ASYMMETRIC ORGANOCATALYTIC CONJUGATE ADDITIONS WITH VINYL SULFONES

ZHU QIANG

NATIONAL UNIVERSITY OF SINGAPORE

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ZHU QIANG

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Summary

This thesis studies the direct asymmetric organocatalytic conjugate additions to vinyl sulfones. Various nucleophiles were studied as donors in the conjugate addition reactions, and six chapters are covered.

Chapter 1 reviews recent development in asymmetric organocatalysis, and some selected important organocatalysts are illustrated. In particular, the development of asymmetric conjugate addition reactions via enamine activation or hydrogen-bonding catalysis in the past ten years has been described.

Chapter 2 describes prolinol silyl ether as an efficient organocatalyst for the asymmetric conjugate additions of aldehydes to vinyl sulfones. High yields and nearly perfect enantioselectivities were obtained.

Chapter 3 presents the asymmetric conjugate reaction of ketones to vinyl sulfone mediated by cinchonidine-derived primary amine catalyst. The reactions between ketones and vinyl sulfone proceeded in good yields and with excellent enantioselectivities. To illustrate synthetic utility, the conjugate adduct was converted to sodium cyclamate.

Chapter 4 depicts the conjugate addition of branched aldehydes to vinyl sulfone with creation of quaternary carbon centers. Natural primary amine catalysts derived from L-serine and L-threonine were designed, synthesized and investigated as novel organocatalysts in the above asymmetric conjugate additions.

Chapter 5 discloses the conjugate addition of nitroalkanes to vinyl sulfone

mediated by quinidine-derived thiourea catalyst. Up to 87% yield and 86% ee were obtained for the reaction. In order to illustrate the synthetic value of the reaction, the conjugate adduct was used to synthesize (*R*)-3-ethyl-1,2,3,4-tetrahydroisoquinoline.

Chapter 6 studies the conjugate addition of 3-aryl-oxindoles to vinyl sulfone mediated by quinidine-derived thiourea catalyst to generate quaternary carbon centers, and good yields and high enantioselectivities were obtained for these reactions. However, 3-alkyl-oxindoles were not applicable. New multi-hydrogen bonding catalysts containing primary amino acids were designed and synthesized from *epi*-cinchonidine-derived primary amine. With the newly developed catalysts, conjugate addition of 3-alkyl-oxindoles to vinyl sulfone could proceed in good yields and with high enantioselectivities.

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List of Abbreviations

^{o}C	degrees Celsius
Ac	acetyl
Ar	aromatic group
Boc	*tert*-butoxycarbonyl
Bn	benzyl
br	broad
CAM	ceric ammonium molybdate
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
C-C bond	carbon-carbon bond
DCM	dichloromethane
DMAP	dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
d	doublet
dr	diastereomeric ratio
EA	ethyl acetate
ee	enantiomeric excesses
ESI	electrospray ionisation
Et	ethyl

h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectra
IPA	isopropanol
LUMO	lowest unoccupied molecular orbital
m	*meta*
m	multiplet
m/z	mass-to-charge ratio
mmol	millimole
Me	methyl
MP	melting point
mL	milliliter
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*
PTC	phase-transfer catalysis
q	quartet
rac	*racemic*
rt	room temperature
s	singlet
TBAF	*tetra*-butyl ammonium fluoride

TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilane
t	triplet
t_R	retention time (HPLC)
Ts	toluenesulfonyl
ts	transition state

List of Publications & Awards

Journal Articles:

1. Qiang Zhu, and Yixin Lu*. "Organocatalytic Michael Addition of Aldehydes to Vinyl Sulfones: Enantioselective α-alkylations of Aldehydes and Their Derivatives". *Org. Lett.* **2008**, *10*, 4803-4806 (one of the most read articles in November 2008).

2. Qiang Zhu, Lili Cheng, and Yixin Lu*. "Asymmetric Michael addition of ketones to vinyl sulfone". *Chem. Commun*. **2008**, 6315-6317.

3. Qiang Zhu, and Yixin Lu*. "Enantioselective Conjugate Addition of Nitroalkanes to Vinyl Sulfone: an Organocatalytic Access to Chiral Amines". *Org. Lett*. **2009**, *11*, 1721-1724 (highlighted in *SYNFACTS* **2009**, 683).

