Methyl sulfonyl
Naph (Np)	Naphthyl
NR	No reaction
Ph	Phenyl
PMP	*p*-methoxylphenyl
Pr	Propyl
PTC	Phase transfer catalyst
PTSA (TsOH)	*p*-Toluenesulfonic acid
Py (pyr)	Pyridine
R.T.	Room temperature

TBME	*tert*-Butylmethylether
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	Triethylamine
TFA	Trifluoromethylacetic acid
THF	Tetrahydrofuran
TIPB	1,3,5-Triisopropylphenyl
TPP	Triphenylphosphine
TPS	Triphenylsilane
TS	Transition state
Ts (Tos)	*p*-Toluenesulfonyl

List of Publications

1. Han, X.; Wang, Y.; Zhong, F.; Lu, Y. "Enantioselective [3+2] Cycloaddition of Allenes to Acrylates Catalyzed by Dipeptide-derived Novel Phosphines: Facile Creation of Functionalized Cyclopentenes Containing Quaternary Stereogenic Centers", *J. Am. Chem. Soc.* **2011**, *133*, 1726. (**No. 1 *JACS* most-read article in January/February 2011; highlighted in *SYNFACTS* 2011, 442**)

2. Han, X.; Zhong, F.; Wang, Y.; Lu, Y. "Versatile Enantioselective [3+2] Cyclization between Imines and Allenoates Catalyzed by Dipeptide-Based Phosphines", *Angew. Chem. Int. Ed.* **2012**, *51*, 767. (**highlighted in *SYNFACTS* 2012, 331**)

3. Han, X.; Wang, Y.; Zhong, F.; Lu, Y. "Enantioselective Morita–Baylis–Hillman (MBH) Reaction Promoted by L-Threonine-Derived Phosphine–Thiourea Catalysts", *Org. Biomol. Chem.* **2011**, *9*, 6734.

4. Han, X.; Wang, S.-X.; Zhong, F.; Lu, Y. "Formation of Functionalized Cyclopentenes via Catalytic Asymmetric [3+2] Cycloaddition of Acrylamides with an Allenoate Promoted by Dipeptide-Derived Phosphines", *Synthesis* **2011**, 1859.

5. Zhong, F.; Han, X.; Wang, Y.; Lu, Y. "Highly Enantioselective [3+2] Annulation of Morita-Baylis-Hillman Adducts Mediated by L-Threonine-Derived Bifunctional Phosphines: Synthesis of 3-Spirocyclopentene-2-oxindoles having Two Contiguous Quaternary Centers", *Angew. Chem. Int. Ed.* **2011**, *50*, 7837. (**highlighted in *SYNFACTS* 2011, 1020**)

6. Wang, S.-X.; Han, X.; Zhong, F.; Lu, Y. "Novel Amino Acid-Based Bifunctional Chiral Phosphines", *Synlett* **2011,** 2766.

7. Dou, X.; Han, X.; Lu, Y. "From Feist–Bénary Reaction to Organocatalytic Domino Michael–Alkylation Reaction: Asymmetric Synthesis of 3(2*H*)-Furanones", *Chem. Eur. J.* **2012**, 18, 85.

8. Zhao, Q.-Y.; Han, X.; Wei, Y.; Shi, M.; Lu, Y. "Asymmetric [3+2] Annulation of Allenes with Maleimides Catalyzed by Dipeptide-Derived Phosphines: Facile

Creation of Functionalized Bicyclic Cyclopentenes Containing Two Tertiary Stereogenic Centers", *Chem. Commun.* **2012**, *48*, 970.

9. Zhong, F.; Han, X.; Wang, Y.; Lu, Y. "Highly enantioselective [4+2] annulations catalyzed by amino acid-based phosphines: Synthesis of functionalized cyclohexenes and 3-spirocyclohexene-2-oxindoles ", *Chem. Sci.* **2012**, *3*, 1231.

10. Zhong, F.; Wang, Y.; Han, X.; Huang, K.-W.; Lu, Y. "L-Threonine-Derived Bifunctional Phosphine-Sulfonamide Catalyst-Promoted Enantioselective Aza-Morita–Baylis–Hillman Reaction", *Org. Lett.* **2011**, *13*, 1310. (**highlighted in *SYNFACTS* 2011, 551**).

Chapter 1 Nucleophilic Phosphine Organocatalysis

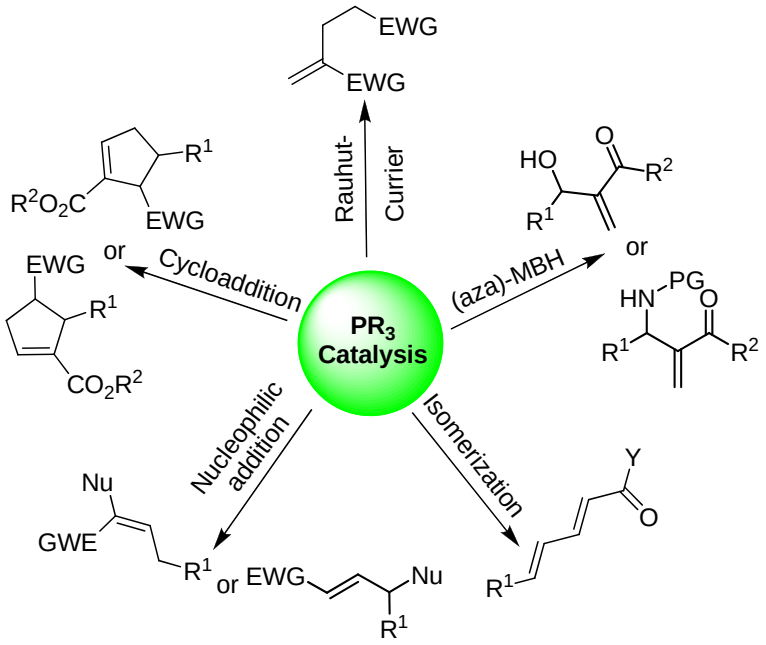
1.1 Introduction

Nucleophilic catalysis refers to the acceleration of chemical reaction by utilizing a nucleophilic compound, which is involved in the rapid formation of a low-energy covalent intermediate, and does not end up in the reaction product. The nucleophilic catalyst enhances the reactivity of a reactant through donation of its electron pair to an electrophile reactant other than a proton. Moreover, nucleophilicity of a nucleophilic catalyst is closely related to the polarizability of the nucleophilic atom, and is also very sensitive to steric hindrance.

Nucleophilic catalysis plays an important role in organic synthesis. Numerous Lewis bases, such as tertiary phosphines, pyridines, 4-dimethylaminopyridine (DMAP), *N*-heterocyclic carbenes (NHCs), have been employed as nucleophilic catalysts in a wide array of organic reactions. These compounds accelerate a broad spectrum of reactions, including rearrangement of *O*-acylated enolates,[1] isomerization of alkynes to dienes,[2] acylation of alcohols by anhydrides[3] and addition of alcohols to ketones.[4]

Organophosphorus compounds have been widely used in synthetic organic chemistry for more than a century. The well-known applications include Wittig reaction, Mitsunobu and Staudinger reactions, furthermore, phosphines are commonly employed ligands in transition metal-mediated processes.[5] However, the most significant important developments in nucleophilic phosphine catalysis only emerged in the last two decades. The triphenylphosphine and its derivatives, which are commercially available or easily accessible, can be directly used as organocatalysts in Michael-type additions of activated alkenes and alkynes or 1,2-addition of carbonyl

groups.[6] As compared to similarly substituted amines, phosphines are generally less basic and more nucleophilic, which consequently contribute to their divergent catalytic behaviors and unique properties in organic processes. The reaction cycles of phosphine-promoted processes start from the formation of the phosphonium ylide-type intermediates through donation of the non-bonded phosphorus lone pair of electrons to eletronphilic species, such as activated alkynes and olefins. The resultant ylide intermediates undergo subsequent coupling reactions with the other reaction partners, such as olefins, imines and aldehydes, affording a variety of highly functionalized molecular frameworks. The relevant examples are Morita–Baylis–Hillman-type reactions,[7] the isomerization of alkynes to dienes,[8] the nucleophilic additions of alkynes,[9] the Rauhut-Currier reactions[10] and the cycloadditions of allenoates (Scheme 1.1).[11]



Scheme 1.1 Selective examples of phosphine-promoted organic reactions

The catalytic ability of organophosphorus compounds can be attributed primarily to their pronounced nucleophilicity and the exceptional stability of the phosphonium enolate zwitterions. There are several important features of phosphine organocatalysis: (1) the nucleophilicity of phosphines are easily tunable by simply varying the substitutents (alkyl or aryl) on the phosphorus atom; (2) modification of chiral phosphine backbones could result in asymmetric induction; (3) the availability of many known phosphine ligands makes the catalyst development more readily; (4) most phosphine compounds are not only cheap and stable, but also completely free from contamination as compared with some metal catalysts, which is an especially attractive feature for industrial synthesis.[12]

Asymmetric organocatalysis has been growing rapidly in the past decade, and has been established as an important tool in the preparation of chiral molecules. Despite the importance of tertiary phosphines in organocatalysis, it was only till the late 1990s that Vedejs and co-workers reported the first enantioselective example utilizing phosphine- catalysts,[13] in which they showed the effectiveness of cyclic phosphines in the asymmetric acylations. Shortly after, Zhang et al. disclosed the highly enantioselective [3+2] cycloaddition between allenoates and acrylates catalyzed by a bicyclic chiral phosphine.[14] Since then, phosphine-mediated nucleophilic catalysis has attracted much attention from synthetic community and became an intensively investigated research area. In the following sections, recent development in this field will be discussed in detail.

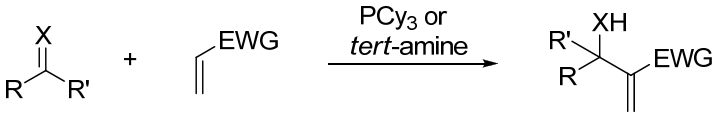
1.2 Phosphine-Promoted Enantioselective Organic Reactions

In this section, several types of asymmetric organic reactions promoted by chiral phosphine catalysts will be introduced. The unique reactivity of phosphines has

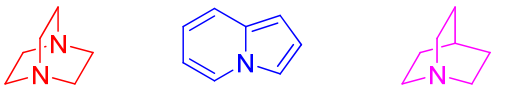
allowed the discovery of the Michael-type addition of activated alkenes and alkynes, enantioselective nucleophilic additions at the α- or γ-position of unsaturated carbonyl compounds, as well as novel [3+2] and [4+2] cyclizations of electron-deficient allenes and alkynes. Additionally, the divergent phosphine catalyst has also made the acylation of secondary alcohol occurred in an enantioselective fashion.

1.2.1 Morita–Baylis–Hillman (MBH) Reactions

The origin of Morita–Baylis–Hillman (MBH) reaction dates back to 1968, when Morita and coworkers demonstrated that the reaction of acrylonitrile or methyl acrylate with various aldehydes under the catalytic influence of tricyclohexylphosphine (PCy_3) led to densely functionalized products (Scheme 1.2).[15] In 1972, Baylis and Hillman disclosed a German patent describing the tertiary bicyclic amine-catalyzed C–C bond formation of aldehydes (aliphatic, aromatic and α,β-unsaturated) with activated alkenes (acrylic esters, acrylonitriles, vinyl ketones, phenyl vinyl sulfone, phenyl vinyl sulfonate ester, vinyl phosphonate and acrolein) (Scheme 1.2).[16]



R = aryl, alkyl, heteroaryl; R' = H, COOR, alkyl
X = O, NCOOR, NTs, NSO_2Ph
EWG = electron withdrawing group:
COR, CHO, CN, COOR, $PO(OEt)_2$, SO_2Ph, SO_3Ph, SOPh

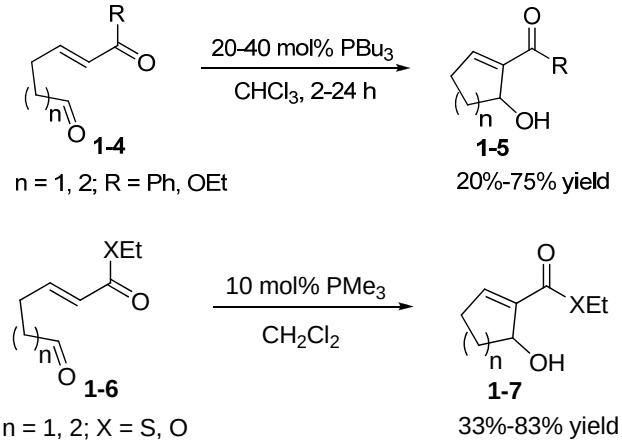
tert-amine = 

DABCO **1-1** | indolizine **1-2** | Quinuclidine **1-3**

Scheme 1.2 Reactions embodied in patents by Morita, Baylis and Hillman

The applications of the MBH reaction were very limited in the early days due to the low reaction rates and conversions, as well as the highly substrate-dependent nature of the MBH reaction. An important improvement in reaction efficiency was achieved by Kawanisi and coworkers by using cocatalysts tributylphosphine and triethylaluminum to promote the MBH reaction between α,β-unsaturated carbonyl compounds and aldehydes.[17] Even though the tertiary amine-catalyzed MBH reaction dominated in the 1980s, the value of phosphine-mediated MBH reaction were later recognized.[18]

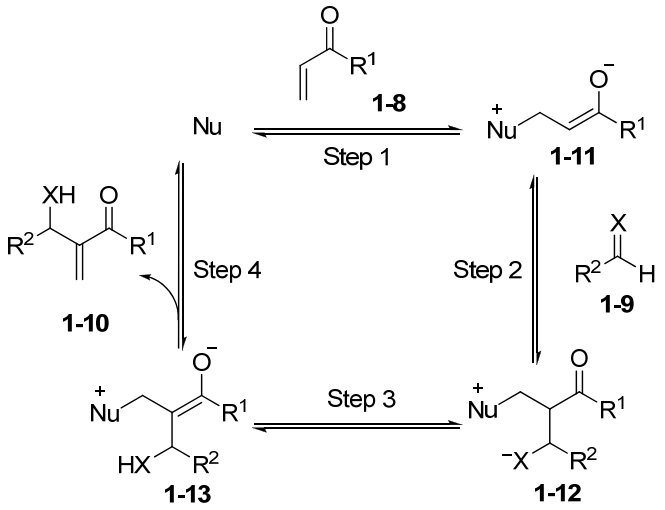
The intramolecular variant of the MBH reaction, which is an excellent strategy for the construction of the cyclic framework, has seen significant progress since the first report by Frater et al. in 1992.[19] Further investigations resulted in the synthesis of cyclopentenes and cyclohexene derivatives using trialkyl phosphines as catalysts (Scheme 1.3).[20]



Scheme 1.3 Interamolecular Morita–Balysi–Hillman reaction

The MBH reaction formally comprises a sequence of Michael addition, aldol reaction and β-elimination, and the commonly accepted mechanism of MBH reaction is depicted in Scheme 1.4. The catalytic cycle is initiated by the reversible conjugate

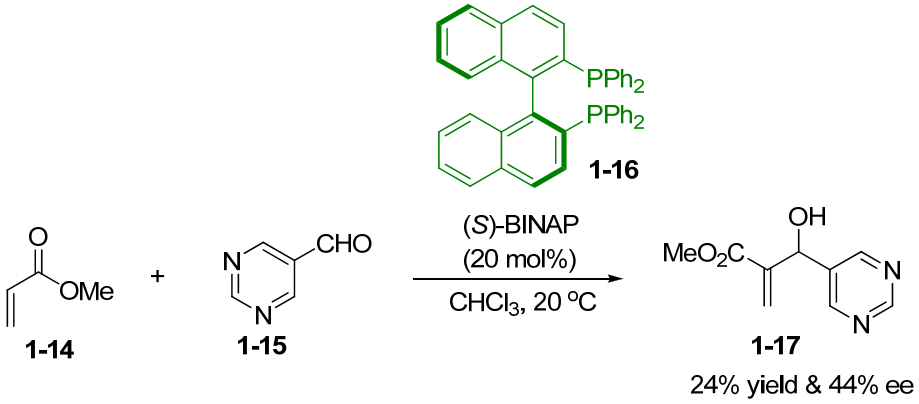
addition of the nucleophilic catalyst to the α,β-unsaturated carbonyl compound **1-8**, generating the zwitterionic enolate **1-11** (step 1), which subsequently intercept the aldehyde or the acylimine **1-9** to afford the second zwitterionic intermediate **1-12** (step 2). Following a proton migration from the α-carbon atom to the β-alkoxide/amide (step 3), β-elimination of the catalyst affords the MBH adduct **1-10** (step 4).[21] The detailed mechanistic studies were carried out and reported by the groups of Aggarwal[22] and McQuade [23] in the past few years.



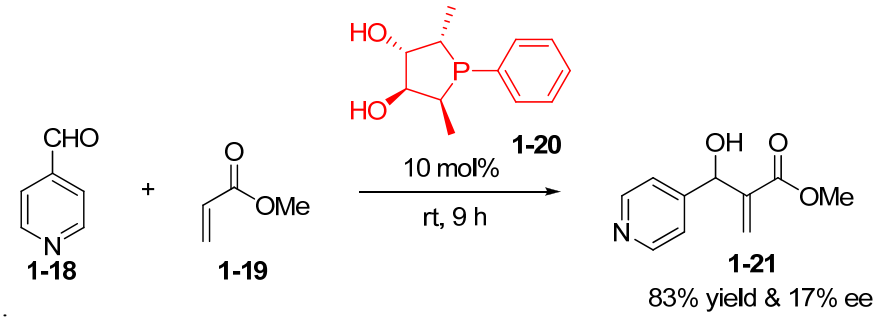
Scheme 1.4 Proposed mechanism for the MBH reaction

Following the initial report by Morita, many new phosphine catalysts, including chiral ones, have been developed and widely applied in the enantioselective condensation of electron-deficient olefins with aldehydes and ketones in both inter- and intramolecular MBH reactions. The first significant advance in enantioselective variant was reported by Soai and co-workers in 1998.[24] The intermolecular MBH reaction between methyl acrylate and pyrimidine-5-carbaldehyde could proceeded smoothly in the presence of 20 mol% (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl [(*S*)-BINAP] **1-16** (Scheme 1.5). The corresponding MBH adduct **1-17** was obtained

with up to 44% ee value. Later, a chiral hydroxyl phospholane **1-20** was prepared and used as a catalyst for the coupling of 4-pyridinecarboaldehyde and methyl acrylate. However, only 17% enantiomeric excess was obtained (Scheme 1.6).[25]



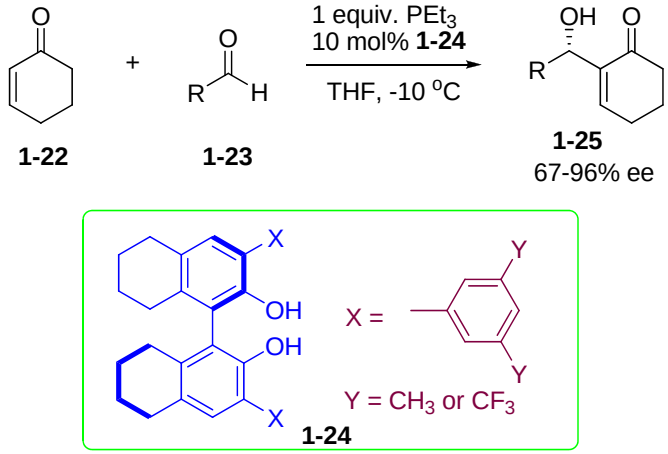
Scheme 1.5 (*S*)-BINAP-catalyzed MBH reaction



Scheme 1.6 Phosphine-catalyzed asymmetric MBH reaction

In 2003, Schaus and coworkers reported the successful use of chiral BINOL-derived Brønsted acids **1-24** catalysts in coordination with triethylphosphine (1 eq.) in the asymmetric MBH reactions of cyclohexenone **1-22** with aldehydes **1-23** (Scheme 1.7).[26] Good to excellent enantioselectivities were achieved with aliphatic aldehydes, while the conjugated aldehydes such as benzaldehyde and cinnamaldehyde led to products in low yields and enantioselectivities. In a plausible mechanism, the

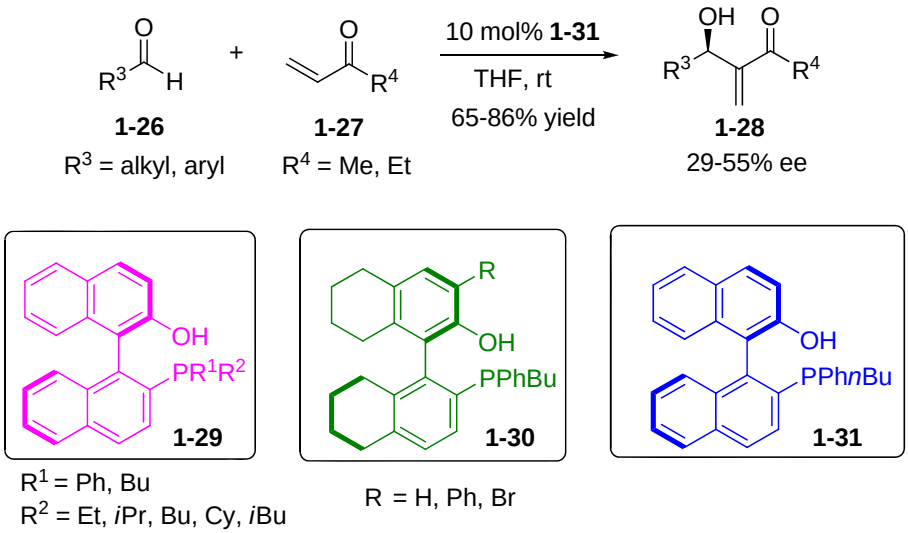
Brønsted acid was suggested to stabilize the phosphonium enolate formed in the Michael addition of triethylphosphine to cyclohexenone, while the hydrogen-bonding interaction between Lewis catalyst and reactant played an important role in the subsequent enantio-determining addition to the aldehyde. Catalysts with two hydrogen bonding partners are necessary for the higher level of enantioselectivity as the mono-*O*-methylated Lewis acid catalyst resulted in diminished catalytic activity, affording **1-25** with only 3% ee.[6]



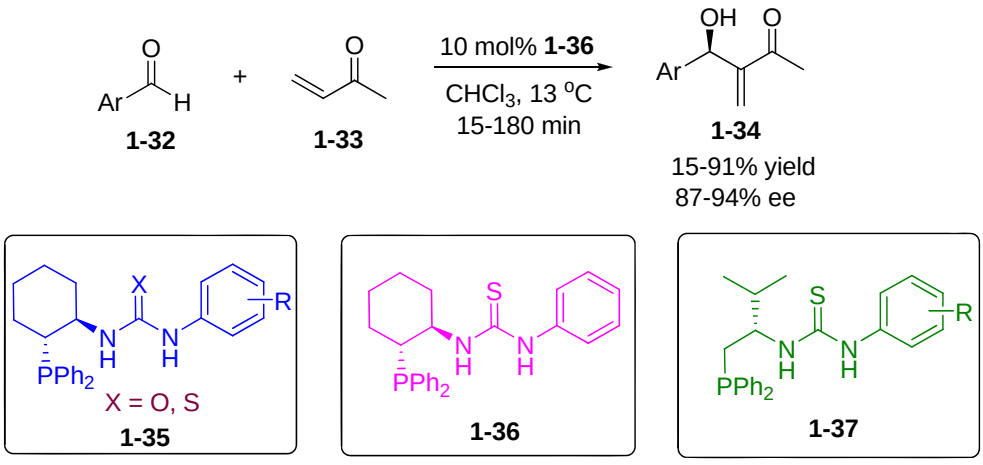
Scheme 1.7 Brønsted-acid-catalyzed asymmetric MBH reactions

Recently, a series of novel chiral bifunctional phosphine catalysts (**1-29**–**1-31**) were designed and synthesized by the Shi group. Lewis base catalyst **1-31** proved to be the most effective for the asymmetric MBH reaction of aldehydes with methyl vinyl ketone (MVK) and ethyl vinyl ketone (EVK), affording the corresponding products in good yields with moderate ee's (Scheme 1.8).[27] Wu and coworkers later reported that *trans*-2-amino-1-(diphenylphosphino)-cyclohexane-derived phosphino(thio)ureas **1-35** were highly effective for the MBH reaction between various aromatic aldehydes and MVK leading to the MBH adducts with excellent

enantiomeric excesses under mild conditions in relative short reaction time (Scheme 1.9).[28] Further exploration was reported by the same group utilizing the L-valine-derived phosphinothioureas (**1-37**, Scheme 1.9) in the reaction of aromatic aldehydes with acrylates. It was found that reaction with electron-rich arylaldehyde turned out to be more difficult resulted in complex reaction mixtures.[29]

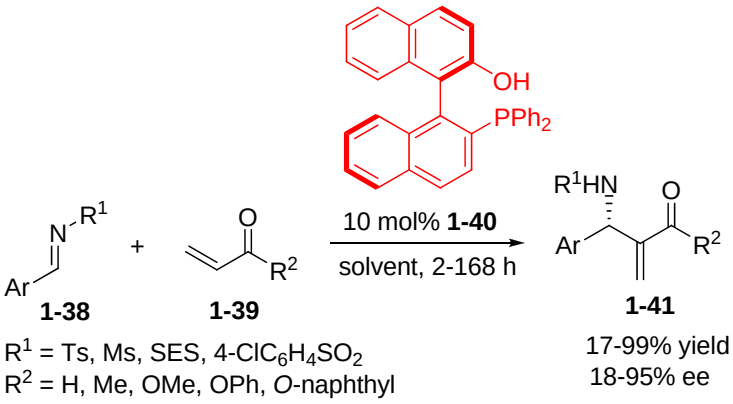


Scheme 1.8 Bifunctional chiral phosphine-catalyzed asymmetric MBH reaction of aldehydes with activated vinyl ketones



Scheme 1.9 MBH reactions of MVK with aromatic aldehydes

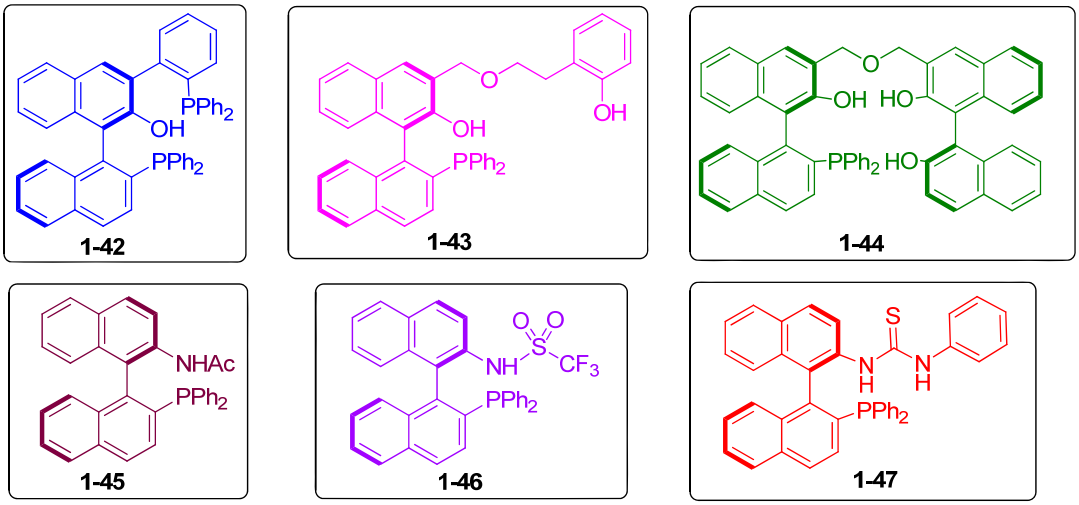
As a modification to the traditional MBH reaction, the aza-Mortia–Baylis–Hillman (aza-MBH) reaction pioneered by Perlmutter and Teo[30] involves the coupling of electron-deficient alkenes with more reactive imines.[31] The first phosphine catalyzed enantioselective variant was demonstrated by Shi in 2003. The best results were obtained using bifunctional phosphine catalyst **1-34** in the reaction of Ts-imines with activated alkenes.[32] Products **1-41** were generally obtained with good to excellent enantioselectivity (Scheme 1.10). The mechanistic studies indicated the bifunctional activation mode of the catalyst – the phosphine acting as a Lewis base to initiate the reaction, whereas the phenol serving as a Brønsted acid to activate the electrophile and stabilize the phosphonium enolate intermediate through hydrogen-bonding interactions.



Scheme 1.10 Catalytic asymmetric aza-MBH reaction

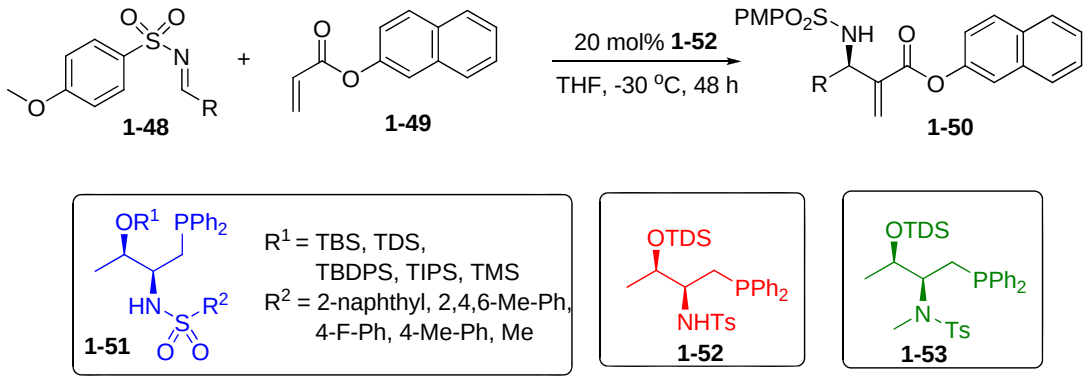
Over the past few years, various organophosphine catalysts have been developed and employed in aza-MBH reactions. These include phosphine bearing multiple phenol moieties, such as compound **1-42**[33], **1-43**,[34] and **1-44**,[35] phosphine–amide **1-45**,[36] phosphine–sulfonamide **1-46**,[37] and phosphinethiourea **1-47** (scheme 1.11).[37] Aromatic imines and vinyl ketones are the most commonly explored substrates. Excellent enantioselectivities have been achieved in these and analogous aza-MBH

reactions.



Scheme 1.11 Selective phosphine catalysts in the aza-MBH reactions

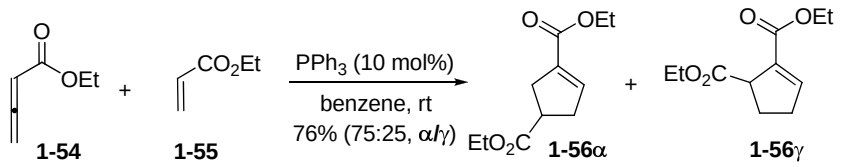
Our research group recently introduced a novel class of amino acid derived bifunctional phosphine–sulfonamide catalysts **1-51** (Scheme 1.12).[38] We demonstrated that these phosphine catalysts were highly effective for the enantioselective aza-MBH reactions of *N*-(*p*-methoxybenzene-sulfonyl)imines with acrylates. Excellent chemical yields (76-96%) and very high enantioselectivities (88-97%) were attainable with 20 mol% phosphine catalyst **1-52** in a wide range of aromatic imines within 48 hours. Further mechanistic studies and the experimental observations suggested that the hydrogen bonding donor moiety of Brønsted acidic sulfonamide in the catalyst contributed significantly to the aza-MBH reaction and was crucial for the asymmetric induction. Employing *N*-methylated sulfonamide phosphine **1-53** as reaction catalyst resulted in the dramatically decreased enantioselectivity (25% ee).



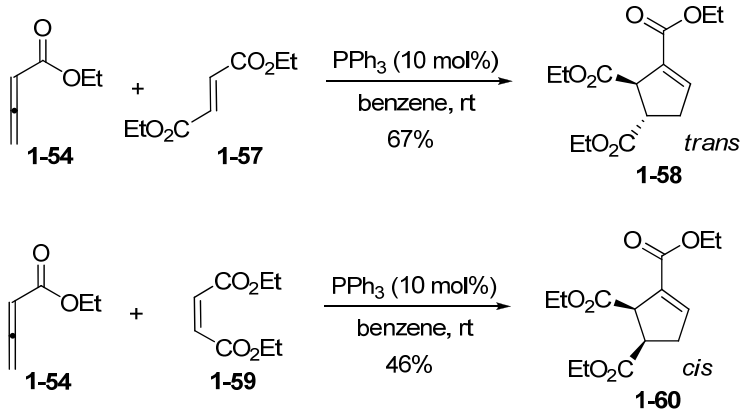
Scheme 1.12 Phosphine–sulfonamide mediated enantioselective Aza-MBH reactions

1.2.2 [3+2] Cycloaddition Reactions of Activated Allenes and Alkynes

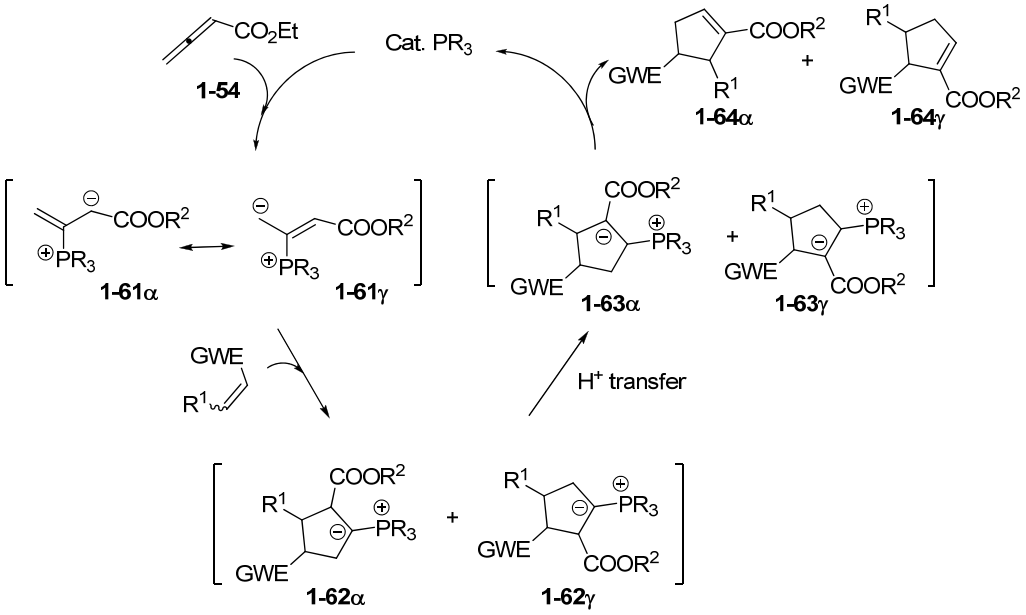
In 1995, Lu's pioneering work on [3+2] cycloadditions of allenoates with α,β-unsaturated carbonyl compounds has established a novel synthetic approach to functionalized five-membered carbocycles from readily available starting materials.[39] It was found that the treatment of 2,3-butadienoate **1-54** with triphenyphosphine or more reactive tributylphosphine in the presence of the activated olefins such as ethyl acrylate **1-55** afforded the corresponding cycloadducts with good regioselectivity (~ 4:1) and isolated combined yield (Scheme 1.13). Further attempted cycloaddition with diethyl fumarate **1-57** and diethyl maleate **1-59** succeeded with furnishing the single product trans-1-**1-58** and cis-**1-60** respectively (Scheme 1.14). In addition to allenoate esters, alkynyl esters were also shown to be suitable substrates for this annulation in the presence of 10 mol% tributylphosphine, while triphenylphosphine failed to catalyze the reaction even at a higher temperature (135 °C) for a long time (24 h) due to the respective weaker catalytic activity.



Scheme 1.13 [3+2] Cycloaddition between allenoate and ethyl acrylate



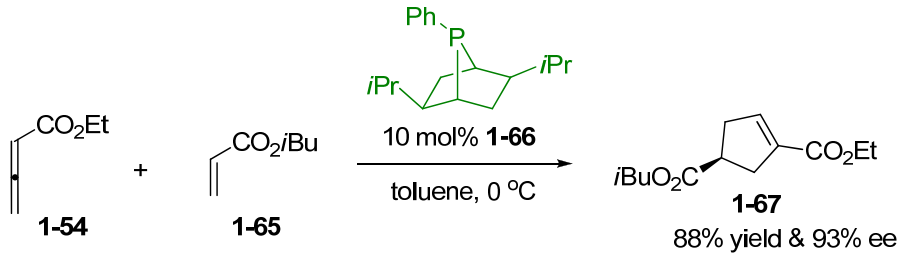
Scheme 1.14 Stereospecific [3+2] cycloaddition with diethyl fumarate and maleate



Scheme 1.15 Proposed mechanism for allenoate–acrylate [3+2] cycloaddition

The proposed mechanism for the [3+2] cycloaddition reaction stems from nucleophilic addition of the phosphine to the β-carbon of the allenoate **1-54** (Scheme 1.15). The generated zwitterionic enolate **1-61α** or **1-61γ** will react with activated alkene to yield the cyclic intermediate **1-62α** and **1-62γ**, which are in equilibrium with **1-63α** and **1-63γ** respectively. Following proton transfer and elimination, the regioisomeric cyclopentenes **1-64α** and **1-64γ** are formed.

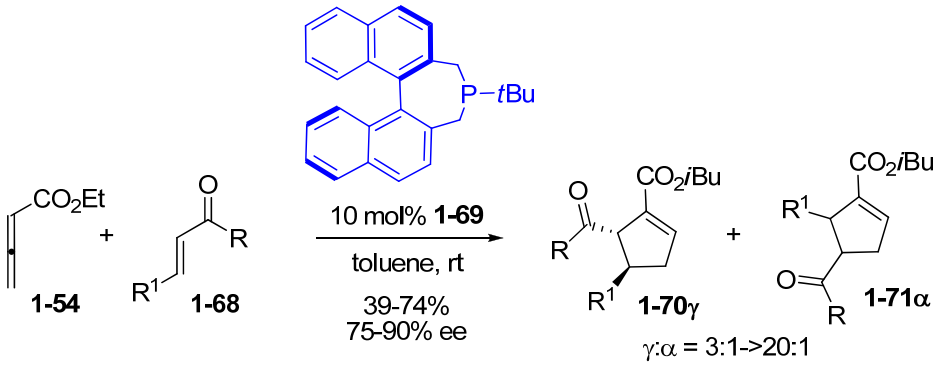
The first enantioselective [3+2] cycloaddition of allenes with olefins was reported by Zhang shortly after Lu's original disclosure.[40] In this work, a variety of chiral mono- and bisphosphines were explored in the annulations between allenoates and acrylate substrates. Structurally rigid *P*-chiral phosphabicyclo[2.2.1]heptane catalyst **1-66** led to the formation of single regioisomer **1-67** in 88% yield and 93% ee in the reaction system of ethyl 2,3-butadienoate **1-54** with isobutyl acrylate **1-65** (Scheme 1.16). Although high level of enantioselectivity was achieved in most cases, the range of activated olefins is limited to α,β-unsubstituted acrylate esters and diethyl maleate.



Scheme 1.16 Enantioselective [3+2] cycloaddition with acrylate

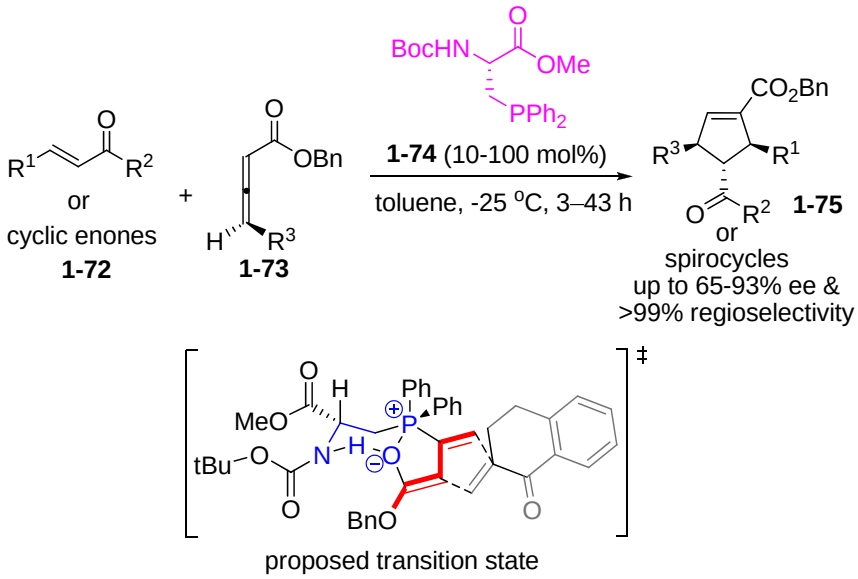
Following Zhang's work, Fu and coworkers revealed their findings with binaphthyl-based *C2*-symmetric chiral phosphine **1-69** in cyclizations reactions with allenoates **1-54** (Scheme 1.17).[41] The scope of activated olefins was broadened to

include β-substituted enones **1-68**, and functionalized spirocyclic products **1-70γ** were obtained in high regioselectivity (up to > 20 :1) and enantiocontrol (up to 90% ee).



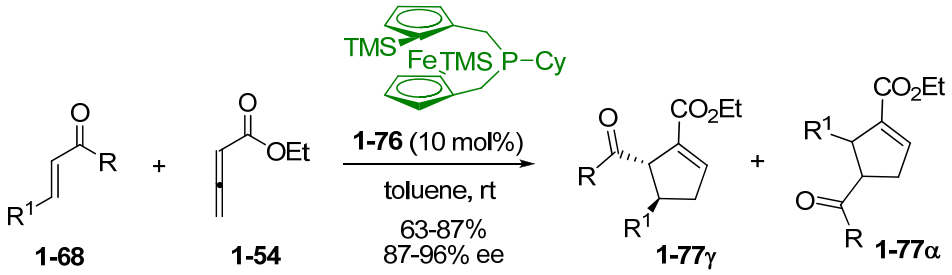
Scheme 1.17 Enantioselective [3+2] cycloadditions with chalcones

Subsequently, Cowen and Miller demonstrated that amino acid-derived chiral phosphine–amide **1-74** could effectively induce the enantioselective variant of [3+2] cycloaddition of allenoate esters **1-73** with acyclic and cyclic enones **1-72** (Scheme 1.18).[42] Under optimized reaction conditions, this simple peptide-like chiral phosphine gave the products **1-75** as only α-isomer in up to 95% isolated yield and 93% ee. Notably, this reaction provides a new methodology for efficient construction of chiral cyclic and acyclic exomethylenes, even though a full equivalent of catalyst loading is required in the case of less reactive chalcones as coupling partners. A six-membered cyclic transition state was considered, in which an intermolecular hydrogen bonding interactions were assumed to exist between the zwitterionic enolate intermediate and the N–H group of the amide moiety in phosphine catalyst. Presumably due to the steric shielding of phenyl rings on the catalyst, the substrate approaches the generated zwitterion from the π-face, resulting in the formation of the major enantiomer.



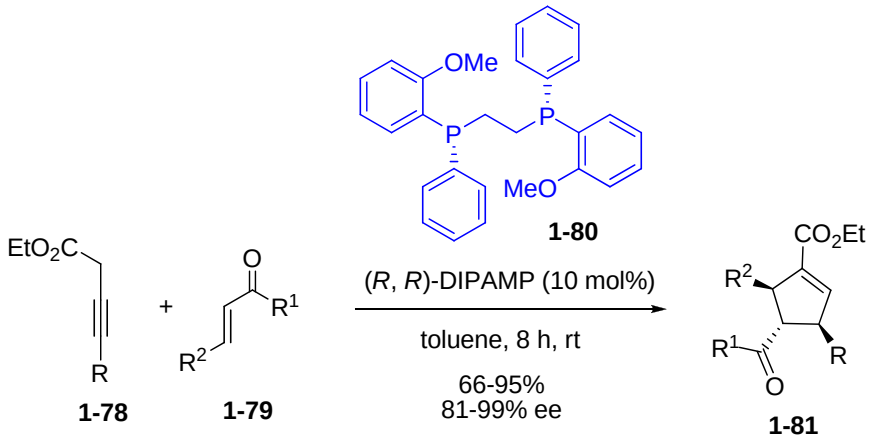
Scheme 1.18 Asymmetric [3+2] cycloaddition of allenoates and enones promoted by phosphine–amide catalyst

A report further expanding the range of chiral phosphines for enantioselective cycloadditon processes to the ferrocenophane derivatives was disclosed by Marinetti and coworkers in 2008.[43] In their approach, a new class of chiral phosphines based on a planar chiral 2-phospha[3]ferrocenophane scaffold was synthesized and examined in the asymmetric [3+2] annulation of ethyl 2,3-butadienoate with α,β-unsaturated esters and ketones (Scheme 1.19). Two regioisomeric cycloadducts **1-77γ** and **1-77α** could be obtained from reactions of **1-54** with **1-68** in high yields (63-87%), regio- (up to >20 : 1), and enantioselectivities (87-96% ee). It should be noted that catalyst **1-76** displays good good air-stability and ease of handling, even though the P-center is trialkylated.



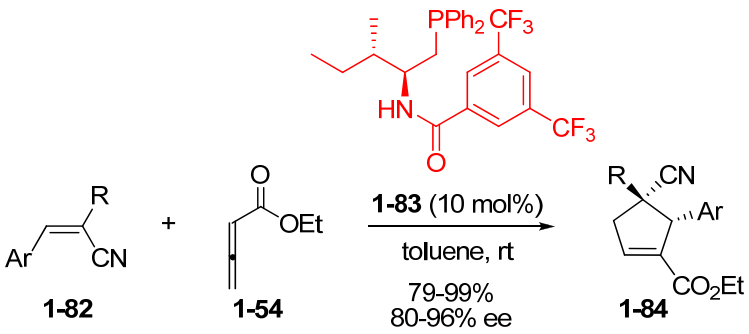
Scheme 1.19 2-Phospha[3]ferrocenophane-promoted enantioselective [3+2] cycloadditions of allenoates with ketones

Usually, alkynes are regarded as less reactive coupling partners as compared to allenes containing the same electron-withdrawing substitutes. Loh et al. recently reported the direct applicability of 3-butynoates **1-78** in the [3+2] cycloaddition reaction of a series of electron-deficient enones **1-79** (Scheme 1.20).[44] Commercially available chiral phosphine, (*R*,*R*)-DIPAMP **1-80** showed the best efficiency for the cycloaddition reaction, affording various cyclopentene derivatives **1-81** with high optical purities (81-99% ee). However, their methodology suffers from the high price of the phosphine catalysts in contrast to the previously presented phosphine catalysts.