4. Qiang Zhu, and Yixin Lu*. "Chiral Amine-Mediated Asymmetric Conjugate Additions to Vinyl Sulfones". *Aust. J. Chem*. **2009**, *62*, 951-955 (invited paper for a UQ-NUS special issue of AJC).

5. Qiang Zhu, and Yixin Lu*. "Chiral primary amine mediated conjugate addition of branched aldehydes to vinyl sulfone: asymmetric generation of quaternary carbon centers". *Chem. Commun.* **2010**, 2235-2237.

6. Qiang Zhu, and Yixin Lu*. "Stereocontrolled Generation of Quaternary Stereocent-centers by Organocatalytic Conjugate Addition of Oxindoles to Vinyl Sulfone". *Angew. Chem., Int. Ed.*, **2010**, 49, 7753-7756.

7. Qiang Zhu, and Yixin Lu*. "Facile Synthesis of Bicyclic Amidines and Imidazolines from 1,2-Diamines". *Org. Lett*. **2010**, *12*, 4156-4158.

Conferences & Posters:

1. Qiang, Zhu. "Development of Asymmetric Organocatalytic Synthetic Methods based on Vinyl Sulfones", **Poster Presentation**, *1st SG-HK Bilateral Graduate Student Congress*, Singapore, May 26-30, **2009**.

2. Qiang, Zhu. "Asymmetric Conjugate Additions with Vinyl Sulfones Catalyzed by Small Chiral Molecules", **Oral Presentation**, *1st SG-HK Bilateral Graduate Student Congress,* Singapore, May 26-30, **2009**.

3. Qiang, Zhu. "Enantioselective Conjugate Additions With Vinyl Sulfones", **Oral Presentation**, *6th Singapore International Chemical Conference* (*SICC-6*), Singapore, December 17-20, **2009**.

4. Qiang, Zhu. "Asymmetric Organocatalytic Conjugate Additions With Vinyl Sulfones", **Oral Presentation**, *Workshop on chemical science and engineering for young chemists and mechanical engineers in National University of Singapore*, Singapore, January 29, **2010**.

5. Qiang, Zhu. "Asymmetric Organocatalytic Michael Additions With Vinyl Sulfones", **Poster Presentation**, *The 6th Asian European Symposium*, Singapore, May 06-10, **2010**.

Awards:

1. **Best Teaching Assistance Award** (CM 3291) from Department of Chemistry, Faculty of Science, National University of Singapore, **2008**.

2. **Best Poster Presentation Award** for the *1st SG-HK Bilateral Graduate Congress,* Singapore, **2009**.

Chapter 1 Introduction

1.1 Molecular Chirality

Molecular chirality (handedness) plays an important role in human life. Precise molecular recognition between enzymes, receptors, other natural binding sites and different chiral molecules exists in most of the biological and physical functions. Consequently, molecular chirality is a major concern in modern pharmaceutical industry.[1] Much effort has to be put in the studies of the properties of both enantiomers of a racemic drug because the two stereoisomers may have unique pharmacological activities, as well as display different pharmacokinetic and pharmacodynamic effects,[2,3] as the body is extremely chiral-selective and interacts with each enantiomer of a racemic drug differently. Thus, one isomer could generate the desired therapeutic activities, while the other one might be less efficient or, in the worst cases, produces obvious side effects. Therefore, an important task for synthetic chemists is to find more efficient methods to synthesize optically pure compounds.

1.2 Asymmetric Catalysis

Traditionally, optically pure compounds were obtained either by resolving a racemic mixture of the two enantiomers, or by chemical transformation of an enantiomerically enriched precursor, which was directly or indirectly derived from

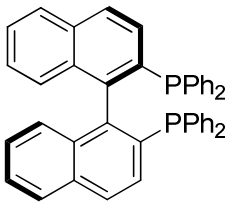
nature's chiral pool. However, potentially severe drawbacks were associated with both approaches. The former in typically yielded only up to 50% of the desired enantiomer and the latter required stoichiometric amounts of a suitable precursor. Asymmetric catalysis is arguably the best way to synthesize optically pure compounds,[4-6] which involves a catalytic amount of transition metal complexes, enzymes, or small chiral organic molecules binding temporarily to starting materials and induce chirality in the final products. In general, asymmetric catalysis includes enzymatic catalysis, metal-based catalysis and organic catalysis.