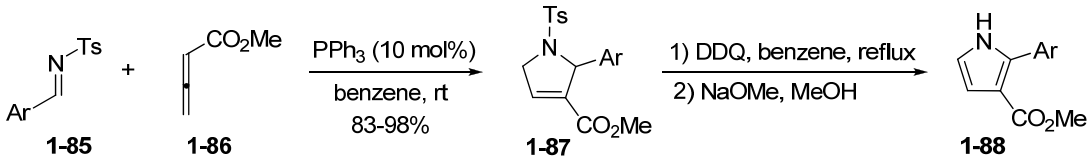
Scheme 1.20 Asymmetric [2+3] cycloaddition reaction using (*R*,*R*)-DIPAMP

Very recently, the Zhao group extended the enantioselective [3+2] cycloaddition scope to the dual activated olefins **1-82**.[45] The cyclization reactions were performed well with allenoates and a variety of α,α-disubstituted alkene in the presence of bifunctional *N*-acyl aminophosphine catalyst **1-83** (Scheme 1.21). The good accessibility of the catalyst, high yields (79-99%), good to excellent enantioselectivities (80-96%), and mild reaction conditions made their methodology a valuable complement to currently existing methods for accessing synthetically useful multifunctionalized chiral cyclopentenes.



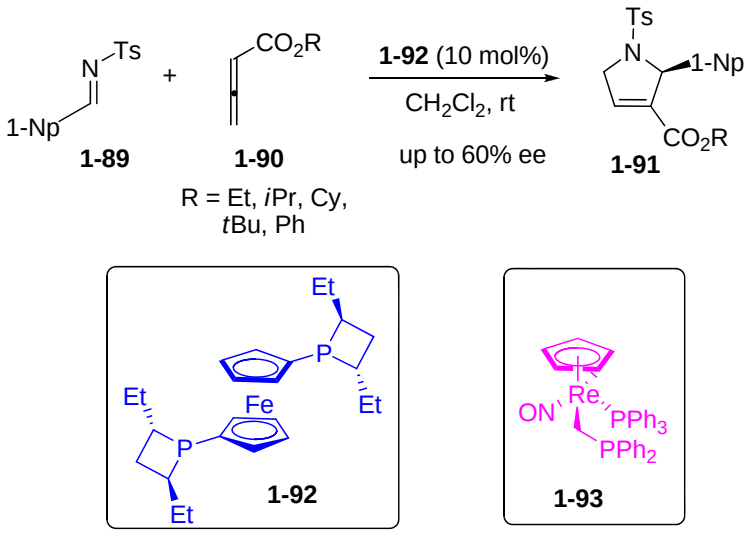
Scheme 1.21 Enantioselective [3+2] cycloadditions of ethyl 2,3-butadienoate with *N*-acyl aminophosphine catalyst

The dipolarophiles in the phosphine-promoted [3+2] cycloadditions are not limited to electron-deficient olefins, as activated aldimines were also found to be competent coupling partners in these types of transformations. Again, Lu and coworkers pioneered this subfield establishing that *N*-tosylimines participated in formal [3+2] cyclization reactions with 2,3-butadienoates catalyzed by triphenylphosphine to afford pyrrolines **1-87** in good to excellent yield (83-98%) (Scheme 1.22).[46] Subsequent transformation of the cycloaddition products produced the pyrroles **1-88** in moderate to good yields in two steps.



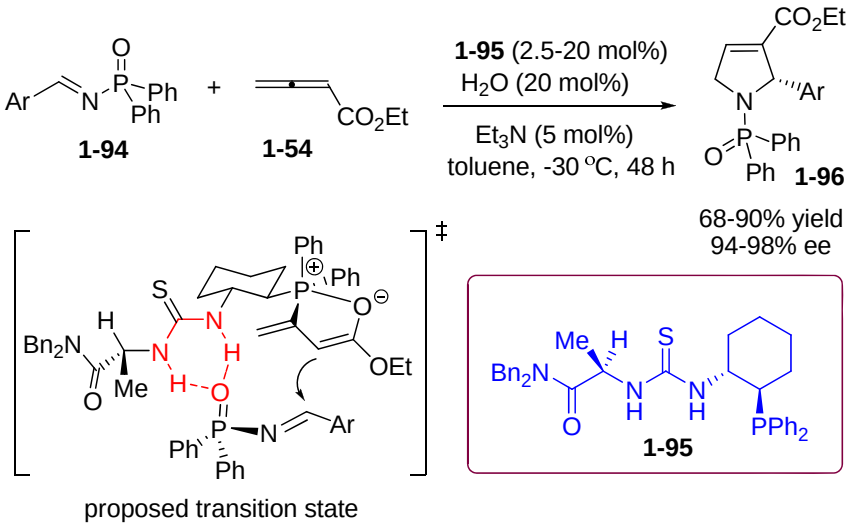
Scheme 1.22 Formal [3+2] cycloaddition with Ts-imines

Lu's methodologies involving phosphine-promoted annulations of allenoates to activated aldimines provide a potentially convenient, nevertheless underdeveloped tool for the synthesis of five-membered multi-functionalized pyrrolines and derivatives, which are useful intermediates for the synthesis of natural products[46b] and pharmaceutically relevant compounds[47]. Due to its significant synthetic potential, the development of an enantioselective variant by using chiral phosphines catalysts would be an important objective. The first example of the asymmetric cycloaddition between allenoate and imine was not reported until 2006. Marinetti and coworkers demonstrated the potential utility of readily available chiral phosphine ligands in the enantioselective synthesis of 2-aryl-3-pyrrolines via the [3+2] cyclizations of imines with allenic esters.[48] The corresponding cyclization adducts 2-naphthyl-substituted pyrrolinic esters **1-91** were obtained in moderate to good yields with ee values ranging from 46% to 60% in the presence of phosphine (*R*,*R*)-Et-FerroTANE **1-92** and coupling partners **1-89** and **1-90** (Scheme 1.23). Scherer and Gladysz later reported similar ee values in analogous systems using rhenium phosphine catalyst **1-93**. Although high chemical yields were achieved, the enantiomeric excesses were still in moderate levels.[49]



Scheme 1.23 Phosphine-promoted enantioselective [3+2] cycloaddition

The breakthrough came when Jacobsen introduced phosphinothiourea catalysis of imine–allene cyclization; by utilizing diphenylphosphinoyl (DPP) imines **1-94**,[50] substituted 2-aryl-2,5-dihydropyrroles **1-96** were formed in good yields and with excellent enantioselectivities (Scheme 1.24). Catalyst **1-95** bearing an alanine unit gave the best results in the reaction system containing substoichiometric triethylamine (Et_3N; 5 mol%) and water (20 mol%). The existence of additives (Et_3N and H_2O) in the reaction medium resulted in significantly increased reaction rates, which presumably is due to the beneficial effect on proton transfer and catalyst regeneration steps in the reaction mechanism—a hypothesis supported experimentally and computationally by the study from other groups.[30,51]



Scheme 1.24 Asymmetric [3+2] cycloadditions of allenoates and imines promoted by phosphine–thiourea catalysts

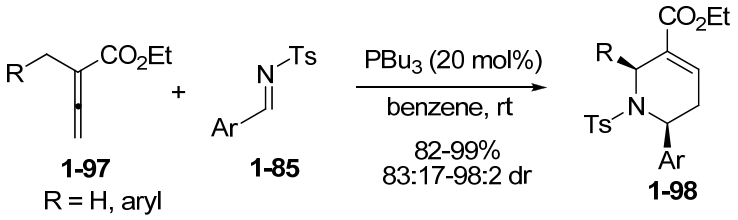
In a plausible mechanism, it was suggested that the thiourea moiety is responsible for the activation of phosphonyl imines through hydrogen bonding interaction. The generated zwitterionic enolate may then attack the imine from the *Re* face in an intramolecular manner resulting in the observed enantiomer of the cycloadduct.

1.3 [4+2] Cycloaddition Reactions of Electron-Deficient Allenoates

The phosphine-promoted reaction between allenes and activated imines, which usually affords the [3+2] adducts, may follow a different reaction pathway, whereby an alkyl group replaces the hydrogen at the α-position of the starting allenic ester. In such a case, a formal [4+2] cycloaddition process takes place, leading to a highly functionalized piperidine, which is prevalent structural motif in bioactive molecules and natural products.

In 2003, Kwon and co-workers reported the [4+2] cyclizations reactions for the

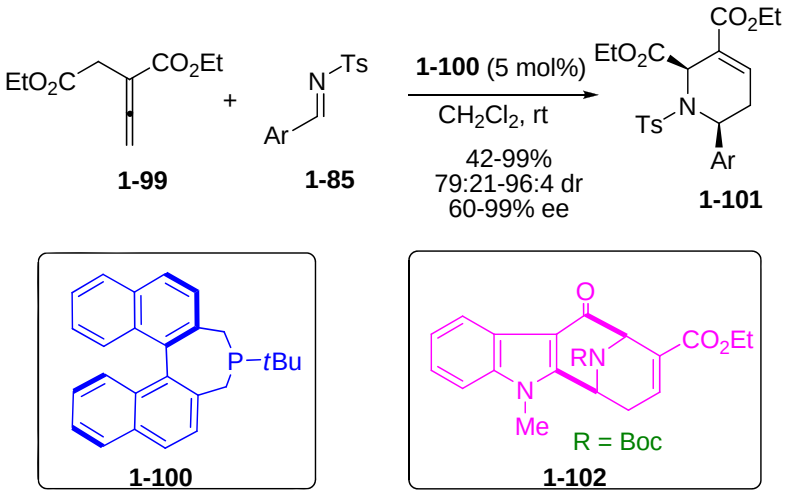
first time. In their work, the tetrahydropyridine derivatives **1-98** were obtained from reactions of allenoate **1-97** with Ts-imine **1-85** in excellent yields with complete regioselectivity and high diastereoselectivities (Scheme 1.25).[52] The potential utility of this [4+2] annulation was demonstrated subsequently by the same group for the synthesis of two biologically active naturally occurring alkaloids, (±)-alstonerine and (±)-macroline.[53]



Scheme 1.25 Enantioselective [4+2] cyclizations between α-substituted allenic esters and *N*-tosyl-substituted imines

A very successful asymmetric variant was later described by Wurz and Fu in 2005.[54] Several known chiral phosphine ligands were examined in the formal [4+2] cycloadditions of Ts-imines to α-substituted allenic esters (Scheme 1.26). BINEPINE **1-100** was found to be the most effective catalyst providing six-membered nitrogen heterocycles **1-101** with excellent diastereo- (up to 96:4) and enantioselectivity (up to 99%). A facile transformation of the [4+2] cycloadduct afforded a framework common to an array of important natural products **1-102**.

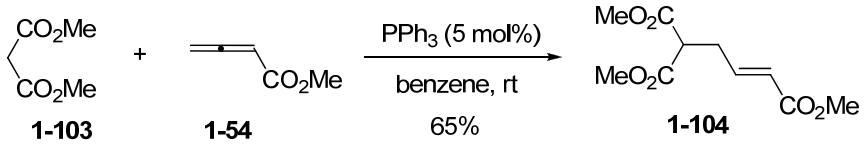
This recent study opens up promising and interesting perspectives in the field of enantioselective [4+2] cycloaddition reaction by using phosphine catalysts. Further progress is expected in the near future.



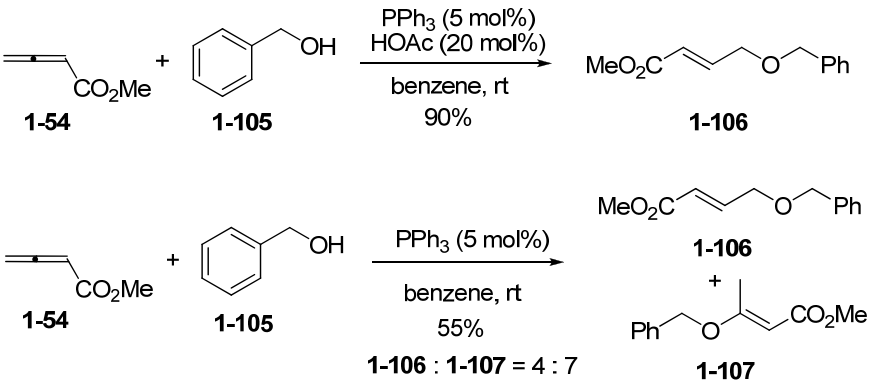
Scheme 1.26 Enantioselective [4+2] cyclizations promoted by BINEPINE

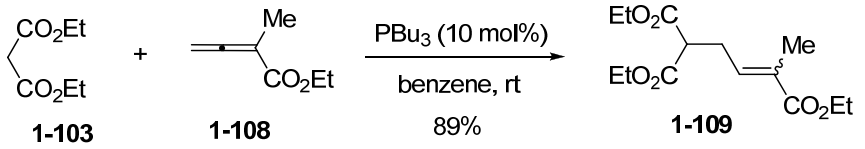
1.2.4 Nucleophilic Addition of Electron-Deficient Substrates

In the mid-1990s, Lu's group and Trost's group independently developed a series of new synthetic reactions derived from nucleophilic addition of tertiary phosphines to electron-deficient allenoates or alkynes.[55,56] Trost first reported the phosphine-promoted γ-addition of nucleophiles to 2-alkynoates (Scheme 1.27). Treatment of dimethyl malonate **1-103** with methyl 2,3-butadienoate **1-54** in the presence of 5 mol% triphenylphosphine in benzene at room temperature afforded the product **1-104** in 65% isolated yield.[57] On the basis of this work, Lu studied the similar addition of carbon and oxygen nucleophiles to the allenoates.[58] When alcohols were used as nucleophiles in the γ-addition, a catalytic amount of an acid (e.g. acetic acid) as a cocatalyst was essential for prohibiting the formation of Michael adduct **1-107**. Moreover, the more nucleophilic tributylphosphine was required for the reaction involving the α-substituted 2,3-butadienoate **1-108** as coupling partners (Scheme 1.28).



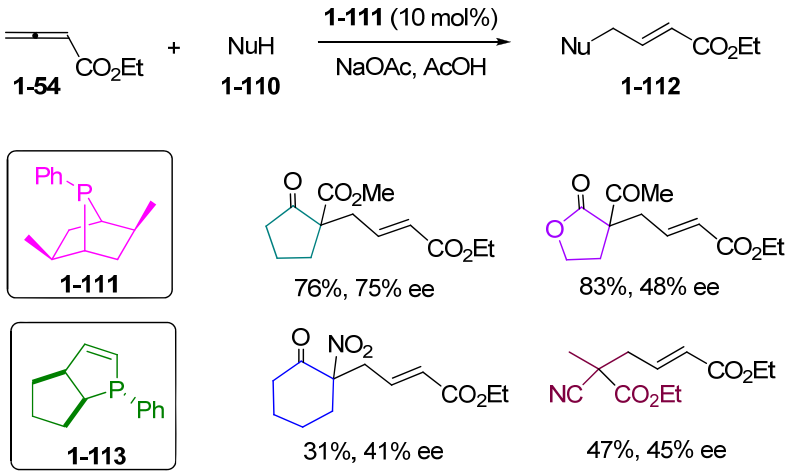
Scheme 1.27 Umpolung γ-addition of allenoate with dimethyl malonate





Scheme 1.28 Phosphine-catalyzed γ-addition of allenoate with nuclephiles

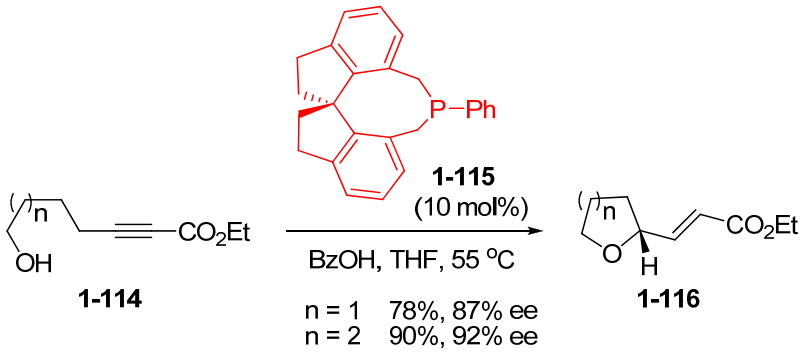
Based on Lu and Trost' discovery, the potential for asymmetric synthesis was demonstrated later by Zhang and coworkers.[59] It was shown that ethyl 2,3-butadienoate reacts with a variety of carbon acids **1-110** to yield γ-addition products **1-112** in moderate enantioselectivity under the conditions of phosphine catalysis (Scheme 1.29). Bicyclic phosphine **1-111** was found to be the optimal catalyst giving the products with enantiomeric excesses of up to 81%. The additive of a sodium acetate-acetic acid buffer could enhance the enantioselectivity considerablely at the expense of slowing the reaction rate significantly.



Scheme 1.29 Chiral phosphine-catalyzed asymmetric nucleophilic addition

Another report further attempted the same reaction of allenic esters with cyclic β-keto esters was disclosed by Pietrusiewicz and coworker in 2004. However, their novel bicyclic phosphine **1-113** (Scheme 1.29) was unable to improve the enantioselectivity; only a maximum 51% ee was obtained.[60]

A major advance in the development of highly enantioselective nucleophilic addition was reported by Chung and Fu in 2009.[61] Spirocyclic monophosphine **1-115**, which had previously proved effective as a chiral ligand in transition-metal chemistry, was utilized as a catalyst in the synthesis of an array of oxygen heterocycles **1-114** from hydroxy-2-alkynoates **1-110**. The nuclephilic addition adducts—tetrahydrofurans and tetrahydropyrans, were obtained in good yields and high enantiomeric excesses in the presence of phosphine **1-115** and benzoic acid as reaction additive (Scheme 1.30). Significantly, this reaction has been used not only to synthesize simple, saturated rings, but also to access a wide range of substituted and benzo-fused species.



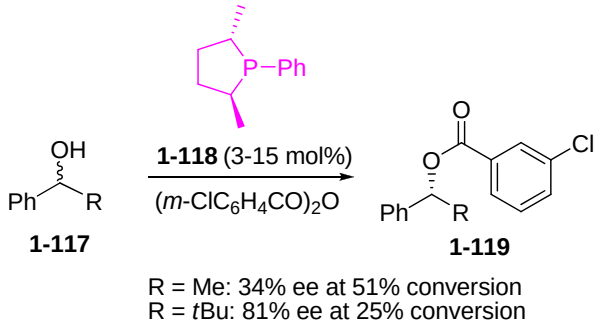
Scheme 1.30 Enantioselective cyclization of hydroxy-substituted 2-alkynoates

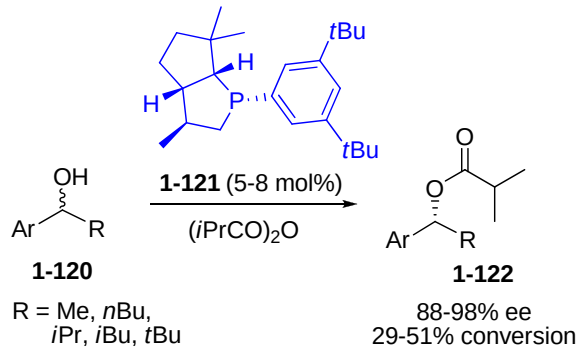
1.2.5 Alcohols Acylation and Kinetic Resolution

Nucleophiles as well as bases are known to catalyze the acylation of alcohols by acid anhydrides. Significant catalysis was therefore anticipated with tributylphosphine, a weak base but a potent nucleophile. In 1993, Vedejs and coworkers surprisingly found that addition of catalytic *n*-Bu_3P to the solution of cyclohexanol in dichloromethane containing 3 equivalence of acid anhydride resulted in the formation of cyclohexyl acetate with 88% conversion.[62] The reaction rates of alcohol acetylation or benzoylation using Bu_3P were remarkably fast, with efficiency similar to those of DMAP catalyst.[63] The reagents Bz_2O/PBu_3 and Ac_2O/PBu_3 acylated typical alcohol substrates including menthol, tertiary alcohols and hindered phenols. A likely mechanistic pathway involves a tight ion pair $[Bu_3P^+COR][RCO_2^-]$ transition state, derived from a *P*-acylphosphonium carboxylate intermediate.

Following the discovery of phosphine-catalyzed alcohol acylations with acid anhydrides, Vedejs and coworkers reported the first examples of enantioselective acyl transfer reactions catalyzed by a chiral phosphine.[64] It was showed that *trans*-2,5-dimethyl-1-phenylphospholane **1-118** could activate *m*-chlorobenzoic anhydride for the chlorobenzoylation of alcohols **1-117** with significant enantioselectivity (Scheme

1.31). However, the reaction was very slow and required two weeks to reach 25% conversion to **1-119** at room temperature using 15 mol% of the phosphine catalyst. Many prior attempts had been made subsequently to develop more efficient chiral nucleophilic acylation phosphine catalysts, including a variety of mono- and disubstituted phospholanes. Among them, bicyclic derivative **1-121** based on the 2-phosphabicyclo-[3.3.0]octane (PBO) skeleton appeared to be remarkably more reactive, giving the acylation products **1-122** with impressive levels of enantioselectivity (Scheme 1.31).[65]

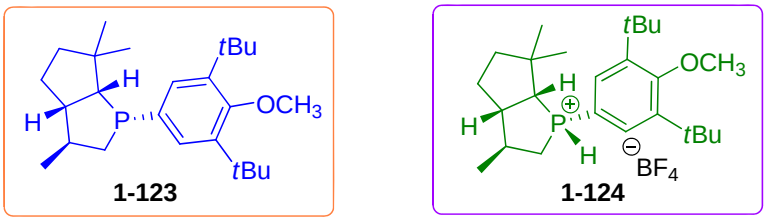




Scheme 1.31 Chiral phosphines as enantioselective acylating catalysts

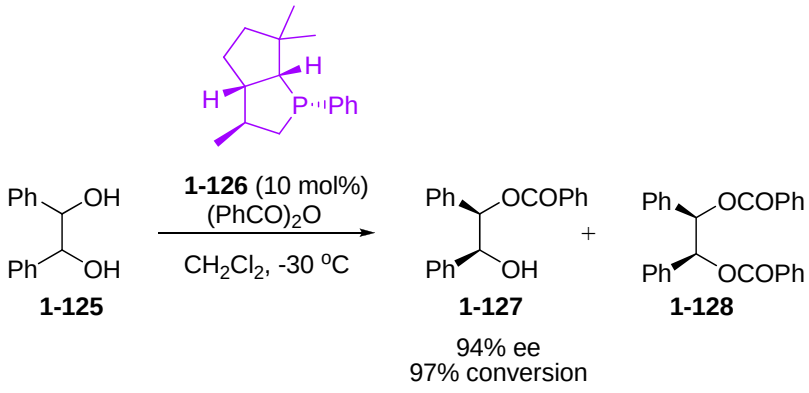
Because PBO catalysts are rather air-sensitive, an improvement was made later by using the air-stable, easy-to-handle phosphonium tetrafluoroborate salts as effective precursors. In situ deprotonation of these phosphonium salts with Et_3N

releases the free phosphine catalyst in typical acylation experiments. Precatalyst **1-123** gave products with enantioselectivities comparable to those with PBO **1-124** for the kinetic resolution of nicotinoylation reactions with nicotinic anhydride (Scheme 1.32).[66]



Scheme 1.32 PBO Derived chiral phosphine salts

Much progress has been made in the kinetic resolution of aryl-substituted and allylic secondary alcohols using specifically designed phosphine catalysts, however, the desymmetrization of diols had not been explored until the year of 2004. Vedejs et al. described the chiral phosphine-promoted desymmetrization of *meso*-hydrobenzoin for the first time.[67] Catalyst **1-126** offered the best efficiency in terms of reactivity and enantioselectivity in the benzoylation reaction, affording product dibenzoate **1-127** with up to 94% enantiomeric excess (Scheme 1.33).

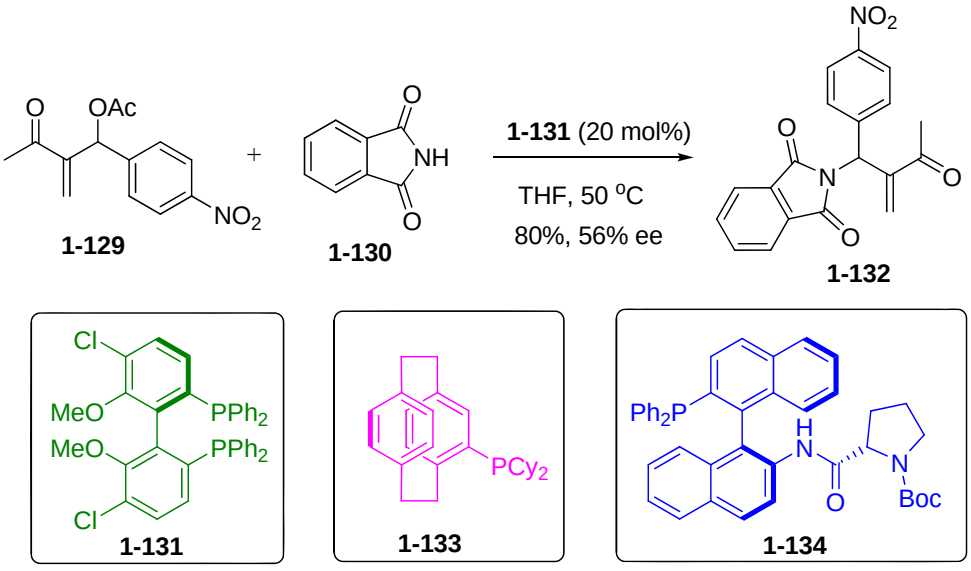


Scheme 1.33 Chiral phosphine-promoted desymmetrization of *meso*-hydrobenzoin

1.2.6 Allylic Substitutions and [3+2] Cyclizaitons of MBH Adducts

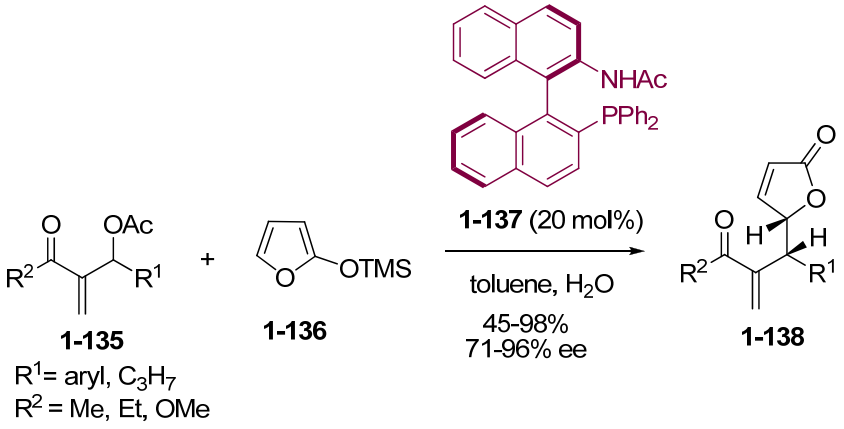
The Morita–Baylis–Hillman (MBH) reaction provides a convenient and atom-economic synthetic method for the synthesis of α-methylene-β-hydroxy-carbonyl compounds, which have proven to be versatile and valuable synthetic intermediates in organic transformations. The MBH adducts have been widely used in organic synthesis, including tertiary amines and metal catalyzed amination and allylic alkylation of MBH adducts, as well as their application in natural products synthesis.[68]

In 2004, Krische and co-workers demonstrated the first examples of chiral phosphine catalyzed allylic amination of MBH acetates. With (*R*)-Cl-MeO-BIPHEP **1-131** as the catalyst, the substitution of 4-nitrophenyl-substituted allylic acetate **1-129** with phthalimide **1-130** furnished the corresponding product **1-132** in 80% isolated yield and 56% enantiomeric excess (Scheme 1.34).[69] Hou[70] and Shi[71] later attempted the same reaction by using phosphine **1-133** and **1-134**, but only moderate enantioselectivity was observed.



Scheme 1.34 Asymmetric allylic aminations of MBH acetates

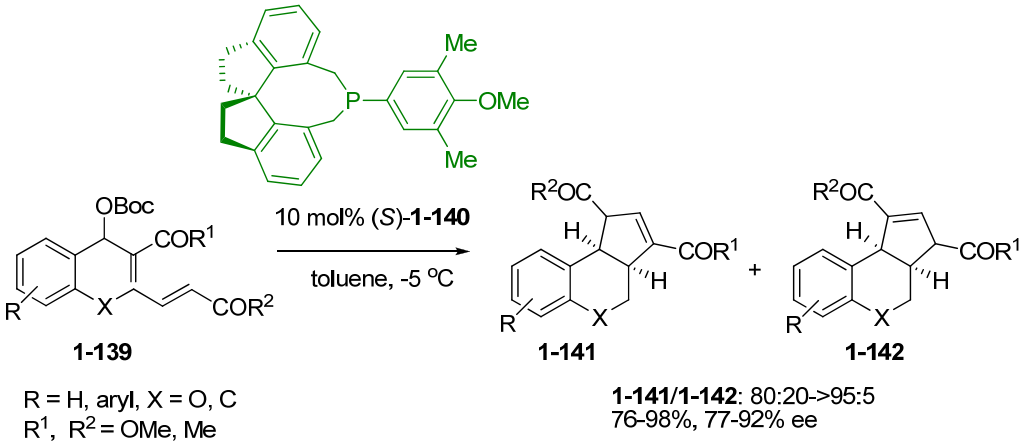
Striking improvement in enantioselectivity became possible when Shi et al. introduced the multifunctional chiral phosphine **1-137** in the nucleophilic substitutions of MBH acetates **1-135** with 2-trimethylsilyloxy furan **1-136**.[72] γ-Butenolides **1-138** were obtained with high *syn*-diastereoselectivity and excellent enantiomeric excesses for a range of substrates (Scheme 1.35).



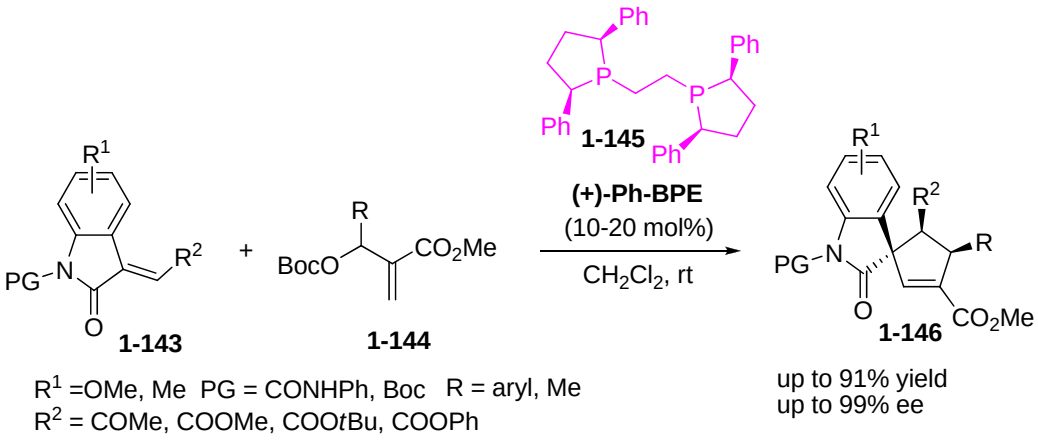
Scheme 1.35 Substitution of MBH acetates with 2-(trimethylsiloxy)furan

In addition to the allylic substitution, Lu and coworkers reported that the simple allylic compounds, which can be easily obtained by a one-step transformation of the MBH product, underwent readily formal [3+2] and [3+6] cycloaddition reactions with electron-deficient olefins in good to excellent yields in the presence of 10 mol% PPh_3.[73] On the basis of these findings, Tang and Zhou recently demonstrated a catalytic asymmetric version of the intramolecular [3+2] annulations using a modified allylic phosphonium ylide.[74] It was found that the spirobiindane-based chiral phosphine **1-140** could be an excellent organocatalyst, leading to the formation of benzobicyclo [4.3.0] compounds with high diastereo- and enantioselectivities (Scheme 1.36). Further transformations of these products provided a direct and practical access to the sprio-, heterocyclic derivatives with four contiguous

stereocenters.



Scheme 1.36 Synthesis of functionalized benzobicyclo-[4.3.0] compounds through a catalytic asymmetric formal [3+2] cycloaddition

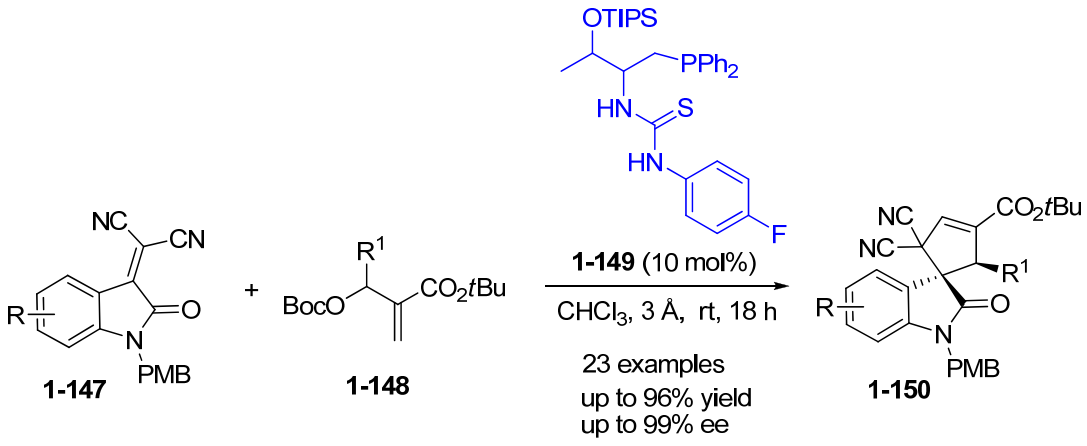


Scheme 1.37 Phosphine-promoted [3+2] cycloadditions with allylic compounds

Very recently, Barbas and coworkers observed that in the presence of 10 mol% chiral phosphine (+)-Ph-BPE, the [3+2] cycloaddition reaction between methyleneindolinones **1-143** and allylic compounds **1-144** could afford complex spirocyclopentaneoxindoles with excellent enantioselectivity (up to 99% ee) and structural diversity (Scheme 1.37),[75] which opens a new route for the direct

construction of spirocyclopenteneoxindole derivatives containing three chiral centers from simple starting materials under mild conditions.

Almost at the same time, our group reported the same type of [3+2] cycloaddition process between the MBH carbonates and isatin-derived tetrasubstituted alkenes.[76] Novel threonine-derived phosphine thiourea **1-149** was found to be the optimal catalyst, providing biologically important 3-spirocyclopentene-2-oxindoles containing two contiguous quaternary centers with excellent regio- and enantioselectivities. A variety of different isatin-derived α,α-dicyanoalkenes were explored as coupling partners in this novel [3+2] annulation reactions (Scheme 1.38). It should be noted that the addition of 3Å molecular sieves to the reaction mixture significantly enhanced the reaction rate and afforded the final cycloaddition product with a better enantioselectivity meanwhile.

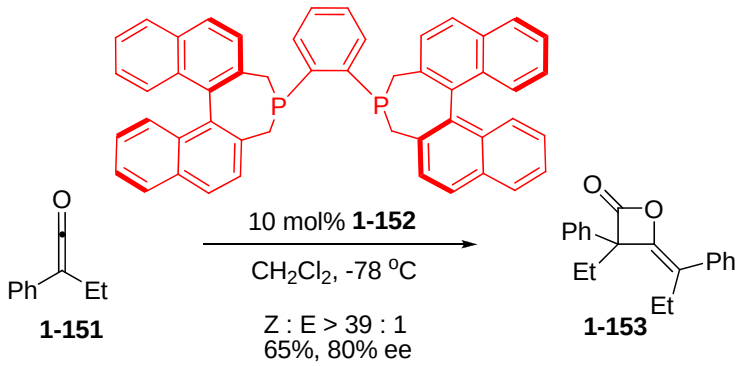


Scheme 1.38 Asymmetric [3+2] annulations of MBH adducts with isatin-derived activated alkenes

1.2.7 Other Reactions

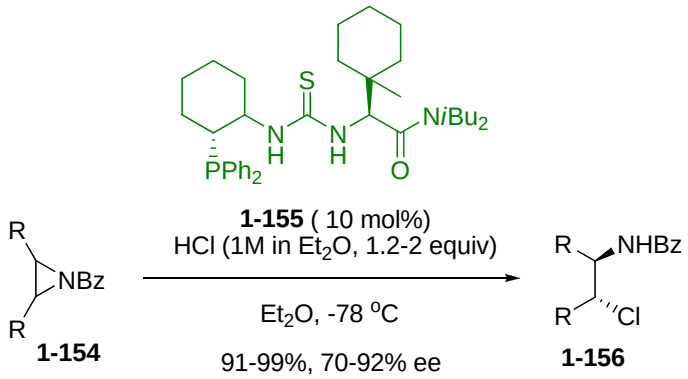
Enantioselective variants of the organocatalytic *dimerization of ketenes* have met,

so far, with limited examples. Only one report showed that chiral phosphine (*R*,*R*) BINAPHANE **1-152** could be used as a catalyst to afford the dimeric product of ethyl(phenyl) ketene as the *Z*-isomer in good enantiomeric excess of 80% (Scheme 1.39).[77]



Scheme 1.39 Enantioselective dimerization of a ketene

The enantioselective ring opening of aziridines with hydrogen chloride, was recently described by Mita and Jacobsen (Scheme 1.40).[78] A broad range of cyclic as well as acyclic substrates underwent clean addition in the presence of phosphine–thiourea **1-155** to afford the corresponding β-chlorobenzamide derivatives in high yields and with high enantioselectivities. A proposed transition state model was suggested, the phosphorus functionality of the bifunctional catalyst was assumed to activate hydrogen chloride by deprotonation, and the hydrogen bonding formation between the chloride and thiourea moiety resulted in a highly stereochemical and enantiometic control.



Scheme 1.40 Phosphine–thiourea-promoted enantioselective ring opening of aziridines

1.3 Project objectives

The phosphine-triggered organic transformations have become a practical and powerful tool in organic chemistry. The unique reactivity of organophosphines compared to their amine counterparts has led to the discovery of a variety of novel reactions, such as [3+2] and [4+2] cyclizations, Michael and nucleophilic additions of activated allenes and alkynes. Over the past few years, many chiral mono- and bifuctional phosphine catalysts have been developed and proved to be efficient in a wide range of enantioselective variants. These catalytic methodologies allow easy access to some sprio-, heterocyclic and polycyclic compounds from readily available materials.

Although great progress has been made in the field of phosphine catalysis, in general, phosphine-catalyzed reactions suffer from the large catalyst loading, poor regioselectivities and enantioselectivities. Furthermore, phosphine catalysts are usually air-sensitive, particularly when substituted by the alkyl groups. In light of this, how to increase the air-stability and catalytic efficiency, and how to develop highly enantioselective catalytic processes will be the aim of further investigations.

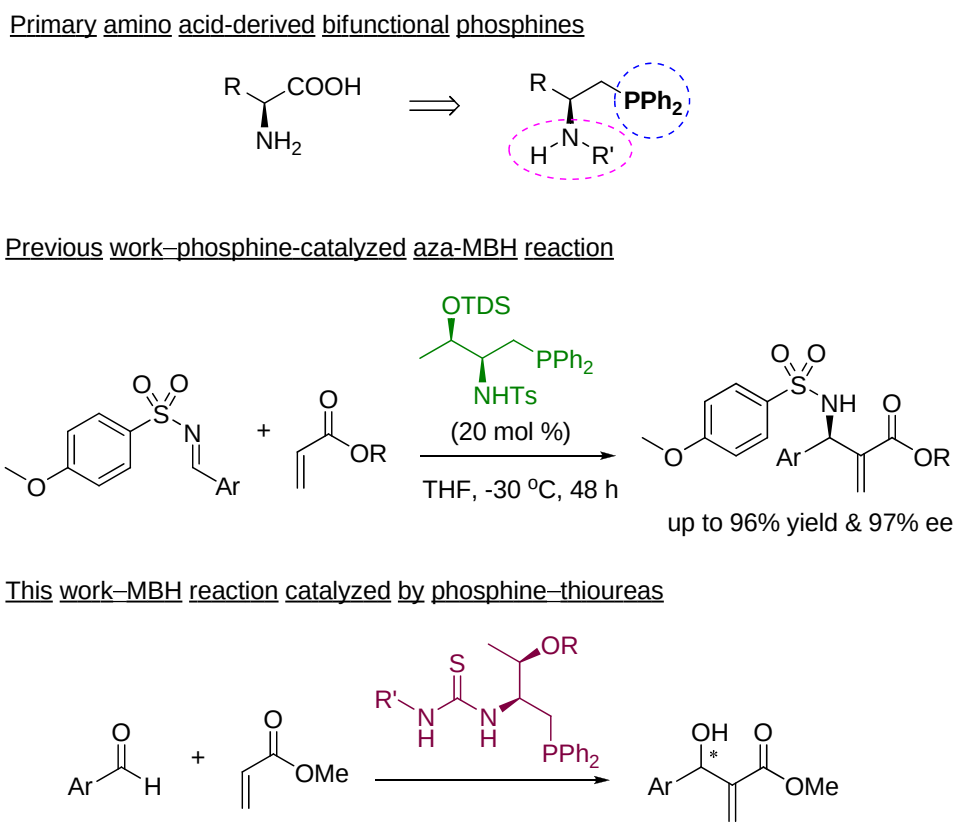
Moreover, phosphine catalysis may complement the amino catalysis well in asymmetric synthesis.

The aim of this project is to design and synthesize novel bifunctional or multifunctional phosphine catalysts derived from amino acid scaffolds, and to employ them in the enantioselective MBH reactions and [3+2] cycloadditions. We are also interested in applying the newly developed methodologies to the synthesis of biologically and pharmaceutically useful compounds.

Chapter 2 Enantioselective Morita–Baylis–Hillman Reaction Promoted by L-Threonine-Derived Phosphine–Thiourea Catalysts

2.1 Introduction

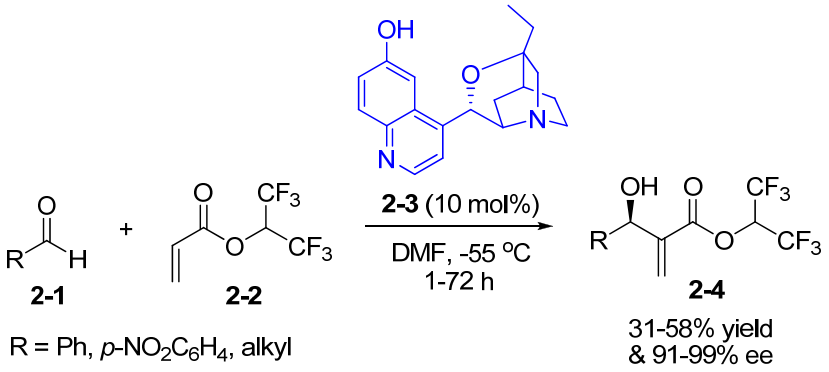
Trivalent phosphines, traditionally utilized as ligands in the transition metal mediated processes, have recently emerged as versatile Lewis base catalysts in synthetic organic chemistry.[6,12,56c,79] As a significant complement to the amine-based catalysts, phosphines often display remarkable and unique properties in the nucleophilic catalysis due to their weaker basicity and stronger nucleophilicity. Comparing to the extensive studies carried out on phosphine-triggered organic transformations, the development of efficient and versatile chiral phosphine catalysts and their applications in enantioselective organic reactions remain to be a less-explored research area.[40-45,80] As our continuous efforts toward the evolution of amino acid-derived organic catalysts for enantioselective organic transformations,[81] we recently embarked on an exciting journey of exploring novel bifunctional chiral phosphines derived from amino acid structural scaffolds (Scheme 2.1). We showed that novel bifunctional phosphine–sulfonamide catalysts could efficiently promote the enantioselective aza-Morita–Baylis–Hillman (aza-MBH) reaction *N*-(*p*-methoxy-benzene-sulfonyl)imines with acrylates, affording corresponding adducts in excellent chemical yields and with very high enantioselectivities (Scheme 2.1, Chapter 2; Scheme 1.12, Chapter 1).[38] It is thus highly desirable to further extend the utility of amino acid-based phosphine catalysts to other important organic reactions.



Scheme 2.1 Applications of amino acid-derived bifunctional phosphines in the (aza)-MBH reactions

The MBH reaction is one of the most valuable carbon–carbon bond-forming reactions, which provides easy access to heavily functionalized and synthetic uesful MBH adducts from readily available activated olefins and aldehydes.[82] In the past decade, the development of enantioselective versions of the MBH reactions has received increasing attention from the synthetic community. Among the activated alkenes suitable for the MBH reactions, enones are most commonly employed; a number of elegant asymmetric MBH reactions between enones and aldehydes have been developed in the past few years.[83] On the other hand, the examples using acrylates as a reaction partner in highly enantioselective MBH reactions are very

limited.[84] In 1999, Hatakeyama and co-workers disclosed a highly enantioselective MBH reaction between hexafluoroisopropyl acrylate (HFIPA) and aldehydes, catalyzed by a novel quinine-derived β-isocupreidine (β-ICD).[85] Although HFIPA had to be employed, and the chemical yields were modest in many cases (Scheme 2.2), nevertheless, the Hatakeyama method represented a breakthrough in the field; highly enantioselective MBH reaction of acrylates was shown to be feasible.[86] Recently, there were a few reports on organocatalytic enantioselective MBH reactions between aldehydes and acrylates.[28,87] Those methods, however, suffered from limited substrate scope, moderate yields or low enantioselectivities. There clearly exists a need for an enantioselective MBH reaction in which simple acrylates can be used directly.



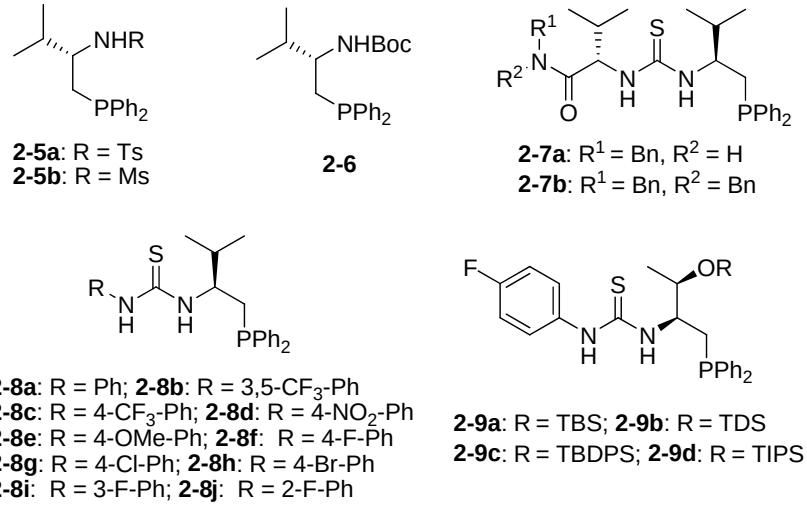
Scheme 2.2 β-ICD-Catalyzed MBH reaction

Herein, we describe the development of amino acid-derived phosphine–thiourea catalysts, and their applications in enantioselective MBH reaction between aromatic aldehydes and simple acrylates. The corresponding MBH adducts were obtained with with up to 90% ee. Moreover, to gain mechanistic insights into the reaction, effects of adding various additives on the MBH reaction were also investigated.