1.2.1 Enzymatic Catalysis and Metal-Based Catalysis

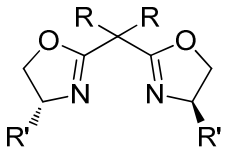
Optically pure compounds are produced in nature by chirality transfer from enzymic catalysts. In such processes, enzymes exhibit extraordinary degrees of stereoselectivity and displays remarkable substrate specificity, allowing for very high level of selectivities. However, enzymes have specific environmental conditions at which they will function best due to their sensitivities to acid, base and temperature.

Metal-based catalysis began predominantly in 1980 and progressed remarkably due to the contributions made by Sharpless,[7-10] Noyori,[11-15] and Jacobsen.[16] For example, with the combination of Ruthenium(II) and BINAP **1-1** (Scheme 1-1) developed by Noyori,[11] hydrogenation of many unsaturated substrates (C=C or C=O double bonds) proceeded in good yields and with high enantioselectivities. In this field, different chiral ligands were developed and several representative ligands are

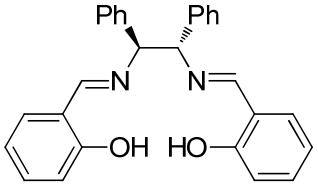
shown in Scheme 1-1.[17-20]



1-1
(R)-BINAP



1-2



1-3

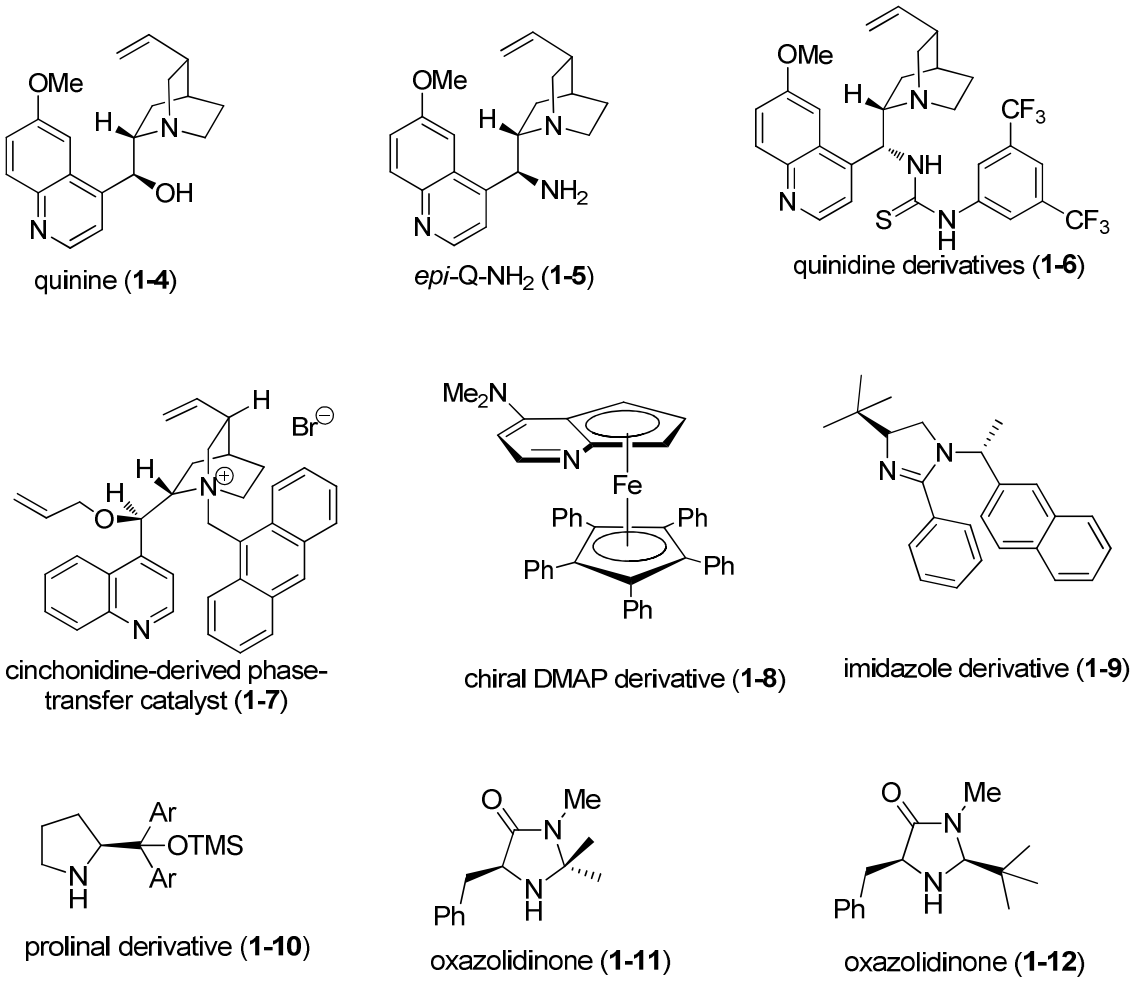
Scheme 1-1 Representative chiral ligands used in transition metal-based catalysis