2.2 Results and Discussion

2.2.1 Catalysts Design and Synthesis

Amino acids serve as an excellent starting point for derivatizing various bifunctional chiral phosphine catalysts. The phosphine group in the catalysts is derived from the carboxylic acid via simple functional group transformations. Moreover, the presence of a neighbouring primary alkyl carbon makes the phosphorus center highly nucleophilic, as we demonstrated in our previous reports.[38] By installing different Brønsted acid moieties at the amino sites, and selecting valine or threonine as the chiral backbone, a number of bifunctional phosphine catalysts (**2-5a**–**2-9d**) were prepared (Scheme 2.3). We chose to prepare L-threonine-based phosphine catalysts, since the effectiveness of the threonine motif in stereochemical control has been amply demonstrated by us.[38,81b-d] The isopropyl group in valine serves as a convenient gauge for evaluating steric effects in the asymmetric induction, and the preparation of valine-based catalysts is also more straightforward.



2-5a: R = Ts
2-5b: R = Ms

2-6

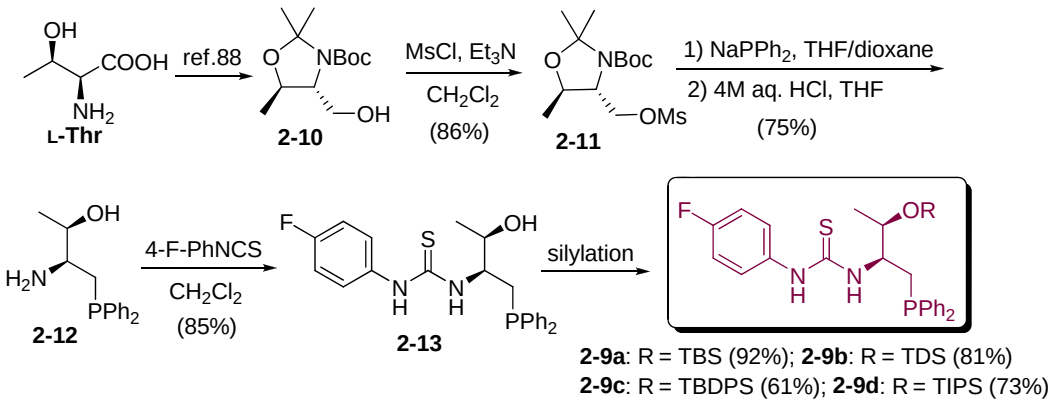
2-7a: R^1 = Bn, R^2 = H
2-7b: R^1 = Bn, R^2 = Bn

2-8a: R = Ph; **2-8b**: R = 3,5-CF_3-Ph
2-8c: R = 4-CF_3-Ph; **2-8d**: R = 4-NO_2-Ph
2-8e: R = 4-OMe-Ph; **2-8f**: R = 4-F-Ph
2-8g: R = 4-Cl-Ph; **2-8h**: R = 4-Br-Ph
2-8i: R = 3-F-Ph; **2-8j**: R = 2-F-Ph

2-9a: R = TBS; **2-9b**: R = TDS
2-9c: R = TBDPS; **2-9d**: R = TIPS

Scheme 2.3 Amino acid-derived bifunctional phosphines

Preparation of bifunctional phosphine–thiourea catalysts from L-threonine is illustrated in Scheme 2.4. Following the literature procedure,[88] threonine was protected as an oxazolidine **2-10**. The hydroxy group was converted to a mesylate, and a substitution reaction with $NaPPh_2$ introduced the phosphine moiety in the catalyst. Acidic treatment yielded phosphine **2-12** with the free amino group, which smoothly reacted with thioisocynate to afford the advanced intermediate **2-13**. Finally, silylation gave phosphine–thiourea catalysts **2-9a** to **2-9d**. It is noteworthy that the above phosphine catalysts and phosphorus-containing synthetic intermediates are stable in the air at room temperature, and have shelf life for at least a few months.



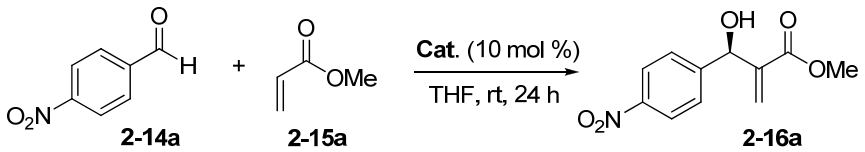
Scheme 2.4 Preparation of L-threonine-derived phosphine–thiourea catalysts

2.2.2 Reaction Optimization

The MBH reaction between *p*-nitrobenzaldehyde and methyl acrylate was chosen as a model reaction to evaluate the effectiveness of our phosphine catalysts (Table 2.1). L-Valine-based bifunctional phosphines with different Brønsted acid moieties were tested first to establish the influence of Brønsted acids on the reaction. Phosphine–sulfonamides **2-5a** and **2-5b** displayed high reactivity; however, the

enantioselectivity was disappointing (entries 1–2). Phosphine **2-6** containing a Boc group led to the formation of the desired product with moderate ee (entry 3). Dipeptide-derived phosphine–thioureas **2-7a** and **2-7b** turned out to be quite good catalysts, and the MBH adducts were formed in high yields and with good enantioselectivities (entries 4–5). The thiourea moieties in the catalysts seemed important in the asymmetric induction, thus, a number of phosphines bearing different aryl thioureas (catalysts **2-8a**–**2-9j**) were next prepared and screened (entries 6–15), and it was found the *p*-F-phenyl-thiourea moiety was most efficient in chiral induction (entry 11, 85% yield, 83% ee). Having established the importance of steric effects in asymmetric induction with valine-derived phosphines, we then focused on derivatization of phosphine–thiourea catalysts (**9a–9d**) based on threonine backbone. Very similar reactivities and selectivities were observed with different silyloxy groups (entries 16–19), catalyst with the TBS group (**2**–**9a**) was chosen for further studies as it gave slightly better results than other silyloxy-containing catalysts, and its preparation was more economical.

Table 2.1 Screening of amino acid-based bifunctional phosphines in the MBH reaction[a]



Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	**2-5a**	88	40
2	**2-5b**	92	37
3	**2-6**	67	53
4	**2-7a**	85	79

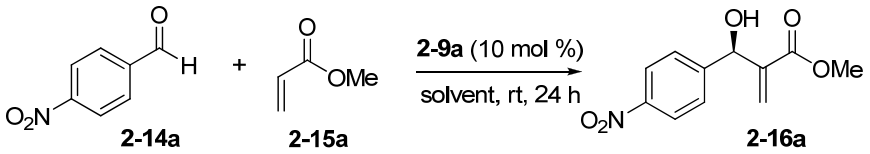
5	**2-7b**	70	72
6	**2-8a**	89	80
7	**2-8b**	90	76
8	**2-8c**	83	80
9	**2-8d**	80	77
10	**2-8e**	84	77
11	**2-8f**	85	83
12	**2-8g**	88	79
13	**2-8h**	91	78
14	**2-8i**	78	77
15	**2-8j**	81	69
16	**2-9a**	**90**	**85**
17	**2-9b**	78	85
18	**2-9c**	88	84
19	**2-9d**	79	84

[a] The reaction was performed with **2-14a** (0.1 mmol), **2-15a** (0.15 mmol) and the catalyst (0.01 mmol) in anhydrous THF (0.2 mL) under N_2 at room temperature for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase.

The influence of different solvents on **2-9a**-catalyzed MBH reaction was next investigated, and the results are summarized in Table 2.2. 1,4-Dioxane was found to be a suitable solvent, offering slightly inferior results to those obtained with THF (entry 2). All the other common organic solvents were shown to be unsuitable, affording products in low yields and with poor enantioselectivities (entries 3–8). The protic solvent, e.g. methanol, proved to be an extremely poor medium, and the desired MBH adduct was obtained in 36% yield and with only 13% ee (entry 9). This result seemed to suggest hydrogen bonding interactions might be very important in stereochemical control, as methanol likely disrupted such key interactions. When a THF/water solvent pair was employed, a very low yield and poor enantioselectivity were observed, contrasting with the excellent results attainable using THF alone as

the solvent. Under the optimized reaction conditions in which molecular sieves were added, the MBH adduct was obtained in 92% yield and 87% ee (entry 12).

Table 2.2 Solvent screening for **2-9a**-catalyzed MBH reaction[a]



Entry	Solvent	Yield (%)[b]	ee (%)[c]
1	THF	90	85
2	1,4-Dioxane	88	82
3	Toluene	49	65
4	CH_2Cl_2	45	42
5	Ether	48	61
6	CH_3CN	25	45
7	DMSO	24	45
8	DMF	32	51
9	MeOH	36	13
10	THF/H_2O (4/1)	15	39
11[d]	THF	85	87
12[e]	**THF**	**92**	**87**
13[f]	THF	84	86

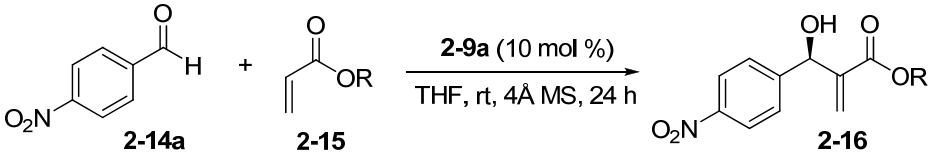
[a] The reaction was performed with **2-14a** (0.1 mmol), **2-15a** (0.15 mmol) and **2-9a** (0.01 mmol) in anhydrous THF (0.2 mL) under N_2 at room temperature for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 0.4 mL THF was used. [e] 4Å molecular sieves were added. [f] The reaction was performed at 10 ^oC for 72 h.

2.2.3 Substrate Scope

With the best catalyst and the most appropriate solvent in hand, we next examined different acrylates in **2-9a**-catalyzed MBH reaction (Table 2.3). Simple alkyl acrylates gave best results, excellent yields and enantioselectivities were

attainable (entries 1–4); the enantioselectivity seemed to be dependent on the steric hindrance of the ester group, and the most sterically hindered *t*-butyl acrylate led to decreased enantioselectivity comparing with less hindered acrylates. The aryl acrylates, on the other hand, were found to be unsuitable for the reaction (entries 5–6).

Table 2.3 Employment of different acrylate in the MBH Reaction[a]



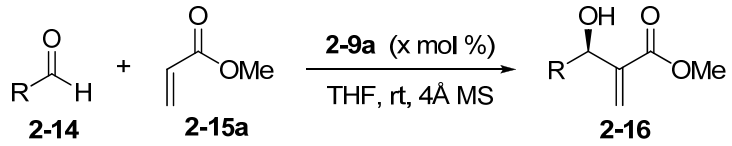
Entry	R	Yield (%)[b]	ee (%)[c]
1	Me	92	87
2	Et	92	85
3	Bn	94	84
4	*t*-Bu	84	82
5	Ph	trace	-[d]
6	1-naphthyl	32	11

[a] The reaction was performed with **2-14a** (0.1 mmol), **2-15** (0.15 mmol) and **2-9a** (10 mol %) in anhydrous THF (0.4 mL) containing 4Å molecular sieves (50 mg) under N_2 at room temperature for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Not determined.

The substrate scope for **2-9a**-catalyzed MBH reactions was next investigated (Table 2.4). The reaction is applicable to aromatic aldehydes with various electron-withdrawing groups at differernt positions of the aryl ring, and high yields and enantioselectivities were generally attainable (entries 1–7). In contrast to the related examples in the literature in which virtually only electron-poor aldehydes could be utilized,[86-88] our reaction was applicable to a wide range of aryl aldehydes. The

reaction worked well for the halogenated aromatic aldehydes and benzaldehyde, and consistent high enantioselectivities were achieved (entries 8–13). Moreover, electron-rich aromatic aldehydes could be employed as well, and the reactions proceeded with good enantioselectivities, even though the chemical yields were poor (entries 14–15). In addition, aromatic aldehydes bearing naphthyl or heterocyclic rings were also found to be suitable (entries 16–18). However, aliphatic aldehydes could not be efficiently activated in our system. It should be noted that only the desired MBH adducts were observed in **2-9a**-catalyzed MBH reactions, undesired dioxanones[1] were not observed under our reaction conditions.

Table 2.4 Substrate scope of **2-9a**-catalyzed MBH reaction[a]



Entry	x	*t* (h)	Product (R)	Yield (%)[b]	ee (%)[c]
1	10	24	**2-16b** (3-NO_2-Ph)	84	85
2	10	24	**2-16c** (2-NO_2-Ph)	91	69
3	10	36	**2-16d** (4-CN-Ph)	92	87
4	10	36	**2-16e** (3-CN-Ph)	89	85
5	10	40	**2-16f** (4-CF_3-Ph)	80	87
6	10	40	**2-16g** (3,5-CF_3-Ph)	74	84
7	10	40	**2-16h** (3-NO_2-2-Cl-Ph)	89	85
8	20	60	**2-16i** (4-F-Ph)	72	81
9	20	60	**2-16j** (4-Cl-Ph)	67	84
10	20	60	**2-16k** (3-Cl-Ph)	63	82
11	20	60	**2-16l** (4-Br-Ph)	73	83
12	20	60	**2-16m** (3-Br-Ph)	77	84
13	20	72	**2-16n** (Ph)	43	80
14	20	96	**2-16o** (4-Me-Ph)	25	76
15	20	96	**2-16p** (3-Me-Ph)	27	77

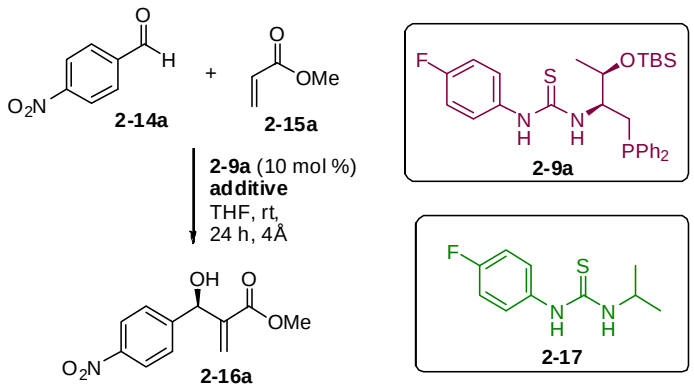
16	20	72	**2-16q** (2-naphthyl)	53	90
17	20	72	**2-16r** (3-pyridine)	87	84
18	20	72	**2-16s** (2-thiophenyl)	52	70
19	20	96	**2-16t** (CH_2Ph)	-[d]	-

[a] The reaction was performed with **2-14** (0.1 mmol), **2-15a** (0.15 mmol for entries 1–7 and 0.2 mmol for entries 8–19) and **2-9a** in anhydrous THF (0.4 mL for entries 1–12 and 0.2 mL for entries 13–19) containing 4Å molecular sieves under N_2 at room temperature. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] No reaction.

2.2.4 Additives Effects and Plausible Reaction Mechanism

Given the widespread uses of thiourea as the hydrogen bonding catalyst in asymmetric catalysis,[89] a mechanistic proposal involving hydrogen bonding interactions between the bifunctional phosphines and the substrate/intermediates seems to be plausible. We focused on the potential roles that thiourea moiety might have played in our catalytic systems. Toward this end, the effects of adding various external proton donors on **2-9a**-catalyzed MBH reaction were next investigated (Table 2.5). The presence of methanol slightly decreased the enantioselectivity of the reaction (entry 2). The addition of thiourea **2-17**, which mimics the thiourea moiety in catalyst **2-9a**, did not have much influence on the stereoselectivity of the reaction, even in a large excess (entries 3–6). However, the addition of a stronger hydrogen bond donor, phenol or 2-naphthol, clearly lowered the enantioselectivity of the reaction (entries 7–8). Interestingly, inclusion of a strong acid in the reaction system, e.g. benzoic acid, virtually had no effect on the enantioselectivity, but resulted in a dramatically decreased chemical yield (entry 9). On the other hand, adding excess benzoic acid or a much stronger trifluoroacetic acid completely stopped the reaction (entries 10–11).

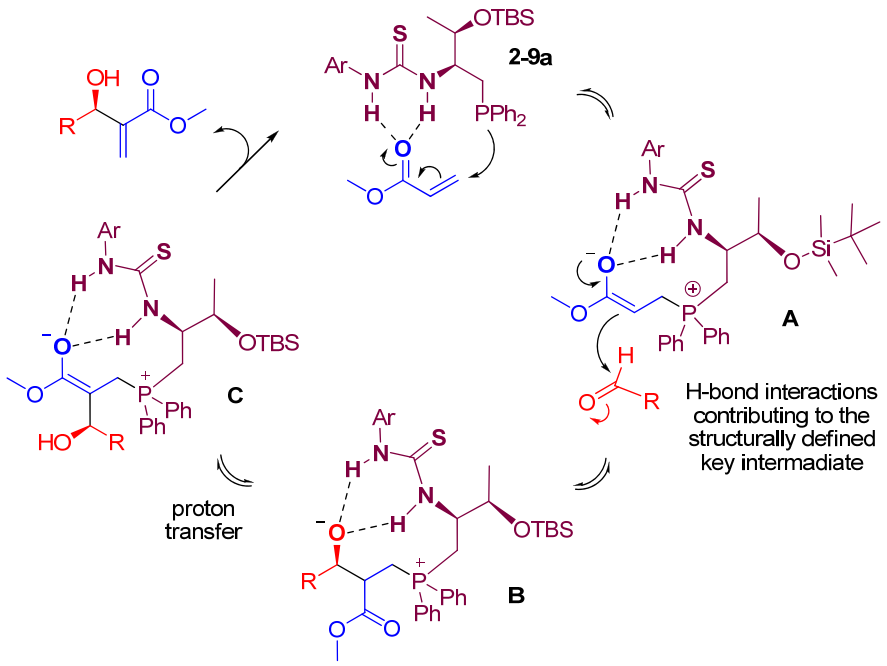
Table 2.5 Examination of the effects of various additives on **2-9a**-catalyzed MBH reaction[a]



Entry	Additive	Yield (%)[b]	ee (%)[c]
1	none	92	87
2	MeOH (10 mol%)	93	84
3	2-17 (10 mol%)	90	85
4	2-17 (20 mol%)	89	85
5	2-17 (50 mol%)	86	84
6	2-17 (100 mol%)	81	83
7	PhOH (10 mol%)	84	77
8	2-Naphthol (10 mol%)	88	74
9	PhCOOH (10 mol%)	37	85
10	PhCOOH (20 mol%)	-[d]	-
11	TFA (10 mol%)	-[d]	-

[a] The reaction was performed with **2-14a** (0.1 mmol), **2-15a** (0.15 mmol) and **2-9a** (0.01 mmol) in anhydrous THF (0.2 mL) under N_2 at room temperature for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Not determined.

Based on the above additive studies, as well as recent elegant mechanistic investigations on the (aza)-MBH reactions,[90] we propose the mechanism of **2-9a**-catalyzed MBH reaction as shown in Scheme 2.5. The reaction is initiated by a reversible conjugate addition of phosphine **2-9a** to the acrylate to generate phosphonium enolate intermediate **A**, which then undergoes aldol reaction with the



Scheme 2.5 Proposed mechanism for phosphine–thiourea promoted MBH Reaction

aldehyde to create intermediate **B**. The subsequent proton transfer, followed by β-elimination, affords the final MBH adduct and regenerates the phosphine catalyst **2-9a**. We propose the strong intramolecular hydrogen bonding interactions between thiourea and the enolate facilitates the formation of a structurally well-defined intermediate **A**, which reacts with the aldehyde substrate in a highly stereochemically selective manner, accounting for the high enantioselectivity observed. This proposal is supported by the results obtained with the additive studies. Relatively weak external hydrogen bond donors competed unfavourably with the intramolecular thiourea in their interactions with the enolate, thus had no significant influence on the enantioselectivity (Table 2.5, entries 2–6). Stronger hydrogen bond donors disrupted thiourea–enolate interaction more, resulting in decreased enantioselectivity (Table 2.5, entries 7–8). The addition of carboxylic acids, such as benzoic acid or TFA, may

partially/completely protonate the enolate intermediate **A**, thus leading to a marked decrease in chemical yield or a complete stop of the reaction. Had the external proton donors participate in the proton transfer step, a more dramatic decrease in enantioselectivity is anticipated, as we had observed in a related study.[91]

2.3 Conclusions

In summary, we have designed and prepared a series of phosphine–thiourea organic catalysts based on the structural scaffolds of natural amino acids. In particular, L-threonine-derived bifunctional phosphine **2-9a** was prepared for the first time and found to be an effective catalyst for the enantioselective MBH reaction of acrylates with aromatic aldehydes. The desired MBH adducts were obtained with good to very good enantioselectivities. We studied the influences of various additives on **2-9a**-catalyzed MBH reaction, and we proposed the hydrogen bonding interactions between the thiourea and the phosphonium enolate intermediate **A** are crucial for the high enantioselectivity observed. The reaction described in this report provides a general and practical solution to the enantioselective MBH reaction of simple acrylates, and is anticipated to find wide applications in organic synthesis in the future.

2.4 Experimental section

2.4.1 Material and General Methods

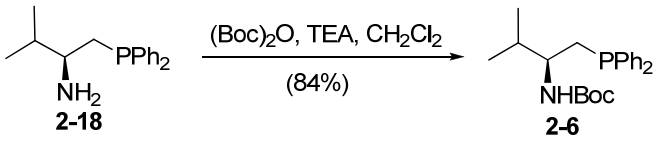
All the starting materials were obtained from commercial sources and used without further purification unless otherwise stated. Toluene, THF and diethyl ether were dried and distilled from sodium benzophenone ketyl prior to use. $CHCl_3$ and CH_2Cl_2 were distilled from CaH_2 prior to use. Dioxane was dried and distilled from

Na prior to use. All the solvents used in reactions involving phosphorus-containing compounds were de-gassed by N_2. 1H and ^{13}C NMR spectra were recorded on a Bruker ACF300 or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Coupling constants were reported in Hertz (Hz). All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254) were used, and compoundswere visualized with a UVlight at 254 nm. Further visualizationwas achieved by staining with iodine, or ceric ammonium molybdate followed by heating on a hot plate. Flash chromatographic separationswere performed on Merck 60 (0.040–0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by HPLC analysis on a chiral stationary phase.

The absolute configuration of **2-16a** was assigned by comparing its specific rotation with that of known compound reported in the literature.[86b] The configurations of other MBH adducts were assigned by analogy.

2.4.2 Catalysts Preparation

(*S*)-*tert*-Butyl 1-(diphenylphosphino)-3-methylbutan-2-ylcarbamate (**2-6**)

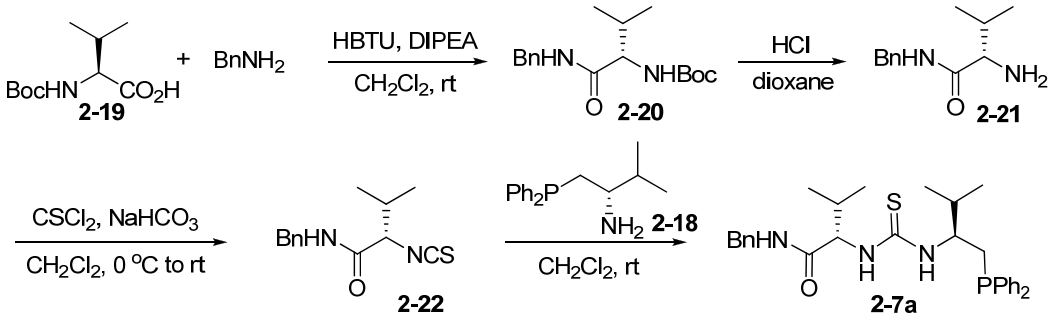


To a solution of (*S*)-1-(diphenylphosphino)-3-methylbutan-2-amine[92] (150 mg, 0.55 mmol) and Et_3N (153 μL, 1.10 mmol) in CH_2Cl_2 (5 mL) under N_2 was added

$(Boc)_2O$ (143 mg, 0.66 mmol). The reaction mixture was stirred at room temperature for 2 hrs, solvent was then removed under reduced pressure, and the residue was directly purified by column chromatography on silica gel (hexane/ethyl acetate = 15:1 to 10: 1) to afford catalyst **2-6** as a white solid (171 mg, 84% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.32 (m, 10H), 4.40-4.38 (m, 1H), 3.59 (br, 1H), 2.30-2.12 (m, 2H), 1.93-1.87 (m, 1H), 1.43 (s, 9H), 0.88 (d, *J* = 4.4 Hz, 3H), 0.86 (d, *J* = 4.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 115.3, 146.8, 138.9, 138.8, 138.5, 133.1, 132.9, 132.8, 132.7, 128.7, 128.5, 128.5, 128.5, 128.5, 128.4, 85.2, 78.8, 53.6 (d), 32.5, 28.4, 27.4, 18.9, 17.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ -22.2; HRMS (ESI) m/z calcd for $C_{22}H_{31}NO_2P$ $[M+H]^+$ = 372.2087, found = 372.2079.

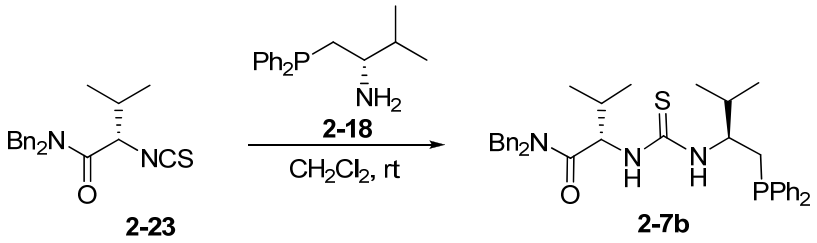
(*S*)-*N*-Benzyl-4-((*S*)-1-(diphenylphosphino)-3-methylbutan-2-ylamino)-2-isopropyl-4-thioxobutanamide (**2-7a**)



To a solution of isothiocyanide **2-22**[50] (82 mg, 0.33 mmol) in CH_2Cl_2 (1 mL) under N_2 was added (*S*)-1 (diphenylphosphino)-3-methylbutan-2-amine (81.4 mg, 0.3 mmol). The mixture was stirred at room temperature for 24 h, the solvent was then removed under reduced pressure, and the residue was directly subjected to column chromatographic separation on silica gel (hexane/ethyl acetate = 15:1 to 8: 1) to afford catalyst **2-7a** as a white solid (135 mg, 79% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44-7.40 (m, 4H), 7.31-7.24 (m, 11H), 6.84 (br, 1H), 4.81 (s, 1H), 4.46-4.42 (m, 3H), 2.40-2.36 (m, 1H), 2.28-2.13 (m, 1H), 2.07 (s, 1H), 2.03-1.98 (m, 1H), 0.98-0.89 (m, 6H), 0.83(s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.3, 132.8 (dd), 128.6, 128.4 (d), 127.4, 64.1, 57.6 (d), 43.5, 31.9 (d), 30.9, 19.4, 18.8, 18.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ -23.1; HRMS (ESI) m/z calcd for $C_{30}H_{39}N_3OPS$ $[M+H]^+$ = 520.2551, found = 520.2550.

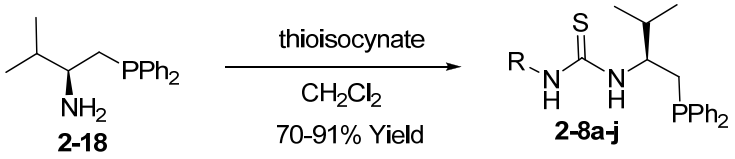
(*S*)-*N*,*N*-Dibenzyl-4-((*S*)-1-(diphenylphosphino)-3-methylbutan-2-ylamino)-2-isopropyl-4-thioxobutanamide (**2-7b**)



Catalyst **2-7b** was prepared from *N*-Boc-L-Valine, following the same procedure described for the synthesis of **2-7a**.

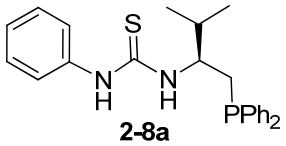
A white solid (67% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (br, 1H), 7.41-7.27(m, 18H), 7.25 (d, *J* = 5.1 Hz, 2H), 5.80 (br, 1H), 4.72 (s, 4H), 4.38 (d, *J* = 13.8 Hz, 1H), 2.38-2.35 (m, 1H), 2.34-2.22 (m, 2H), 2.14-1.97 (m, 1H), 0.98 (d, *J* = 6.3 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.81 (d, *J* = 5.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 136.3 (d), 132.9 (dd), 132.8, 128.6 (d), 128.3 (d), 127.9 (d), 127.4, 57.3 (d), 50.5, 47.9, 31.9 (dd), 19.6 (d), 18.8, 17.9; ^{31}P NMR (202 MHz, $CDCl_3$) δ -23.4; HRMS (ESI) m/z calcd for $C_{37}H_{45}N_3OPS$ $[M+H]^+$ = 610.3021, found = 610.3023.

Typical procedure for preparation of catalysts 2-8a–j



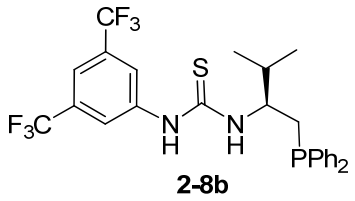
To a solution of (*S*)-1-(diphenylphosphino)-3-methylbutan-2-amine (81 mg, 0.30 mmol) in CH_2Cl_2 (2 mL) under N_2 was added isothiocyanate (1.1 eq., 0.33 mmol), and the reaction mixture was stirred at room temperature for 24 hrs. Solvent was then removed under reduced pressure, and the residue was directly subjected to column chromatographic separation on silica gel (hexane/ethyl acetate = 12:1 to 8: 1) to afford catalyst **2-8a-j** as a white solid (71-95% yield).

(*S*)-1-(1-(Diphenylphosphino)-3-methylbutan-2-yl)-3-phenylthiourea (**2-8a**)



A white solid (86% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (br, 1H), 7.42-7.16(m, 13H), 7.00 (d, *J* = 10.3 Hz, 4H), 5.92 (d, *J* = 11.4 Hz, 1H), 4.50 (br, 1H), 2.36-2.30 (m, 1H), 2.24-2.17 (m, 1H), 2.09-2.00 (m, 1H), 0.80 (d, *J* = 9.0 Hz, 3H), 0.75 (d, *J* = 9.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.1, 135.9, 132.9 (d), 132.7 (d), 130.1, 128.5 (dd), 127.1, 125.2, 58.5 (d), 31.7 (d), 31.2 (d), 18.8, 17.9; ^{31}P NMR (121 MHz, $CDCl_3$) δ -23.9; HRMS (ESI) m/z calcd for $C_{24}H_{28}N_2PS$ $[M+H]^+$ = 407.1711, found = 407.1711.

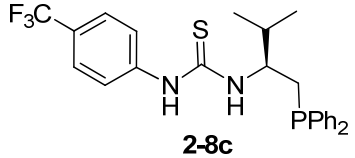
(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1-(diphenylphosphino)-3-methylbutan-2-yl) thiourea (**2-8b**)



2-8b

A white solid (86% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (br, 1H), 7.66 (d, *J* = 12.6 Hz, 6H), 7.44 (t, *J* = 2.9 Hz, 4H), 7.42-7.29 (m, 6H), 6.22 (br, 1H), 4.62(br, 1H), 2.54-2.52 (m, 1H), 2.51-2.49 (m, 1H), 2.34-2.16 (m, 1H), 0.95 (t, *J* = 7.8 Hz, 6H); ^{31}P NMR (202 MHz, $CDCl_3$) δ -23.2; HRMS (ESI) m/z calcd for $C_{26}H_{26}F_6N_2PS$ $[M+H]^+$ = 543.1459, found = 543.1459. The characterization data were in agreement with the values reported in the literature.[28]

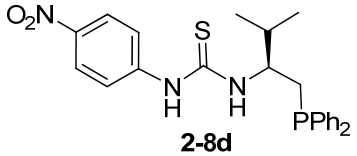
(*S*)-1-(1-(Diphenylphosphino)-3-methylbutan-2-yl)-3-(4 (trifluoromethyl) phenyl) thiou- rea (**2-8c**)



2-8c

A white solid (81% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (br, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.47-7.41 (m, 4H), 7.31(d, *J* = 3.8 Hz, 6H), 7.22 (d, *J* = 7.6 Hz, 2H), 6.19 (br, 1H), 4.64 (br, 1H), 2.50-2.46 (m, 1H), 2.32-2.27 (m, 1H), 2.19-2.15 (m, 1H), 0.91 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.6, 139.8, 137.9, 132.8 (d), 132.6, 128.8 (d), 128.5 (dd), 127.9, 127.7, 128.2, 126.9, 124.8, 123.6, 122.7, 58.7 (d), 31.9, 30.8 (d), 18.5 (d); ^{31}P NMR (202 MHz, $CDCl_3$) δ -24.1; HRMS (ESI) m/z calcd for $C_{25}H_{27}F_3N_2PS$ $[M+H]^+$ = 475.1585, found = 475.1582.

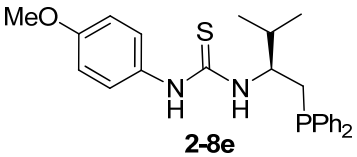
(*S*)-1-(1-(Diphenylphosphino)-3-methylbutan-2-yl)-3-(4-nitrophenyl)thiourea (**2-8d**)



2-8d

A white solid (86% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (br, 1H), 8.14-8.11 (m, 2H), 7.46-7.30 (m, 12H), 6.49 (br, 1H), 4.62 (br, 1H), 2.55-2.53 (m, 1H), 2.50-2.48 (m, 1H), 2.35-2.15 (m, 1H), 0.95 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4, 143.9, 143.3, 138.0 (d), 137.4, 132.7 (d), 128.8 (dd), 125.3, 122.1, 58.6 (d), 32.0, 30.7, 18.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ -23.7; HRMS (ESI) m/z calcd for $C_{24}H_{27}N_3O_2PS$ $[M+H]^+$ = 452.1562, found = 452.1560.

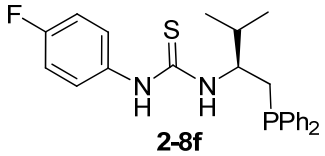
(*S*)-1-(1-(Diphenylphosphino)-3-methylbutan-2-yl)-3-(4-methoxyphenyl)thiourea (**2-8e**)



2-8e

A white solid (75% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (br, 1H), 7.48-7.41 (m, 4H), 7.36-7.31 (m, 6H), 7.00-6.96 (m, 2H), 6.89-6.84 (m, 2H), 5.78 (d, *J* = 8.2 Hz, 1H), 4.55 (br, 1H), 3.80 (s, 3H), 2.44-2.37 (m, 1H), 2.29-2.21 (m, 1H), 2.16-2.05 (m, 1H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.7, 158.8, 132.9 (d), 132.6 (d), 128.6, 128.3 (dd), 127.68, 115.1, 58.3 (d), 55.4, 31.7 (d), 31.2 (d), 18.8, 17.9, ^{31}P NMR (121 MHz, $CDCl_3$) δ -24.1; HRMS (ESI) m/z calcd for $C_{25}H_{30}N_2O_3PS$ $[M+H]^+$ = 437.1816, found = 437.1811.

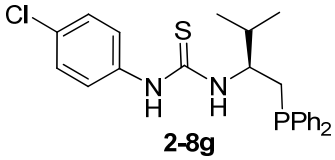
(*S*)-1-(1-(Diphenylphosphino)-3-methylbutan-2-yl)-3-(4-fluorophenyl)thiourea (**2-8f**)



2-8f

A white solid (91% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (br, 1H), 7.46-7.40 (m, 4H), 7.32-7.31(m, 6H), 7.04 (d, *J* = 6.8 Hz, 4H), 5.83 (d, *J* = 5.9 Hz, 1H), 4.57 (br, 1H), 2.47-2.44 (m, 1H), 2.42-2.40 (m, 1H), 2.28-2.04 (m, 1H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.3, 162.9, 159.6, 138.1, 132.9 (d), 132.6 (d), 131.8, 128.7, 128.5 (dd), 127.7, 127.6, 117.0, 116.7, 58.44(d), 31.8 (d), 31.1 (d), 18.7, 18.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ -24.3; HRMS (ESI) m/z calcd for $C_{24}H_{27}FN_2PS$ $[M+H]^+$ = 425.1617, found = 425.1624.

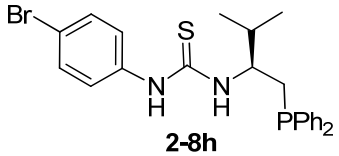
(*S*)-1-(4-Chlorophenyl)-3-(1-(diphenylphosphino)-3-methylbutan-2-yl)thiourea (**2-8g**)



2-8g

A white solid (81% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (br, 1H), 7.46-7.41 (m, 4H), 7.32-7.29 (m, 7H), 7.02 (d, *J* = 8.2 Hz, 2H), 5.95 (br, 1H), 4.60 (br, 1H), 2.47-2.45 (m, 1H), 2.44-2.42 (m, 1H), 2.28-2.11 (m, 1H), 0.88 (d, *J* = 6.3 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.9, 138.2 (d), 132.8 (d), 132.5 (dd), 130.1, 128.8 (d), 128.5 (d), 128.5, 126.3, 58.5 (d), 31.8 (d), 31.0 (d), 18.7, 18.2; ^{31}P NMR (202 MHz, $CDCl_3$) δ -24.2; HRMS (ESI) m/z calcd for $C_{24}H_{27}ClN_2PS$ $[M+H]^+$ = 441.1321, found = 441.1322.

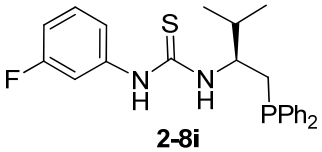
(*S*)-1-(4-Bromophenyl)-3-(1-(diphenylphosphino)-3-methylbutan-2-yl)thiourea (**2-8h**)



2-8h

A white solid (75% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (br, 1H), 7.41-7.36 (m, 6H), 7.27-7.25 (m, 6H), 6.90 (d, *J* = 8.2 Hz, 2H), 5.90 (br, 1H), 4.54 (br, 1H), 2.42-2.38 (m, 1H), 2.23-2.18 (m, 1H), 2.10-2.07 (m, 1H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.9, 138.2 (d), 135.1, 132.8 (dd), 128.8 (d), 128.5 (d), 126.5, 120.2, 58.6 (d), 31.85 (d), 30.9 (d), 18.7, 18.3; ^{31}P NMR (202 MHz, $CDCl_3$) δ -24.2; HRMS (ESI) m/z calcd for $C_{24}H_{27}BrN_2PS$ $[M+H]^+$ = 485.0816, found = 485.0815.

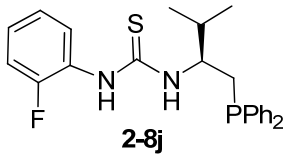
(*S*)-1-(1-(Diphenylphosphino)-3-methylbutan-2-yl)-3-(3-fluorophenyl)thiourea (**2-8i**)



2-8i

A white solid (79% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (br, 1H), 7.41-7.34 (m, 4H), 7.33-7.17 (m, 7H), 6.88-6.74 (m, 3H), 6.02 (d, *J* = 11.6 Hz, 1H), 4.52 (br, 1H), 2.40-2.38 (m, 1H), 2.36-2.34 (m, 1H), 2.23-2.02 (m, 1H), 0.86 (d, *J* = 2.9 Hz, 3H), 0.82 (d, *J* = 2.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.7, 164.8, 161.5, 138.1 (d), 137.8 (d), 132.8 (dd), 131.1 (d), 128.7, 128.5 (dd), 119.9 (d), 113.5 (d), 111.8 (d), 58.6 (d), 31.8 (d), 31.0 (d), 18.7, 18.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ -24.1; HRMS (ESI) m/z calcd for $C_{24}H_{27}FN_2PS$ $[M+H]^+$ = 425.1617, found = 425.1621.

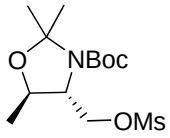
(*S*)-1-(1-(Diphenylphosphino)-3-methylbutan-2-yl)-3-(2-fluorophenyl)thiourea (**2-8j**)



2-8j

A white solid (82% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (br, 1H), 7.49-7.40 (m, 4H), 7.33-7.21 (m, 8H), 7.16-7.10 (m, 2H), 6.05 (br, 1H), 4.60 (br, 1H), 2.42-2.39 (m, 1H), 2.38-2.32 (m, 1H), 2.31-2.13 (m, 1H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.3, 156.9, 154.9, 138.0 (d), 132.8 (d), 132.7 (d), 128.7, 128.4 (dd), 128.1 (d), 126.7, 124.9, 116.8 (d), 58.6 (d), 31.6, 31.1 (d), 18.7, 17.9; ^{31}P NMR (202 MHz, $CDCl_3$) δ -24.1; HRMS (ESI) m/z calcd for $C_{24}H_{27}FN_2PS$ $[M+H]^+$ = 425.1617, found = 425.1617.

(4*S*,5*R*)-*tert*-Butyl-2,2,5-trimethyl-4-((methylsulfonyloxy) methyl)oxazolidine-3-car-boxylate (**2-11**)

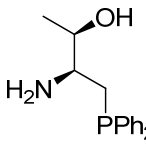


2-11

To a solution of alcohol **2-10**[88](2.33 g, 9.5 mmol) in CH_2Cl_2 (30 mL) at 0 ^{o}C was added Et_3N (3.30 mL, 23.7 mmol), followed by dropwise addition of $MeSO_2Cl$ (970 μL, 12.50 mmol) over 10 minutes. The reaction mixture was stirred at room temperature for 3 hours. The mixture was then washed with water, and the aqueous layer was back extracted with CH_2Cl_2 several times (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Purification by silica gel column chromatography (hexanes/ethyl acetate = 10:1 to 5:1) afforded the desired product **7** as a colorless oil (2.64 g, 86% yield).

^{1}H NMR (500 MHz, DMSO, 50 ^{o}C) δ 4.43 (br, 1H), 4.34-4.31 (m, 1H), 4.15-4.12 (m, 1H), 3.62-3.59 (m, 1H), 3.17 (s, 3H), 1.54 (s, 3H), 1.44 (s, 9H), 1.41 (s, 3H), 1.29 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, DMSO, 50 ^{o}C) δ 150.8, 93.3, 79.5, 78.9, 72.2, 66.6, 61.2, 36.6, 27.7, 25.6, 19.1; HRMS (ESI) m/z calcd for $C_{13}H_{26}NO_6S$ [M+H]+ = 324.1403, found = 324.1400.

(2*R*,3*S*)-3-Amino-4-(diphenylphosphino)butan-2-ol (**2-12**)



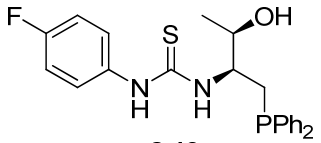
2-12

To a solution of **2-11** (2.6 g, 8.0 mmol) in anhydrous THF (20 mL) under N_2 at 0 ^{o}C was slowly added a solution of $NaPPh_2$ in THF/dioxane (0.2 M in THF/dioxane, 52.0 mL, 10.40 mmol). The resulting mixture was stirred at 0 ^{o}C for 2 hrs. The reaction was then quenched by adding H_2O (25 mL), and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. A THF solution of HCl (4 M, 25 ml) was added to the residue, and the resulting mixture was stirred for 1h. The pH value of the mixture was adjusted to 10 by slow addition of 2 M aqueous NaOH solution at 0 ^{o}C. The mixture was then extracted with ethyl acetate several times (3 x 30 mL), and the combined organic layers were washed with brine and dried over Na_2SO_4. Purification by column chromatography (hexane/ethyl acetate = 5:1 to 1:1, hexanes containing 5% Et_3N) afforded **2-12** as a white solid (1.7 g, 78%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.30 (m, 10H), 3.59-3.54 (m, 1H), 2.61-2.55 (m, 1H), 2.42 (t, *J* = 3.5 Hz, 1H), 2.40-2.25 (m, 3H), 2.05-1.99 (m, 1H), 1.14 (d, *J*

= 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8 (dd), 132.7 (dd), 129.1, 128.6 (dd), 71.0 (d), 56.7 (d), 34.6 (d), 20.0; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ -22.3 (s); HRMS (ESI) m/z calcd for $C_{16}H_{21}NOP$ $[M+H]^+$ = 274.1361, found = 274.1362.

1-((2*S*,3*R*)-1-(Diphenylphosphino)-3-hydroxybutan-2-yl)-3-(4-fluorophenyl)-thiourea (**2-13**)

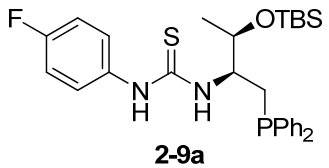


2-13

To a solution of **2-12** (0.81 g, 3.0 mmol) in CH_2Cl_2 (5 mL) under N_2 was added 4-fluorophenyl isothiocyanate (0.51 g, 3.3 mmol), and the reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated *in vacuo*, and the residue was directly purified by column chromatography (hexane/ethyl acetate = 15:1 to 5:1) to afford **2-13** as a white solid (1.14 g, 90% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.51-7.41 (m, 4H), 7.33-7.29 (m, 6H), 7.10-6.98 (m, 4H), 6.47 (d, *J* = 7.7 Hz, 1H), 4.60 (br, 1H), 4.21-4.19 (m, 1H), 2.49-2.47 (m, 2H), 1.14 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 161.0 (d), 137.8 (d), 137.2 (d), 132.8 (d), 132.6 (d), 132.1, 128.8 (d), 128.6 (d), 128.5 (d), 127.1 (d), 127.1, 116.7 (d), 68.9 (d), 58.1 (d), 31.6 (d), 20.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ -23.9; HRMS (ESI) m/z calcd for $C_{23}H_{25}FN_2OPS$ $[M+H]^+$ = 427.1409, found = 427.1409.

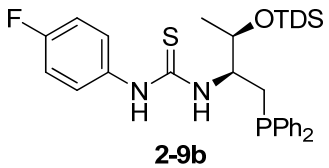
1-((2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-1-(diphenylphos-phino)butan-2-yl)-3-(4-fluorophenyl)thiourea (**2-9a**)



2-9a

To the solution of thiourea **2-13** (0.50 g, 1.17 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 ^oC was added DIPEA (0.61 mL, 3.51 mmol), followed by slow addition of TBSOTf (0.11 mL, 0.69 mmol). The resulting mixture was allowed to warm to room temperature and continued stirring for an additional hour. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ (10 mL), and then extracted with CH_2Cl_2 (2×20 mL). The combined organic extracts were washed with brine, and dried over Na_2SO_4. Purification by column chromatography (hexane/ethyl acetate = 10:1) afforded **2-9a** (0.58 g, 92% yield) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (br, 1H), 7.70-7.64 (m, 2H), 7.40-7.35 (m, 5H), 7.29-7.23 (m, 3H), 7.15-7.09 (m, 2H), 7.07-7.02 (m, 2H), 6.37 (d, *J* = 8.9 Hz, 1H), 4.45 (s, 1H), 4.35 (d, *J* = 5.7 Hz, 1H), 2.66 (dd, *J* = 4.4 Hz, 8.8 Hz, 1H), 2.04-2.00 (m, 1H), 1.09 (d, *J* = 6.3 Hz, 3H), 0.69 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.4, 161.4 (d), 139.1, 139.0, 137.0, 136.9, 133.2(d), 132.8, 132.7, 131.9, 128.8, 128.5, 128.5, 128.4, 128.3, 127.9 (d), 117.0 (d), 68.5 (d),-4.6, 58.6 (d), 31.9 (d), 21.5, 17.6, -4.3, -4.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ -22.60; HRMS (ESI) m/z calcd for $C_{29}H_{39}FN_2OPSSi$ $[M+H]^+$ = 541.2274, found = 541.2269.

1-((2*S*,3*R*)-3-(((2,3-Dimethylbutan-2-yl)dimethylsilyl)oxy)(diphenylphosphino) butan-2-yl)-3-(4-fluorophenyl)thiourea (**2-9b**)

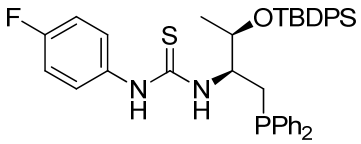


2-9b

To a solution of **2-13** (57.5 mg, 0.14 mmol) in THF (1 mL) at 0 ^{o}C was added NaH (22.4 mg, 0.60 mmol, 60% (w/w) in mineral oil). The mixture was stirred at 0 ^{o}C for 20 minutes, followed by the addition of *tert*-butyldimethylsilyl chloride (32.5 mg, 0.18 mmol). The mixture was then allowed to warm to room temperature and the stirring was continued for 2 hours. The reaction was quenched by the addition of water (2 mL), and the mixture was extracted with EtOAc several times (3 x 5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (hexane/ethyl acetate = 10:1 to 5:1) to afford **2-9b** as a white solid (64.5 mg, 81% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (br, 1H), 7.70-7.65 (m, 2H), 7.40-7.26 (m, 8H), 7.15-7.03 (m, 4H), 6.31 (s, 1H), 4.47 (s, 1H), 4.32 (d, *J* = 6.0 Hz, 1H), 2.68-2.65 (m, 1H), 2.10-2.03 (m, 1H), 1.45-1.36 (m, 1H), 1.09 (d, *J* = 6.2 Hz, 3H), 0.69 (d, *J* = 6.9 Hz, 6H), 0.64 (d, *J* = 2.0 Hz, 6H), 0.08 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 161.0 (d), 133.3, 133.1, 132.8, 132.6, 131.9, 128.9, 128.5, 128.6, 128.4, 128.3, 128.0 (d), 117.0 (d), 68.7 (d), 58.6 (d), 33.8, 31.7 (d), 24.6, 20.1, 18.4, 18.4, 2.4, 2.2, -2.4, -2.4; ^{31}P NMR (121 MHz, $CDCl_3$) δ -24.2; HRMS (ESI) m/z calcd for $C_{31}H_{43}FN_2OPSSi$ $[M+H]^+$ = 569.2587, found = 569.2589.

1-((2*S*,3*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)-1-(diphenylpho-sphino)butan-2-yl)-3-(4-fluorophenyl)thiourea (**2-9c**)

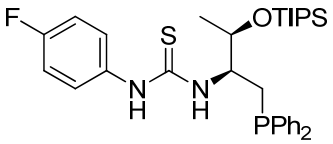


2-9c

Following the procedure described for the preparation of **2-9b**, catalyst **2-9c** (61% yield) was prepared similarly.

A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (br, 1H), 7.58-7.51 (m, 4H), 7.49-7.40 (m, 4H), 7.36-7.30 (m, 7H), 7.28-7.26 (m, 5H), 7.19-7.14 (m, 2H), 7.07-7.01 (m, 2H), 6.47 (d, *J* = 8.8 Hz, 1H), 4.49 (s, 1H), 4.28-4.23 (m, 1H), 2.66-2.60 (m, 1H), 2.17-2.10 (m, 1H), 0.96 (d, *J* = 4.5 Hz, 3H), 0.89 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.7, 161.5 (d), 137.5, 135.9, 135.8, 134.8, 133.5, 133.3, 133.0, 132.8, 132.8, 132.6, 129.9, 129.8, 129.6, 128.8, 128.5, 128.4, 128.3, 128.3, 128.1 (d), 127.7, 127.5, 117.1 (d), 70.7 (d), 58.8 (d), 32.5 (d), 29.7, 26.9, 21.4, 19.2; ^{31}P NMR (121 MHz, $CDCl_3$) δ -23.8; HRMS (ESI) m/z calcd for $C_{39}H_{43}FN_2OPSSi$ $[M+H]^+$ = 665.2587, found = 665.2592.

1-((2*S*,3*R*)-1-(Diphenylphosphino)-3-((triisopropylsilyl)oxy)butan-2-yl)-3-(4-fluoro- phenyl)thiourea (**2-9d**)



2-9d

Following the procedure described for the preparation of **2-9b**, catalyst **2-9d** (73% yield) was prepared similarly. A white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (br, 1H), 7.53-7.48 (m, 2H), 7.27-7.12 (m, 8H), 7.00-6.92 (m, 2H), 6.90-6.87 (m, 2H), 6.25 (d, *J* = 8.5 Hz, 1H), 4.34 (d, *J* = 5.7 Hz, 2H), 2.58-2.51 (m, 1H), 2.06 (t, *J* = 10.5 Hz, 1H), 1.01 (d, *J* = 6.2 Hz, 3H),

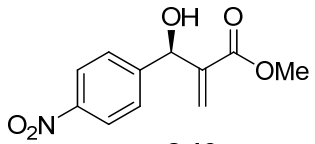
0.80 (br, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.5, 161.5 (d), 139.0, 137.5, 137.3, 133.2, 132.9, 132.9, 132.6, 131.8, 128.7, 128.5, 128.4, 128.4, 128.3, 128.1 (d), 116.9 (d), 69.2 (d), 58.9 (d), 32.1 (d), 18.1, 18.1, 12.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ -23.7; HRMS (ESI) m/z calcd for $C_{32}H_{45}FN_2OPSSi$ $[M+H]^+$ =583.2665, found = 583.2746.

2.4.3 Representative Procedure for MBH Reactions

To a flame-dried round bottom flask with a magnetic stirring bar under N_2 were added methyl acrylate **2-15a** (14 ml, 0.15 mmol), anhydrous THF (0.4 mL), **2-9a** (5.4 mg, 0.01 mmol) and 4 Å molecular sieves (50 mg). The resulting mixture was stirred for 2 min, followed by the addition of *p*-nitrobenzaldehyde **2-14a** (15.1 mg, 0.1 mmol). The flask was then sealed, and the mixture was stirred at room temperature for 24 h. The reaction mixture was filtered (to remove molecular sieves) and concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane/EtOAc = 10 : 1 to 1 : 1) to afford **2-16a** (21.8 mg, 92%) as a yellow solid.

2.4.4 Analytical Data of MBH Products

(*R*)-Methyl 2-(hydroxy(4-nitrophenyl)methyl)acrylate (**2-16a**)

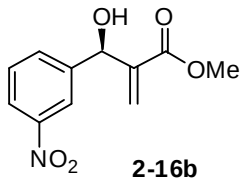


2-16a

A yellow solid; $[\alpha]^{27}_D$ = -83.4 (c 1.00, MeOH), (lit.[85]: $[\alpha]^{25}_D$ = -86.6 (c, 0.54, MeOH)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 6.39

(s, 1H), 5.87 (s, 1H), 5.29 (d, *J* = 5.1 Hz, 1H), 3.74 (s, 3H), 3.32 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 148.6, 147.5, 140.9, 127.3, 127.2, 123.6, 72.75, 52.19; HRMS (ESI) m/z calcd for $C_{11}H_{12}NO_5$ $[M+H]^+$ = 238.0715, found = 238.0705; the ee value was 87%, t_R (minor) = 25.2 min, t_R (major) = 33.6 min (Chiralcel IC-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

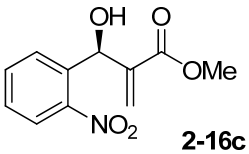
(*R*)-Methyl 2-(hydroxy(3-nitrophenyl)methyl)acrylate (**2-16b**)



2-16b

A yellow solid; $[\alpha]^{27}_D$ = -2.7 (c 0.85, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13-8.15 (m, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.9 Hz, 1H), 6.41 (s, 1H), 5.90 (s, 1H), 5.64 (d, *J* = 5.1 Hz, 1H), 3.74 (s, 3H), 3.32 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 148.4, 143.6, 140.9, 132.6, 129.3, 127.2, 122.8, 121.5, 72.6, 52.2; HRMS (ESI) m/z calcd for $C_{11}H_{12}NO_5$ $[M+H]^+$ = 238.0715, found = 238.0706; The ee value was 85%, t_R (minor) = 13.4 min, t_R (major) = 16.1 min (Chiralcel IC-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*R*)-Methyl 2-(hydroxy(2-nitrophenyl)methyl)acrylate (**2-16c**)

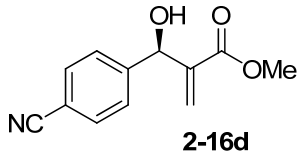


2-16c

A yellow solid; $[\alpha]^{27}_D$ = -16.9 (c 0.80, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 1.3 Hz, 8.2 Hz), 7.74-7.76 (m, 1H), 7.64 (d, *J* = 7.3 Hz, 1H), 7.44-7.48 (m, 1H), 6.36 (s, 1H), 6.12 (s, 1H), 5.73 (s, 1H), 3.73 (s, 3H), 3.43 (br, 1H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 166.4, 148.3, 140.7, 136.1, 133.4, 128.9, 128.7, 126.5, 124.6, 67.7, 52.1; HRMS (ESI) m/z calcd for $C_{11}H_{12}NO_5$ $[M+H]^+$ = 238.0715, found = 238.0712; The ee value was 69%, t_R (minor) = 14.4 min, t_R (major) = 16.9 min (Chiralcel OD-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

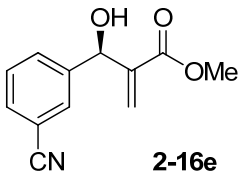
(*R*)-Methyl 2-((4-cyanophenyl)(hydroxy)methyl)acrylate (**2-16d**)



2-16d

A colorless oil; $[\alpha]^{27}_D$ = -4.4 (c 0.85, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 6.37 (s, 1H), 5.85 (s, 1H), 5.58 (d, *J* = 4.4 Hz, 1H), 3.73 (s, 3H), 3.29 (d, *J* = 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 146.6, 141.0, 132.2, 127.2, 127.1, 118.7, 111.6, 72.8, 52.1; HRMS (ESI) m/z calcd for $C_{12}H_{12}NO_3$ $[M+H]^+$ = 218.0817, found = 218.0816; The ee value was 87%, t_R (minor) = 16.3 min, t_R (major) = 22.0 min (Chiralcel IC-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*R*)-Methyl 2-((3-cyanophenyl)(hydroxy)methyl)acrylate (**2-16e**)

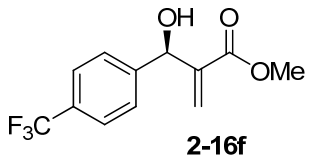


2-16e

A colorless oil; $[\alpha]^{27}_D$ = +11.5 (c 0.87, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 6.39 (s, 1H), 5.86 (s, 1H), 5.56 (d, *J* = 5.7 Hz, 1H), 3.74 (s, 3H), 3.28 (d, *J* = 6.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 142.9, 141.1, 131.4, 131.0, 130.2, 129.1, 127.0,

118.7, 112.5, 72.5, 52.1; HRMS (ESI) m/z calcd for $C_{12}H_{12}NO_3$ $[M+H]^+$ = 218.0817, found = 218.0824; The ee value was 85%, t_R (minor) = 17.1 min, t_R (major) = 24.4 min (Chiralcel IC-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

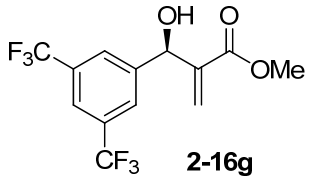
(*R*)-Methyl 2-(hydroxy(4-(trifluoromethyl)phenyl)methyl)acrylate (**2-16f**)



2-16f

A colorless oil; $[\alpha]^{27}_D$ = -4.3 (c 0.71, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 6.36 (s, 1H), 5.84 (s, 1H), 5.59 (d, *J* = 5.7 Hz, 1H), 3.73 (s, 3H), 3.27 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 145.3, 141.4, 129.9 (q), 126.8, 126.8, 125.4 (q), 125.2, 123.0, 72.9, 52.1; HRMS (ESI) m/z calcd for $C_{12}H_{12}F_3O_3$ $[M+H]^+$ = 261.0714, found = 261.0717; The ee value was 87%, t_R (minor) = 12.9 min, t_R (major) = 20.4 min (Chiralcel IC-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

(*R*)-Methyl 2-((3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)acrylate (**2-16g**)

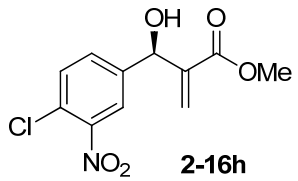


2-16g

A colorless oil; $[\alpha]^{27}_D$ = 20.9 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 2H), 7.80 (s, 1H), 6.24 (s, 1H), 5.88 (s, 1H), 5.65 (s, 1H), 3.76 (s, 3H), 3.34 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 144.0, 140.8, 132.1, 131.6, 127.5, 126.8, 124.4, 122.2, 121.8, 121.7, 121.7, 72.5, 52.3; HRMS (ESI) m/z calcd for $C_{13}H_{11}F_6O_3$ $[M+H]^+$ = 329.0612, found = 329.0620; The ee value was 84%, t_R (minor) = 12.7 min, t_R

(major) = 10.7 min (Chiralcel OD-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

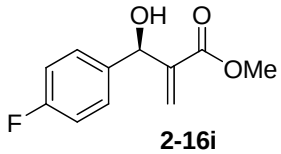
(*R*)-Methyl 2-((4-chloro-3-nitrophenyl)(hydroxy)methyl)acrylate (**2-16h**)



2-16h

A colorless oil; $[\alpha]^{27}_{D}$ = -7.7 (c 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 1.9 Hz, 1H), 7.49-7.55 (m, 2H), 6.39 (s, 1H), 5.91 (s, 1H), 5.56 (s, 1H), 3.74 (s, 3H), 3.43 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 147.8, 142.1, 140.7, 131.7, 131.1, 127.3, 126.0, 123.6, 71.9, 52.2; HRMS (ESI) m/z calcd for $C_{11}H_{11}ClNO_5$ $[M+H]^+$ = 272.0326, found = 272.0329; The ee value was 85%, t_R (minor) = 19.0 min, t_R (major) = 23.4 min (Chiralcel IC-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

(*R*)-Methyl 2-((4-fluorophenyl)(hydroxy)methyl)acrylate (**2-16i**)

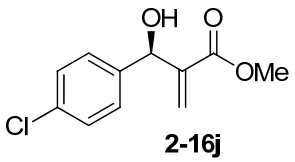


2-16i

A colorless oil; $[\alpha]^{27}_{D}$ = -20.0 (c 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.36 (m, 2H), 7.02 (t, *J* = 8.8 Hz, 2H), 6.33 (s, 1H), 5.82 (s, 1H), 5.54 (d, *J* = 5.1 Hz, 1H), 3.73 (s, 3H), 3.06 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 163.3, 161.4, 141.9, 137.0 (d), 128.3 (d), 126.1, 115.3 (d), 72.6, 52.9; HRMS (ESI) m/z calcd for $C_{11}H_{12}FO_3$ $[M+H]^+$ = 211.0770, found = 211.0772; The ee value was

81%, t_R (minor) = 13.9 min, t_R (major) = 24.2 min (Chiralcel IC-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

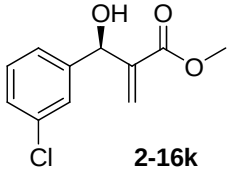
(*R*)-Methyl 2-((4-chlorophenyl)(hydroxy)methyl)acrylate (**2-16j**)



2-16j

A colorless oil; $[\alpha]^{27}_D$ = -22.4 (c 1.31, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 4H), 6.32 (s, 1H), 5.83 (s, 1H), 5.51 (d, *J* = 5.0 Hz, 1H), 3.71 (s, 3H), 3.23 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 141.6, 139.8, 133.5, 128.5, 127.9, 126.2, 72.5, 51.9; (ESI) m/z calcd for $C_{11}H_{12}ClO_3$ $[M+H]^+$ = 227.0475, found = 227.0480; The ee value was 84%, t_R (minor) = 13.6 min, t_R (major) = 21.0 min (Chiralcel IC-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

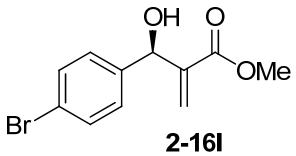
(*R*)-Methyl 2-((3-chlorophenyl)(hydroxy)methyl)acrylate (**2-16k**)



2-16k

A colorless oil; $[\alpha]^{27}_D$ = -6.6 (c 0.63, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 1.9 Hz, 7.6 Hz, 1H), 7.22-7.36 (m, 3H), 6.33 (s, 1H), 5.98 (s, 1H), 5.58 (s, 1H), 3.77 (s, 3H), 3.33 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 140.6, 138.2, 132.8, 129.4, 129.0, 128.1, 127.0, 126.9, 69.3, 52.1; HRMS (ESI) m/z calcd for $C_{11}H_{11}ClO_3$ $[M+H]^+$ = 227.0475, found = 227.0476; The ee value was 82%, t_R (minor) = 20.5 min, t_R (major) = 31.1 min (Chiralcel IC-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

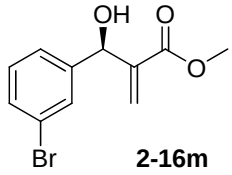
(*R*)-Methyl 2-((4-bromophenyl)(hydroxy)methyl)acrylate (**2-16l**)



2-16l

A colorless oil; $[\alpha]^{27}_{D}$ = +7.9 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.2 Hz, 2H), 7.45 (dd, *J* = 2.6 Hz, 8.9 Hz, 2H), 6.33 (s, 1H), 5.82 (s, 1H), 5.49 (d, *J* = 5.1 Hz, 1H), 3.71 (s, 3H), 3.22 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 141.6, 140.3, 131.5, 128.3, 126.3, 121.7, 72.6, 51.9; (ESI) m/z calcd for $C_{11}H_{12}BrO_3$ $[M+H]^+$ = 270.9970, found = 270.9961; The ee value was 83%, t_R (minor) = 14.2 min, t_R (major) = 21.8 min (Chiralcel IC-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

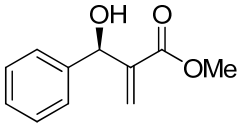
(*R*)-Methyl 2-((3-bromophenyl)(hydroxy)methyl)acrylate (**2-16m**)



2-16m

A colorless oil; $[\alpha]^{27}_{D}$ = -14.9 (c 0.80, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 8.2 Hz, 1H), 6.35 (s, 1H), 5.84 (s, 1H), 5.50 (s, 1H), 3.73 (s, 3H), 3.22 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 143.6, 141.4, 130.8, 129.9, 129.6, 126.6, 125.2, 122.5, 72.6, 52.0; HRMS (ESI) m/z calcd for $C_{11}H_{12}BrO_3$ $[M+H]^+$ = 270.9949, found = 270.9952; The ee value was 84%, t_R (minor) = 14.6 min, t_R (major) = 20.7 min (Chiralcel IC-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

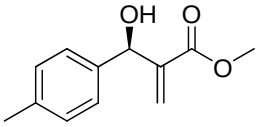
(*R*)-Methyl 2-(hydroxy(phenyl)methyl)acrylate (**2-16n**)



2-16n

A colorless oil; $[\alpha]^{27}_{D}$ = -94.3 (c 0.42, MeOH), (lit.[85]: $[\alpha]^{28}_{D}$ = -109.3 (c, 0.54, MeOH)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.38 (m, 4H), 7.26-7.29 (m, 1H), 6.33 (s, 1H), 5.84 (s, 1H), 5.56 (s, 1H), 3.71 (s, 3H), 3.15 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 142.0, 141.3, 128.4, 127.8, 126.6, 126.1, 73.2, 51.9; HRMS (ESI) m/z calcd for $C_{11}H_{13}O_3$ $[M+H]^+$ = 193.0865, found = 193.0866; The ee value was 80%, t_R (minor) = 14.8 min, t_R (major) = 29.1 min (Chiralcel IC-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

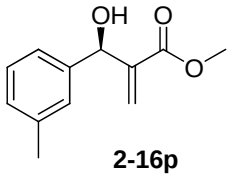
(*R*)-Methyl 2-(hydroxy(p-tolyl)methyl)acrylate (**2-16o**)



2-16o

A colorless oil; $[\alpha]^{27}_{D}$ = -57.4 (c 0.52, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 6.6 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.33 (s, 1H), 5.85 (d, *J* = 1.3 Hz, 1H), 5.53 (s, 1H), 3.71 (s, 3H), 2.99 (br, 1H), 2.34 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 142.1, 138.3, 137.5, 129.1, 126.5, 125.8, 73.0, 51.9, 21.1; HRMS (ESI) m/z calcd for $C_{12}H_{15}O_3$ $[M+H]^+$ = 207.1021, found = 207.1022; The ee value was 76%, t_R (minor) = 21.6 min, t_R (major) = 37.5 min (Chiralcel IC-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

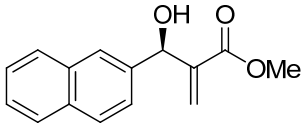
(*R*)-Methyl 2-(hydroxy(m-tolyl)methyl)acrylate (**2-16p**)



2-16p

A colorless oil; $[\alpha]^{27}_{D}$ = -46.7 (c 0.45, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15-7.26 (m, 3H), 7.10 (d, *J* = 6.9 Hz, 2H), 6.34 (s, 1H), 5.85 (s, 1H), 5.53 (s, 1H), 3.72 (s, 3H), 3.05 (br, 1H), 2.35 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 141.9, 141.2, 138.0, 128.5, 128.3, 127.2, 125.9, 123.6, 73.2, 51.9, 21.4; HRMS (ESI) m/z calcd for $C_{12}H_{15}O_3$ $[M+H]^+$ = 207.1021, found = 207.1015; The ee value was 77%, t_R (minor) = 9.9 min, t_R (major) = 17.3 min (Chiralcel IC-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

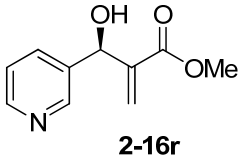
(*R*)-Methyl 2-(hydroxy(naphthalen-2-yl)methyl)acrylate (**2-16q**)



2-16q

A white solid; $[\alpha]^{27}_{D}$ = -12.6 (c 0.43, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82-7.86 (m, 4H), 7.48 (d, *J* = 7.6 Hz, 3H), 6.38 (s, 1H), 5.88 (s, 1H), 5.75 (d, *J* = 3.2 Hz, 1H), 3.72 (s, 3H), 3.15 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 141.9, 138.6, 133.2, 133.0, 128.2, 128.1, 127.6, 126.4, 126.1, 126.0, 125.5, 124.6, 73.4, 52.9; HRMS (ESI) m/z calcd for $C_{15}H_{15}O_3$ $[M+H]^+$ = 243.1021, found = 243.1021; the ee value was 90%, t_R (minor) = 13.0 min, t_R (major) = 18.6 min (Chiralcel IC-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

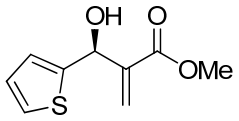
(*R*)-Methyl 2-(hydroxy(pyridin-3-yl)methyl)acrylate (**2-16r**)



2-16r

A colorless oil; $[\alpha]^{27}_{D}$ = -44.5 (c 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.4 Hz, 1H), 7.71-7.73 (m, 1H), 7.23-7.26 (m ,1H), 6.37 (s, 1H), 5.95 (s, 1H), 5.59 (m, 1H), 3.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 148.6, 148.3, 141.6, 137.4, 134.5, 126.2, 123.4, 70.7, 51.9; HRMS (ESI) m/z calcd for $C_{10}H_{12}NO_3$ $[M+H]^+$ = 194.0817, found = 194.0813; the ee value was 84%, t_R (minor) = 12.0 min, t_R (major) = 19.2 min (Chiralcel IC-H, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*S*)-Methyl 2-(hydroxy(thiophen-2-yl)methyl)acrylate (**2-16s**)



2-16s

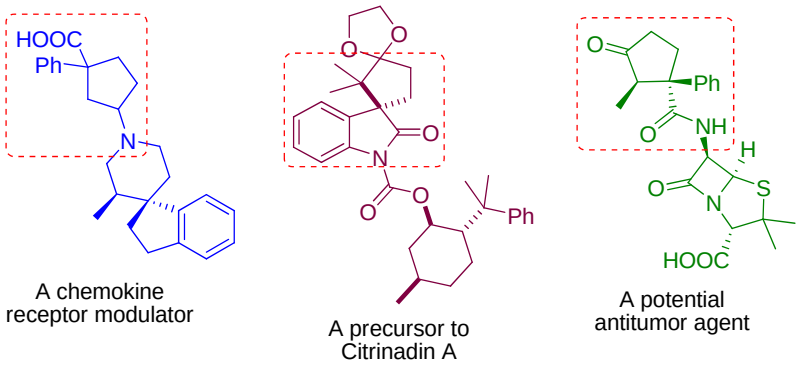
A colorless oil; $[\alpha]^{27}_{D}$ = +46.7 (c 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.26 (m, 1H), 6.94 (m, 2H), 6.35 (s, 1H), 5.95 (s, 1H), 5.76 (d, *J* = 6.3 Hz, 1H), 3.74 (s, 3H), 3.44 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 145.7, 141.3, 126.8, 126.1, 125.2, 124.7, 69.6, 51.9; HRMS (ESI) m/z calcd for $C_9H_{11}O_3S$ $[M+H]^+$ = 199.0429, found = 199.0427; The ee value was 70%, t_R (minor) = 11.6 min, t_R (major) = 17.1 min (Chiralcel IC-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

Chapter 3 Enantioselective [3+2] Cycloaddition of Allenes to Acrylates Catalyzed by Dipeptide-Derived Phosphines: Facile Creation of Functionalized Cyclopentenes Containing Quaternary Stereogenic Centers

3.1 Introduction

Functionalized five-membered carbocycles are structural motifs often found in natural products and medicinally important agents.[93] Among the known synthetic methods, phosphine-catalyzed [3+2] cycloaddition, developed by Lu in 1995,[39,94] is considered to be one of the most efficient synthetic approaches. By employing electron-deficient olefins and imines, cyclopentenes and pyrrolidines can be prepared via phosphine-catalyzed cycloadditions, respectively.[6,12,56c,79] The first asymmetric [3+2] cycloaddition between allenoates and acrylates catalyzed by a bicyclic chiral phosphine was reported by Zhang in 1997.[40] Recently, enantioselective cyclizations of allenoates and enones were achieved by Fu[41] and Miller,[42] utilizing a binaphthyl-based *C2*-symmetric chiral phosphine and a multifunctional phosphine-containing α-amino acid, respectively. Jacobsen designed a series of bifunctional phosphine–thiourea catalysts and applied them to the enantioselective imine–allene annulations.[50] Planar chiral 2-phospha[3]ferrocenophanes, introduced by Marinetti, were shown to promote enantioselective [3+2] additions of allenic esters and phosphonates with enones.[43,95] Very recently, Loh discovered that commercially available chiral phosphines could promote the cycloaddition of 3-butynoates to enones.[44] Zhao reported bifunctional *N*-acyl amino phosphines were effective catalysts for the asymmetric [3+2] cycloadditions of allenoates and activated olefins.[45] Despite the above impressive achievements, comparing to the widespread applications

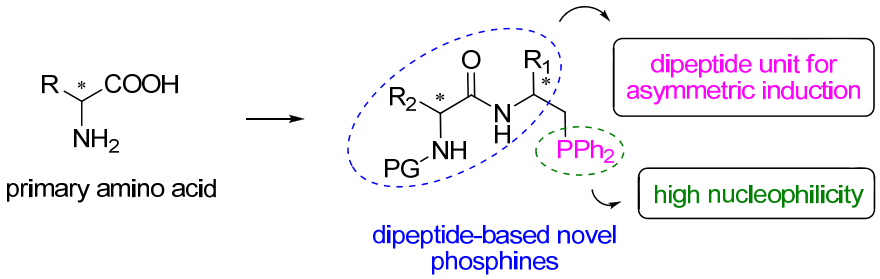
of phosphine-mediated processes, the design and development of chiral phosphine catalysts are still under-explored. When the phosphine-catalyzed [3 + 2] cyclizations are concerned, acrylates remain as elusive substrates;[40,43] thus an enantioselective [3+2] cycloaddition applicable to substituted acrylates is highly desirable.



Scheme 3.1 Cyclopentane structures with a quaternary carbon

Creation of quaternary stereocenters is a challenging task in organic synthesis,[96] and we recently became interested in devising organocatalytic methods to access molecules with chiral quaternary centers.[97] Five-membered carbocycles with a quaternary stereogenic center are interesting substructures often found in many natural products and bioactive molecules (Scheme 3.1),[98] we envisioned that phosphine-catalyzed [3+2] annulations between α-substituted acrylates and allenes may be utilized to construct such five-memebered ring systems. Our group has been actively investigating asymmetric organic transformations that can be promoted by organocatalysts derived from primary amino acids in the past few years,[81,98] thus we have keen interest in deriving versatile amino acid-based novel phosphines. To ensure effective chiral communications with the substrates, and to make the catalysts readily accessible, we chose dipeptide[99] as the basic chiral backbone for our catalyst

development (Scheme 3.2). The carboxylic acid group can be easily converted to a phosphine, which is expected to be highly nucleophilic as the phosphorus atom is connected to a primary carbon. The substrate-interacting chiral pocket derived from the dipeptide is highly tunable by simply varying the amino acid side chains. Herein, we describe the first enantioselective [3+2] cycloaddition between α-substituted acrylates and allenoates mediated by dipeptide-based novel phosphine catalysts, creating chiral cyclopentenes containing a quaternary stereogenic center.

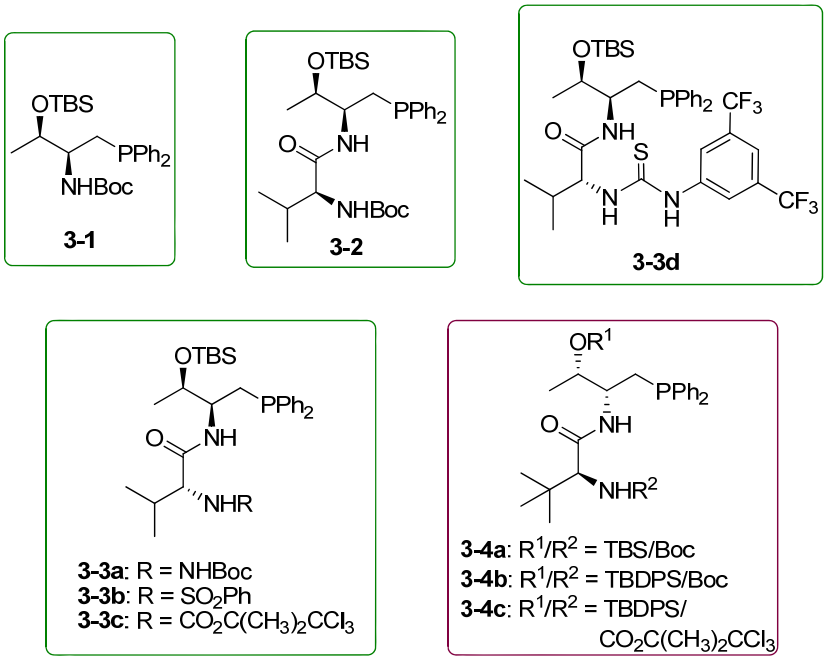


Scheme 3.2 Phosphine catalysts based on dipeptides

3.2 Results and Discussion

3.2.1 Reaction Optimization

We began our investigation by selecting [3+2] cycloaddition between 2-phenyl-substituted acrylate **5a** and benzyl allenoate **6a** as a model reaction (Table 3.1). It should be noted that employment of α-substituted acrylates in asymmetric [3+2] cycloadditions is virtually unexplored.[39,100] For the design of effective catalysts, given our success in threonine-based catalytic systems,[38,81] we chose threonine as the first amino acid residue, and a number of dipeptide-derived phosphines **3-1–3-4** were prepared. We hypothesize judicious selection of the side chains may facilitate the

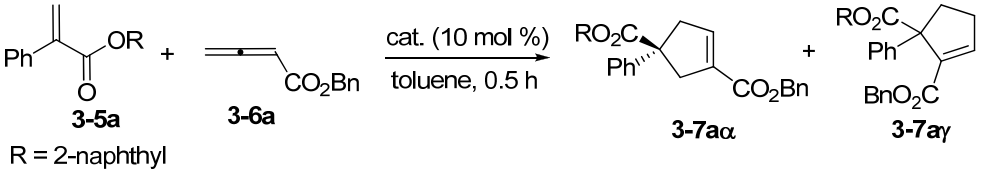


Scheme 3.3 Amino acid-based phosphine catalysts

dipeptide catalyst to adopt a relatively rigid conformation, favoring its interactions with substrates. L-Threonine-derived phosphine **3-1** led to the formation of α-selective product with low ee (entry 1). On the other hand, dipeptide-based phosphines turned out to be more effective. L-Thr-L-Val-derived 3-**2** led to substantially improved results, moderate ee was attainable (entry 2). Combining L-Thr and D-Val yielded a better catalytic system, and the ee value was further improved to 60% (entry 3). Employment of sulfonamide as Brønsted acid moiety in the catalyst did not offer better results (entry 4). L-Thr-D-Val-derived phosphine–thiourea catalyst **3-3d** was also prepared and examined in the cyclization, and the reaction was completed only after 24 hrs. The cycloaddition products were obtained in 85% yield, with an α to γ ratio of 90:10, and -28% ee for the α-isomer. Higher α-selectivity was achieved by utilizing an even more sterically hindered carbamate (entry 6). The catalyst structures were further tuned by engaging *tert*-leucine as the second amino

acid residue and varying the siloxy groups on the OH of threonine. To make the catalyst more economical, D-Thr-L-*tert*-Leu dipeptidic backbone was selected for structural elaborations. Finally, *O*-TBDPS-D-Thr-L-*tert*-Leu-derived **3-4c** was found to be the best catalyst, affording the desired adduct **3-7aα** in 96% yield, with an α to γ ratio of 95:5 and 78% ee (entry 9).

Table 3.1 [3+2] Cycloaddition of allenoates with acrylates catalyzed by different amino acid-based phosphines[a]



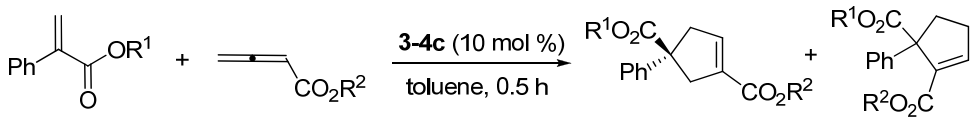
Entry	Catalyst	**3-7a**:**3-7γ**[b]	Yield (%)[c]	ee (%)[d]
1	**3-1**	83:17	88	-36
2	**3-2**	84:16	90	-52
3	**3-3a**	89:11	96	-60
4	**3-3b**	74:26	90	-57
5	**3-3c**	92:8	93	-61
6[e]	**3-3d**	90:10	85	-28
7	**3-4a**	93:7	93	63
8	**3-4b**	94:6	95	74
9	**3-4c**	**95:5**	**96**	**78**

[a] Reactions were conducted with **3-5a** (0.05 mmol), **3-6a** (0.075 mmol) and the catalyst (10 mol%) in toluene (0.5 mL) at room temperature. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yield. [d] The ee value of the major stereroisomer, determined by HPLC analysis on a chiral stationary phase.

Having identified the best catalyst **3-4c**, we then focused on tuning the ester moieties in acrylates and allenoates (Table 3.2). The *tert*-butyl ester proved to be superior to other esters in the allenoate structures, the ratio of α to γ-isomer could be

improved to 96:4, and ee of the major isomer reached 84% (entries 1–5). Among the different acrylate esters, 9-phenanthryl acrylate was found to be the best, and its cycloaddition with *tert*-butyl allenoate led to the formation of only α-isomer in 95% yield and 91% ee (entry 11).

Table 3.2 [3+2] Cycloaddition of allenoates with acrylates[a]



3-5 **3-6** **3-7α** **3-7γ**

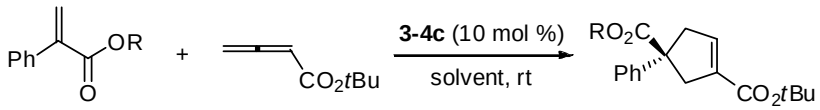
Entry	R^1/R^2	α : γ[b]	Yield (%)[c]	ee (%)[d]
1	2-Napthyl/Et	94:4	91	74
2	2-Napthyl/Bn	95:5	96	78
3	2-Napthyl/9-CH_2An	93:7	87	76
4	2-Napthyl/*t*-Bu	96:4	94	84
5	2-Natphyl/Ph	89:11	95	84
6	*i*-Pr/*t*-Bu	97:3	72	24
7	Bn/*t*-Bu	94:6	68	20
8	Ph/*t*-Bu	97:3	92	76
9	2,6-CH_3Ph/*t*-Bu	98:2	94	72
10	1-Napthyl/*t*-Bu	98:2	93	81
11	**9-Phenanthryl/*t*-Bu**	**>99: 1**	**95**	**91**
12	9-Anthryl/*t*-Bu	>99 : 1	95	80

[a] Unless otherwise specified, reactions were conducted with **3-5** (0.05 mmol), **3-6** (0.075 mmol) and **3-4c** (10 mol%) in toluene (0.5 mL) at room temperature. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yield. [d] The ee value of the major stereoisomer, determined by HPLC analysis on a chiral stationary phase.

Performing reaction in different solvents and lowering the reaction temperature did not result in further improvement (Table 3.3). Toluene still turned out to be the best solvent, offering the corresponding [3+2] adduct in 95% yield with 91% ee (entry

1). All the other common organic solvents were shown to be unsuitable, affording products in low yields and with poor enantioselectivities. The protic solvent, e.g. methanol, proved to extremely poor medium, and no desired product was observed under this reaction condition (entry 12). Furthermore, with the decrease of the temperature from room temperature to -20 °C, the reaction became much slower and the enantioselectivity was not improved at all; only 84% yield was obtained (entry 15).

Table 3.3 Solvents screening for **3-4c**-promoted [3+2] cycloaddition[a]



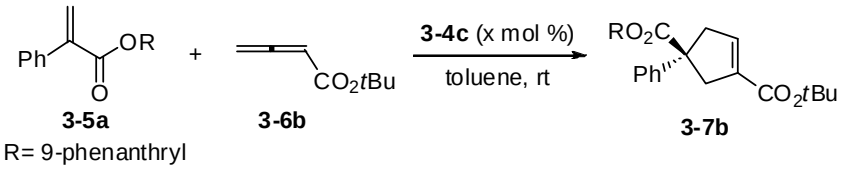
3-5a R= 9-phenanthryl **3-6b** **3-7b**

Entry	Solvent	*t* (h)	Yield (%)[b]	ee (%)[c]
1	**toluene**	**0.5**	**95**	**91**
2	1,2-dichlorobenzene	0.5	90	77
3	PhBr	0.5	91	82
4	benzene	0.5	94	88
5	xylene	0.5	89	88
6	4-fluorotoluene	0.5	94	74
7	CH_2Cl_2	0.5	92	70
8	$CHCl_3$	2	81	76
9	THF	0.5	93	67
10	Et_2O	0.5	95	87
11	$CNCH_3$	6	53	12
12	MeOH	6	-[d]	-[d]
13	DMF	6	21	13
14[e]	toluene	1.2	95	89
15[f]	toluene	5	84	88

[a] Unless otherwise specified, reactions were conducted with **3-5a** (0.05 mmol), **3-6b** (0.075 mmol) and **3-4c** (10 mol%) in solvent (0.5 mL) at room temperature. [b] Isolated yield. [c] The ee value of the major stereoisomer, determined by HPLC analysis on a chiral stationary phase. [d] Not determined. [e] The reaction was performed at 4 °C. [f] The reaction was performed at -20 °C.

Additionally, the molecular sieves (MS) were revealed to be useless in improving the asymmetric induction (entry 2–4, Table 3.4). To make the methodology more practical, catalyst loading was further decreased. With 5 mol% **3-4c**, the [3+2] cycloaddition could be completed with half an hour, furnishing α-isomer in 95% yield and with 91% ee (entry 7). It should be noted that the catalyst loading could go as low as 2 mol%, with marginally reduced yield and enantioselectivity (entry 8).

Table 3.4 The effects of additives and catalyst loading on **3-4c**-promoted [3+2] cycloaddition



3-5a R= 9-phenanthryl **3-6b** **3-7b**

Entry	x (mol %)	Additive	*t* (h)	Yield (%)[b]	ee (%)[c]
1	10	none	0.5	95	91
2	10	3Å MS	0.5	95	91
3	10	4Å MS	0.5	94	91
4	10	5Å MS	0.5	94	90
6	10	H_2O	0.5	90	87
7	5	none	0.5	95	91
8	2	none	0.5	93	90
9	1	none	6	56	88

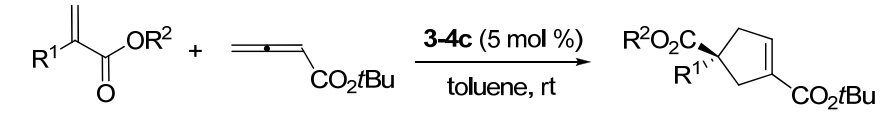
[a] Unless otherwise specified, reactions were conducted with **3-5a** (0.05 mmol), **3-6b** (0.075 mmol) and **3-4c** (10 mol%) in toluene (0.5 mL) at room temperature. [b] Isolated yield. [c] The ee value of the major stereoisomer, determined by HPLC analysis on a chiral stationary phase.

3.2.2 Substrate Scope

With the optimized reaction conditions in hand, the substrate scope of **3-4c**-

catalyzed enantioselective [3+2] cycloaddition between allenes and acrylates was examined (Table 3.5). Different α-aryl-substituted acrylates could be employed, α-isomers were regiospecifically formed, and enantioselectivities were excellent in all the examples examined. Reactions of acrylates bearing electronwithdrawing aryl substituents proceeded very fast, typically completing in 10 min, while longer reaction time was required for the cyclization of the acrylate with electron-rich phenyl group at its α-position (entry 4–8). The acrylate with 1- or 2-naphthyl substitution, or disubstituted phenyl was well-tolerated for the reaction (entries 12–13). However, the use of α-alkyl substituted acrylate resulted in the formation of the desired product in high yield, but only with moderate enantioselectivity (entry 15–17), which presumably due to the rather flexible conformation of acrylate with a alkyl substitution compared to that of other α-aryl substituents. The absolute configurations of the cycloaddition products were determined on the basis of the X-ray crystal structure of **3-7l**.

Table 3.5 Enantioselective allene–acrylates [3+2] cycloadditions catalyzed by **3-4c**[a]



3-5 **3-6b** **3-7**

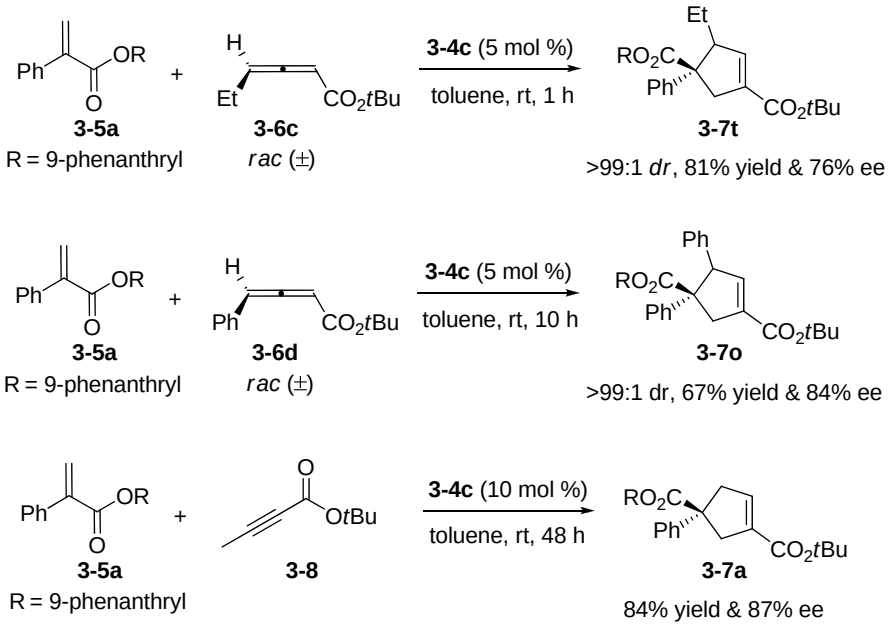
R^2 = 9-phenanthryl

Entry	Product (R^1)	time	Yield (%)[c]	ee (%)[d]
1	**3-7b** (Ph)	0.5 h	95	91
2	**3-7c** (4-ClC_6H_5)	10 min	96	94
3	**3-7d** (4-BrC_6H_5)	10 min	97	93
4	**3-7e** (4-MeC_6H_5)	3 h	81	90
5	**3-7f** (4-$OMeC_6H_5$)	24 h	61	87
6	**3-7g** (4-*t*-BuC_6H_5)	3 h	87	90
7	**3-7h** (4-CN C_6H_5)	10 min	97	94

8	**3-7i** (3-MeC_6H_5)	3 h	96	88
9	**3-7j** (2-$NO_2C_6H_5$)	0.5 h	96	90
10	**3-7k** (2-FC_6H_5)	0.5 h	95	83
11	**3-7l** (3,4-ClC_6H_4)	0.5 h	94	92
12	**3-7m** (1-naphtyl)	0.5 h	96	80
13	**3-7n** (2-naphtyl)	0.5 h	92	91
14	**3-7o** (9-phenanthryl)	0.5 h	95	82
15	**3-7p** (Bn)	5 h	91	68
16	**3-7q** (CH_3)	20 h	51	51
17	**3-7r** (cyclohexyl)	48 h	44	47
18	**3-7s** (H)	10 min	96	62

[a] Unless otherwise specified, reactions were conducted with **3-5** (0.05 mmol), **3-6b** (0.075 mmol) and **3-4c** (5 mol%) in toluene (0.5 mL) at room temperature. [b] Isolated yield. [c] The ee value of the major stereoisomer, determined by HPLC analysis on a chiral stationary phase.