Obviously, metal-based catalysis is an important approach to access optically pure compounds. With the combination of chiral ligands and metals, good selectivity on a range of reactions can be achieved. However, metal-based catalysis suffers from potentially severe drawbacks, such as: toxic and expensive transition metals involved and stringent reaction conditions (e.g. anhydrous and inert).

1.2.2 Organic Catalysis

In contrary to metal-based catalysis, organic catalysis only relies on chiral small molecules and no metals are involved in the catalytic process. Although some progresses were made in the first half of the 20th century,[21-26] considerably less attention had been paid to this approach. In the early 2000s, The groups of Denmark,[27-30] Jacobsen,[31-33] List,[34-39] MacMillan,[40-42] and Maruoka[43-47] developed different organocatalysts to mediate various types of reactions. These catalysts can be classified into several kinds, including cinchona alkaloid derivatives,[48-51] DMAP

derivatives,[52,53] imidazole derivatives,[54,55] proline derivatives,[56] thiourea derivatives,[57-59] and phase- transfer catalysts.[60] Some selective organocatalysts are shown in Scheme 1-2.



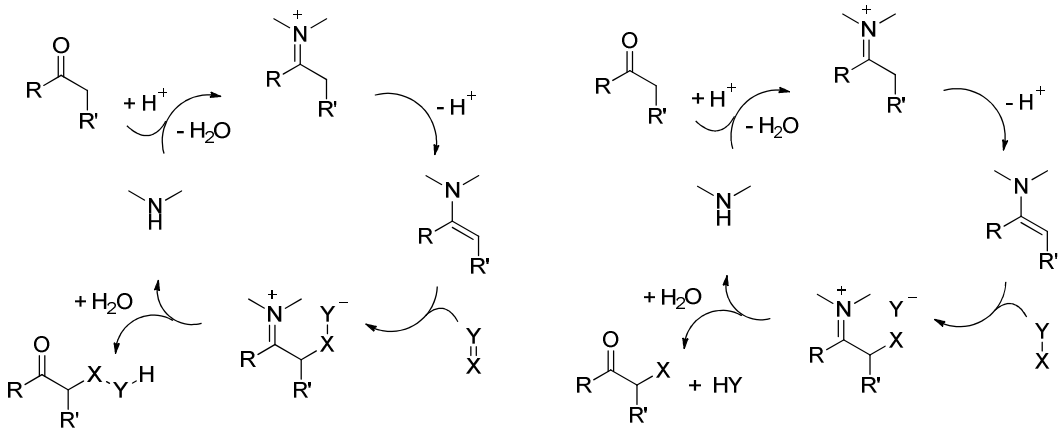
Scheme 1-2 Selected typical chiral catalysts used in organic catalysis

Organic catalysts show some notable advantages: they are usually robust, inexpensive, easy to prepare, and non-toxic. Additionally, most of the organocatalyzed reactions are not sensitive to moisture and oxygen. All these properties make organic catalysts suitable for industrial applications.

1.3 Asymmetric Aminocatalysis

1.3.1 Secondary Amine-Mediated Enamine and Iminium Catalysis

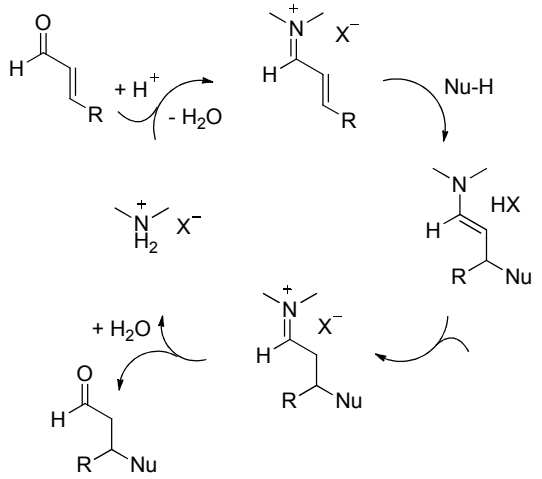
The use of chiral secondary amines as catalysts for the generation of enamine or iminium intermediates has resulted in a huge number of asymmetric processes that directly transform aldehydes and ketones into useful functionalized molecules.[61] Molecules such as amino acids, peptides, alkaloids, and synthetic amine-containing compounds, are frequently used in amine catalysis to promote various asymmetric reactions. Generally, nucleophiles are activated through the enamine intermediates (enamine catalysis) or electrophiles are activated via the iminium ion formation (iminium catalysis).



Scheme 1-3 Enamine catalysis of nucleophilic addition (left) and substitution reaction (right)

The catalytic cycle of enamine catalysis[62] is shown in Scheme 1-3. The enamine intermediate, which is formed from a secondary amine and a carbonyl compound, can react with an electrophile X=Y, such as aldehyde,[63] imine,[64] azodicarboxylate,[65,66]

nitrosobenzene,[67] electron-withdrawing-alkene[68] or alkyl halides (X-Y)[69-71] to give an α-modified iminium ion intermediate. After hydrolysis, the α-modified carbonyl product (and HY) is finally generated.

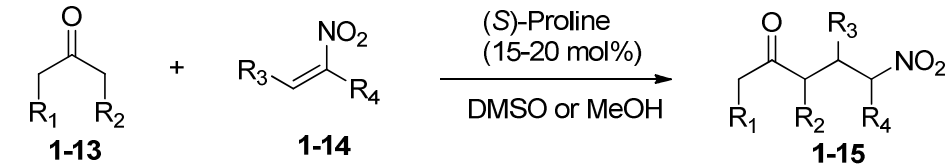


Scheme 1-4 Iminium catalysis of conjugate addition

Following the first asymmetric organocatalytic Diels-Alder reaction via iminium intermediate reported by MacMillan in 2000,[72-74] iminium catalysis has become a flourishing research area. A catalytic cycle involving an iminium intermediate is shown in Scheme1-4. The iminium intermediate resulted from α,β-unsaturated aldehyde and a secondary amine function reacts with a nucleophile to give an enamine intermediate, the hydrolysis of which then generates the desired product. In iminium catalysis, different types of organocatalytic reactions involving the activation of α,β-unsaturated aldehydes were reported, such as 1,3-dipolar cycloadditions,[75] and conjugate addition[76] catalyzed by chiral amino acid-derived imidazolidinones **1-12**. Other types of reactions, such as epoxidations,[77] cyclopropanations,[78] and conjugate reductions[79,80] were also explored.

1.3.2 Asymmetric Conjugate Addition Catalyzed by Proline and Its Derivatives

Conjugate addition represents one of the most important methods for the C-C bond formation. Although the combination of ligands and transition-metals has been successfully applied to catalyze various conjugate additions, only recently using small molecules as chiral induction has attracted much attention.[81-83] The use of chiral secondary amines has resulted in development of plenty of conjugate additions. The pioneering work of introducing enamines, prepared from pyrrolidine and ketones, in conjugate additions was reported by Stork.[84] Subsequently, enamines as nucleophiles in conjugate additions were described by Seebach,[85-87] and Yamada.[88,89]