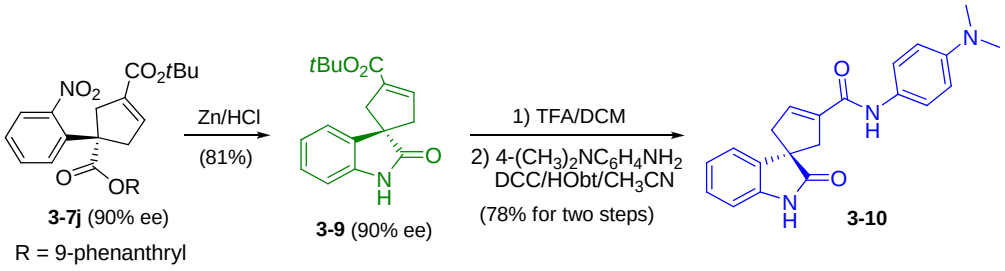
α-Substituted acrylate, moreover, could undergo a unique deracemization reaction upon cycloaddition with racemic γ-substituted allenoate (Scheme 3.4). We were pleased to find that when (±)-**3-6c** was exposed to acrylate **3-5a** in the presence of 5 mol % catalyst **3-4c**, a 81% yield of cyclopentene **3-7t** was formed within 1 h and that the corresponding product exhibited 76% ee. When γ-phenyl-substituted allenoate **3-6d** was employed, a similar result was observed, although the reaction rate was diminished (Scheme 3.4, 67% yield within 10 h, 84% ee). In each of these cases, these highly substituted cycloadducts were formed as single regio- and diastereomers via chiral phosphine-catalyzed [3+2] cycloaddition. Furthermore, alkynoate **3-8**, which is generally much less reactive as compared to allenoate, was found to be suitable coupling partner, affording product **3-7a** in 84% yield with 87% ee in the presence of 10 mol % catalyst.



Scheme 3.4 Phosphine **3-4c**-promoted [3+2] cycloaddition involving γ-substituted allenoates and alkynoate as reaction substrates

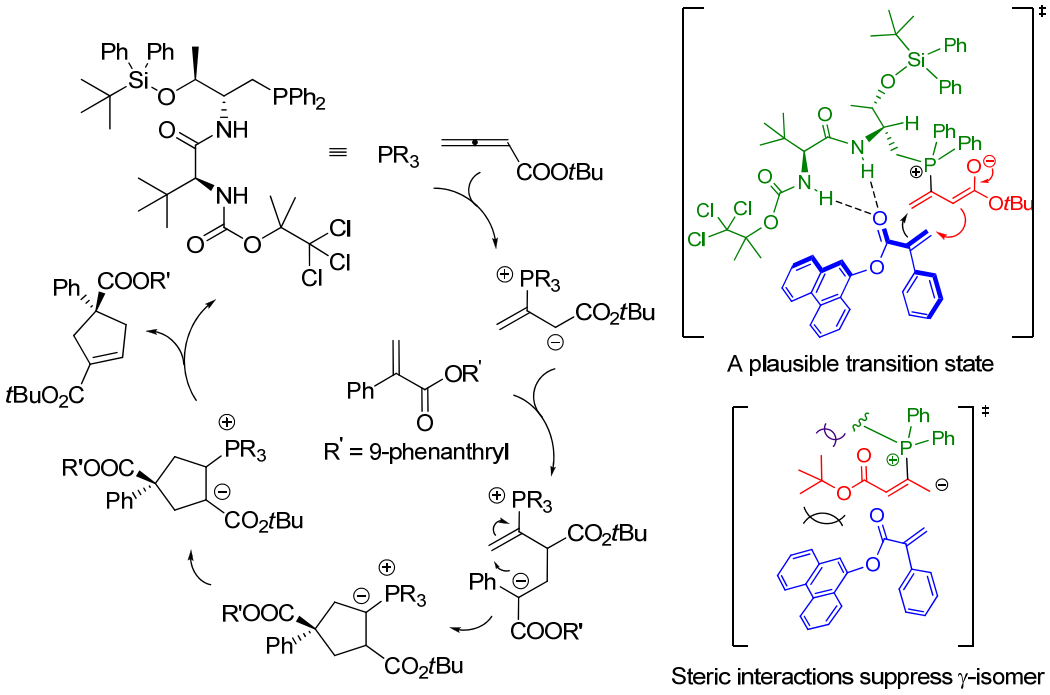
3.2.3 Derivative Synthesis

The optically enriched functionalized cyclopentenes **3-7** are valuable molecules, due to the importance of five-membered ring structures in natural products and medicinal chemistry.[98] With the established synthetic protocols,[101] such structures are also attractive synthetic intermediates. As oxindoles are important structural scaffolds in pharmaceutical industry,[102] synthetic value of the cycloaddition products was further demonstrated by converting **3-7j** into a spiral oxindole. As illustrated in Scheme 3.5, reduction of the nitro group resulted in a spontaneous lactam formation and yielded spiral oxindole core **3-9**, which was readily transformed to **3-10**, an agent displaying interesting cytotoxic activities.[103]



Scheme 3.5 Preparation of a spiral oxindole derivative

3.2.4 Plausible Mechanism and Transition State Model



Scheme 3.6 Proposed mechanism and transition state model

Mechanism of this reaction has not been rigorously investigated at this stage, based on Lu's initial proposal[39] and recent excellent mechanistic studies,[104] a plausible mechanism and transition state model are presented in Scheme 3.6. We propose that the dipeptidic backbone of the catalyst adopts a conformation favoring its

hydrogen bonding interactions with the acrylate substrate. The phosphonium enolate intermediate, generated from the nucleophilic attack of the phosphine catalyst at the allene, approaches the acrylate from its *Re* face to yield the major stereoisomer. The formation of the γ-regioisomer is suppressed by the unfavorable steric interactions of the bulky *tert*-butyl group with the acrylate substrate and the sterically hindered carbamate moiety in the catalyst, which is analogous to Lu's utilization of *tert*-butyl allenoate in an α-selective cycloaddition.

3.3 Conclusions

In summary, we have developed a new family of dipeptide-based chiral phosphines; such phosphine catalysts are highly reactive, and their structures are easily tunable. We have also employed α-substituted acrylates in the enantioselective cycloaddition reactions for the first time. D-Thr-L-tert-Leu-based phosphine **4c** catalyzed the allene-acrylate [3+2] cyclizations efficiently, affording functionalized cyclopentenes containing quaternary stereocenters in a regiospecific and enantioselective manner. Detailed mechanistic investigations and applications of this class of novel catalysts to other organic transformations are currently ongoing in our laboratory.

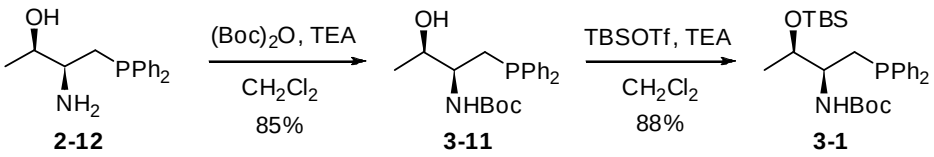
3.4 Experimental Section

3.4.1 General Methods

^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF300 or DPX300 (300 MHz) or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference.

Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in ESI mode, and a Finnigan/MAT 95XL-T mass spectrometer in FAB mode. All high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. Flash chromatography separation was performed on Merck 60 (0.040 - 0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by HPLC analysis on a chiral stationary phase.

3.4.2 Catalysts Preparation



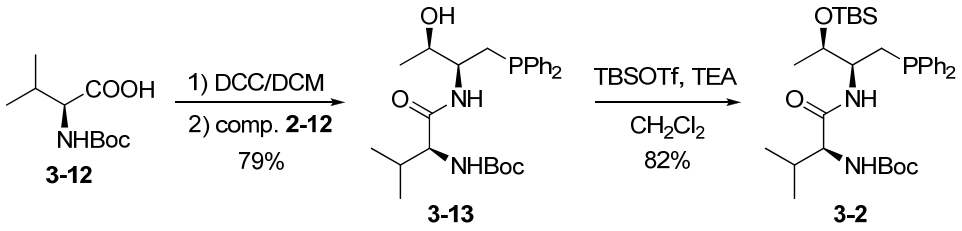
tert-Butyl(2*S*,3*R*)-3-(*tert*-butyldimethylsilyloxy)-1-(diphenylphosphino)butan-2-yl-ca-rbam- ate (**3-1**)

To a solution of **2-12** (150 mg, 0.55 mmol) in CH_2Cl_2 (5 mL) at 0 ^oC was added Et_3N (153 μL, 1.10 mmol) and $(Boc)_2O$ (143 mg, 0.66 mmol) under N_2. The reaction mixture was allowed to warm to room temperature and stirring was continued for additional 2 hrs. After concentration in *vacuo*, the residue was directly purified by column chromatography (hexane:ethyl acetate = 10:1 to 5:1) to afford compound **3-11** as a white solid (174 mg, 85% yield). To the crude **3-11** (174 mg, 0.46 mmol) in anhydrous CH_2Cl_2 (5 mL) at 0 ^oC was added triethylamine (95 mL, 0.69 mmol), followed by slow addition of TBSOTf (0.16 mL, 0.69 mmol). Then the mixture was stirred at room temperature for 1 hr. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL), and the resulting mixture was extracted with

CH_2Cl_2 (2 × 20 mL). The organic extracts were combined and washed with brine, and dried over Na_2SO_4. Purification by column chromatography (hexane: ethyl acetate = 10:1) afforded catalyst **3-1** (0.197 g, 88% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.30 (m, 10H), 4.73 (d, *J* = 9.5 Hz, 1H), 4.13 (d, *J* = 5.0 Hz, 1H), 3.59-3.43 (m, 1H), 2.36-2.20 (m, 2H), 1.46 (s, 9H), 1.11 (d, *J* = 6.5 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 138.8 (d), 132.7 (dd), 129.3, 128.4 (dd), 78.9, 76.7, 69.4, 53.5 (d), 32.3 (d), 28.5, 25.9, 20.4, 18.0, -4.6; ^{31}P NMR (202.5 MHz, $CDCl_3$) δ -22.7 (s); HRMS (ESI) m/z calcd for $C_{27}H_{43}NO_3PSi$ $[M+H]^+$ = 488.2744, found = 488.2750; $[\alpha]^{27}_D$ = -9.0 (c 0.5, $CHCl_3$).

tert-Butyl (*S*)-1-((2*S*,3*R*)-3-(*tert*-butyldimethylsilyloxy)-1-(diphenylphosphino)butan-2-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (**3-2**)

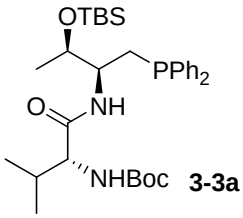


To a stirred solution of *N*-Boc L-valine (0.176 g, 0.82 mmol) in anhydrous CH_2Cl_2 (5 mL) was added DCC (84 mg, 0.41 mmol), and the resulting mixture was stirred at room temperature for 2 hrs. The solution was then cooled down to 0 ^oC and a solution of **2-12** (0.1 g, 0.37 mmol) in CH_2Cl_2 (1 mL) was added dropwise over 2 minutes. The reaction mixture was further stirred for 0.5 h at 0 ^oC and 0.5 h at room temperature. Water (10 mL) was added to quench the reaction, and the resulting mixture was extracted with dichloromethane several times (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered, concentrated, and the residue was purified by column chromatography (hexane: ethyl acetate = 10:1) to

afford **3-13** (0.138 g, 79%) as a white solid. To a solution of **3-13** in anhydrous CH_2Cl_2 (5 mL) at 0 ^oC was added TEA (61 μL, 0.44 mmol), followed by addition of TBSOTf (0.11 mL, 0.69 mmol) slowly. Then the mixture was allowed to warm to room temperature and continued stirring for additional 1 hour. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine, and dried over Na_2SO_4. Purification by column chromatography (hexane: ethyl acetate = 10:1) afforded catalyst **3-2** (0.140 g, 82% yield) as a white solid.

^1H NMR (300 MHz, $CDCl_3$) δ 7.56-7.28 (m, 10H), 6.33, (s, 1H), 5.03 (s, 1H), 4.32-4.26 (m, 1H), 3.95-3.75 (m, 2H), 2.38 (dd, J_1 = 3.9 Hz, J_2 = 10.5 Hz, 1H), 2.20-2.12 (m, 2H), 1.42 (s, 9H), 1.07 (d, J = 6.0 Hz, 3H), 0.98-0.90 (m, 15H), 0.10 (d, J = 2.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 138.6, 132.9, 132.7 (d), 132.5, 128.4 (dd), 79.6, 68.2(d), 60.0, 52.3 (d), 31.7 (d), 20.8, 19.2, 17.7 (d), -4.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ -23.9 (s); HRMS (ESI) m/z calcd for $C_{32}H_{52}N_2O_4PSi$ $[M+H]^+$ = 587.3428, found = 587.3449; $[\alpha]^{27}_D$ = -19.7 (c 0.73, $CHCl_3$).

tert-Butyl (*R*)-1-((2*S*,3*R*)-3-(*tert*-butyldimethylsilyloxy)-1-(diphenylphosphino)butan-2-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (**3-3a**)

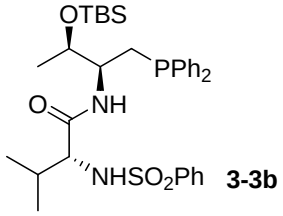


3-3a

The catalyst **3-3a** was prepared in an overall yield of 66% (2 steps), following the procedure described for the preparation of compound **3-2**.

A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56-7.28 (m, 10H), 6.25, (d, *J* = 8.4 Hz, 1H), 4.98 (d, *J* = 8.1 Hz, 1H), 4.24 (d, *J* = 6.0 Hz, 1H), 3.90-3.85 (m, 2H), 2.40 (dd, J_1 = 6.6 Hz, J_2 = 13.5 Hz, 1H), 2.23-2.11 (m, 2H), 1.44 (s, 9H), 1.07 (d, *J* = 6.3 Hz, 3H), 0.96-0.91 (m, 15H), 0.10 (d, *J* = 2.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 155.7, 138.9 (d), 137.4, 132.7 (d), 128.4 (dd), 79.7, 68.5(d), 60.0, 52.3 (d), 31.8 (d), 28.3, 25.6 (d), 21.0, 19.2, 17.9, 17.6, -4.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ -23.6 (s); HRMS (ESI) m/z calcd for $C_{32}H_{52}N_2O_4PSi$ $[M+H]^+$ = 587.3428, found = 587.3453; $[\alpha]^{27}_D$ = -21.4 (c 0.30, $CHCl_3$).

(*R*)-*N*-((2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-1-(diphenylphosphino)butan-2-yl)-3-met-hyl-2 (phenylsulfonamido)butanamide (**3-3b**)

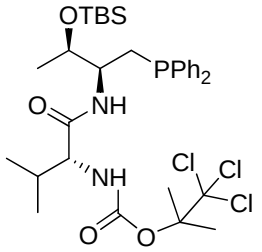


3-3b

The catalyst **3-3b** was prepared in an overall yield of 70% (2 steps), following the procedure described for the preparation of compound **3-2**.

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89, (d, *J* = 5.0 Hz, 1H), 7.34-7.25 (m, 13H), 6.05, (d, *J* = 8.0 Hz, 1H), 5.38 (d, *J* = 8.0 Hz, 1H), 4.26 (t, *J* = 4.5 Hz, 1H), 3.66-3.60 (m, 1H), 3.45 (dd, J_1 = 5.0 Hz, J_2 = 8.0 Hz, 1H), 2.05-1.79 (m, 3H), 1.03 (d, *J* = 5.5 Hz, 3H), 0.91-0.85 (m, 15H), 0.11 (d, *J* = 4.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 139.7, 132.9, 132.7 (d), 132.6, 129.0, 128.9, 128.6 (dd), 127.2, 67.8 (d), 62.2, 52.7 (d), 31.9, 28.3, 25.9, 21.1, 19.0, 18.0, 17.4, -4.5; ^{31}P NMR (202 MHz, $CDCl_3$) δ -24.1 (s); HRMS (ESI) m/z calcd for $C_{33}H_{48}N_2O_4PSSi$ $[M+H]^+$ = 627.2836, found = 627.2867; $[\alpha]^{27}_D$ = -37 (c 0.53, $CHCl_3$).

1,1,1-Trichloro-2-methylpropan-2-yl (*R*)-1-((2*S*,3*R*)-3-(*tert*-butyldimethylsilyloxy)-1-(di-phenylphosphino)butan-2-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (**3-3c**)

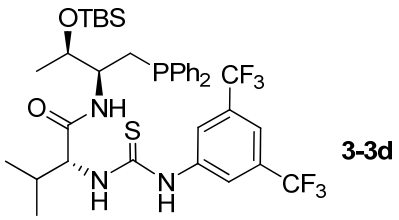


3-3c

The catalyst **3-3c** was prepared in an overall yield of 67% (2 steps), following the procedure described for the preparation of compound **3-2**.

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53, (t, *J* = 7.0 Hz, 2H), 7.40-7.28 (m, 8H), 6.06, (d, *J* = 7.5 Hz, 1H), 5.39 (d, *J* = 7.5 Hz, 1H), 4.24 (d, *J* = 5.5 Hz, 1H), 3.92-3.85 (m, 2H), 3.42 (dd, J_1 = 7.0 Hz, J_2 = 13.5 Hz, 1H), 2.18-2.13 (m, 2H), 1.91 (d, *J* = 6.0 Hz, 6H), 1.08 (d, *J* = 6.0 Hz, 3H), 0.96-0.90 (m, 15H), 0.10 (d, *J* = 4.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 154.0, 138.8 (d), 137.4 (d), 132.7 (d), 128.5 (dd), 106.4, 88.3, 68.7 (d), 60.4, 52.6 (d), 32.0 (d), 31.0, 25.7 (d), 21.6 (d), 21.0, 19.0, 18.0, 17.9, -4.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ -23.6 (s); HRMS (ESI) m/z calcd for $C_{32}H_{49}Cl_3N_2O_4PSi$ $[M+H]^+$ = 689.2259, found = 689.2281; $[\alpha]^{27}_D$ = +3.6 (c 0.53, $CHCl_3$).

(*R*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)-*N*-((2*S*,3*R*)-3-(*tert*butyldimethyl siloxy)-1-(diphenylphosphino)butan-2-yl)-3-methylbutanamide (**3-3d**)

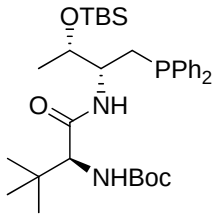


3-3d

To a stirred solution of **3-2** (0.052 g, 0.089 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added TFA (0.1 mL), and the resulting mixture was stirred at room temperature for 2 hrs. The reaction was then quenched with saturated aqueous $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 several times (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated. To a solution of the above residue in anhydrous CH_2Cl_2 (0.5 mL) at 0 ^oC was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (20 μL, 0.098 mmol), and the mixture was stirred at 0 ^oC for 1 h. Purification by flash column chromatography (hexane/ethyl acetate = 15 : 1 to 8 : 1) afforded **3-3d** as a white solid (48 mg, 72% yield).

A white solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.66 (s, 1H), 7.82 (s, 2H), 7.33 (s, 1H), 7.16-7.07 (m, 10H), 6.64 (d, J = 9.9 Hz, 1H), 4.84 (t, J = 7.6 Hz, 1H), 4.25 (d, J = 6.3 Hz, 1H), 3.80-3.74 (m, 1H), 2.33 (dd, J_1 = 6.3 Hz, J_2 = 13.2 Hz, 1H), 2.26-2.16 (m, 2H), 1.16 (d, J = 7.0 Hz, 3H), 1.11 (t, J = 5.7 Hz, 6H), 0.95 (s, 9H), 0.11 (d, J = 15.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.8, 173.4, 139.9, 137.4 (q), 132.7 (d), 131.9 (d), 131.0 (q), 128.8, 128.4 (d), 128.3 (d), 126.2, 124.5, 124.0, 121.9, 117.9, 68.6 (d), 65.3, 53.6, 33.1 (d), 30.9, 25.9, 21.7, 19.5 (d), 17.9, -4.2, -4.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ -23.4 (s); HRMS (ESI) m/z calcd for $C_{36}H_{47}F_6N_3O_2PSSi$ $[M+H]^+$ = 758.2795, found = 758.2789; $[\alpha]^{27}_D$ = +34.6 (c 1.0, $CHCl_3$).

tert-Butyl (*S*)-1-((2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-1-(diphenylphosphino)butan-2yl-amino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (**3-4a**)

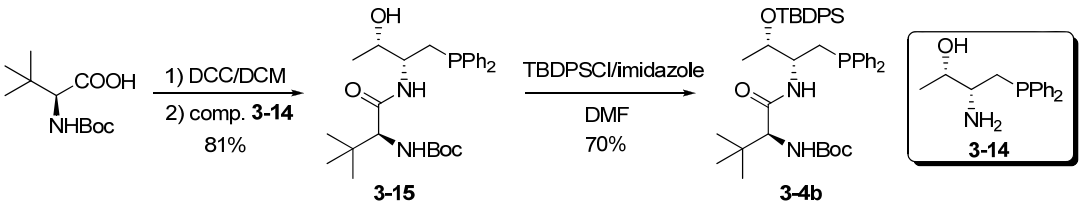


3-4a

The catalyst **3-4a** was prepared in an overall yield of 68% (2 steps), following the procedure described for the preparation of compound **3-2**.

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52, (t, *J* = 6.5 Hz, 2H), 7.39-7.29 (m, 8H), 5.99, (d, *J* = 7.5 Hz, 1H), 5.31 (d, *J* = 8.0 Hz, 1H), 4.28 (d, *J* = 6.5 Hz, 1H), 3.88-3.77 (m, 2H), 2.38 (dd, J_1 = 5.0 Hz, J_2 = 13.5 Hz, 1H), 2.19-2.14 (m, 1H), 1.44 (s, 9H), 1.10 (d, *J* = 5.5 Hz, 3H), 1.00 (s, 9H), 0.89 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 155.8, 138.8, 137.4 (d), 132.7 (d), 128.6 (dd), 79.5, 68.4 (d), 62.9, 52.4 (d), 34.6, 32.2 (d), 29.7, 28.3, 26.8, 25.9, 21.5, 18.0, -4.4; ^{31}P NMR (202 MHz, $CDCl_3$) δ -23.6 (s); HRMS (ESI) m/z calcd for $C_{33}H_{54}N_2O_4PSi$ $[M+H]^+$ = 601.3585, found = 601.3615; $[\alpha]^{27}_D$ = +8.3 (c 0.40, $CHCl_3$).

tert-Butyl (*S*)-1-((2*R*,3*S*)-3-(*tert*-butyldiphenylsilyloxy)-1-(diphenylphosphino)butan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (**3-4b**)

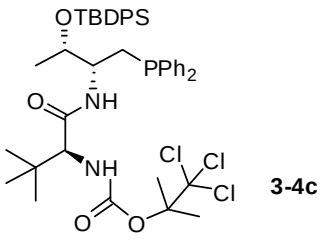


To a stirred solution of *N*-Boc-L-lucine (0.379 g, 1.64 mmol) in anhydrous CH_2Cl_2 (8 mL) was added DCC (0.169 mg, 0.82 mmol), and the resulting mixture was stirred at room temperature for 2 hrs. The solution was then cooled down to 0 ^{o}C, and a solution of **3-14** (0.2 g, 0.74 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 2 minutes. The reaction mixture was further stirred at 0 ^{o}C for 0.5 h and then at room temperature for another 0.5 h. Water (10 mL) was added to quench the reaction, and the resulting mixture was extracted with dichloromethane several times (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and

concentrated, and the residue was purified by column chromatography (hexane: ethyl acetate = 10:1) under N_2 to yield the intermediate **3-15** (0.292 g, 81%) as a white solid. To a solution of **3-15** in anhydrous DMF (138 μL, 1.8 mmol) at room temperature under N_2 was added imidazole (54.4 mg, 1.2 mmol), followed by TBDPSCl (198 mg, 0.72 mmol). The resulting mixture was stirred for 24 h, and then quenched by additing water (3 mL), and extracted with diethyl ether several times (3 x 3 mL). The organic extracts were combined, washed with brine, and dried over Na_2SO_4. Purification by column chromatography (hexane: ethyl acetate = 20:1 to 10:1) afforded catalyst **3-4b** (0.3 g, 70% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70-7.66, (m, 4H), 7.45-7.27 (m, 16H), 6.09, (d, *J* = 8.5 Hz, 1H), 5.34 (d, *J* = 8.0 Hz, 1H), 4.23 (d, *J* = 5.5 Hz, 1H), 3.91-3.85 (m, 2H), 2.38 (dd, J_1 = 7.5 Hz, J_2 = 14.0 Hz, 1H), 2.24-2.20 (m, 1H), 1.47 (s, 9H), 1.09 (s, 9H), 1.05 (s, 9H), 0.98 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 155.8, 138.7 (d), 137.8 (d), 135.9 (d), 134.8, 133.8, 133.2, 132.8 (d), 132.6, 129.8(d), 128.5 (dd), 127.8 (d), 127.5, 79.5, 70.5(d), 63.0, 52.5 (d), 34.6, 32.6 (d), 27.1, 26.8, 21.8, 21.5, 21.2, 19.4; ^{31}P NMR (202 MHz, $CDCl_3$) δ -23.3 (s); HRMS (ESI) m/z calcd for $C_{43}H_{58}N_2O_4PSi$ $[M+H]^+$ = 725.3898, found = 725.3918; $[\alpha]^{27}_D$ = -17.6 (c 0.33, $CHCl_3$).

1,1,1-Trichloro-2-methylpropan-2-yl(*R*)-1-((2*S*,3*R*)-3-(*tert*-butyldiphenylsilyloxy)-1-(di- phenylphosphino)butan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (**3-4c**)

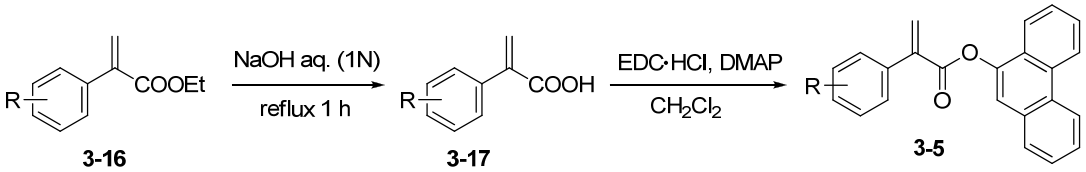


3-4c

The catalyst **3-4c** was prepared in an overall yield of 55% (2 steps), following the procedure described for the preparation of compound **3-4b**.

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71-7.68, (m, 4H), 7.49-7.28 (m, 16H), 6.00, (d, *J* = 9.0 Hz, 1H), 5.70 (d, *J* = 7.5 Hz, 1H), 4.22 (t, *J* = 6.0 Hz, 1H), 3.92-3.87 (m, 2H), 2.43 (dd, J_1 = 7.5 Hz, J_2 = 14.0 Hz, 1H), 2.25-2.20 (m, 1H), 1.95 (s, 9H), 1.10 (s, 9H), 1.07 (s, 9H), 1.00 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 154.1, 138.4 (d), 137.8 (d), 135.9 (d), 133.8, 132.8 (dd), 129.8 (d), 128.5 (dd), 127.7 (d), 106.4, 88.2, 70.7 (d), 63.2, 52.5 (d), 34.8, 32.6 (d), 27.1, 21.9, 21.6, 21.2, 19.3; ^{31}P NMR (202 MHz, $CDCl_3$) δ -22.2 (s); HRMS (ESI) m/z calcd for $C_{43}H_{55}Cl_3N_2O_4PSi$ $[M+H]^+$ = 827.2729, found = 827.2740; $[\alpha]^{27}_D$ = -20.0 (c 0.82, $CHCl_3$).

3.4.3 Preparation of α-Substituted Acrylates

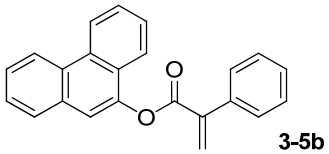


3-16 **3-17** **3-5**

An aqueous solution of 1 N sodium hydroxide (10 mL) was added to different ethyl acrylate[105-108] (5 mmol), then the reaction mixture was refluxed for 1 h. After cooling down to room temperature, the resulting mixture was extracted with diethyl ether several times (2 x 20 mL). The aqueous layer was then acidified with 3 N aqueous HCl solutions (pH < 1.0 by litmus paper test), and extracted with ethyl ether (3 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated. The crude acrylic acids **3-17** (80-95%) were used directly for the subsequent reactions without further purification.

To a solution of acrylic acid (2 mmol) in CH_2Cl_2 (5 mL) at 0 ^oC was added 9-phenanthrol (1.1 eq, 2.2 mmol), followed by EDC·HCl (1.2 eq, 2.4 mmol), and DMAP (0.2 eq, 0.4 mmol). The mixture was allowed to warm up to room temperature and continued stirring for 12 hrs. Saturated aqueous solution of $NaHCO_3$ (15 mL) was added to quench the reaction, and the resulting mixture was extracted with CH_2Cl_2 several times (3 x 15 mL). The combined organic extracts were washed with brine, and dried over Na_2SO_4. Purification by column chromatography (hexane: ethyl acetate = 20:1 to 10:1) afforded **3-5** as a white solid or colorless oil in 55-82% yield.

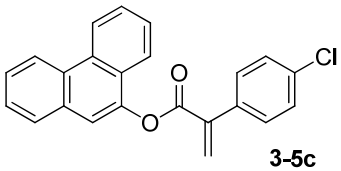
Phenanthren-9-yl 2-phenylacrylate (**3-5b**)



3-5b

A white solid; ^1H NMR (300 MHz, $CDCl_3$) δ 8.76-8.68 (m, 2H), 8.06-8.03 (m, 1H), 7.93-7.92 (m, 1H), 7.90-7.73 (m, 7H), 7.70-7.42 (m, 3H), 6.88 (d, *J* = 0.9 Hz, 1H), 6.26 (d, *J* = 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 145.1, 140.7, 136.3, 131.5, 131.4, 128.9, 128.7, 128.5, 128.4, 128.2, 127.2, 127.0, 126.9, 126.5, 126.4, 122.9, 122.6, 121.8, 117.7; HRMS (ESI) m/z calcd for $C_{23}H_{16}NaO_2$ $[M+Na]^+$ = 347.1042, found = 347.1044.

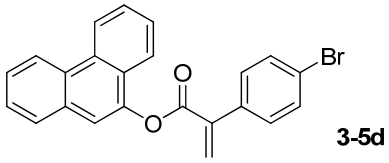
Phenanthren-9-yl 2-(4-chlorophenyl)acrylate (**3-5c**)



3-5c

A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75-8.66 (m, 2H), 7.97-7.87 (m, 2H), 7.74-7.62 (m, 4H), 7.59-7.55 (m, 2H), 7.43-7.40 (m, 2H), 6.87 (s, 1H), 6.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 145.0, 139.6, 134.7, 134.6, 131.6, 131.4, 129.8, 129.2, 129.0, 128.5, 127.3, 127.1, 127.0, 126.5, 126.4, 123.0, 122.7, 121.8, 117.7; HRMS (ESI) m/z calcd for $C_{23}H_{15}ClNaO_2$ $[M+Na]^+$ = 381.0653, found = 381.0650.

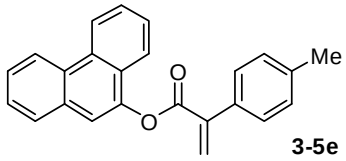
Phenanthren-9-yl 2-(4-bromophenyl)acrylate (**3-5d**)



3-5d

A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75-8.67 (m, 2H), 7.80-7.86 (m, 2H), 7.75-7.49 (m, 9H), 6.87 (d, *J* = 0.6 Hz, 1H), 6.26 (d, *J* = 0.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 145.0, 139.7, 135.1, 131.6, 131.4, 130.1, 129.2, 129.0, 128.5, 127.3, 127.1, 127.0, 126.5, 126.4, 123.0, 122.8, 122.7, 121.8, 117.7; HRMS (ESI) m/z calcd for $C_{23}H_{15}BrNaO_2$ $[M+Na]^+$ = 425.0153, found = 425.0158.

Phenanthren-9-yl 2-p-tolylacrylate (**3-5e**)

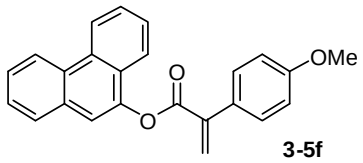


3-5e

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75-8.67 (m, 2H), 8.01-7.87 (m, 2H), 7.74-7.53 (m, 7H), 7.26 (d, *J* = 7.8 Hz, 2H), 6.79 (d, *J* = 0.9 Hz, 1H), 6.20 (d, *J* = 0.9 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 145.1, 140.6, 138.4, 133.4, 131.6, 131.5, 129.0, 128.9, 128.5, 128.3, 128.0, 127.2, 127.0, 126.9, 126.6, 126.4,

123.0, 122.6, 121.9, 117.7, 21.2; HRMS (ESI) m/z calcd for $C_{24}H_{18}NaO_2$ $[M+Na]^+$ = 361.1200, found = 361.1206.

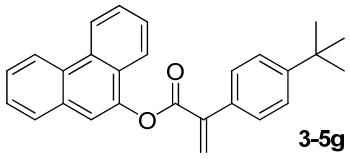
Phenanthren-9-yl 2-(4-methoxyphenyl)acrylate (**3-5f**)



3-5f

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (dd, J_1 = 8.0 Hz, J_2 = 25.0 Hz, 2H), 8.00 (d, J = 7.5 Hz, 1H), 7.89 (d, J = 7.5 Hz, 1H), 7.73-7.59 (m, 7H), 6.97 (d, J = 7.8 Hz, 2H), 6.79 (d, J = 9.0 Hz, 1H), 6.77 (s, 1H), 6.18 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 159.9, 145.2, 140.1, 131.6, 131.5, 129.7, 128.9, 128.7, 128.5, 127.2, 127.0, 126.9, 126.6, 126.4, 123.0, 122.6, 121.9, 117.7, 113.7, 55.3; HRMS (ESI) m/z calcd for $C_{24}H_{18}NaO_3$ $[M+Na]^+$ = 377.1148, found = 377.1150.

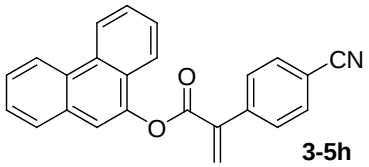
Phenanthren-9-yl 2-(4-tert-butylphenyl)acrylate (**3-5g**)



3-5g

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (dd, J_1 = 8.5 Hz, J_2 = 25.0 Hz, 2H), 8.00 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.73-7.59 (m, 7H), 7.48 (d, J = 7.5 Hz, 2H), 6.81 (s, 1H), 6.22 (s, 1H), 1.39 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 151.7, 145.2, 140.6, 133.4, 131.7, 131.6, 129.0, 128.6, 128.2, 128.1, 127.2, 127.1, 127.0, 126.7, 126.5, 125.3, 123.0, 122.7, 122.0, 117.8, 34.7, 31.3; HRMS (ESI) m/z calcd for $C_{27}H_{24}NaO_2$ $[M+Na]^+$ = 403.1668, found = 403.1667.

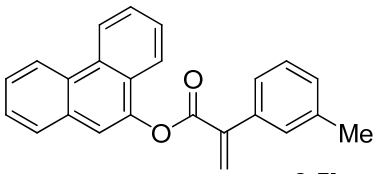
Phenanthren-9-yl 2-(4-cyanophenyl)acrylate (**3-5h**)



3-5h

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74-8.67 (m, 2H), 7.95-7.71 (m, 2H), 7.70-7.60 (m, 9H), 6.91 (s, 1H), 6.26 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 154.0, 145.0, 139.9, 138.7, 137.1, 131.7, 131.5, 130.1, 129.9, 129.0, 128.9, 128.5, 127.2, 127.0, 126.6, 126.5, 126.4, 123.1, 122.7, 121.8, 117.8; HRMS (ESI) m/z calcd for $C_{24}H_{15}NNaO_2$ $[M+Na]^+$ = 372.0094, found = 372.0090.

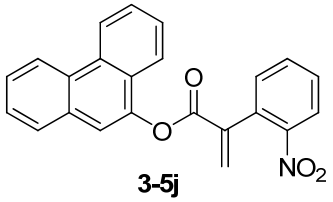
Phenanthren-9-yl 2-m-tolylacrylate (**3-5i**)



3-5i

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (dd, J_1 = 8.0 Hz, J_2 = 25.5 Hz, 2H), 7.99 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.73-7.60 (m, 5H), 7.44 (d, J = 11.0 Hz, 2H), 7.34 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 6.82 (s, 1H), 6.21 (s, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 145.1, 140.9, 137.9, 136.3, 131.6, 131.5, 129.3, 129.2, 128.9, 128.5, 128.4, 128.2, 127.2, 127.1, 126.9, 126.6, 126.4, 125.6, 123.0, 122.7, 121.9, 117.7, 21.4; HRMS (ESI) m/z calcd for $C_{27}H_{24}NaO_2$ $[M+Na]^+$ = 403.1668, found = 403.1662.

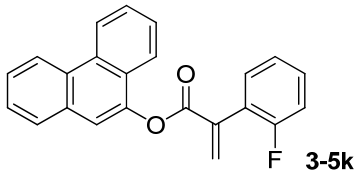
Phenanthren-9-yl 2-(2-nitrophenyl)acrylate (**3-5j**)



3-5j

A yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (dd, J_1 = 8.0 Hz, J_2 = 25.0 Hz, 2H), 8.18 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 3.0 Hz, 1H), 7.92 (d, J = 3.0 Hz, 1H), 7.87-7.47 (m, 8H), 6.91 (s, 1H), 6.11 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6, 147.5, 144.8, 139.5, 135.7, 133.9, 132.5, 132.2, 131.3, 131.2, 130.0, 129.6, 129.2, 128.8, 128.4, 127.1, 126.9, 126.8, 126.4, 126.2, 124.7, 123.7, 122.8, 121.5, 121.7, 117.6; HRMS (ESI) m/z calcd for $C_{23}H_{15}NNaO_4$ $[M+Na]^+$ = 392.0893, found = 392.0894.

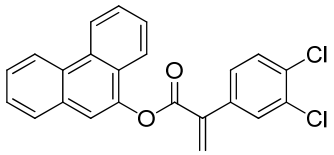
Phenanthren-9-yl 2-(2-fluorophenyl)acrylate (**3-5k**)



3-5k

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (dd, J_1 = 7.5 Hz, J_2 = 23.5 Hz, 2H), 7.96 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.71-7.59 (m, 5H), 7.50-7.47 (m, 2H), 7.42-7.38 (m, 2H), 6.91 (s, 1H), 6.18 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 161.1, 159.1, 145.2, 136.3, 131.6, 131.5, 131.2, 131.0, 130.9, 130.5, 130.4, 129.0, 128.5, 127.2, 127.0, 126.9, 126.6, 126.4, 124.9, 124.8, 124.2, 124.1, 122.9, 121.6, 122.0, 117.6, 115.7, 115.6; HRMS (ESI) m/z calcd for $C_{23}H_{15}FNaO_2$ $[M+Na]^+$ = 365.0954, found = 365.0971.

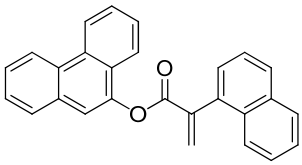
Phenanthren-9-yl 2-(3,4-dichlorophenyl)acrylate (**3-5l**)



3-5l

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (dd, J_1 = 8.0 Hz, J_2 = 27.0 Hz, 2H), 7.93 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.74-7.61 (m, 6H), 7.51-7.45 (m, 2H), 6.91 (s, 1H), 6.26 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9, 138.7, 136.1, 132.8, 132.5, 131.7, 131.4, 130.5, 130.2, 130.0, 129.0, 128.5, 127.9, 127.3, 127.2, 127.0, 126.6, 126.4, 123.1, 122.7, 121.7, 117.8; HRMS (ESI) m/z calcd for $C_{23}H_{14}Cl_2NaO_2$ $[M+Na]^+$ = 415.0264, found = 415.0268.

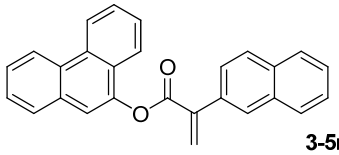
Phenanthren-9-yl 2-(naphthalen-1-yl)acrylate (**3-5m**)



3-5m

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (dd, J_1 = 8.5 Hz, J_2 = 15.0 Hz, 2H), 8.07 (d, J = 9.0 Hz, 1H), 7.96-7.93 (m, 2H), 7.83 (d, J = 9.0 Hz, 1H), 7.65-7.46 (m, 9H), 7.09 (d, J = 1.3 Hz, 1H), 6.18 (d, J = 1.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 144.9, 140.5, 134.9, 133.5, 131.9, 131.7, 131.4, 128.9, 128.8, 128.5, 128.4, 127.2, 127.1, 127.0, 126.7, 126.5, 126.4, 126.1, 125.4, 125.3, 122.8, 122.6, 121.9, 117.3; HRMS (ESI) m/z calcd for $C_{23}H_{14}Cl_2NaO_2$ $[M+Na]^+$ = 415.0263, found = 415.0259.

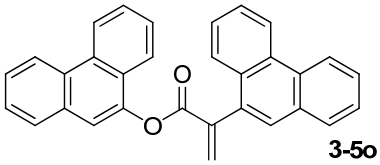
Phenanthren-9-yl 2-(naphthalen-2-yl)acrylate (**3-5n**)



3-5n

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75-8.68 (m, 2H), 8.14 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.92-7.83 (m, 2H), 7.76-7.61 (m, 7H), 7.56-7.49 (m, 3H), 6.93 (s, 1H), 6.36 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 145.1, 140.8, 133.7, 133.3, 133.1, 129.0, 128.5, 128.4, 127.8, 127.6, 127.2, 127.1, 127.0, 126.9, 126.6, 126.5, 126.4, 126.3, 126.1, 123.0, 122.7, 121.9, 117.8; HRMS (ESI) m/z calcd for $C_{23}H_{14}Cl_2NaO_2$ $[M+Na]^+$ = 415.0264, found = 415.0270.

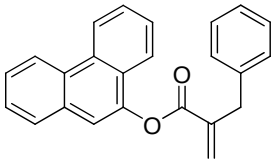
Phenanthren-9-yl 2-(phenanthren-9-yl)acrylate (**3-5o**)



3-5o

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83-8.80 (m, 2H), 8.76-8.58 (m, 2H), 8.16-8.12 (m, 1H), 8.00-7.56 (m, 12H), 7.45 (t, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 1.2 Hz, 1H), 6.29 (t, *J* = 1.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 144.8, 140.7, 133.7, 131.7, 131.3, 130.9, 130.5, 130.4, 128.8, 128.7, 128.4, 128.1, 127.1, 127.0, 126.9, 126.8, 126.7, 126.6, 126.4, 126.3, 126.1, 123.1, 122.7, 122.6, 122.5, 121.8, 117.3; HRMS (ESI) m/z calcd for $C_{31}H_{20}NaO_2$ $[M+Na]^+$ = 447.1361, found = 415.0270.

Phenanthren-9-yl 2-benzylacrylate (**3-5p**)

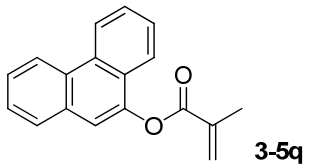


3-5p

A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (dd, J_1 = 8.5 Hz, J_2 = 15.0 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.67-7.54 (m, 6H), 7.43-7.34 (m, 5H), 6.71 (s, 1H), 5.84 (s, 1H), 3.92 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 145.0, 139.7, 138.4,

131.5, 131.4, 129.1, 128.9, 128.6, 128.4, 128.3, 127.1, 127.0, 126.8, 126.6, 126.5, 126.4, 122.9, 122.6, 121.9, 117.7; HRMS (ESI) m/z calcd for $C_{24}H_{18}NaO_2$ $[M+Na]^+$ = 361.1200, found = 361.1202.

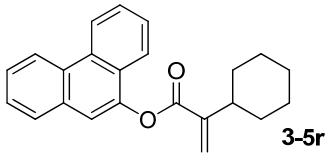
Phenanthren-9-yl methacrylate (**3-5q**)



3-5q

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (dd, J_1 = 8.0 Hz, J_2 = 15.0 Hz, 2H), 7.98 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.74-7.58 (m, 5H), 6.58 (d, J = 6.0 Hz, 1H), 5.90 (d, J = 5.5 Hz, 1H), 2.21-2.20 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 145.1, 135.8, 131.5, 128.9, 128.4, 127.6, 127.0, 126.9, 126.7, 126.4, 122.9, 122.6, 121.8, 117.7, 18.5; HRMS (ESI) m/z calcd for $C_{18}H_{14}NaO_2$ $[M+Na]^+$ = 285.0851, found = 285.0844.

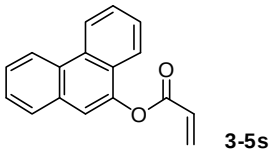
Phenanthren-9-yl 2-cyclohexylacrylate (**3-5r**)



3-5r

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (dd, J_1 = 8.5 Hz, J_2 = 15.0 Hz, 2H), 7.94 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.72-7.58 (m, 5H), 6.60 (s, 1H), 6.82 (s, 1H), 2.68 (t, J = 5.0 Hz, 1H), 2.02-1.75 (m, 5H), 1.45-1.20 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 145.9, 145.3, 131.7, 131.6, 128.9, 128.4, 127.1, 127.0, 126.8, 126.3, 124.2, 122.9, 122.6, 121.9, 117.4, 39.4, 32.7, 26.6, 26.2; HRMS (ESI) m/z calcd for $C_{22}H_{22}NaO_2$ $[M+Na]^+$ = 353.1517, found = 353.1500.