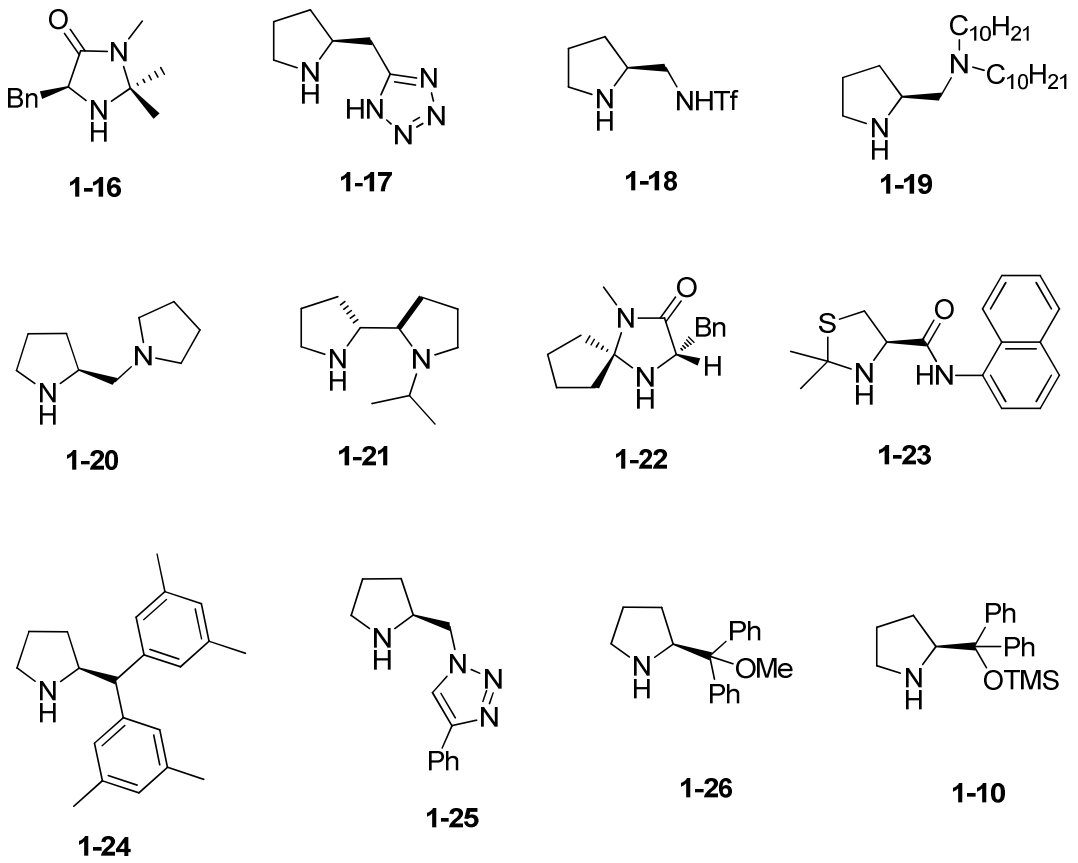


Scheme 1-5 L-Proline-catalyzed conjugate addition of ketones to nitrostyrenes

Prepared enamines were frequently used in conjugate additions, but chemical equivalent of chiral amines had to be used.[84-89] In 2001, List investigated the first asymmetric enamine-catalyzed conjugate addition of ketones to nitroolefins (Scheme 1-5).[90,91] Catalytic amounts of L-proline were used to mediate the reaction in good yields and in moderate enantioselectivities. Subsequently, Barbas,[92] Enders,[93] Toma,[94] and Salunkhe[95] revisited the reaction. They used L-proline for the reactions in polar

solvents and ionic liquids to achieve higher yields and better enantioselectivities.

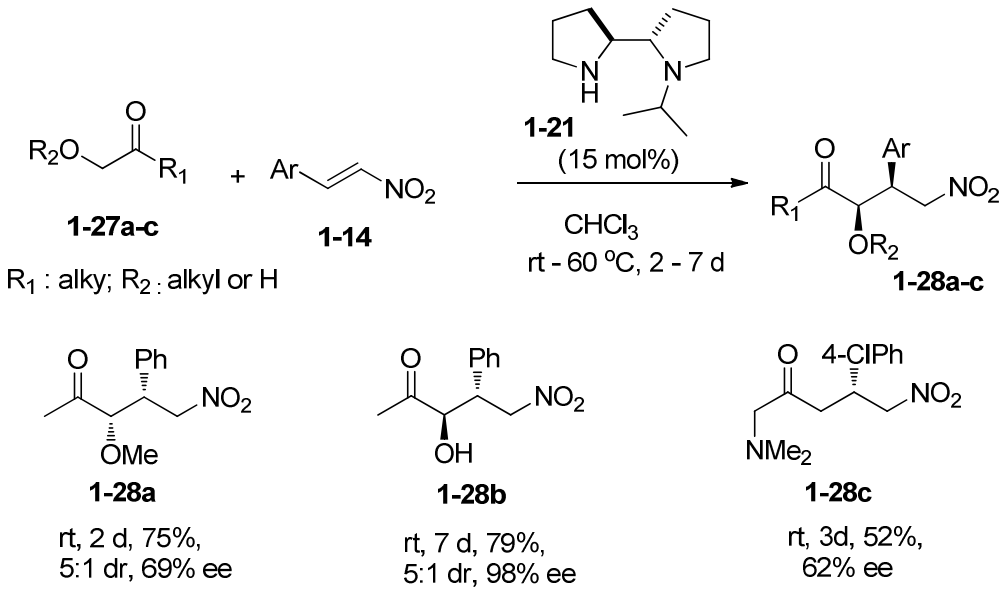
Although good results associated with L-proline were obtained, some problems still remained unsolved, such as limited solvent compatibility, high catalyst loading, long reaction time and low stereoselectivities. In order to solve these problems, Alexakis,[96-99] Barbas,[100] Wang,[101-103] Hayashi and Jørgensen,[105-107] and other groups[104] developed various structurally diverse proline analogs. Some selected examples are shown in Scheme 1-6.



Scheme 1-6 Selected L-proline derivatives used in asymmetric conjugate addition

The catalytic activities of L-proline-derived secondary amines in the conjugate additions may be improved either by introducing another hydrogen bonding site or by

increasing the steric hindrance of the catalyst. For example, secondary amine **1-21** developed by Alexakis was used to catalyze the asymmetric conjugate addition of hydroxyl acetone to nitroolefines (Scheme 1-7).[96-99] *Syn*-isomer was obtained with α-methoxyacetone used as a donor, but unexpected *anti*-isomer was obtained when α-hydroxyacetone was used. It was believed that an additional hydrogen bond between the hydroxyl group of the substrate and the tertiary amine of the catalyst leaded to the *cis*- instead of the *trans*-enamine (TS-A and TS-B in Figure 1-1).



Scheme 1-7 Secondary amine **1-21**-catalyzed conjugate addition of acyclic ketones to nitroolefines

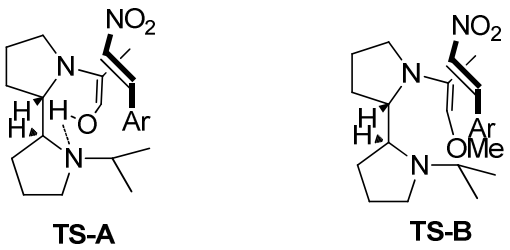
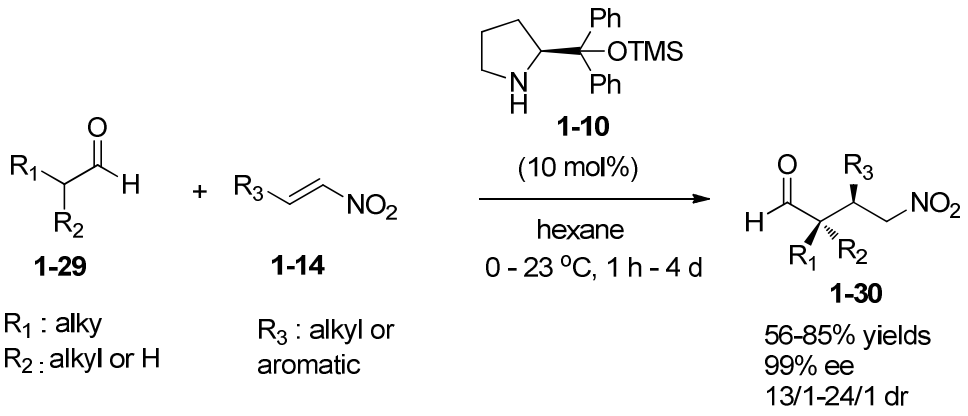


Figure 1-1 Proposed transition state for the asymmetric conjugate addition mediated by bipyrrolidine

Another interesting example was the secondary amine **1-18** containing sulfonamide function developed by Wang.[101-103] The catalyst was efficient for the addition of aldehydes and ketones to nitrostyrenes, affording the desired adducts in good dr's and with high enantioselectivities. It was also proposed that in the transition states for the rate-limiting C-C bond forming steps, the preferential *E*-enamines of both aldehydes and ketones would be added to the less hindered face of a nitroolefin.