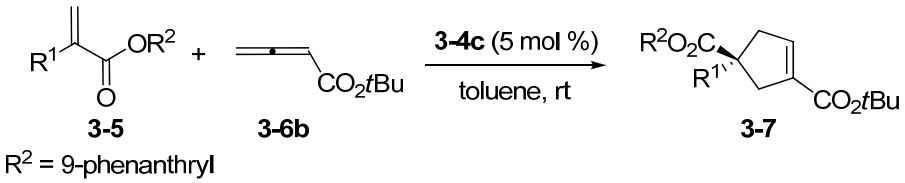
Phenanthren-9-yl acrylate (**3-5s**)



3-5s

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (dd, J_1 = 8.0 Hz, J_2 = 15.0 Hz, 2H), 7.97 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.73-7.60 (m, 5H), 6.78 (d, J = 6.0 Hz, 1H), 6.57-6.51 (m, 1H), 6.13 (d, J = 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 144.8, 133.1, 131.6, 131.5, 128.9, 128.5, 127.7, 127.2, 127.0, 126.9, 126.5, 122.9, 122.6, 121.8, 117.7; HRMS (ESI) m/z calcd for $C_{17}H_{12}NaO_2$ $[M+Na]^+$ = 271.0735, found = 271.0721.

3.4.4 Representative Procedure for [3+2] Cycloadditions



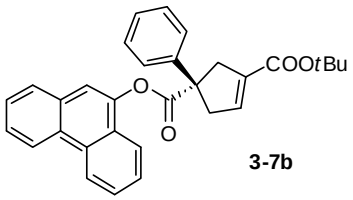
3-5 **3-6b** **3-7**

R^2 = 9-phenanthryl

To a flame-dried round bottle flask with a magnetic stirring bar were added catalyst **3-4c** (2.1 mg, 0.0025 mmol) and acrylate **3-5** (0.05 mmol) under N_2, followed by the addition of anhydrous toluene (0.5 mL). Allenoate **3-6b** (11 μL, 0.075 mmol) was then added, and the reaction mixture was stirred at room temperature for a given period (as specified in Table 3.4. At the end of the reaction, the mixture was subjected directly to flash column chromatographic separation using a mixture of hexane/ethyl acetate (15 : 1 to 10 : 1) as the eluent to afford cycloaddtion products **3-7** (61-97% yield).

3.4.5 Analytical Data of [3+2] Adducts

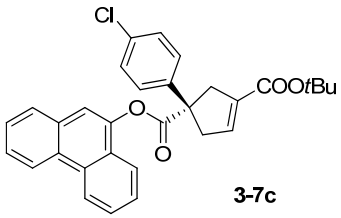
(*S*)-3-*tert*-Butyl 1-phenanthren-9-yl 1-phenylcyclopent-3-ene-1,3-dicarboxylate (**3-7b**)



3-7b

A white solid; $[\alpha]^{27}_D$ = +10.9 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, *J* = 13.4 Hz, 1H), 8.66 (d, *J* = 12.6 Hz, 1H), 7.95 (d, *J* = 12.9 Hz, 1H), 7.87-7.84 (m, 1H), 7.72-7.57 (m, 4H), 7.52 (s, 1H), 6.67 (d, *J* = 3.1 Hz, 1H), 3.45-3.12 (m, 2H), 2.92-2.73 (m, 2H), 2.19-2.09 (m, 1H), 1.91-1.75 (m, 5H), 1.54 (s, 9H), 1.49-1.18 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ175.3, 164.0, 145.0, 140.0, 136.1, 131.5, 131.4, 128.7, 128.4, 127.1, 127.0, 126.8, 126.7, 126.3, 122.9, 122.6, 121.7, 117.3, 80.5, 57.6, 45.7, 39.7, 38.7, 28.2, 28.1, 28.0, 26.5, 26.3; HRMS (ESI) m/z calcd for $C_{31}H_{28}NaO_4$ $[M+Na]^+$ = 487.1880, found = 487.1891; the ee value was 91%, t_R (major) = 28.6 min, t_R (minor) = 31.4 min (Chiralcel IB-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

(*S*)-3-*tert*-Butyl1-phenanthren-9-yl 1-(4-chlorophenyl)cyclopent-3-ene-1,3-dicarboxylate (**3-7c**)

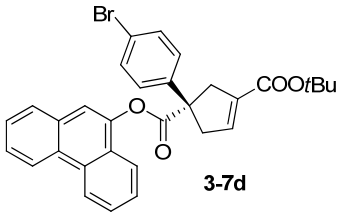


3-7c

A white solid; $[\alpha]^{27}_D$ = +1.4 (c 0.93, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 8.2 Hz, 1H), 8.62 (d, *J* = 8.2 Hz, 1H), 7.81-7.79 (m, 1H), 7.65-7.56 (m, 3H), 7.54-7.52 (m, 2H), 7.47-7.43 (m, 3H), 7.37 (s, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 6.83 (s, 1H),

3.98 (dd, *J* = 1.3 Hz, 16.4 Hz, 1H), 3.88 (d, *J* = 18.3 Hz, 1H), 3.27-3.23 (m, 1H), 3.10-3.05 (m, 1H), 1.58 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ173.5, 163.7, 144.9, 140.5, 139.7, 136.6, 133.6, 131.5, 131.3, 129.0, 128.9, 128.4, 127.1, 127.0, 126.8, 126.5, 126.4, 122.9, 122.6, 121.4, 117.3, 80.8, 58.5, 43.0, 41.3, 28.2; HRMS (ESI) m/z calcd for $C_{31}H_{27}ClNaO_4$ $[M+ Na]^+$ = 521.1487, found = 521.1486; the ee value was 94%, t_R (major) = 21.2 min, t_R (minor) = 25.6 min (Chiralcel IB-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

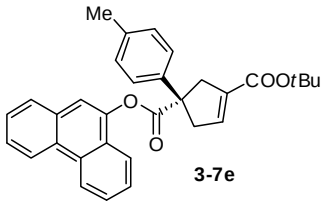
(*S*)-3-*tert*-Butyl1-phenanthren-9-yl1-(4-bromophenyl)cyclopent-3-ene-1,3-dicarboxy-late (**3-7d**)



3-7d

A white solid; $[\alpha]^{27}_D$ = -6.6 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 8.2 Hz, 1H), 8.62 (d, *J* = 8.2 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.65-7.56 (m, 5H), 7.47-7.43 (m, 3H), 7.36 (s, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 6.82 (s, 1H), 3.96 (dd, *J* = 1.3 Hz, 16.4 Hz, 1H), 3.87 (dd, *J* = 1.3 Hz, 18.3 Hz, 1H), 3.25-3.21 (m, 1H), 3.09-3.05 (m, 1H), 1.56 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 163.7, 144.9, 141.1, 139.7, 136.6, 132.0, 131.5, 131.3, 128.9, 128.8, 128.4, 127.2, 127.1, 126.8, 126.5, 126.4, 122.9, 122.6, 121.7, 121.4, 117.3, 80.9, 58.6, 42.9, 41.2, 28.2; HRMS (ESI) m/z calcd for $C_{31}H_{27}BrO_4$ $[M+ Na]^+$ = 565.1009, found = 565.1007; the ee value was 93%, t_R (major) = 14.4 min, t_R (minor) = 16.7 min (Chiralcel IB-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

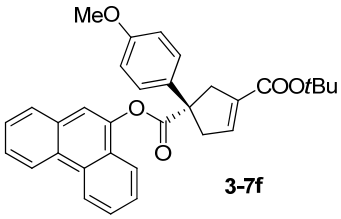
(*S*)-3-*tert*-Butyl 1-phenanthren-9-yl 1-*p*-tolylcyclopent-3-ene-1,3-dicarboxylate (**3-7e**)



3-7e

A white solid; $[\alpha]^{27}_{D}$ = -12.8 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, *J* = 8.2 Hz, 1H), 8.62 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.63-7.55 (m, 3H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.41-7.37 (m, 2H), 7.31-7.28 (m, 3H), 6.82 (s, 1H), 3.96 (d, *J* = 16.4 Hz, 1H), 3.87 (d, *J* = 18.3 Hz, 1H), 3.26 (dd, *J* = 2.5 Hz, 16.4 Hz,1H), 3.10 (dd, *J* = 2.5 Hz, 18.3 Hz, 1H), 1.56 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ174.1, 163.9, 145.1, 140.0, 139.1, 137.3, 236.7, 131.5, 131.4, 129.54, 128.9, 128.4, 127.0, 130.0, 126.9, 126.7, 126.6, 126.4, 122.8, 122,6, 121.7, 117.3, 80.7, 58.7, 43.1, 41.2, 28.2, 21.0; HRMS (ESI) m/z calcd for $C_{32}H_{30}NaO_4$ $[M+ Na]^+$ = 501.2036, found = 501.2059; the ee value was 90%, t_R (major) = 11.2 min, t_R (minor) = 13.5 min (Chiralcel IC-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*S*)-3-*tert*-Butyl1-phenanthren-9-yl1-(4-methoxyphenyl)cyclopent-3-ene-1,3-dicarboxylate (**3-7f**)

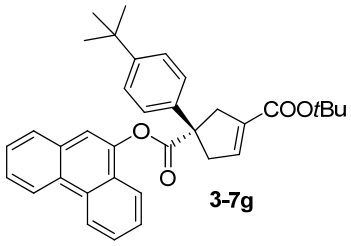


3-7f

A white solid; $[\alpha]^{27}_{D}$ = -1.2 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 8.2 Hz, 1H), 8.62 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.63-7.55 (m, 5H), 7.52-7.49 (m, 1H), 7.44-7.40 (m, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 7.01-6.99 (m, 2H), 6.82 (s, 1H), 3.96 (dd, *J* = 1.3 Hz, 16.4 Hz, 1H), 3.87 (d, *J* = 9.5 Hz, 1H), 3.26-3.22

(m, 1H), 3.11-3.07 (m, 1H), 1.56 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 163.9, 159.0, 145.1, 140.0, 136.7, 134.0, 131.5, 131.4, 128.9, 128.4, 128.2, 127.0, 127.0, 126.7, 126.6, 126.4, 122.8, 122.6, 121.6, 117.3, 114.2, 80.7, 58.4, 55.3, 43.1, 41.3, 28.2; HRMS (ESI) m/z calcd for $C_{32}H_{30}O_5$ $[M+ Na]^+$ = 517.1985, found = 517.2004; the ee value was 87%, t_R (major) = 10.7 min, t_R (minor) = 12.8 min (Chiralcel IC-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

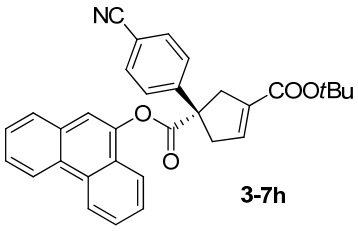
(*S*)-3-*tert*-Butyl1-phenanthren-9-yl1-(4-*tert*-butylphenyl)cyclopent-3-ene-1,3-dicarboxylate (**3-7g**)



3-7g

A white solid; $[\alpha]^{27}_D$ = -12.9 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65-8.60 (m, 2H), 7.82-7.79 (m, 1H), 7.64-7.51 (m, 7H), 7.48 (d, *J* = 15.5 Hz, 1H), 7.39 (s, 1H), 7.35-7.29 (m, 1H), 7.16-7.14 (m, 1H), 6.82 (d, *J* = 1.9 Hz, 1H), 3.99-3.86 (m, 2H), 3.32-3.26 (m, 1H), 3.17-3.10 (m, 1H), 1.56 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 163.9, 150.6, 145.0, 140.0, 139.0, 136.7, 131.5, 131.4, 128.9, 128.4, 127.0, 126.9, 126.7, 126.6, 126.3, 125.8, 122.8, 122.6, 121.6, 117.4, 80.7, 58.6, 43.0, 41.1, 34.6, 31.4, 28.2; HRMS (ESI) m/z calcd for $C_{35}H_{36}NaO_4$ $[M+ Na]^+$ = 543.2511, found = 543.2506; the ee value was 90%, t_R (major) = 13.0 min, t_R (minor) = 17.0 min (Chiralcel IB-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

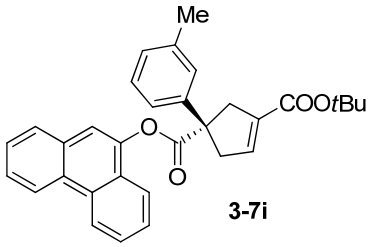
(*S*)-3-*tert*-Butyl1-phenanthren-9-yl1-(4-cyanophenyl)cyclopent-3-ene-1,3-dicarboxylate (**3-7h**)



3-7h

A white solid; $[\alpha]^{27}_{D}$ = -15.2 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67-8.62 (m, 2H), 7.79-7.78 (d, *J* = 7.5 Hz, 1H), 7.66-7.58 (m, 7H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.45-42 (m, 1H), 7.41 (s, 1H), 7.36 (s, 1H), 6.81(s, 1H), 3.99-3.23 (m, 2H), 3.12 (d, *J* = 2.5 Hz, 1H), 3.08 (d, *J* = 1.9 Hz, 1H), 1.55 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 163.6, 154.0, 144.9, 144.8, 139.5, 136.6, 136.5, 131.5, 131.3, 128.9, 128.4, 127.2, 127.1, 127.0, 126.8, 126.5, 126.4, 122.9, 122.6, 121.4, 117.2, 80.7, 58.6, 43.0, 41.1, 34.6, 31.4, 28.2; HRMS (ESI) m/z calcd for $C_{32}H_{27}NaNO_4$ [M+ Na]$^+$ = 512.1832, found = 512.1827; the ee value was 94%, t_R (major) = 22.1 min, t_R (minor) = 17.0 min (Chiralcel AD-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*S*)-3-*tert*-Butyl 1-phenanthren-9-yl 1-m-tolylcyclopent-3-ene-1,3-dicarboxylate (**3-7i**)

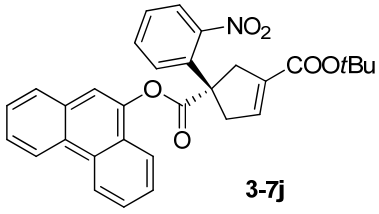


3-7i

A white solid; $[\alpha]^{27}_{D}$ = +5.2 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 8.2 Hz, 1H), 8.62 (d, *J* = 8.2 Hz, 1H), 7.80 (d, *J* = 2.6 Hz, 1H), 7.63-7.56 (m, 3H), 7.41-7.36 (m, 5H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 6.83 (s, 1H), 3.97 (d, *J* = 16.4 Hz, 1H), 3.89 (d, *J* = 17.7 Hz, 1H), 3.26-3.20 (m, 1H), 3.15-3.11 (m, 1H), 2.44 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ174.0, 163.9, 145.1, 141.9, 134.0, 138.6, 136.7, 131.5, 131.4, 128.9, 128.8, 128.4, 128.3, 127.7, 127.1,

127.0, 126.8, 126.6, 126.4, 124.0, 122.8, 122.6, 121.7, 117.4, 80.7, 58.9, 43.0, 41.2, 28.2, 21.6; HRMS (ESI) m/z calcd for $C_{32}H_{30}NaO_4$ $[M+ Na]^+$ = 501.2036, found = 501.2054; the ee value was 88%, t_R (major) = 9.8 min, t_R (minor) = 11.9 min (Chiralcel IB-H, λ = 254 nm, 10% iPrOH/hexanes, flow rate = 1.0 mL/min).

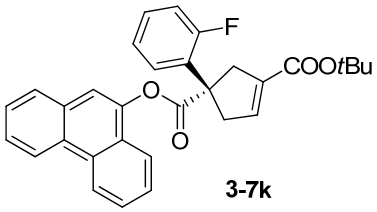
(*S*)-3-*tert*-Butyl1-phenanthren-9-yl1-(2-nitrophenyl)cyclopent-3-ene-1,3-dicarboxy-late (**3-7j**)



3-7j

A yellow solid; $[\alpha]^{27}_D$ = -24.5 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, *J* = 8.2 Hz, 1H), 8.65 (d, *J* = 8.2 Hz, 1H), 8.10-8.08 (m, 1H), 7.92-7.90 (m, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.72-7.59 (m, 8H), 7.53-7.50 (m, 1H), 6.80 (d, *J* = 1.9 Hz, 1H), 3.97 (dd, *J* = 2.6 Hz, 18.9 Hz, 1H), 3.91-3.86 (m, 1H), 3.53 (d, *J* = 17.1 Hz, 1H), 3.23 (d, *J* = 18.9 Hz, 1H), 1.58 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 163.4, 148.2, 144.6, 139.0, 137.7, 135.5, 133.5, 131.5, 131.4, 128.9, 128.8, 128.7, 128.4, 127.1, 127.0, 126.8, 126.5, 126.4, 125.7, 122.9, 122.5, 121.4, 117.6, 81.1, 56.7, 45.5, 44.2, 28.1; HRMS (ESI) m/z calcd for $C_{31}H_{27}NaNO_6$ $[M+ Na]^+$ = 532.1731, found = 532.1729; the ee value was 90%, t_R (major) = 15.6 min, t_R (minor) = 22.4 min (Chiralcel IB-H, λ = 254 nm, 30% iPrOH/hexanes, flow rate = 1.0 mL/min).

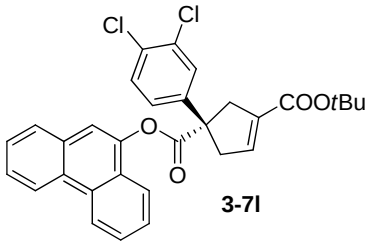
(*S*)-3-*tert*-Butyl1-phenanthren-9-yl1-(2-fluorophenyl)cyclopent-3-ene-1,3-dicarboxy-late (**3-7k**)



3-7k

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54 (s, 9H), 3.13 (dd, J = 1.9 Hz, 18.3 Hz, 1H), 3.40 (dd, J = 1.9 Hz, 17.0 Hz, 1H), 3.78-3.87 (m, 2H), 6.76 (t, J = 1.9 Hz, 1H), 7.19-7.25 (m, 2H), 7.35-7.40 (m, 1H), 7.48-7.57 (m, 3H), 7.58-7.66 (m, 4H), 7.83-7.85 (m, 1H), 8.63 (d, J = 8.2 Hz, 1H), 8.66 (d, J = 8.2 Hz, 1H); HRMS (ESI) m/z calcd for $C_{31}H_{27}NaFO_4$ $[M+ Na]^+$ = 505.1795, found = 505.1788; the ee value was 83%, t_R (major) = 13.3 min, t_R (minor) = 18.6 min (Chiralcel IB-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*S*)-3-*tert*-Butyl1-phenanthren-9-yl1-(3,4-dichlorophenyl)cyclopent-3-ene-1,3dicarboxylate (**3-7l**)

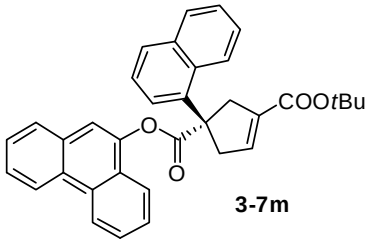


3-7l

A white solid; $[\alpha]^{27}_D$ = +5.5 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (dd, *J* = 8.2 Hz, 20.0 Hz, 2H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.68-7.54 (m, 5H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.43-7.37 (m, 3H), 6.81 (s, 1H), 3.95 (d, *J* = 16.4 Hz, 1H), 3.86 (d, *J* = 17.7 Hz, 1H), 3.21 (dd, *J* = 1.9 Hz, 16.4 Hz, 1H), 3.07 (dd, *J* = 1.9 Hz, 18.3 Hz, 1H), .56 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 163.5, 144.8, 142.2, 139.4, 136.6, 133.1, 132.0, 131.5, 131.2, 130.8, 129.1, 128.9, 128.4, 127.2, 127.1, 126.9, 126.6, 126.4, 126.3, 123.0, 122.6, 121.3, 117.3, 81.0, 58.4, 43.0, 41.4, 28.2; HRMS (ESI) m/z calcd for $C_{31}H_{26}Cl_2NaO_4$ $[M+ Na]^+$ = 555.1100, found = 555.1122; the ee value was 92%, t_R

(major) = 16.5 min, t_R (minor) = 21.7 min (Chiralcel IB-H, λ = 254 nm, 10% iPrOH/hexanes, flow rate = 1.0 mL/min).

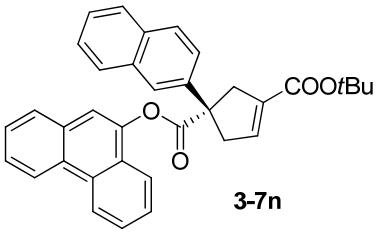
(S)-3-*tert*-Butyl1-phenanthren-9-yl1-(naphthalen-1-yl)cyclopent-3-ene-1,3-dicarboxylate (**3-7m**)



3-7m

A white solid; $[\alpha]^{27}_D$ = +9.4 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 3.2 Hz, 8.2 Hz, 2H), 8.21-8.19 (m, 1H), 8.02-7.99 (m, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.76-7.71 (m, 2H), 7.60-7.52 (m, 6H), 7.29 (s, 1H), 7.22-7.19 (m, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.77 (d, *J* = 2.5 Hz, 1H), 3.99-3.90 (m, 2H), 3.69 (d, *J* = 16.4 Hz, 1H), 3.43 (d, *J* = 18.9 Hz, 1H), 1.55 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 163.8, 144.9, 139.2, 137.7, 135.7, 134.8, 131.3, 131.3, 131.2, 129.6, 128.8, 128.7, 128.4, 127.0, 126.9, 126.7, 126.5, 126.4, 126.3, 125.7, 125.3, 124.3, 124.1, 122.6, 122.5, 121.6, 117.1, 80.8, 57.9, 44.3, 42.6, 28.2; HRMS (ESI) m/z calcd for $C_{35}H_{30}NaO_4$ $[M+ Na]^+$ = 537.2036, found = 537.2043; the ee value was 80%, t_R (major) = 16.2min, t_R (minor) = 20.0 min (Chiralcel IB-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

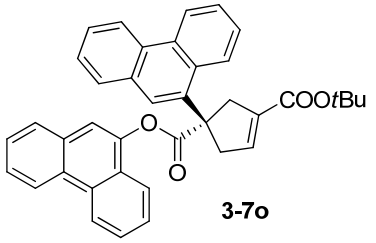
(*S*)-3-*tert*-Butyl 1-phenanthren-9-yl 1-(naphthalen-2-yl)cyclopent-3-ene-1,3-dicarboxylate (**3-7n**)



3-7n

A white solid; $[\alpha]^{27}_{D}$ = -9.8 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (t, *J* = 8.8 Hz, 2H), 8.04 (s, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.93-7.91 (m, 2H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.72 (dd, *J* = 1.9 Hz, 8.2 Hz, 1H), 7.60-7.54 (m, 5H), 7.37 (s, 1H), 7.29-7.23 (m, 2H), 6.88 (s, 1H), 4.10-3.98 (m, 2H), 3.44-3.41 (m, 1H), 3.28-3.24 (m, 1H), 1.58 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 163.9, 145.1, 139.9, 139.3, 136.7, 133.3, 132.6, 131.4, 131.3, 128.9, 128.8, 128.4, 128.2, 127.6, 127.0, 127.0, 126.7, 126.5, 126.5, 126.4, 126.3, 125.6, 125.1, 122.8, 122.6, 121.6, 117.3, 80.8, 59.1, 43.1, 41.3, 28.2; HRMS (ESI) m/z calcd for $C_{35}H_{30}NaO_4$ $[M+ Na]^+$ = 537.2036, found = 537.2041; the ee value was 91%, t_R (major) = 8.8 min, t_R (minor) = 9.7 min (Chiralcel IB-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*S*)-3-*tert*-Butyl1-phenanthren-9-yl1-(phenanthren-9-yl)cyclopent-3-ene-1,3-dicarboxylate (**3-7o**)

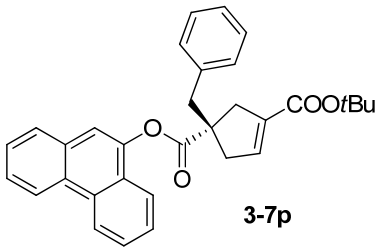


3-7o

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (s, 9H), 3.53 (d, J = 17.8 Hz, 1H), 3.78 (d, J = 16.9 Hz, 1H), 3.95-4.00 (m, 2H), 6.82 (s, 1H), 7.10 (d, J = 8.2 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.27 (s, 1H), 7.51-7.59 (m, 3H), 7.63-7.71 (m, 2H), 7.98 (d, J = 7.0 Hz, 2H), 8.26 (d, J = 8.2 Hz, 1H), 8.56 (d, J = 8.2 Hz, 1H), 8.73 (d, J = 8.2 Hz,

1H), 8.88 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.21, 42.63, 44.32, 57.78, 80.88, 117.10, 121.66, 122.41, 122.53, 122.62, 123.94, 125.06, 125.28, 126.32, 126.46, 126.51, 126.89, 126.94, 126.94, 127.01, 127.08, 127.16, 128.39, 128.82, 129.10, 130.35, 131.27, 131.31, 131.76, 135.65, 135.83, 139.06, 145.00, 163.82, 175.62; HRMS (ESI) m/z calcd for $C_{39}H_{32}NaO_4$ $[M+ Na]^+$ = 587.2203, found = 587.2215; the ee value was 82%, t_R (minor) = 15.3 min, t_R (major) = 26.0 min (Chiralcel AD-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

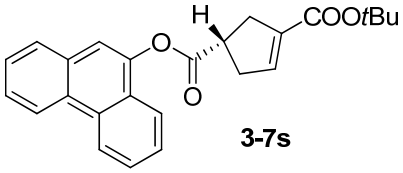
(*R*)-3-*tert*-Butyl 1-phenanthren-9-yl 1-benzylcyclopent-3-ene-1,3-dicarboxylate (**3-7p**)



3-7p

A white solid; $[\alpha]^{27}_D$ = +19.2 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, *J* = 7.6 Hz, 1H), 8.65 (d, *J* = 7.6 Hz, 1H), 7.84-7.82 (m, 1H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.70-7.59 (m, 3H), 7.55 (t, *J* = 6.9 Hz, 1H), 7.43 (s, 1H), 7.36-7.31 (m, 5H), 6.70 (t, *J* = 1.9 Hz, 1H), 3.49-3.35 (m, 4H), 3.29 (d, *J* = 13.9 Hz, 1H), 3.02 (dd, *J* = 1.9 Hz, 17.0 Hz, 1H), 2.88 (dd, *J* = 1.3 Hz, 18.9 Hz, 1H), 1.55 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 163.9, 144.9, 139.6, 137.3, 136.1, 131.5, 131.4, 130.7, 129.930.0, 128.8, 128.5, 128.5, 127.9, 127.1, 127.0, 126.9, 126.5, 126.4, 122.9, 122.6, 121.8, 117.3, 80.6, 54.9, 44.3, 42.1, 41.6, 28.2; (ESI) m/z calcd for $C_{32}H_{30}NaO_4$ $[M+ Na]^+$ = 501.2036, found = 501.2040; the ee value was 68%, t_R (major) = 22.8 min, t_R (minor) =27.9 min (Chiralcel IB-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

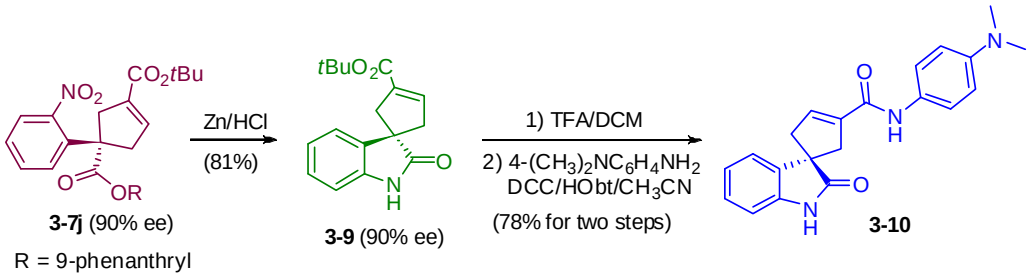
(*S*)-3-*tert*-Butyl 1-phenanthren-9-yl cyclopent-3-ene-1,3-dicarboxylate (**3-7s**)



3-7s

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (s, 9H), 3.01-3.07 (m, 1H), 3.13-3.20 (m, 3H), 3.70 (dd, J = 7.6 Hz, 11.4 Hz, 1H), 6.70 (s, 1H), 7.55 (s, 1H), 7.59-7.72 (m, 4H), 7.85 (d, J = 7.6 Hz, 1H), 7.94 (d, J = 7.6 Hz, 1H), 8.67 (d, J = 8.2 Hz, 1H), 8.72 (d, J = 8.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.16, 35.57, 36.70, 42.01, 80.63, 117.59, 121.67, 122.64, 123.02, 126.46, 126.50, 126.94, 127.07, 127.13, 127.22, 128.46, 128.91, 131.46, 131.57, 136.62, 139.90, 144.86, 163.93, 173.63; (ESI) m/z calcd for $C_{25}H_{24}NaO_4$ $[M+ Na]^+$ = 411.1576, found = 411.1560; the ee value was 68%, t_R (major) = 32.0 min, t_R (minor) = 47.2 min (Chiralcel IB-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

3.4.6 Synthesis of Spiral Oxindole Derivative



3-7j (90% ee)
R = 9-phenanthryl

3-9 (90% ee)

3-10

(*S*)-*tert*-Butyl 2'-oxospiro[cyclopent[3]ene-1,3'-indoline]-3-carboxylate (**3-9**)

To a solution of **3-7j** (0.102 g, 0.2 mmol) in MeOH (1.6 mL) and H_2O (0.4 mL) was added activated Zn dust (0.13 g, 2 mmol) and 7.0 M HCl (0.3 mL), and the reaction mixture was brought to reflux for 1 h. The mixture was then filtered through Celite, the filtrate was diluted with H_2O, and extracted with ethyl acetate several times

(3 x 10 mL). The combined organic extracts were washed with brine, and dried over Na_2SO_4. Purification by column chromatography (hexane: ethyl acetate = 10:1) afforded **3-9** (46.2 mg, 81%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.30-7.19 (m, 2H), 7.05-6.95 (m, 2H), 6.79 (s, 1H), 3.29-3.17 (m, 2H), 2.91-2.76 (m, 2H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.8, 163.5, 139.9, 139.5, 136.8, 136.3, 127.9, 122.9, 122.0, 110.0, 80.6, 52.5, 44.8, 43.5, 28.0; (ESI) m/z calcd for $C_{17}H_{19}NaNO_3$ $[M+Na]^+$ = 308.1257, found = 308.1263; $[\alpha]^{27}_D$ = -28.2 (c 0.9, $CHCl_3$); the ee value was 90%, t_R (major) = 19.5 min, t_R (minor) = 17.9 min (Chiralcel IB-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

(*S*)-*N*-(4-(Dimethylamino)phenyl)-2'-oxospiro[cyclopent[3]ene-1,3'-indoline]-3-carb-oxamide (**3-10**)

To a solution of **3-9** (0.1 g, 0.35 mmol) in anhydrous CH_2Cl_2 (3 mL) was added TFA (0.26 mL, 3.5 mmol), and the resulting mixture was then stirred at room temperature for 15 hrs. Solvent was removed to afford the crude acid, which was then dissolved in anhydrous MeCN (3 mL), the solution was then cooled down to 0 ^{o}C, to which HOBt (45.5 mg, 0.35 mmol) and *N*, *N*-dimethylaminoaniline (53 mg, 0.39 mmol) were added. The mixture was stirred at 0 ^{o}C for 10 min, EDC·HCl (68 mg, 0.35 mmol) was then introduced. The reaction mixture was allowed to warm up slowly to room temperature and stirred for 12 h, and subsequently at 60 ^{o}C for 2 h. The solvent was removed *in vacuo*, and the residue was extracted with CH_2Cl_2 (3 x 10 mL) and washed successively with H_2O and brine. Purification by column chromatography (hexane: ethyl acetate = 5:1 to 2:1) afforded oxindole **3-10**[109] (95 mg, 78% yield) as a white solid.

^{1}H NMR (500 MHz, DMSO) δ 10.39 (s, 1H), 9.49 (s, 1H), 7.51-7.48 (m, 2H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.20-7.17 (m, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.70 (dd, *J* = 2.5 Hz, 6.9 Hz, 3H), 3.07 (d, *J* = 1.9 Hz), 3.04 (d, *J* = 2.6 Hz, 1H), 3.00 (s, 6H), 2.99-2.69 (m, 2H); ^{13}C NMR (125 MHz, DMSO) δ 181.6, 161.9, 147.1, 141.0, 138.0, 136.5, 134.2, 128.6, 127.8, 122.0, 121.5, 121.4, 112.4, 109.3, 51. 6, 44.5, 43.6, 40.4; (ESI) m/z calcd for $C_{21}H_{21}N_3NaO_2$ $[M+Na]^+$ = 370.1526, found = 370.1524.

3.4.7 X-Ray Crystallographic Analysis and Determination of Absolute Configurations of [3+2] Adducts

The absolute configuration of the product **3-7l** (*S*) was assigned by X-ray crystallographic analysis of a single crystal of **3-7l** (Figure 3.1). The configurations of other [3+2] cycloaddition products were assigned by analogy.

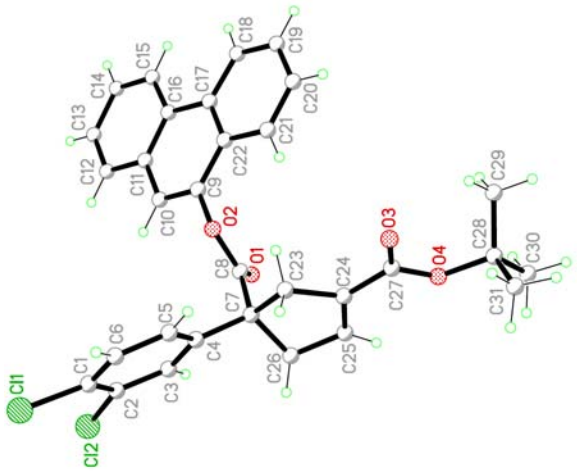


Figure 3.1 X-ray structure of **3-7l**

Table 3.6 Crystal data and structure refinement for A477

Identification code	A477
Empirical formula	C31 H26 Cl2 O4

Formula weight	533.42	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.3201(4) Å	α = 90°.
	b = 15.3584(7) Å	β = 90°.
	c = 20.8270(9) Å	γ = 90°.
Volume	2661.3(2) Å3	
Z	4	
Density (calculated)	1.331 Mg/m3	
Absorption coefficient	0.279 mm-1	
F(000)	1112	
Crystal size	0.30 x 0.26 x 0.10 mm3	
Theta range for data collection	1.65 to 27.49°.	
Index ranges	-10<=h<=10, -19<=k<=19, -20<=l<=27	
Reflections collected	18918	
Independent reflections	6090 [R(int) = 0.0714]	
Completeness to theta = 27.49°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9726 and 0.9209	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	6090 / 0 / 337	
Goodness-of-fit on F2	1.031	
Final R indices [I>2sigma(I)]	R1 = 0.0770, wR2 = 0.1388	

R indices (all data)	R1 = 0.1294, wR2 = 0.1576
Absolute structure parameter	0.03(10)
Largest diff. peak and hole	0.347 and -0.362 e.Å-3

Chapter 4 Formation of Functionalized Cyclopentenes via Catalytic Asymmetric [3+2] Cycloaddition of Acrylamides with An Allenoate Promoted by Dipeptide-Derived Phosphines

4.1 Introduction

Phosphine-mediated [3+2] cycloaddition between electron-deficient alkenes and allenes or alkynes is a powerful approach for the construction of functionalized cyclopentenes;[6,12,56c,79] these structural motifs are often found in natural products and medicinally important agents.[110] Significant progress has been made in phosphine-catalyzed enantioselective [3+2] cycloadditions.[40-45] The C_2 synthons employed for such annulations were mainly enones, and occasionally acylates and imines. To the best of our knowledge, the direct application of acrylamides in the phosphine-catalyzed asymmetric [3+2] cycloaddition has not been reported. Thus, it is highly desirable to develop a synthetic variant in which acrylamides can be used directly in such a cyclization. We have discussed in Chapter 3 novel types of chiral phosphines based on simple dipeptides, and demonstrated that such catalysts could promote effectively the enantioselective [3+2] cycloaddition of allenoates with acrylates, affording functionalized cyclopentenes in high yields and with excellent enantioselectivities. Given the high efficiency and reactivity of our catalysts, we reasoned that their application in the catalytic asymmetric [3+2] cycloaddition between acrylamides and allenes may be feasible. For the design of an efficient [3+2]-annulation reaction, the allenoate, *tert*-butyl buta-2,3-dienoate (**4-2**) appeared to be an excellent reaction component, since its effectiveness in inducing the formation of α-regioisomers was demonstrated in our earlier studies (Chapter 3). For the acrylamide substrates, we focused on 3,5-dimethyl-1*H*-pyrazole-derived acrylamides.[111] The

pyrazole nitrogen atoms are expected to form hydrogen bonds with hydrogen bond donors in the bifunctional phosphine catalysts, reinforcing the hydrogen bonding interactions between the carbonyl group and the amide N–H moiety. Moreover, the presence of the two methyl groups on the pyrazole ring was anticipated to introduce steric hindrance, thus facilitating the formation of sterically less demanding regioisomers (Figure 4.1). Herein, we describe the first asymmetric acrylamide–allene [3+2] cycloaddition mediated by dipeptide derived bifunctional phosphines; the reactions proceed efficiently at room temperature, and functionalized cyclopentenes with a quaternary stereogenic center were obtained in high yields and with moderate enantioselectivities.

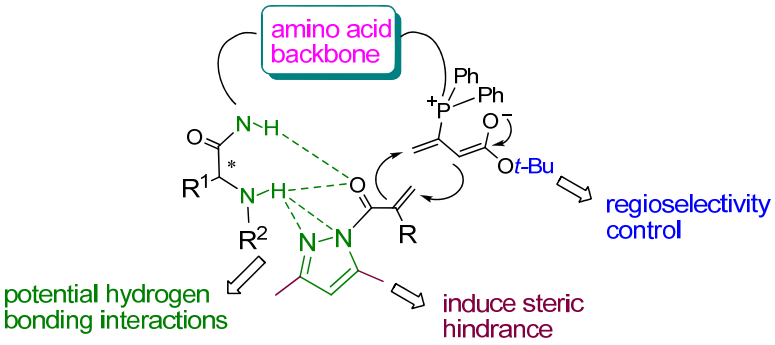


Figure 4.1 Working hypothesis

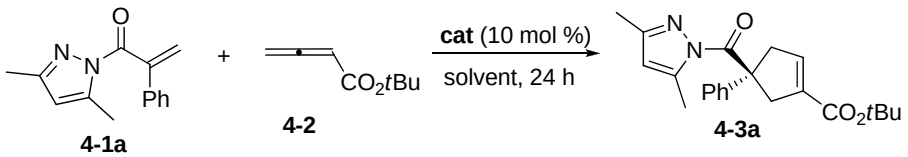
4.2 Results and Discussion

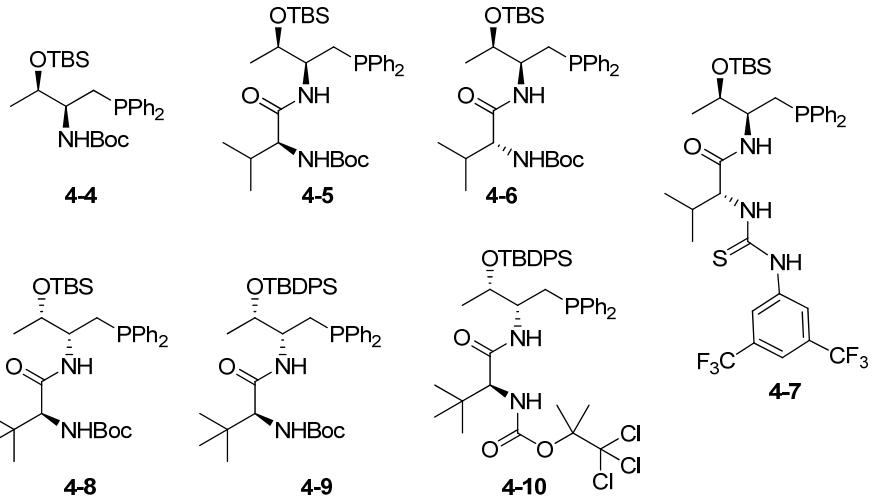
4.2.1 Reaction Optimization

We chose the [3+2] cycloaddition between a-phenyl-substituted acrylamide **4-1a** and allenoate **4-2** as a model reaction, and investigated the catalytic effects of various phosphines derived from amino acids. The results are summarized in Table 4.1. Given the success we achieved with threonine-based catalytic systems,[98] the threonine core was incorporated into our catalytic systems. In all the examples examined, the

corresponding α-regioisomers were formed exclusively. L-Threonine-derived phosphine **4-4** promoted the reaction, but the enantioselectivity was very poor (Table 4.1, entry 1). Combining L-threonine and D-valine led to a more effective catalytic system than that based on L-threonine and L-valine (Table 4.1, entries 2 and 3). The thiourea–phosphine catalyst **4-7**, however, was found to be an extremely poor catalyst (Table 4.1, entry 4). Introduction of a *tert*-leucine residue rendered further improvement; when D-threonine-L-*tert*-leucine-derived phosphine **4-8** or **4-9** was employed the enantioselectivity was improved to 49% (Table 4.1, entries 5 and 6). The presence of a carbamate moiety at the terminus of the dipeptide was found to be important, since catalyst **4-10** containing the more hindered carbamate group proved to be superior, affording the desired cycloaddition product in 86% yield and with 66% ee (Table 4.1, entry 7). Carrying out the reaction in different solvents and lowering the reaction temperature did not result in any further improvements (Table 4.1, entries 8–16). It is noteworthy that the dipeptide-based phosphine catalysts described here are easily tunable, allowing specific interactions with different substrates. Hence, their application in a wide array of asymmetric organic reactions is well anticipated.

Table 4.1 [3+2] Cycloaddition of acrylamide **4-1a** with allenoate **4-2** catalyzed by amino acid derived phosphines[a]





Entry	Catalyst	Solvent	Yield (%)[b]	ee (%)[c]
1	**4-4**	toluene	71	7
2	**4-5**	toluene	76	19
3	**4-6**	toluene	81	-39
4[d]	**4-7**	toluene	41	-17
5	**4-8**	toluene	78	47
6	**4-9**	toluene	80	49
7	**4-10**	toluene	86	66
8	**4-10**	benzene	79	41
9	**4-10**	xylene	82	43
10	**4-10**	4-fluorotoluene	75	11
11	**4-10**	CH_2Cl_2	73	47
12	**4-10**	$CHCl_3$	77	40
13	**4-10**	Et_2O	80	58
14	**4-10**	THF	75	26
15	**4-10**	DMF	31	4
16[e]	**4-10**	toluene	80	61

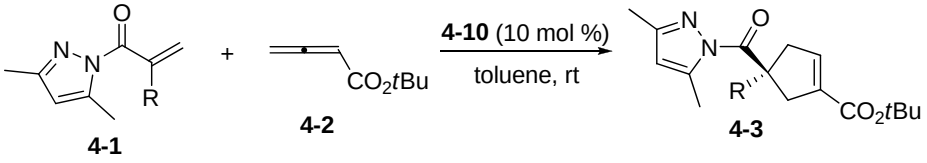
[a] Reaction conditions: **4-1a** (0.05 mmol), **4-2** (0.075 mmol), catalyst (10 mol%), solvent (0.25 mL), r.t. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction time was 48 h. [e] The reaction was performed at –20 °C over 60 h.

4.2.2 Substrate Scope

The scope of the reaction was next investigated (Table 4.2). Different α-aryl-

substituted acrylamides were examined in this cyclization, and α-regioisomeric products were obtained exclusively in good to excellent yields in each case. Satisfactory enantioselectivities were obtained for the pyrazole-derived acrylamides with *para* substituted aryl groups at their a-positions (Table 4.2, entries 2–4). The acrylamides containing *meta*- or *ortho*-substituted aromatic rings turned out to be less suitable substrates (Table 4.2, entries 5 and 6), and moderate enantioselectivity was obtained when a naphthyl-substituted acrylamide was employed (Table 4.2, entry 7). Moreover, acrylamides with α-alkyl substituents could also be used, and up to 61% ee was attained (Table 4.2, entries 8 and 9). To account for the observed regiospecific formation of the α-isomer, we propose that steric hindrance due to the presence of the bulky *tert*-butyl group on the allenoate and the 3,5-dimethylpyrazole moiety make formation of the γ-isomer highly unfavorable (Figure 4.2).

Table 4.2 Asymmetric allene–acrylamide [3+2] cycloadditions catalyzed by dipeptide-derived phosphine **4-10**[a]



Entry	product (R)	*t* (h)	Yield (%)[b]	ee (%)[c]
1	**4-3a** (Ph)	24	86	66
2	**4-3b** (4-BrC_6H_4)	24	84	60
3	**4-3c** (4-ClC_6H_4)	24	88	60
4	**4-3d** (4-PhC_6H_4)	20	93	62
5	**4-3e** (3-ClC_6H_4)	24	88	44
6	**4-3f** (2-FC_6H_4)	20	91	36
7	**4-3h** (2-naphthyl)	24	91	56
8	**4-3i** (CH_3)	48	71	47

9	**4-3j** (CH_2Ph)	48	81	61

[a] Reaction conditions: **4-1** (0.05 mmol), **4-2** (0.075 mmol), catalyst **4-10** (10 mol%), toluene (0.25 mL), r.t. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase.

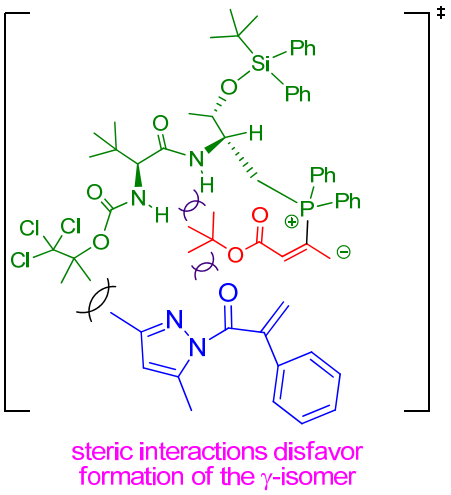
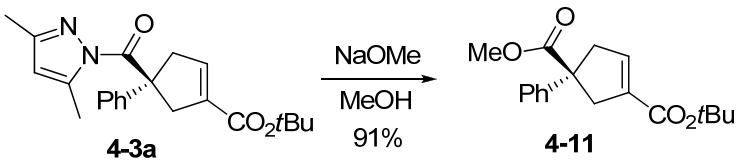


Figure 4.2 Suppression of formation of the γ-isomer

4.2.3 Derivative Synthesis



Scheme 4.1 Derivatization of *N*-acylpyrazole-containing cyclopentene

The optically-enriched functionalized cyclopentenes resulting from the [3+2] cycloadditions are useful synthetic intermediates. In particular, the *N*-acylpyrazoles can be converted readily into various acyl derivatives via reactions with different nucleophiles, such as alcohols,[112] amines,[113] and organometallic reagents.[114] When cyclopentenes **4-3a** was treated with sodium methoxide, the corresponding methyl

ester **4-11** was obtained in excellent yield (Scheme 4.1). The absolute configuration of **4-3a** was determined to be *S* by comparing the optical rotation value of **4-11** with literature data.[115]

4.3 Conclusions

In summary, we have utilized 3,5-dimethyl-1*H*-pyrazolederived acrylamides in asymmetric [3+2] cycloadditions with an allenoate for the first time. The annulation reaction was promoted effectively by dipeptide-derived phosphines, affording only the α-regioisomers in excellent yields and moderate enantioselectivities. This is the first example in which acrylamides are used directly in phosphine-catalyzed asymmetric [3+2]-cycloaddition reactions. We are currently investigating the mechanistic aspects of this novel reaction and are developing new catalytic systems to further improve the enantioselectivities of the reported reactions.

4.4 Experimental Section

4.4.1 General Methods

All starting materials were obtained from commercial sources and were used without further purification unless otherwise stated. Toluene, THF and Et_2O were dried and distilled from sodium benzophenone prior to use. $CHCl_3$ and CH_2Cl_2 were distilled from CaH_2 prior to use. All solvents used in reactions involving phosphorus-containing compounds were degassed using N_2. Melting points were determined using a Büchi B-540 melting point apparatus. Optical rotations were measured using a Jasco DIP-1000 polarimeter. ^1H and ^{13}C NMR spectra were recorded on a Bruker ACF300 or AMX500 (500 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton

($CHCl_3$, δ 7.26), carbon ($CHCl_3$, δ 77.0). Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet). Coupling constants are reported in hertz (Hz). High-resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. TLC was accomplished using Merck pre-coated TLC plates (Merck 60 F254), and compounds were made visual with UV light at 254 nm. Flash chromatographic separations were performed on Merck 60 (0.040–0.063 mm) mesh silica gel. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase.

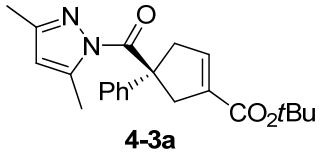
All the α-substituted acrylic acids were prepared according to our previous reported method.[115] Acrylamides **4-1a-g** were prepared by reaction of the corresponding acids with oxalyl chloride and 3,5-dimethyl-1*H*-pyrazole in the presence of pyridine in CH_2Cl_2;[116] acrylamides **4-1h** and **4-1i** were prepared using EDC·HCl, HOBt and 3,5-dimethyl-1*H*-pyrazole following the procedures reported in the literature.[117]

4.4.2 Representative Procedure for [3+2] Cycloadditions

To a flame-dried, round bottom flask were added catalyst **4-10** (4.2 mg, 0.005 mmol) and acrylamide **4-1** (0.05 mmol) under N_2, followed by the addition of anhydrous toluene (0.25 mL). Allenoate **4-2** (11 mL, 0.075 mmol) was then added, and the mixture stirred at r.t. for a given period as specified in Table 4.2. Following completion of the reaction the mixture was subjected directly to flash column chromatographic separation using a mixture of hexane–EtOAc as the eluent to afford cycloaddition products **4-3**.

4.4.3 Analytical Data of [3+2] Adducts

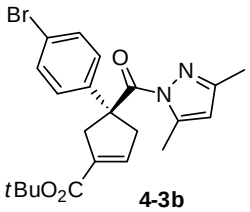
tert-Butyl (4*S*)-4-[(3,5-Dimethyl-1*H*-pyrazol-1-yl)carbonyl]-4-phenylcyclopent-1-ene-ca-rboxylate (**4-3a**)



4-3a

Yield: 15.7 mg (86%); white solid; mp 94.0–95.0 °C; $[\alpha]^{26}_{D}$ = –47.2 (*c* 0.65, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26-7.17 (m, 4 H), 7.16-7.13 (m, 1 H), 6.61 (t, *J* = 1.9 Hz, 1 H), 5.77 (s, 1 H), 3.66-3.58 (m, 2 H), 3.37 (d, *J* = 16.4 Hz, 1 H), 3.14 (d, *J* = 19.0 Hz, 1 H), 2.54 (s, 3 H), 1.98 (s, 3 H), 1.49 (s, 9 H); ^{13}C NMR (125 MHz, CDCl3): d = 174.6, 164.1, 150.9, 144.9, 144.6, 139.0, 135.5, 128.2, 126.1, 125.3, 110.2, 80.3, 60.3, 44.9, 42.7, 28.2, 14.7, 13.7; HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{22}H_{26}N_2O_3Na$: 389.1836; found: 389.1848; HPLC: 66% ee (Chiralcel IC-H, *i*PrOH/hexane, 5:95, flow rate = 0.5 mL/min, λ = 254 nm): t_R (major) = 14.2 min, t_R (minor) = 16.4 min.

tert-Butyl (4*S*)-4-(4-Bromophenyl)-4-[(3,5-dimethyl-1*H*-pyrazol-1 yl)carbonyl]cyclo-pen-1-ene-1-carboxylate (**4-3b**)



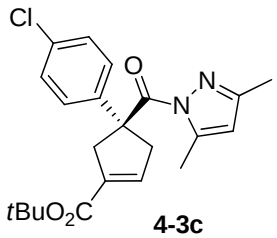
4-3b

Yield: 18.7 mg (84%); white solid; mp 114.5–115.0 °C; $[\alpha]^{26}_{D}$ = –54.7 (*c* 0.70, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.9 Hz, 2 H), 7.12 (d, *J* = 8.8 Hz, 2 H),

6.59 (d, *J* = 2.6 Hz, 1 H), 5.78 (s, 1 H), 3.64-3.56 (m, 2 H), 3.30 (d, *J* = 17.1 Hz, 1 H), 3.08 (d, *J* = 18.9 Hz, 1 H), 2.52 (s, 3 H), 1.99 (s, 3 H), 1.48 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.9, 163.9, 151.3, 144.7, 144.0, 138.8, 135.5, 131.3, 127.2, 119.9, 110.4, 80.5, 59.9, 44.8, 42.7, 28.1, 14.7, 13.7; HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{22}H_{25}BrN_2O_3Na$: 467.0941; found: 467.0922. HPLC: 60% ee (Chiralcel IC-H, *i*PrOH /hexane, 3:97, flow rate = 0.5 mL/min, λ = 254 nm): t_R (major) = 11.2 min, t_R (minor) = 12.5 min.

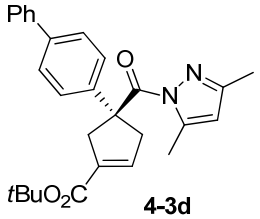
tert-Butyl (4*S*)-4-(4-Chlorophenyl)-4-[(3,5-dimethyl-1*H*-pyrazol-1-yl)carbonyl] cyclopent-1-ene-1-carboxylate (**4-3c**)



4-3c

Yield: 17.6 mg (88%); white solid; mp 114.1–114.5 °C; $[\alpha]^{26}_D$ = –49.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23-7.15 (m, 4 H), 6.60 (t, *J* = 2.0 Hz, 1 H), 5.78 (s, 1 H), 3.66-3.33 (m, 2 H), 3.27 (d, *J* = 16.5 Hz, 1H), 3.06 (d, *J* = 19.4 Hz, 1 H), 2.52 (s, 3 H), 1.99 (s, 3 H), 1.48 (s, 9 H); ^{13}C NMR (75 MHz, CDCl3): δ = 174.0, 163.9, 151.3, 144.7, 143.4, 138.8, 135.4, 131.9, 128.3, 126.8, 80.5, 59.8, 44.8, 42.7, 28.1, 14.7, 13.8; HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{22}H_{25}ClN_2O_3Na$: 423.1446; found: 423.1448; HPLC: 60% ee (Chiralcel IC-H, *i*PrOH/hexane, 5:95, flow rate = 0.5 mL/min, λ = 254 nm): t_R (major) = 9.8 min, t_R (minor) = 10.8 min.

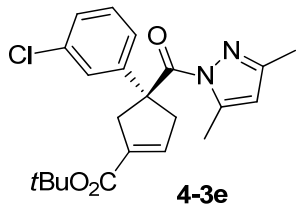
tert-Butyl (4*S*)-4-(Biphenyl-4-yl)-4-[(3,5-dimethyl-1*H*-pyrazol-1-yl)carbonyl]cyclopent-1-ene-1-carboxylate (**4-3d**)



4-3d

Yield: 20.7 mg (93%); white solid; mp 135.6–136.0 °C; $[\alpha]^{26}_{D}$ = –50.0 (*c* 0.9, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57 (t, *J* = 8.2 Hz, 2 H), 7.50 (t, *J* = 14.5 Hz, 2 H), 7.42 (t, *J* = 19.5 Hz, 2 H), 7.39-7.31 (m, 3 H), 6.64 (t, *J* = 1.9 Hz, 1 H), 5.79 (s, 1 H), 3.71-3.61 (m, 2 H), 3.42 (d, *J* = 17.6 Hz, 1 H), 3.21 (d, *J* = 19.0 Hz, 1 H), 2.56 (s, 3 H), 2.00 (s, 3 H), 1.50 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.5, 164.2, 151.1, 144.7, 144.0, 140.7, 139.1, 138.8, 135.6, 128.7, 127.1, 126.9, 126.8, 125.9, 110.4, 80.4, 60.1, 45.0, 42.8, 28.2, 14.8, 13.8; HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{28}H_{30}N_2O_3Na$: 465.2149; found: 465.2149; HPLC: 62% ee (Chiralcel IC-H, *i*PrOH/hexane, 5:95, flow rate = 0.5 mL/min, λ = 254 nm): t_R (major) = 12.3 min, t_R (minor) = 14.5 min.

tert-Butyl (4*S*)-4-(3-Chlorophenyl)-4-[(3,5-dimethyl-1*H*-pyrazol-1-yl)carbonyl] cyclope-nt-1-ene-1-carboxylate (**4-3e**)

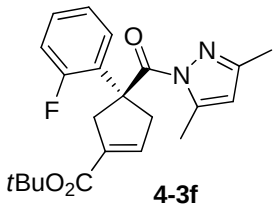


4-3e

Yield: 17.6 mg (88%); white solid; mp 98.8–99.5 °C; $[\alpha]^{26}_{D}$ = –13.7 (*c* 0.9, $CHCl_3$). ^{1}H NMR (500 MHz, CDCl3): δ = 7.26-7.25 (m, 1 H), 7.18-7.09 (m, 3 H), 6.60 (s, 1 H), 5.79 (s, 1 H), 3.64-3.57 (m, 2 H), 3.29 (d, *J* = 17.7 Hz, 1 H), 3.11 (d, *J* = 19.6 Hz, 1 H), 2.54 (s, 3 H), 1.99 (s, 3 H), 1.49 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.8, 163.9, 151.3, 146.9, 144.7, 138.8, 135.4, 134.1, 129.4, 126.3, 125.7, 123.6,

110.4, 80.5, 60.1, 44.8, 42.7, 28.1, 14.7, 13.7; HRMS (ESI): *m*/z $[M+Na]^+$ calcd for $C_{22}H_{25}ClN_2O_3Na$: 423.1446; found: 423.1450; HPLC: 44% ee (Chiralcel IC-H, *i*PrOH/hexane, 5:95, flow rate = 0.5 mL/min, λ = 254 nm): t_R (major) = 10.3 min, t_R (minor) = 12.1 min.

tert-Butyl (4*S*)-4-[(3,5-Dimethyl-1*H*-pyrazol-1-yl)carbonyl]-4-(2-fluorophenyl) cyclopent-1-ene-1-carboxylate (**4-3f**)

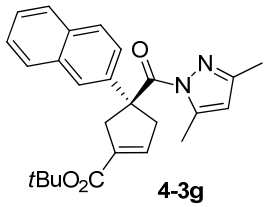


4-3f

Yield: 17.5 mg (91%); yellow oil; $[\alpha]^{26}_D$ = –37.2 (*c* 1.2, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39-7.35 (m, 1 H), 7.16-7.07 (m, 2 H), 6.89-6.84 (m, 1 H), 6.63 (t, *J* = 1.9 Hz, 1 H), 5.77 (s, 1 H), 3.72-3.57 (m, 2 H), 3.34 (d, *J* = 17.7 Hz, 1 H), 3.06 (d, *J* = 18.9 Hz, 1 H), 2.54 (s, 3 H), 1.91 (s, 3 H), 1.49 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.6, 164.0, 160.6, 158.8, 150.6, 144.4, 138.9, 133.0 (d, *J* = 13.7 Hz), 126.8 (d, *J* = 4.6 Hz), 123.7 (d, *J* = 2.7 Hz), 115.2 (d, *J* = 22.8 Hz), 110.1, 80.5, 56.4, 44.0, 42.1, 28.2, 14.4, 13.6; HRMS (ESI): *m*/z $[M+Na]^+$ calcd for $C_{22}H_{25}FN_2O_3Na$: 407.1741; found: 407.1747; HPLC: 36% ee (Chiralcel IC-H, *i*PrOH/hexane, 5:95, flow rate = 0.5 mL/min, λ = 254 nm): t_R (major) = 10.9 min, t_R (minor) = 21.9 min.

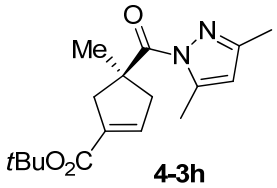
tert-Butyl(4*S*)-4-[(3,5-Dimethyl-1*H*-pyrazol-1-yl)carbonyl]-4-(naphthalen-2-yl)cyclopent-1-ene-1-carboxylate (**4-3g**)



4-3g

Yield: 18.9 mg (91%); white solid; mp 153.0–153.8 °C; $[\alpha]^{26}_{D}$ = –45.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.79-7.71 (m, 4 H), 7.45-7.39 (m, 3 H), 6.65 (t, *J* = 1.9 Hz, 1 H), 5.75 (s, 1 H), 3.73–3.45 (m, 2 H), 3.47 (d, *J* = 17.7 Hz, 1 H), 3.27 (d, *J* = 19.0 Hz, 1 H), 2.56 (s, 3 H), 1.92 (s, 3 H), 1.49 (s, 9 H); ^{13}C NMR (125 MHz, CDCl3): δ = 174.5, 164.1, 151.1, 144.6, 142.2, 139.0, 135.6, 133.4, 132.0, 128.0, 127.9, 127.4, 125.9, 125.5, 124.2, 123.8, 110.3, 80.4, 60.5, 44.9, 42.8, 28.2, 14.7, 13.7; HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{26}H_{28}N_2O_3Na$: 439.1992; found: 439.2003; HPLC: 56% ee (Chiralcel IC-H, *i*PrOH/hexane, 5:95, flow rate = 0.5 mL/min, λ = 254 nm): t_R (major) = 12.3 min, t_R (minor) = 14.0 min.

tert-Butyl (4*S*)-4-[(3,5-Dimethyl-1*H*-pyrazol-1-yl)carbonyl]-4-methylcyclopent-1-ene-1-carboxylate (**4-3h**)



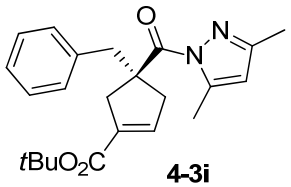
4-3h

Yield: 10.8 mg (71%); yellow oil; $[\alpha]^{26}_{D}$ = +26.0 (*c* 0.3, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.57 (s, 1 H), 5.89 (s, 1 H), 3.30-3.26 (m, 2 H), 3.75 (d, *J* = 15.1 Hz, 1 H), 3.63 (d, *J* = 17.1 Hz, 1 H), 2.51 (s, 3 H), 2.20 (s, 3 H), 1.58 (s, 3 H), 1.49 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.1, 164.6, 151.1, 144.8, 139.1, 135.4, 110.3, 80.2, 51.6, 45.2, 43.5, 28.2, 14.9, 13.9; HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{17}H_{24}N_2O_3Na$: 327.1679; found: 327.1683; HPLC: 47% ee (Chiralcel IC-H, *i*PrOH/hexane, 5:95, flow rate = 0.5 mL/min, λ = 254 nm): t_R (major) = 10.8 min, t_R

(minor) = 13.7 min.

tert-Butyl (4*R*)-4-Benzyl-4-[(3,5-dimethyl-1*H*-pyrazol-1-yl)carbonyl]cyclopent-1-ene-1-carboxylate (**4-3i**)

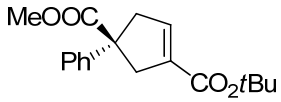


4-3i

Yield: 15.4 mg (81%); yellow oil; $[\alpha]^{26}_{D} = -2.2$ (*c* 0.93, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21-7.16 (m, 3 H), 6.80-6.78 (m, 2 H), 6.57 (d, *J* = 2.5 Hz, 1 H), 5.97 (s, 1 H), 3.52 (d, *J* = 13.3 Hz, 1 H), 3.31 (d, *J* = 13.4 Hz, 1 H), 3.27-3.04 (m, 2 H), 2.90 (d, *J* = 4.4 Hz, 1 H), 2.86 (d, *J* = 3.1 Hz, 1 H), 2.29 (s, 3 H), 1.92 (s, 3 H), 1.51 (s, 9 H); ^{13}C NMR (125 MHz, CDCl3): δ = 175.2, 164.4, 151.3, 144.9, 139.2, 137.7, 135.5, 129.5, 129.1, 128.1, 126.4, 110.4, 80.3, 57.4, 44.6, 42.3, 41.5, 39.9, 28.2, 14.8, 13.9; HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{23}H_{28}N_2O_3Na$: 403.1992; found: 403.1995; HPLC: 61% ee (Chiralcel IC-H, *i*PrOH/hexane, 5:95, flow rate = 0.5 mL/min, λ = 254 nm): t_R (major) = 11.0 min, t_R (minor) = 13.6 min.

3-*tert*-Butyl 1-Methyl (1*S*)-1-Phenylcyclopent-3-ene-1,3-dicarboxylate (**4-11**)



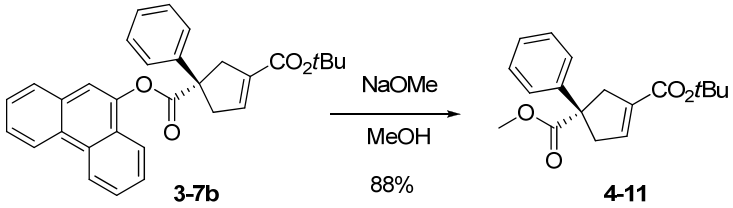
4-11

To a solution of **4-3a** (73 mg, 0.2 mmol) in MeOH (2 mL) at 0 °C was added NaOMe (22 mg, 0.4 mmol) and the mixture stirred at r.t. for 1 h. Next, the reaction was quenched by the addition of H_2O (4 mL), and the resulting mixture was extracted with Et_2O (2 × 8 mL). The combined organic extracts were washed with brine (6 mL)

and dried over Na_2SO_4. Purification by column chromatography (eluent: hexane/EtOAc, 15:1) afforded diester **4-11**.

Yield: 55 mg (91%); white solid; mp 71.0–72.0 °C; $[\alpha]^{26}_D$ = –24.0 (*c* 0.8, $CHCl_3$) {Lit.[115] $[\alpha]^{26}_D$ = –35.2 (*c* 1.0, $CHCl_3$)}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32-7.29 (m, 4 H), 7.26-7.23 (m, 1 H), 6.65 (s, 1 H), 3.66 (s, 3 H), 3.65-3.59 (m, 2 H), 3.03 (d, *J* = 14.5 Hz, 1 H), 2.90 (d, *J* = 14.1 Hz, 1 H), 1.49 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.8, 163.9, 142.9, 139.7, 136.4, 128.5, 126.9, 126.4, 80.5, 58.2, 52.6, 43.4, 41.6, 28.1; HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{18}H_{22}O_4Na$: 325.1410; found: 325.1417.

4.4.4 Determination of Absolute Configurations of the Products



3-7b **4-11**

To a solution of compound **3-7b** (Table 3.5, Chapter 3)[115] (50 mg, 0.11 mmol) in MeOH (1 mL) at 0 °C was added sodium methoxide (12 mg, 0.22 mmol), and the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched by addition of H_2O (2 mL), and the resulting mixture was extracted with ethyl ether (2 × 5 mL). The combined organic extracts were washed with brine (5 mL), and dried over Na_2SO_4. Purification by column chromatography (hexane/ethyl acetate = 15:1) afforded **4-11** (29 mg, 88% yield) as a white solid.

$[\alpha]^{26}_D$ = -35.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.29 (m, 4H), 7.26-7.23 (m, 1H), 6.65 (s, 1H), 3.66 (s, 1H), 3.65-3.59 (m, 2H), 3.03 (d, *J* = 14.5 Hz, 1H), 2.90 (d, *J* = 14.1 Hz, 1H), 1.49 (s, 9H).

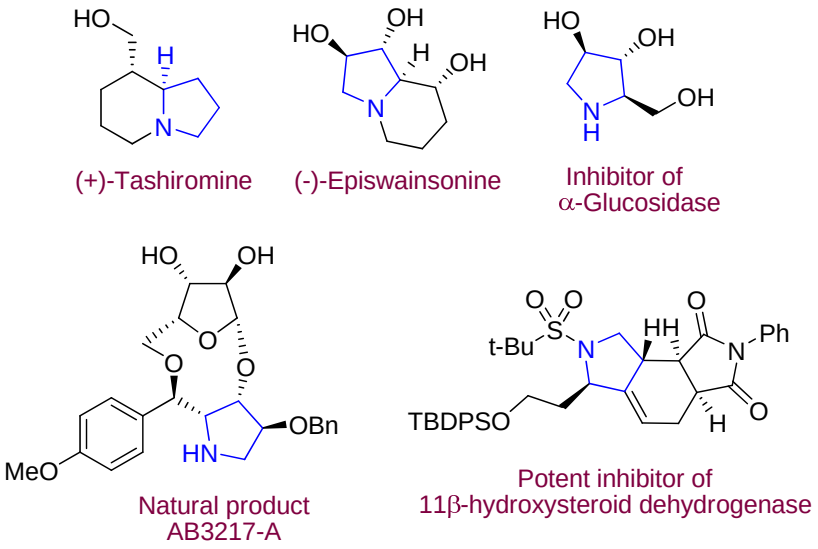
The above-derived compound **4-11** has same configuration as the **4-11** derived from **4-3a**, by comparing the optical rotation values. Thus, the configuration of **4-3a** was assigned as *S*, and the configurations of other annulations products were assigned by analogy.

Chapter 5 Versatile Enantioselective [3+2] Cyclization between Imines and Allenoates Catalyzed by Dipeptide-Based Phosphines

5.1 Introduction

Optically pure five-membered *N*-heterocycles are valuable intermediates in chemical synthesis, and they are also prevalent structural motifs in bioactive molecules and natural products.[118] Over the past decade, many synthetic methods have been devised for the construction of such ring systems.[119] In this context, [3+2] cyclization of imines with allenes or alkynes is one of the most straightforward and efficient methods for the creation of pyrrolines[120] and pyrrolidines,[121] which are classes of compounds of synthetic and biological importance. In 1997, Lu disclosed the [3+2] cycloadditions between imines and alkynes or allenes for the synthesis of pyrroline rings.[46b] However, asymmetric variants of these phosphine-catalyzed [3+2] cyclizations only appeared almost a decade later. Marinetti and Gladysz independently reported chiral phosphine-triggered asymmetric [3+2] annulations of allenes with *N*-tosyl imines, affording functionalized 3-pyrrolines in moderate enantioselectivity.[48,49,122] The breakthrough came when Jacobsen introduced phosphinothiourea catalysis of imine–allene cyclization; by utilizing diphenylphosphinoyl (DPP) imines,[123] substituted 2-aryl-2,5-dihydropyrroles were formed in good yields and with excellent enantioselectivities.[50] Despite all the above advances, the utilization of aliphatic imines in phosphine-catalyzed [3+2] cycloaddition reaction remains elusive. Aliphatic imines are challenging substrates, due to their isomerizable nature[124] and relative instability. Nonetheless, their synthetic values are remarkable. Apparently, accessing five-membered *N*-heterocycles via

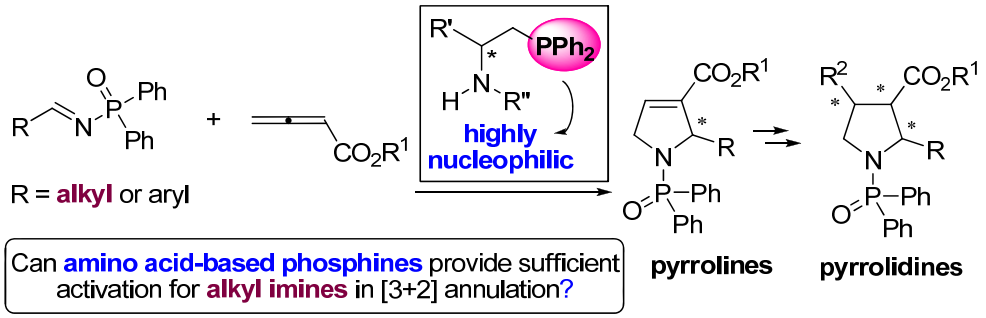
cycloaddition reactions of aliphatic imines holds significant synthetic utilities. As illustrated in Scheme 5.1, pyrrolidines with 2-alkyl substituents are very common substructures in bioactive molecules and natural products.[125]



Scheme 5.1 Pyrrolidine-containing bioactive molecules

We recently embarked on an exciting adventure of developing amino acid-based bifunctional phosphines and their applications in asymmetric organic transformations.[81] We showed that highly enantioselective aza-Morita–Baylis–Hillman (MBH) and MBH reactions could be realized by using L-threonine-derived phosphine–sulfonamides[38] and phosphine–thioureas (Chapter 2), respectively. We also demonstrated that dipeptide-derived phosphines were powerful catalysts for promoting enantioselective [3+2] cycloadditions of allenes to acrylates (Chapter 3) or acrylamides (Chapter 4). Very recently, we discovered that L-threonine-derived phosphine–thioureas were capable of promoting MBH carbonates as C_3-synthons in the [3+2] cyclization.[126] Given the relative instability of aliphatic imines, we reasoned highly reactive phosphines are probably necessary for their effective activations in the

cycloaddition reaction, since potential decomposition of imines may be avoided. It is noteworthy that our amino acid-based phosphines possess remarkably high nucleophilicity. We hypothesize employment of highly nucleophilic bifunctional phosphines may result in a practical asymmetric [3+2] annulation protocol in which alkyl imines can be conveniently utilized (Scheme 5.2).



Scheme 5.2 Phosphine-triggered [3+2] cyclization of imines with allenoates

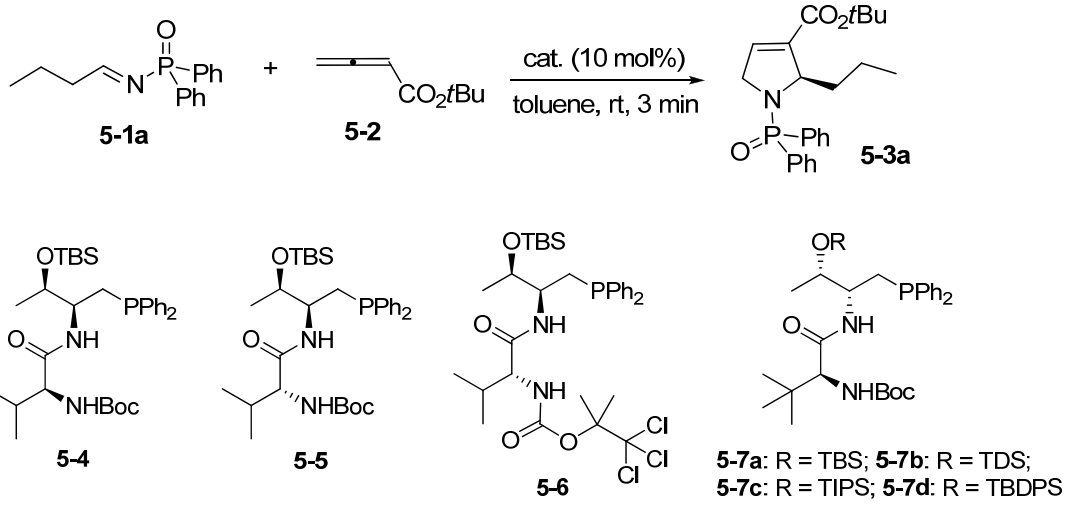
5.2 Results and Discussion

5.2.1 Reaction Optimization

The [3+2] cycloaddition between DPP imine **5-1a** and *tert*-butyl allenoate **5-2** was selected as a model reaction for the initial explorations (Table 5.1). For the catalysts, we chose to focus on dipeptide-based bifunctional phosphines, which were shown to be highly efficient in our previous studies (Chapter 3).[115] To our delight, all the phosphines examined displayed remarkable catalytic effects, affording the desired 3-pyrrolines in just a few minutes. While L-Thr-L-Val-derived phosphine **5-4** induced very low enantioselectivity, catalyst **5-5** consisting of L-Thr and D-Val subunits turned out to be very effective in asymmetric induction (entries 1–2), suggesting the chirality matching is very important in our catalytic system. The structures of the catalysts were optimized by introducing *tert*-Leu as the second amino acid residue and

varying the carbamate group on the *N*-terminal of the dipeptide, and it was discovered that *O*-TBDPS-D-Thr-L-*tert*-Leu-based **5-7d** was the best catalyst (entries 4–7).

Table 5.1 [3+2] Cycloaddition of allenoates with amines catalyzed by dipeptide-based phosphines[a]



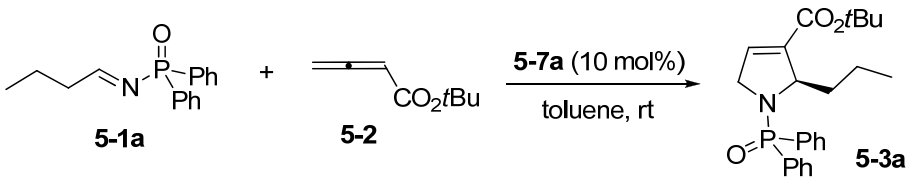
Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	**5-4**	88	-11
2	**5-5**	91	-88
3	**5-6**	86	-82
4	**5-7a**	**91**	**92**
5	**5-7b**	90	85
6	**5-7c**	88	89
7	**5-7d**	90	92

[a] Reactions were performed with **5-1a** (0.05 mmol), **5-2** (0.075 mmol) and the catalyst (10 mol %) in toluene (0.5 mL) at room temperature. [b] Isolated yield. [c] The ee value was determined by HPLC analysis on a chiral stationary phase.

To further improve the enantioselectivity of the reaction, solvent screening was performed and summarized in Table 5.2. To our delight, slightly better result was achieved when this reaction was carried out in ether at room temperature, offering the corresponding [3+2] adduct in 91% yield with 93% ee (entry 7). All the other

common solvents were shown to be unsuitable, affording products in low yields and with poor enantioselectivities. When the reaction was performed with 10 mol% **5-7d** in ether, the product **5-3a** was obtained in 92% yield and with 94% ee (entry 14).

Table 5.2 Solvents screening for **5-7a**-promoted [3+2] cycloaddition[a]



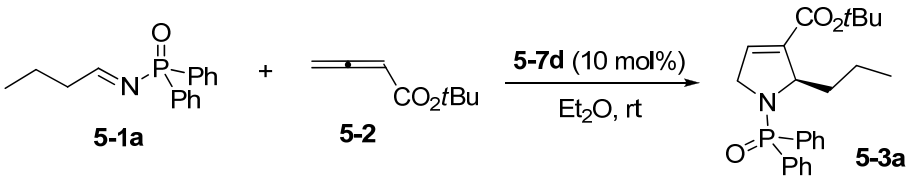
Entry	Solvent	*t* (min)	Yield (%)[b]	ee (%)[c]
1	toluene	3	91	92
2	benzene	3	90	90
3	CH_2Cl_2	3	85	78
4	$CHCl_3$	3	72	69
5	DCE	3	77	79
6	CH_3CN	3	70	69
7	Et_2O	3	91	93
8	THF	3	85	86
9	dioxane	3	< 20%	-[d]
10	DME	3	87	91
11	TBME	3	93	90
12	CH_3OH	3	-[e]	
13	Toluene/ Et_2O	3	90	92
14[f]	**Et_2O**	**3**	**92**	**94**

[a] Reactions were performed with **5-1a** (0.05 mmol), **5-2** (0.075 mmol) and **5-7a** (10 mol %) in corresponding solvent (0.5 mL) at room temperature. [b] Isolated yield. [c] The ee value was determined by HPLC analysis on a chiral stationary phase. [d] Not determined. [e] No reaction. [f] Phosphine **5-7d** was used as the catalyst.

The screening indicated that catalyst **5-7d** was promising (Table 5.2), so further attempts to improve the enantioselectivity were performed by investigations the effects of additive, temperature and catalyst loading on **5-7a**-promoted [3+2]

cycloaddition (Table 5.3). The existence of 5 Å molecular sieves had a positive effect on the enantioselectivity (entry 4). Furthermore, lowering the temperature to 0 ^{o}C enhanced the enantioselectivity (entry 7); however, further cooling prolonged the reaction time but gave no additional improvement in enantioselectivity. Applying the catalyst **5-7d** with 5 mol% under the optimized conditions furnished the pyrroline product **5-3a** in very high yield and excellent enantioselectivity (entry 9).

Table 5.3 The effects of additive, temperature and catalyst loading on **5-7a**-promoted [3+2] cycloaddition



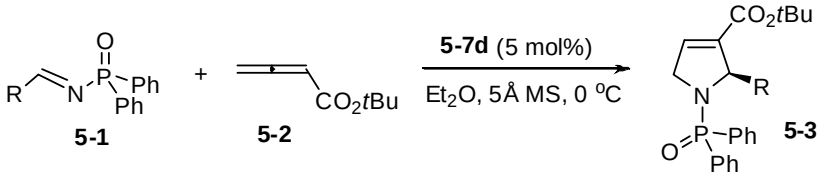
Entry	Additive	Temperature	*t* (min)	Yield (%)[b]	ee (%)[c]
1	none	rt	3	92	94
2	3Å MS	rt	10	90	94
3	4Å MS	rt	10	92	94
4	5Å MS	rt	10	91	95
6	H_2O	rt	3	84	90
7	5Å MS	0 ^{o}C	20	89	96
8	5Å MS	- 20 ^{o}C	60	84	94
9[d]	**5Å MS**	**0 ^{o}C**	**30**	**92**	**96**
10[e]	5Å MS	0 ^{o}C	45	86	95

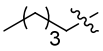
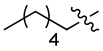
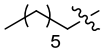
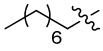
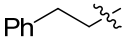
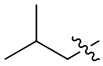
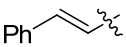
[a] Reactions were performed with **5-1a** (0.05 mmol), **5-2** (0.075 mmol) and **5-7d** (10 mol %) in ether (0.5 mL) at room temperature. [b] Isolated yield. [c] The ee value was determined by HPLC analysis on a chiral stationary phase. [d] Catalyst loading was 5 mol %. [e] Catalyst loading was 2 mol %.

5.2.2 Substrate Scope

Having established the optimal reaction conditions for the preparation of 3-pyrroline, the substrate scope for **5-7d**-catalyzed [3+2] cyclization was then investigated (Table 5.4). A wide range of alkyl imines could be employed, and the enantioselectivity of the reaction was independent to the alkyl substituents of the imines. The reaction was applicable to α-methyl-substituted imine, which tends to form isomeric enamide readily (entry 1). α-Unbranched alkyl imines were found to be excellent substrates; not only simple linear alkyl groups of different length were applicable, the alkyl imine bearing a phenyl group at the end was also suitable (entries 2–7). The reaction also tolerated branched alkyl imines, and the cycloaddition proceeded remarkably well with imines bearing *s*-butyl, isopropyl or cyclohexyl group (entries 8–10). Furthermore, the imine with a vinylic substituent also proved to be a suitable substrate. Notably, only 5 mol% catalyst was sufficient to promote the allenoate–imine cyclizations, affording the 3-pyrrolines in good to excellent yields, and with nearly perfect enantioselectivities. Moreover, the reactions were very fast, and all the cyclizations could be completed in less than 30 minutes. The absolute configuration of [3+2] products were determined by comparing the optical rotation of a **5-3j** derivative with the value reported in the literature.[127]

Table 5.4 Enantioselective [3+2] cycloaddition of allenoates with aliphatic DPP-imines catalyzed by **5-7d**[a]

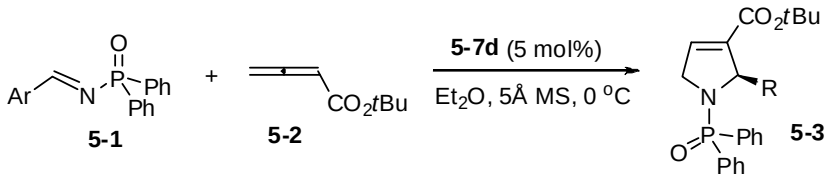


Entry	R	Product	Yield (%)[b]	ee (%)[c]
1		**5-3b**	75	95
2		**5-3c**	78	96
3		**5-3d**	80	97
4		**5-3e**	84	97
5		**5-3f**	85	97
6		**5-3g**	82	96
7		**5-3h**	81	95
8		**5-3i**	90	95
9		**5-3j**	81	99
10		**5-3k**	83	99
11		**5-3l**	81	96

[a] Reactions were performed with **5-1** (0.1 mmol), **5-2** (0.15 mmol) and **5-7d** (0.005 mmol) in Et_2O (1 mL) containing 5Å molecular sieves at 0 ^oC for 30 min. [b] Isolated yield. [c] The ee value was determined by HPLC analysis on a chiral stationary phase.

The broad applicability of dipeptide-based phosphine-catalyzed [3+2] annulation to various alkyl imines suggested such enantioselective process should be applicable to aryl imines. We therefore investigated imine–allenoate cyclization employing aryl imines (Table 5.5). Under the optimized conditions and in the presence of phosphine **5-7d**, the [3+2] cycloadditions of aryl imines with allenes were completed within one hour, and the desired products were obtained in constantly high yields and excellent enantioselectivities. The reaction was applicable to aryl imines with different electronic nature and substitution patterns on the aromatic rings. 2-Naphthyl and heteroaryl imines were also found to be suitable.

Table 5.5 Enantioselective [3+2] cycloaddition of allenoates with aromatic imines catalyzed by **5-7d**.[a]



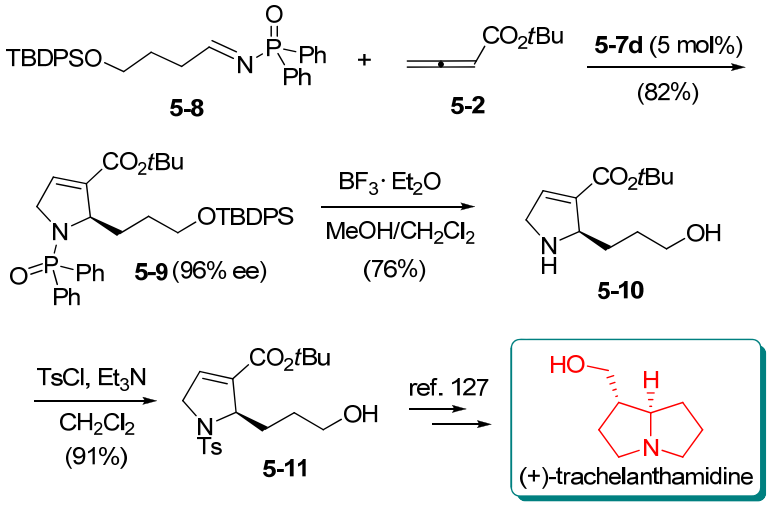
Entry	Ar	Product	Yield (%)[b]	ee (%)[c]
1	Ph	**5-3m**	82	95
2	4-BrC6H4	**5-3n**	83	95
3	3-BrC6H4	**5-3o**	85	96
4	4-OMeC6H4	**5-3p**	94	98
5	3-CNC6H4	**5-3q**	78	93
6	2-naphthyl	**5-3r**	86	96
7	2-furyl	**5-3s**	83	94
8	2-thienyl	**5-3t**	78	95

[a] Reactions were performed with **5-1** (0.1 mmol), **5-2** (0.15 mmol) and **5-7d** (0.005 mmol) in Et_2O (1 mL) containing 5Å molecular sieves at 0 °C for 30 min. [b] Isolated yield. [c] The ee value was determined by HPLC analysis on a chiral stationary phase.

5.2.3 Derivative Synthesis

2-Alkyl-substituted chiral 3-pyrrolines are structures of high synthetic value, which can potentially be elaborated into many biologically useful molecules.[125] As an illustration, a formal synthesis of pyrrolizidine alkaloid (+)-trachelanthamidine using our cyclization protocol as a key step was performed (Scheme 5.3). The [3+2] cycloaddition between imine **5-8** and allenoate **5-2** occurred smoothly in the presence of **5-7d**, affording functionalized pyrroline **5-9** in 82% yield and 96% ee. Treatment of **5-9** with boron trifluoride resulted in simultaneous removal of the DPP protection and cleavage of the silyloxy group, giving intermediate **5-10** in good yield. Installation of a tosyl group on the free NH yielded *N*-tosyl sulfonylamide **5-11**,

which can be converted to (+)-trachelanthamidine following the procedures described in the literature.[127]



Scheme 5.3 A formal synthesis of (+)-trachelanthamidine

5.2.4 Plausible Mechanism and Transition State Model

We propose that amide and carbamate portions of the catalyst interact with imines via hydrogen bonding interactions, which contribute significantly to the key transition state leading to the formation of the major stereoisomer (Figure 5.1). The preferential adoption of an *s*-cis conformation by DPP imines8 facilitates the intramolecular delivery of phosphonium enolate to the imine. The catalytic effects of *N*-methylated catalyst **5-12** were examined, and cyclization product **5-3a** was obtained in 82% yield after 4 h, but with only 59% ee (Scheme 5.4). In comparison, similar catalysts with free carbamate (**5-5** and **5-7d** in Table 5.1) afforded products in excellent yields and around 90% ee in just a few minutes. These results clearly support the importance of the hydrogen bond donor groups in our catalytic systems. Thioureas are known to provide excellent activations and stereochemical controls for reactions involving imines, as demonstrated by Jacobsen et al. in their related report.[50]

However, dipeptide or threonine-based phosphine–thiourea **5-13** or **5-14** was found to be completely ineffective in our reactions. Since catalysts **5-13**/**5-14** are conformationally flexible, we believe the thiourea group of the catalyst preferentially stabilizes the phosphonium enolate, rather than DPP imines, via hydrogen bonding interactions.

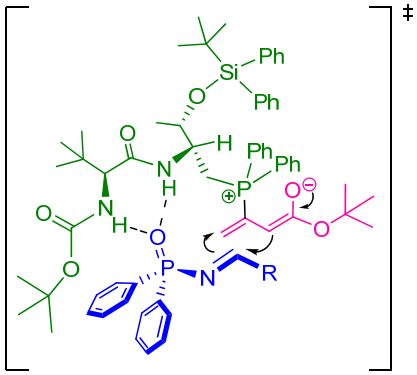
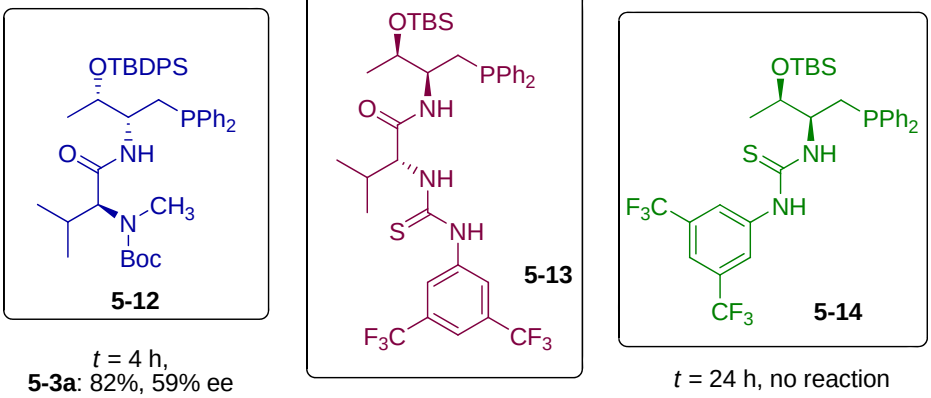


Figure 5.1 Proposed transition state



t = 4 h,
5-3a: 82%, 59% ee

t = 24 h, **5-3a**: <10% yield

t = 24 h, no reaction

Scheme 5.4 The [3+2] annulations between **5-1a** and **5-2** in toluene promoted by different catalysts

5.3 Conclusions

In conclusion, we have developed a highly enantioselective [3+2] cyclization between imines and allenoates, by employing dipeptide-based chiral phosphines as catalysts. Notably, this is the first time that alkyl imines have been applied successfully in the asymmetric [3+2] cycloaddition. Moreover, such enantioselective cyclization is very versatile, worked equally well for aryl imines. The efficiency of the cyclization processes described in this report is noteworthy; in the presence of **5-5** mol% **5-7d**, all the reactions were completed within one hour, and the 2-alkyl/aryl-substituted 3-pyrrolines could be easily prepared in nearly enantiomerically pure form. Synthetic value of our method has been demonstrated by using imine~allene annulation as a key step in a concise formal synthesis of (+)-trachelanthamidine. We are currently investigating the reaction mechanism and applying the methodology described to the synthesis of biologically important molecules.

5.4 Experimental Section

5.4.1 Materials and General Methods

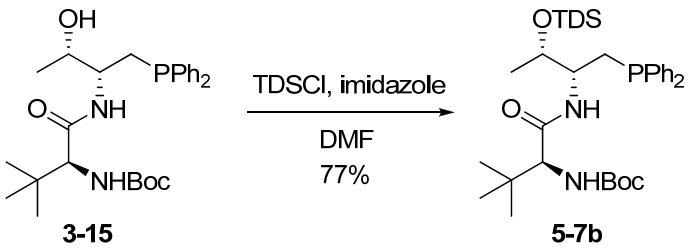
All starting materials were obtained from commercial sources and were used without further purification unless otherwise stated. Toluene, THF and Et_2O were dried and distilled from sodium benzophenone prior to use. $CHCl_3$ and CH_2Cl_2 were distilled from CaH_2 prior to use. All solvents used in reactions involving phosphorus-containing compounds were degassed using N_2. Melting points were determined using a Büchi B-540 melting point apparatus. Optical rotations were measured using a Jasco DIP-1000 polarimeter. ^1H and ^{13}C NMR spectra were recorded on a Bruker ACF300 or AMX500 (500 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton

($CHCl_3$, δ 7.26), carbon ($CHCl_3$, δ 77.0). Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet). Coupling constants are reported in hertz (Hz). High-resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. TLC was accomplished using Merck pre-coated TLC plates (Merck 60 F254), and compounds were made visual with UV light at 254 nm. Flash chromatographic separations were performed on Merck 60 (0.040–0.063 mm) mesh silica gel. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase.

All the alkyl, aryl-, heteroaryl- and alkynel-substituted aldimines were synthesized from the intermediates of the corresponding sulfinyl adducts according to literature reported methods.[128,129] Catalysts **5-4**, **5-5**, **5-6**, **5-7a** and **5-7d** were prepared following the procedures described in Chapter 3.

5.4.2 Catalysts Preparation

tert-Butyl (*S*)-1-((2*R*,3*S*)-3-((2,3-dimethylbutan-2-yl)dimethylsilyloxy)-1-(diphenylphosphino) butan-2-ylamino)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (**5-7b)**



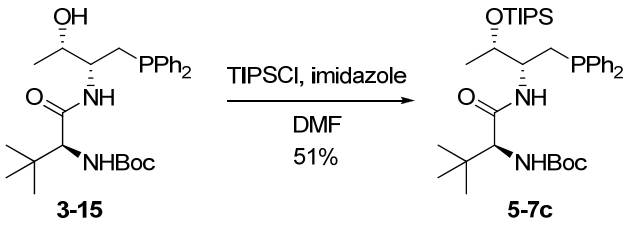
3-15 **5-7b**

To a solution of **3-15** (140 mg, 0.29 mmol) in anhydrous DMF (40 μL) at room temperature under N_2 was added imidazole (39 mg, 0.58 mmol), followed by TDSCl (70 μL, 0.35 mmol). The resulting mixture was stirred at room temperature for 24 h, and then quenched by adding water (5 mL), and extracted with diethyl ether (3 x 5 mL). The organic extracts were combined, washed with brine, and dried over Na_2SO_4.

Purification by column chromatography (hexane: ethyl acetate = 20:1 to 10:1) afforded catalyst **5-7b** (0.140 g, 77% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (t, *J* = 7.3 Hz, 2H), 7.40-7.33 (m, 5H), 7.32-7.28 (m, 3H), 5.97 (d, *J* = 8.8 Hz, 1H), 5.30 (d, *J* = 8.9 Hz, 1H), 4.30 (d, *J* = 6.3 Hz, 1H), 3.87-3.75 (m, 2H), 2.39 (dd, J_1 = 5.1 Hz, J_2 = 12.6 Hz, 1H), 2.17-2.12 (m, 1H), 1.68-1.61 (m, 1H), 1.45 (s, 9H), 1.10 (d, *J* = 6.3 Hz, 3H), 1.00 (s, 9H), 0.91-0.90 (m, 6H), 0.85 (s, 6H), 0.14 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 155.7, 138.9 (d), 137.4 (d), 132.7 (d), 128.6 (dd), 79.4, 68.5 (d), 63.1, 52.5 (d), 34.3 (d), 32.3 (d), 28.3, 26.8, 24.9, 21.5, 20.3 (t), 18.7 (t), -1.5, -2.3, -2.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ -23.7 (s); HRMS (ESI) m/z calcd for $C_{35}H_{58}N_2O_4PSi$ $[M+H]^+$ = 629.3829, found = 629.3840.

tert-Butyl (*S*)-1-((2*R*,3*S*)-1-(diphenylphosphino)-3-(triisopropylsilyloxy)butan-2-ylamino)-3,3-dimethyl-1-oxo-butan-2-ylcarbamate (**5-7c**)



3-15 **5-7c**

The catalyst **5-7c** was prepared from **5-15** in 51% yield, following the same procedure described for the preparation of **5-7b**.

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (t, *J* = 7.3 Hz, 2H), 7.39-7.31 (m, 5H), 7.29-7.28 (m, 3H), 5.97 (d, *J* = 8.9 Hz, 1H), 5.30 (d, *J* = 8.9 Hz, 1H), 4.44-4.40 (m, 1H), 3.90 (t, *J* = 7.3 Hz, 1H), 3.76 (d, *J* = 8.9 Hz, 1H), 2.40- 2.27 (m, 2H), 1.67 (m, 1H), 1.45 (s, 9H), 1.16 (d, *J* = 6.3 Hz, 3H), 1.06 (d, *J* = 7.6 Hz, 21H), 0.99 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 155.7, 137.8 (d), 132.9, 132.6 (d), 128.7, 128.5 (dd), 79.4, 68.6 (d), 63.0, 52.8 (d), 34.6, 31.8 (d), 28.3, 26.8, 21.3, 18.2 (d), 17.7, 12.6;

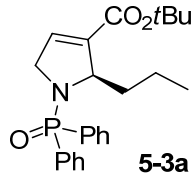
^{31}P NMR (121 MHz, $CDCl_3$) δ -23.2 (s); HRMS (ESI) m/z calcd for $C_{36}H_{60}N_2O_4PSi$ $[M+H]^+$ = 643.3986, found = 643.3999.

5.4.3 Representative Procedure for [3+2] Cycloadditions

To a flame-dried round bottle flask with a magnetic stirring bar was added **5-1a** (27.1 mg, 0.1 mmol), **5-7d** (3.6 mg, 0.005 mmol) and 5Å molecular sieves (60 mg) under N_2, followed by the addition of anhydrous Et_2O (1 mL). The reaction mixture was cooled to 0 ^oC in an ice-bath, allenoate **2** (22 μL, 0.15 mmol) was then added, and the mixture was stirred at 0 ^oC for 30 minutes. The reaction mixture was then filtered (to remove molecular sieves) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 10:1 to 2:1) to afford the cycloaddtion product **5-3a** (37.9 mg, 92% yield) as a colorless oil.

5.4.4 Analytical Data of [3+2] Adducts

(*R*)-*tert*-Butyl 1-(diphenylphosphoryl)-2-propyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-3a**)

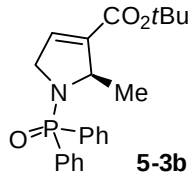


5-3a

A colorless oil; $[\alpha]^{26}_D$ = -23.8 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91-7.81 (m, 4H), 7.52-7.41 (m, 6H), 6.64 (s, 1H), 4.76 (s, 1H), 4.09-3.95 (m, 2 H), 1.61-1.55 (m, 1H), 1.48-1.38 (m, 10H), 1.43-1.27 (m, 1H), 1.18-1.12 (m, 1H), 0.79 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 137.8 (d), 137.1 (d), 132.4 (d), 132.2 (d), 132.0 (d), 131.8 (d), 128.5 (dd), 81.1, 64.2 (d), 53.8 (d), 36.6, 28.1, 16.6, 14.2; ^{31}P NMR (202 MHz, $CDCl_3$) δ 26.5 (s); HRMS (ESI) m/z calcd for

$C_{24}H_{30}NNaO_3P$ $[M+Na]^+$ = 434.1856, found = 434.1873; the ee value was 96%, t_R (major) = 16.1 min, t_R (minor) = 22.5 min (Chiralcel IA-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

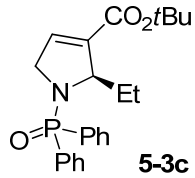
(*R*)-*tert*-Butyl 1-(diphenylphosphoryl)-2-methyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5 -3b**)



5-3b

A colorless oil; $[\alpha]^{26}_D$ = -3.8 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92-7.82 (m, 4H), 7.51-7.41 (m, 6H), 6.60 (s, 1H), 4.64-4.63 (m, 1H), 4.11-3.99 (m, 2 H), 1.45 (s, 9H), 1.17 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 139.8 (d), 136.2 (d), 132.4 (dd), 131.9 (d), 137.6 (d), 131.2 (d), 128.5 (dd), 81.1, 60.5 (d), 53.4 (d), 28.1 (d), 21.9 (d); ^{31}P NMR (202 MHz, $CDCl_3$) δ 25.9 (s); HRMS (ESI) m/z calcd for $C_{22}H_{27}NO_3P$ $[M+H]^+$ = 384.1723, found = 384.1739; the ee value was 95%, t_R (major) = 24.4 min, t_R (minor) = 30.1 min (Chiralcel IA-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*R*)-*tert*-Butyl 1-(diphenylphosphoryl)-2-ethyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-3c**)

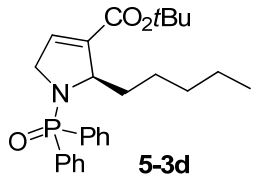


5-3c

A colorless oil; $[\alpha]^{26}_D$ = -22.5 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91-7.81 (m, 4H), 7.54-7.41 (m, 6H), 6.68 (s, 1H), 4.79-4.78 (m, 1H), 4.11-4.05 (m, 1 H), 4.01-3.95 (m, 1 H), 1.68-1.61 (m, 1 H), 1.60 (s, 9H), 1.45-1.32 (m, 1 H), 0.82 (t, *J* =

7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 137.5 (d), 137.1, 132.4 (d), 132.2 (d), 131.8 (d), 131.3, 128.5 (dd), 81.1, 64.9, 55.1 (d), 28.1, 27.0, 7.3; ^{31}P NMR (202 MHz, $CDCl_3$) δ 26.3 (s); HRMS (ESI) m/z calcd for $C_{23}H_{29}NO_3P$ $[M+H]^+$ = 398.1880, found = 398.1898; the ee value was 96%, t_R (major) = 24.5 min, t_R (minor) = 36.5 min (Chiralcel IA-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

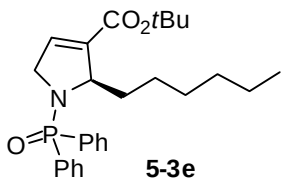
(*R*)-*tert*-Butyl 1-(diphenylphosphoryl)-2-pentyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **(5-3d)**



5-3d

A colorless oil; $[\alpha]^{26}_D$ = -100.3 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91-7.81 (m, 4H), 7.54-7.41 (m, 6H), 6.65 (s, 1H), 4.78 (d, *J* = 4.4 Hz, 1H), 4.11-4.01 (m, 1 H), 4.00-3.96 (m, 1 H), 1.63-1.57 (m, 1 H), 1.45 (s, 9H), 1.41-1.34 (m, 1 H), 1.26-1.20 (m, 3H), 1.17-1.11 (m, 3 H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 137.6 (d), 137.1 (d), 132.4 (d), 132.2 (d), 131.9 (d), 131.8 (d), 131.3, 128.5 (dd), 81.1, 64.3, 54.9 (d), 34.1, 31.8, 28.0, 22.6, 14.0; ^{31}P NMR (202 MHz, $CDCl_3$) δ 26.5 (s); HRMS (ESI) m/z calcd for $C_{26}H_{32}NNaO_3P$ $[M+Na]^+$ = 460.2012, found = 460.2022; the ee value was 97%, t_R (major) = 16.2 min, t_R (minor) = 20.8 min (Chiralcel IA-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

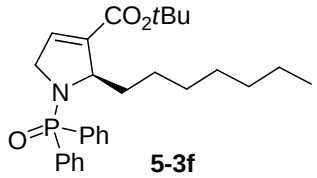
(*R*)-*tert*-Butyl 1-(diphenylphosphoryl)-2-hexyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate **(5-3e)**



5-3e

A colorless oil; $[\alpha]^{26}_D$ = -45.7 (c 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.91-7.81 (m, 4H), 7.54-7.41 (m, 6H), 6.65 (s, 1H), 4.78 (d, *J* = 4.4 Hz, 1H), 4.10-4.05 (m, 1 H), 4.01-3.95 (m, 1 H), 1.63-1.57 (m, 1 H), 1.49-1.45 (m, 10H), 1.39-1.35 (m, 1 H), 1.28-1.23 (m, 3H), 1.20-1.17 (m, 4 H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 137.8 (d), 137.1, 132.4, 132.2 (d), 131.8 (d), 131.4, 128.5 (dd), 81.0, 64.3, 54.9 (d), 34.2, 31.7, 29.3, 28.1, 23.1, 22.5, 14.0; ^{31}P NMR (202 MHz, $CDCl_3$) δ 26.5 (s); HRMS (ESI) m/z calcd for $C_{27}H_{37}NO_3P$ $[M+H]^+$ = 454.2506, found = 454.2515; the ee value was 97%, t_R (major) = 42.4 min, t_R (minor) = 53.5 min (Chiralcel IA-H, λ = 254 nm, 3% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

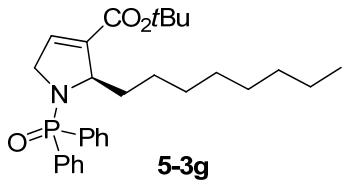
(*R*)-*tert*-Butyl 1-(diphenylphosphoryl)-2-heptyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-3f**)



5-3f

A colorless oil; $[\alpha]^{26}_D$ = -46.6 (c 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.91-7.81 (m, 4H), 7.52-7.41 (m, 6H), 6.65 (s, 1H), 4.78 (d, *J* = 4.4 Hz, 1H), 4.11-4.01 (m, 1 H), 4.00-3.95 (m, 1 H), 1.63-1.45 (m, 1 H), 1.39 (s, 9H), 1.38-1.34 (m, 1H), 1.29-1.25 (m, 4 H), 1.22-1.10 (m, 6H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 137.8 (d), 137.1 (d), 132.4 (d), 132.2 (d), 131.9 (d), 131.7, 131.5 (d), 128.5 (dd), 81.0, 64.4, 54.9 (d), 34.3, 31.8, 29.6, 29.1, 28.1, 23.2, 22.6, 14.0; ^{31}P NMR (202 MHz, $CDCl_3$) δ 26.5 (s); HRMS (ESI) m/z calcd for $C_{28}H_{39}NO_3P$ $[M+H]^+$ = 468.2662, found = 468.2676; the ee value was 97%, t_R (major) = 12.7 min, t_R (minor) = 16.1 min (Chiralcel IA-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

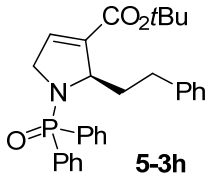
(*R*)-*tert*-Butyl 1-(diphenylphosphoryl)-2-octyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-3g**)



5-3g

A colorless oil; $[\alpha]^{26}_{D}$ = -44.2 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91-7.81 (m, 4H), 7.53-7.41 (m, 6H), 6.65 (s, 1H), 4.78 (d, *J* = 4.4 Hz, 1H), 4.11-4.05 (m, 1 H), 4.01-3.95 (m, 1 H), 1.62-1.46 (m, 1 H), 1.39 (s, 9H), 1.39-1.34 (m, 1H), 1.29-1.10 (m, 12H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 137.9 (d), 137.3 (d), 132.5 (d), 132.2 (d), 131.8 (d), 131.5, 131.5 (d), 128.5 (dd), 81.0, 64.4, 54.9 (d), 34.3, 31.9, 29.7, 29.5, 28.1, 23.2, 22.6, 14.0; ^{31}P NMR (202 MHz, $CDCl_3$) δ 26.4 (s); HRMS (ESI) m/z calcd for $C_{29}H_{41}NO_3P$ $[M+H]^+$ = 482.2819, found = 482.2832; the ee value was 96%, t_R (major) = 12.1 min, t_R (minor) = 15.1 min (Chiralcel IA-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*R*)-*tert*-Butyl 1-(diphenylphosphoryl)-2-phenethyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-3h**)

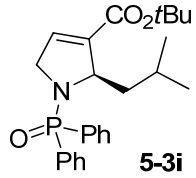


5-3h

A colorless oil; $[\alpha]^{26}_{D}$ = -69.7 (c 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90-7.85 (m, 4H), 7.53-7.43 (m, 6H), 7.25-7.23 (m, 2), 7.17-7.10 (m, 3H), 6.73 (s, 1H), 4.88 (d, *J* = 4.4 Hz, 1H), 4.16-4.02 (m, 2H), 2.77-2.71 (m, 1 H), 2.46-2.40 (m, 1 H), 1.98-1.91 (m, 1 H), 1.67-1.64 (m, 1 H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 142.3, 137.6, 137.3, 132.4 (d), 132.3 (d), 132.2, 131.9 (d), 131.2, 128.5 (dd),

125.6, 81.3, 64.3, 55.0 (d), 36.3, 29.8, 28.1; ^{31}P NMR (202 MHz, $CDCl_3$) δ 26.3 (s); HRMS (ESI) m/z calcd for $C_{29}H_{32}NNaO_3P$ $[M+Na]^+$ = 496.2012, found = 496.2031; the ee value was 95%, t_R (major) = 25.9 min, t_R (minor) = 36.1 min (Chiralcel IA-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

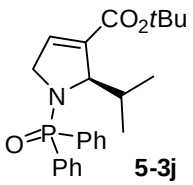
(*R*)-*tert*-Butyl 1-(diphenylphosphoryl)-2-isobutyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-3i**)



5-3i

A colorless oil; $[\alpha]^{26}_D$ = -35.8 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89-7.79 (m, 4H), 7.51-7.39 (m, 6H), 6.61 (s, 1H), 4.74-4.70 (m, 1H), 4.07-3.97 (m, 2 H), 1.67-1.61 (m, 1H), 1.59 (s, 9H), 1.44-1.23 (m, 2H), 0.69 (d, *J* = 6.4 Hz, 3H), 0.66 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 139.5 (d), 137.1 (d), 136.8 (d), 132.5 (d), 132.2 (d), 132.1, 131.8 (d), 131.7 (d), 128.5 (dd), 81.0, 63.2 (d), 53.9 (d), 44.0 (d), 28.0, 24.1, 23.3 (d); ^{31}P NMR (202 MHz, $CDCl_3$) δ 27.0 (s); HRMS (ESI) m/z calcd for $C_{25}H_{33}NO_3P$ $[M+H]^+$ = 426.2193, found = 426.2183; the ee value was 95%, t_R (major) = 18.7 min, t_R (minor) = 28.3 min (Chiralcel IA-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

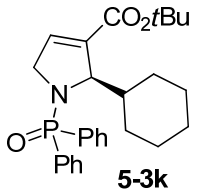
(*R*)-*tert*-Butyl 1-(diphenylphosphoryl)-2-isopropyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-3j**)



5-3j

A colorless oil; $[\alpha]^{26}_D$ = -51.3 (c 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.86-7.77 (m, 4H), 7.53-7.41 (m, 6H), 6.67 (d, *J* = 1.3 Hz, 1H), 4.71-4.68 (m, 1H), 4.05-3.90 (m, 2 H), 1.92-1.86 (m, 1H), 1.47 (s, 9H), 0.77 (d, *J* = 7.0 Hz, 3H), 0.73 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 138.0, 137.6, 132.5 (d), 132.2 (d), 131.9, 131.8 (d), 131.7 (d), 131.4, 131.2, 128.5 (dd), 81.1, 69.2, 55.2 (d), 34.6 (d), 28.0, 18.1 (d); ^{31}P NMR (202 MHz, $CDCl_3$) δ 28.1 (s); HRMS (ESI) m/z calcd for $C_{24}H_{31}NO_3P$ $[M+H]^+$ = 412.2036, found = 412.2044; the ee value was 99%, t_R (major) = 20.1 min, t_R (minor) = 33.1 min (Chiralcel IA-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

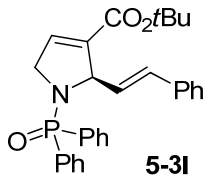
(*R*)-*tert*-Butyl 2-cyclohexyl-1-(diphenylphosphoryl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-3k**)



5-3k

A colorless oil; $[\alpha]^{26}_D$ = -43.3 (c 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.87-7.77 (m, 4H), 7.54-7.41 (m, 6H), 6.63 (d, *J* = 1.3 Hz, 1H), 4.63 (d, *J* = 5.1 Hz, 1H), 4.04-4.00 (m, 1 H), 3.99-3.89 (m, 1 H), 1.66-1.59 (m, 4H), 1.57-1.47 (m, 13H), 1.40-1.33 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 138.0 (d), 137.2 (d), 132.5 (d), 132.2 (d), 131.9 (d), 131.8 (d), 131.7 (d), 131.4, 131.2, 128.5 (dd), 81.1, 68.8, 55.1 (d), 45.1 (d), 28.8 (d), 28.1, 26.7, 26.5 (d); ^{31}P NMR (202 MHz, $CDCl_3$) δ 28.2 (s); HRMS (ESI) m/z calcd for $C_{27}H_{35}NO_3P$ $[M+H]^+$ = 452.2349, found = 452.2362; the ee value was 99%, t_R (major) = 22.0 min, t_R (minor) = 36.5 min (Chiralcel IA-H, λ = 254 nm, 5% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

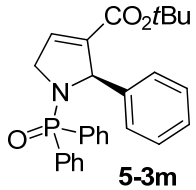
(*R*,*E*)-*tert*-Butyl 1-(diphenylphosphoryl)-2-styryl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-3l**)



5-3l

A colorless oil; $[\alpha]^{26}_{D}$ = -212.7 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92-7.85 (m, 4H), 7.51-7.36 (m, 6H), 7.27-7.15 (m, 5H), 6.73 (s, 1H), 5.99-5.94 (m, 1H), 5.82-5.79 (m, 1H), 5.09-5.06 (m, 1H), 4.20-4.17 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 137.4 (d), 137.0 (d), 136.7, 132.7 (d), 132.4 (d), 132.0, 131.9 (d), 131.8 (d), 131.6, 131.4, 131.2, 130.6, 128.5 (dd), 128.2 (d), 127.4, 126.5, 81.2, 67.0, 53.5 (d), 28.0; ^{31}P NMR (202 MHz, $CDCl_3$) δ 26.3 (s); HRMS (ESI) m/z calcd for $C_{29}H_{31}NO_3P$ $[M+H]^+$ = 472.2036, found = 472.2047; the ee value was 96%, t_R (major) = 14.7 min, t_R (minor) = 17.7 min (Chiralcel IC-H, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*R*)-*tert*-Butyl 1-(diphenylphosphoryl)-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-3m**)

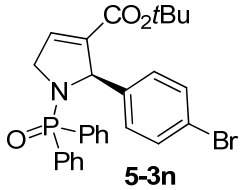


5-3m

A colorless oil; $[\alpha]^{26}_{D}$ = -117.6 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82-7.78 (m, 2H), 7.56-7.52 (m, 2H), 7.48-7.33 (m, 4H), 7.19-7.15 (m, 2H), 7.12-7.05 (m, 3H), 6.81-6.79 (m, 3H), 5.48-5.45 (m, 1H), 4.39-4.32 (m, 1H), 4.28-4.22 (m, 1H), 1.22 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 142.5 (d), 139.0 (d), 136.3 (d), 132.4 (d), 132.2 (d), 131.9 (d), 131.8 (d), 131.5 (d), 131.0, 130.0, 128.5 (dd), 128.0

(d), 127.7, 127.5, 127.0, 81.2, 68.3 (d), 54.6 (d), 27.8; ^{31}P NMR (202 MHz, $CDCl_3$) δ 27.1 (s); HRMS (ESI) m/z calcd for $C_{27}H_{29}NO_3P$ $[M+H]^+$ = 446.1880, found = 446.1865; the ee value was 95%, t_R (minor) = 45.4 min, t_R (major) = 82.6 min (Chiralcel IC-H, λ = 254 nm, 15% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

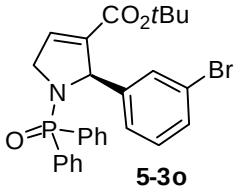
(*R*)-*tert*-Butyl 2-(4-bromophenyl)-1-(diphenylphosphoryl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-3n**)



5-3n

A colorless oil; $[\alpha]^{26}_D$ = -175.9 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82-7.79 (m, 2H), 7.57-7.48 (m, 3H), 7.44-7.37 (m, 3H), 7.24-7.19 (m, 4H), 6.80 (s, 1H), 6.70 (t, *J* = 4.1 Hz, 2H), 5.46-5.43 (m, 1H), 4.38-4.31 (m, 1H), 4.27-4.21 (m, 1H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 141.8, 138.5 (d), 136.7 (d), 132.4 (dd), 132.1 (d), 131.9, 131.8 (d), 131.1 (d), 130.9 (d), 129.2, 128.5 (dd), 121.0, 81.5, 67.7 (d), 54.6 (d), 27.9; ^{31}P NMR (202 MHz, $CDCl_3$) δ 26.9 (s); HRMS (ESI) m/z calcd for $C_{27}H_{28}NO_3P^{81}Br$ $[M+H]^+$ = 526.0964, found = 526.0970; the ee value was 95%, t_R (major) = 28.4 min, t_R (minor) = 40.2 min (Chiralcel IC-H, λ = 254 nm, 15% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

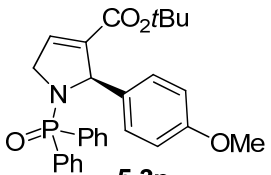
(*R*)-*tert*-Butyl 2-(3-bromophenyl)-1-(diphenylphosphoryl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-3o**)



5-3o

A colorless oil; $[\alpha]^{26}_D$ = -83.4 (c 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.83-7.79 (m, 2H), 7.57-7.49 (m, 3H), 7.45-7.39 (m, 3H), 7.25-7.21 (m, 3H), 7.00 (t, *J* = 7.9 Hz, 1H), 6.87-6.83 (m, 2H), 6.74 (t, *J* = 1.9 Hz, 1H), 5.43-5.39 (m, 1H), 4.39-4.33 (m, 1H), 4.28-4.22 (m, 1H), 1.24 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 144.9, 138.4 (d), 136.7 (d), 137.0 (d), 132.4 (d), 132.1 (d), 131.9 (d), 131.8, 130.8 (d), 130.7, 130.1, 129.9, 129.4, 128.7 (d), 128.1 (d), 125.9, 121.6, 81.5, 67.8 (d), 54.6 (d), 27.8; ^{31}P NMR (202 MHz, $CDCl_3$) δ 26.9 (s); HRMS (ESI) m/z calcd for $C_{27}H_{28}NO_3P^{79}Br$ $[M+H]^+$ = 524.0985, found = 524.0972; $C_{27}H_{28}NO_3P^{81}Br$ $[M+H]^+$ = 526.0964, found = 526.0954; the ee value was 96%, t_R (major) = 35.6 min, t_R (minor) = 40.9 min (Chiralcel IC-H, λ = 254 nm, 15% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

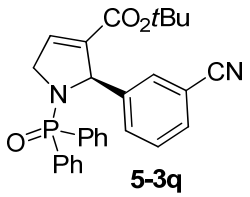
(*R*)-*tert*-Butyl 1-(diphenylphosphoryl)-2-(4-methoxyphenyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-3p**)



5-3p

A colorless oil; $[\alpha]^{26}_D$ = -136.0 (c 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.81-7.77 (m, 2H), 7.58-7.45 (m, 2H), 7.42-7.34 (m, 4H), 7.23-7.19 (m, 2H), 6.76 (s, 1H), 6.72-6.70 (m, 2H), 6.62-6.60 (m, 2H), 5.44-5.41 (m, 1H), 4.35-4.29 (m, 1H), 4.26-4.20 (m, 1H), 3.75 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 158.7, 139.0 (d), 136.0 (d), 134.7 (d), 132.4 (d), 132.3 (d), 131.9 (d), 131.5 (d), 131.2 (d), 130.2, 128.5 (dd), 127.9, 113.0, 81.1, 67.8 (d), 55.2, 54.3 (d), 27.8; ^{31}P NMR (202 MHz, $CDCl_3$) δ 26.8 (s); HRMS (ESI) m/z calcd for $C_{28}H_{31}NO_4P$ $[M+H]^+$ = 476.1985, found = 476.1989; the ee value was 98%, t_R (minor) = 82.2 min, t_R (major) = 85.9 min (Chiralcel IC-H, λ = 254 nm, 3% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

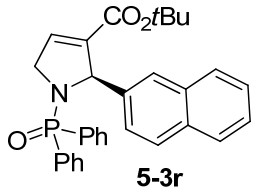
(*R*)-*tert*-Butyl 2-(4-cyanophenyl)-1-(diphenylphosphoryl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-3q**)



5-3q

A colorless oil; $[\alpha]^{26}_{D}$ = -116.3 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81-7.77 (m, 2H), 7.57-7.51 (m, 3H), 7.46-7.40 (m, 4H), 7.26-7.16 (m, 4H), 6.95 (s, 1H), 6.85 (s, 1H), 5.53-5.49 (m, 1H), 4.39-4.26 (m, 2H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 144.3, 137.8 (d), 137.4 (d), 132.3 (d), 132.2 (d), 131.9 (d), 131.8, 131.4, 131.2, 131.0, 130.7, 130.3, 130.0, 128.6 (dd), 128.2, 118.6, 111.7, 81.7, 67.6 (d), 54.8, 27.8; ^{31}P NMR (202 MHz, $CDCl_3$) δ 26.8 (s); HRMS (ESI) m/z calcd for $C_{28}H_{28}N_2O_3P$ $[M+H]^+$ = 471.1832, found = 471.1839; the ee value was 93%, t_R (major) = 26.7 min, t_R (minor) = 40.9 min (Chiralcel IC-H, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*R*)-*tert*-Butyl 1-(diphenylphosphoryl)-2-(naphthalen-2-yl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-3r**)

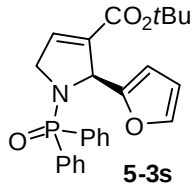


5-3r

A colorless oil; $[\alpha]^{26}_{D}$ = -127.1 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81-7.79 (m, 3H), 7.78-7.52 (m, 1H), 7.68-7.36 (m, 8H), 7.27-7.24 (m, 1H), 7.16-7.14 (m, 1H), 7.07-7.03 (m, 2H), 6.96 (s, 1H), 6.87 (s, 1H), 5.65-5.62 (m, 1H), 4.46-4.42 (m, 1H), 4.41-4.30 (m, 1H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5, 139.5 (d),

138.7 (d), 136.6 (d), 132.7 (d), 132.4 (d), 132.3, 132.1, 131.9 (d), 131.6 (d), 130.0 (d), 128.5 (d), 128.0, 127.9 (d), 127.5 (d), 127.4, 126.9, 125.6 (d), 124.9, 81.2, 68.5 (d), 54.6 (d), 27.8; ^{31}P NMR (202 MHz, $CDCl_3$) δ 27.1 (s); HRMS (ESI) m/z calcd for $C_{31}H_{31}NO_3P$ $[M+H]^+$ = 496.2036, found = 496.2051; the ee value was 96%, t_R (minor) = 21.5 min, t_R (major) = 30.0 min (Chiralcel IC-H, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

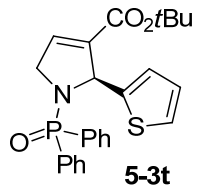
(*S*)-*tert*-Butyl 1-(diphenylphosphoryl)-2-(furan-2-yl)-2,5-dihydro-1*H*-pyrrole-3-carbo-xylate (**5-3s**)



5-3s

A colorless oil; $[\alpha]^{26}_D$ = -99.4 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84-7.80 (m, 2H), 7.66-7.61 (m, 2H), 7.50-7.47 (m, 1H), 7.44-7.40 (m, 3H), 7.32-7.28 (m, 2H), 7.21 (d, *J* = 1.3 Hz, 1H), 6.81 (s, 1H), 6.11-6.10 (m, 1H), 5.63-5.59 (m, 2H), 4.22-4.19 (m, 1H), 1.30 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 153.5 (d), 141.3, 137.7 (d), 135.8 (d), 132.3 (dd), 131.9 (d), 131.6 (d), 131.2, 130.5, 128.6 (d), 128.1 (d), 110.2, 107.4, 81.2, 60.9 (d), 54.2 (d), 27.8; ^{31}P NMR (202 MHz, $CDCl_3$) δ 26.8 (s); HRMS (ESI) m/z calcd for $C_{25}H_{27}NO_4P$ $[M+H]^+$ = 436.1672, found = 436.1678; the ee value was 94%, t_R (minor) = 27.4 min, t_R (major) = 59.9 min (Chiralcel IC-H, λ = 254 nm, 20% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*S*)-*tert*-Butyl 1-(diphenylphosphoryl)-2-(thiophen-2-yl)-2,5-dihydro-1*H*-pyrrole-3-carbo- xylate (**5-3t**)

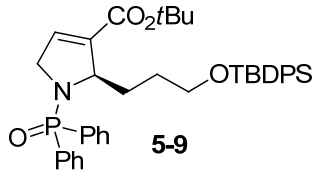


5-3t

A colorless oil; $[\alpha]^{26}_D$ = -106.8 (c 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.90-7.86 (m, 2H), 7.67-7.62 (m, 2H), 7.51-7.43 (m, 4H), 7.40-7.23 (m, 2H), 7.10 (d, *J* = 5.1 Hz, 1H), 6.75 (s, 1H), 6.66-6.65 (m, 1H), 6.26 (d, *J* = 3.2, 1H), 5.85-5.81 (m, 1H), 4.32-4.16 (m, 2H), 1.30 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 146.5 (d), 137.7 (d), 138.6 (d), 136.5 (d), 132.4 (d), 132.3 (d), 131.2 (d), 130.0 (d), 131.6 (d), 131.0 (d), 130.0, 128.6 (d), 128.1 (d), 126.0, 125.4, 124.3, 81.3, 63.2 (d), 53.7 (d), 27.8; ^{31}P NMR (202 MHz, $CDCl_3$) δ 27.5 (s); HRMS (ESI) m/z calcd for $C_{25}H_{27}NO_3PS$ $[M+H]^+$ = 452.1444, found = 452.1449; the ee value was 95%, t_R (minor) = 31.8 min, t_R (major) = 53.5 min (Chiralcel IC-H, λ = 254 nm, 20% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

5.4.5 A Formal Synthesis of (+)-Trachelanthamidine

(*R*)-*tert*-Butyl 2-(3-(tert-butyldiphenylsilyloxy)propyl)-1-(diphenylphosphoryl)-2,5-dihy- 1*H*-pyrrole-3-carboxylate (**5-11**)



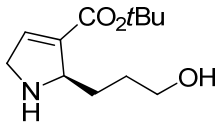
5-9

The cyclization product **5-9** (0.164 g, 82%) was prepared from imine **5-8** (0.158 g, 0.3 mmol) and allene **5-2** (63 μL, 0.45 mmol), following the representative procedure described for the [3+2] annulation reaction.

A colorless oil; $[\alpha]^{26}_D$ = -38.4 (c 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.90-7.78 (m, 4H), 7.66-7.51 (m, 4H), 7.48-7.35 (m, 12H), 6.66 (s, 1H), 4.81 (s, 1H), 4.13-

4.08 (m, 1H), 3.95-3.89 (m, 1H), 3.57 (t, *J* = 5.7 Hz, 2H), 1.73-1.69 (m, 2H), 1.44 (s, 9H), 1.31-1.26 (m, 2H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 137.5, 135.5, 134.0 (d), 132.4 (d), 132.3 (d), 132.2, 132.0, 131.8, 131.3, 131.0, 129.5, 128.6 (d), 128.4 (d), 127.5 (d), 81.1, 64.2, 63.9, 54.8 (d), 30.7, 28.0, 26.9, 26.5, 19.2; ^{31}P NMR (202 MHz, $CDCl_3$) δ 27.1 (s); HRMS (ESI) m/z calcd for $C_{40}H_{49}NO_4PSi$ $[M+H]^+$ = 666.3163, found = 666.3180; the ee value was 96%, t_R (minor) = 26.2 min, t_R (major) = 27.7 min (Chiralcel IB-H, λ = 254 nm, 3% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

(*R*)-*tert*-Butyl 2-(3-hydroxypropyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-10**)[130,131]



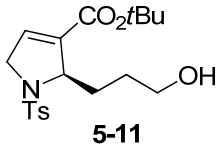
5-10

To a solution of **5-9** (0.164 g, 0.25 mmol) in CH_2Cl_2 (2 mL) at 0 °C were added successively MeOH (2 mL) and $BF_3{\cdot}OEt_2$ (0.55 mL, 2.5 mmol). The mixture was stirred at 0 °C for 30 min and then at room temperature for 4 h. The aqueous layer was then separated, and the pH of which was adjusted to around 10 by with the addition of aqueous K_2CO_3. The aqueous layer was extracted with CH_2Cl_2 several times (3 x 8 mL), and the combined organic extracts were washed with brine, and dried over Na_2SO_4. Purification by column chromatography (hexane: ethyl acetate = 2: 1) afforded **5-10** (56.7 mg, 76%) as a colorless oil.

$[\alpha]^{26}_D$ = +12.3 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.73 (d, *J* = 1.9 Hz, 1H), 4.19 (s, 1H), 3.86-3.82 (m, 4H), 3.65-3.55 (m, 2H), 1.97-1.92 (m, 1H), 1.71-1.64 (m, 3H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 139.6, 80.9, 63.9, 62.6,

52.1, 32.1, 29.1, 28.1; HRMS (ESI) m/z calcd for $C_{12}H_{22}NO_3$ $[M+H]^+$ = 228.1525, found = 228.1541.

(*R*)-*tert*-Butyl 2-(3-hydroxypropyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-11**)



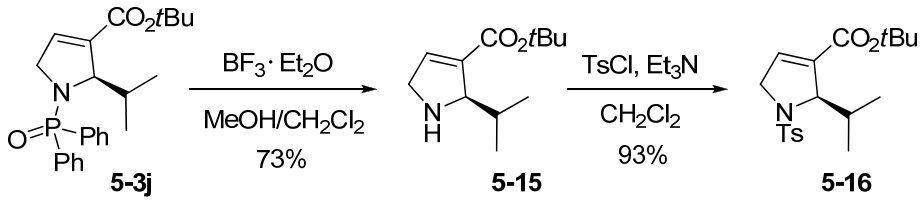
5-11

To a solution of **5-10** (30 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (3 mL) at 0 ^oC was added triethylamine (22 μL, 0.16 mmol), followed by a slow addition of TsCl (25.2 mg, 0.13 mmol) in CH_2Cl_2 (0.5 mL) under N_2. The resulting mixture was stirred at 0 ^oC for 2 hrs. The reaction was then quenched by the addition of H_2O (5 mL), and the mixture was extracted with CH_2Cl_2 (3 × 8 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and purified by column chromatography (hexane: ethyl acetate = 2 : 1) to afford **5-11** (45.1 mg, 91%) as a white solid.

$[\alpha]^{26}_D$ = -119.3 (c 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 7.6 Hz, 2H), 6.46 (d, *J* = 1.3 Hz, 1H), 4.78 (d, *J* = 3.8 Hz, 1H), 4.20 (t, *J* = 2.5 Hz, 2H), 3.65 (t, *J* = 6.0 Hz, 2H), 2.41 (s, 3H), 2.07-2.00 (m, 1H), 1.72-1.50 (m, 3H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5, 143.7, 136.3, 135.4, 134.4, 129.8, 127.4, 81.7, 65.7, 62.7, 55.1, 30.0, 28.0, 27.0, 21.5; HRMS (ESI) m/z calcd for $C_{19}H_{27}NNaO_5S$ $[M+Na]^+$ = 404.1502, found = 404.1508.

5.4.6 Determination of Absolute Configurations of [3+2] Cycloaddition Adducts

5.4.6.1 Determination of Absolute Configurations of [3+2] Cyclization Adducts from Aliphatic DPP Imines



(*R*)-*tert*-Butyl 2-isopropyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**5-15**)

Compound **5-15** (30.8 mg, 73%) was prepared from **5-3j** (0.082 g, 0.2 mmol), following the procedure described for the preparation of **5-10**.

$[\alpha]^{26}_{D}$ = -27.0 (c 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78-6.76 (m, 1H), 4.17 (d, *J* = 2.5 Hz, 1H), 3.84 (t, *J* = 3.5 Hz, 2H), 2.24-2.18 (m, 2H), 1.51 (s, 9H), 1.00 (d, *J* = 6.3 Hz, 3H), 0.79 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 140.1, 138.5, 80.5, 69.3, 53.9, 30.9, 28.1, 20.3, 15.4; HRMS (ESI) m/z calcd for $C_{12}H_{22}NO_2$ $[M+H]^+$ = 212.2576, found = 212.2568.

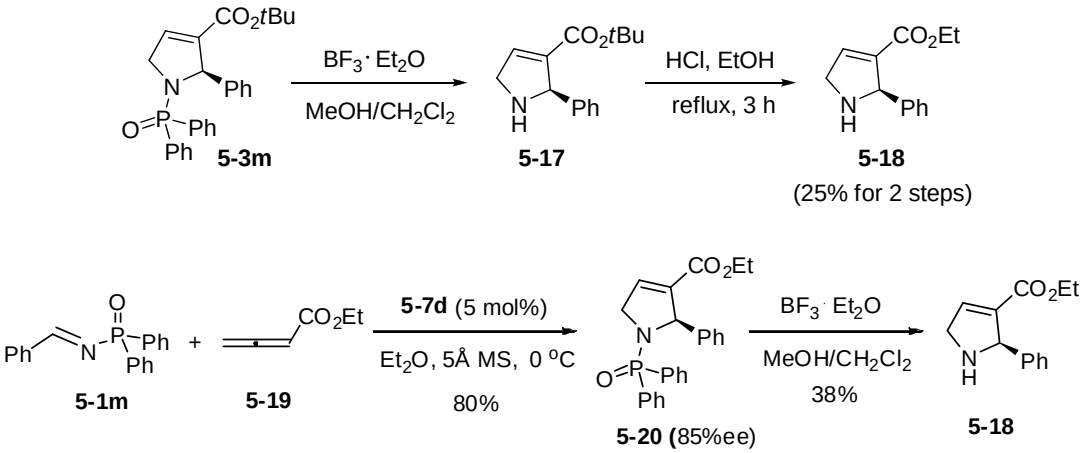
(*R*)-*tert*-Butyl 2-isopropyl-1-tosyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-16**)

Compound **5-16** (34.3 mg, 93%) was prepared from **5-15** (0.021 g, 0.1 mmol), following the procedure described for the preparation of **5-11**.

$[\alpha]^{26}_{D}$ = -165.1 (c 1.00, $CHCl_3$), (lit.[6] $[\alpha]_D$ = +105.6 (c 0.63, $CHCl_3$)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 7.6 Hz, 2H), 6.38 (s, 1H), 4.68 (t, *J* = 3.4 Hz, 1H), 4.21-4.17 (m, 1H), 4.09-4.04 (m, 1H), 2.40 (s, H), 2.17-2.10 (m, 1H), 1.42 (s, 9H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 61.9, 143.5, 137.1, 135.6, 134.7, 129.6, 127.5, 81.4, 71.5, 65.8, 33.2, 21.5, 19.3, 17.2; HRMS (ESI) m/z calcd for $C_{19}H_{28}NO_4S$ $[M+H]^+$ = 366.1734, found = 366.1741.

The absolute configuration of **5-3j** was determined as *R*, by comparing the optical rotation of **5-16** with the value reported in the literature.[131] The absolute configurations of other [3+2] products derived from aliphatic DPP imines were assigned by analogy.

5.4.6.2 Determination of Absolute Configurations of [3+2] Cyclization Adducts Derived from Aromatic DPP Imines



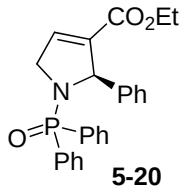
(*R*)-Ethyl 2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-18**)

Compound **5-17** was prepared from **5-3m** (0.15 g, 0.34 mmol), following the procedure described for the preparation of **5-10**. After quickly passing through column, the crude **5-3m** was used directly in the next step.

Compound **5-3m** from the previous step was dissolved in EtOH (3 mL), treated with aqueous HCl (0.6 mL, 12 N), and the mixture was heated to reflux for 3 h. The solvent was then removed, and the residue was diluted with water (4 mL). The aqueous mixture was extracted with EtOAc, the pH was adjusted to 10 with aqueous NaOH solution. The combined extracts were concentrated and further dired over the pump to afford **5-18**[127] (22 mg, 63%) as a colorless oil.

$[\alpha]^{26}_D$ = -65.3 (c 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, D_2O) δ 7.42-7.31 (m, 5H), 7.16 (d, *J* = 1.9 Hz, 1H), 5.30-5.29 (m, 1H), 4.12-4.04 (m, 3H), 3.99-3.95 (m, 1H), 1.10 (t, *J* = 7.3 Hz, 3H); HRMS (ESI) m/z calcd for $C_{13}H_{16}NO_2$ $[M+H]^+$ = 218.1176, found = 218.1178.

(*R*)-Ethyl 1-(diphenylphosphoryl)-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**5-20**)



5-20

The compound **5-20** (67 mg, 80%) was prepared from imine **5-1m** (0.061 g, 0.2 mmol) and allene **5-19** (33 μL, 0.3 mmol), following the representative procedure described for the [3+2] annulation reaction.

A colorless oil; $[\alpha]^{26}_D$ = -136.4 (c 1.00, $CHCl_3$) (lit.[7]: $[\alpha]_D$ = +161 (c 0.94, $CHCl_3$)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82-7.77 (m, 2H), 7.57-7.53 (m, 2H), 7.45 (t, *J* = 3.8 Hz, 1H), 7.41-7.34 (m, 3H), 7.20-7.12 (m, 2H), 7.11-7.09 (m, 3H), 6.86-6.85 (m, 3H), 5.53-5.49 (m, 1H), 4.44-4.37 (m, 1H), 4.34-4.28 (m, 1H), 4.06-3.93 (m, 2H), 1.08 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 142.4 (d), 137.6 (d), 137.0 (d), 132.4 (d), 132.0, 131.9 (d), 131.6 (d), 130.9, 130.0, 128.6 (d), 128.1 (d), 127.8, 127.4, 127.2, 68.4 (d), 60.5, 54.7 (d), 13.9; ^{31}P NMR (202 MHz, $CDCl_3$) δ 27.2 (s); HRMS (ESI) m/z calcd for $C_{25}H_{25}NO_3P$ $[M+H]^+$ = 418.1567, found = 418.1574; the ee value was 85%, t_R (minor) = 39.1 min, t_R (major) = 69.2 min (Chiralcel IC-H, λ = 254 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

The absolute configuration of **5-20** was was determined as *R*, by comparing its optical rotation with the value reported in the literature.[50] Compound **5-20** was deprotected to afford **5-18** (a colorless oil, $[\alpha]^{26}_{D}$ = -52.6 (c 0.6, $CHCl_3$)), which had same configuration as that was prepared from **5-3m**. Thus, the configuration of **5-3m** was assigned as *R*, and the absolute configurations of other [3+2] products derived from aromatic DPP imines were assigned by analogy.

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