Scheme 1-8 Asymmetric conjugate addition of aldehydes to nitrostyrenes mediated by prolinol silyl ether

Catalyst **1-10**, independently developed by Hayashi and Jørgensen,[105-107] was used to catalyze the conjugate additions of aldehydes to nitrostyrenes with good dr's and with high enantioselectivities (Scheme 1-8). For the outcome of stereochemistry, an acyclic synclinal transition state was proposed (Figure 1-2). The catalytic results rely on electrostatic interactions between the nitrogen of the enamine and the nitro group.[108] Selective formation of the *anti*-enamine of the bulky diphenylsiloxymethyl group could efficiently shield the re-face of the enamine intermediate.

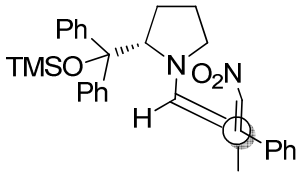
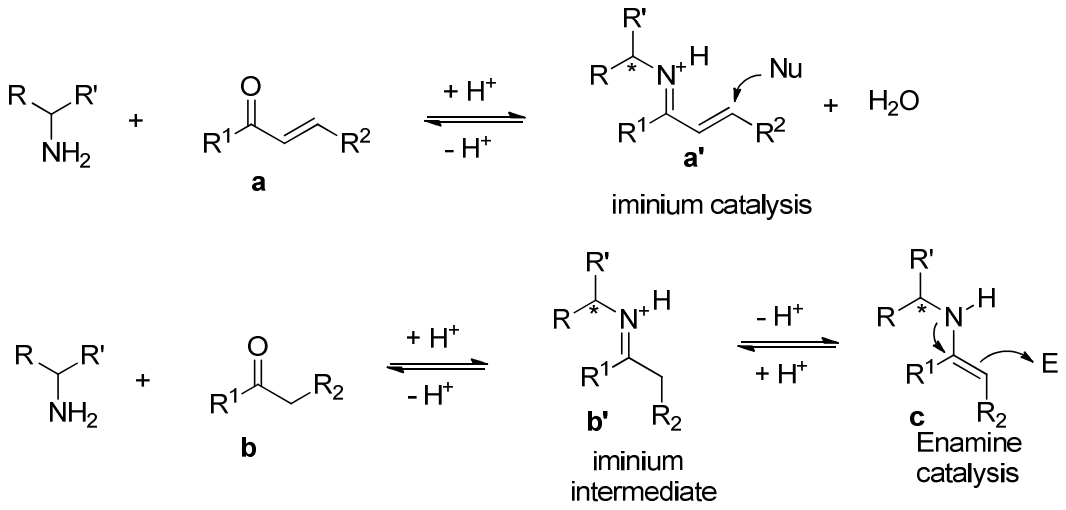


Figure 1-2 Transition state for the conjugate addition catalyzed by prolinol silyl ether

1.3.3 Primary Amine-Induced Enamine and Iminium Catalysis

The use of L-proline and its structurally derived catalysts undoubtedly aroused interest in the asymmetric aminocatalysis via enamine and iminium intermediates. However, the importance of primary amine catalysts has received less attention. In 2000, primary amino acids, such as phenylalanine and valine, were used in asymmetric aldol reaction leading to products with low yields.[109] These discouraging results limited the development of primary amine-based catalysts in asymmetric synthesis. Actually, primary amines are also good catalysts for asymmetric reactions.

The mechanism of primary amine-based catalysis is shown in Scheme 1-9. The primary amine catalyst reacts with α,β-unsaturated ketone to generate the iminium intermediate **a'** which is much more electrophilic than **a**. Another reaction pathway is also shown in Scheme 1-9. The primary amine reacts with the carbonyl compound **b** to generate iminium intermediate **b'** which can be converted into more nucleophilic enamine **c** easily. Compared with secondary amine catalysis, the presence of extra hydrogen on the N-H group facilitates the effective formation of the active catalytic intermediate, especially for ketones. Additionally, the N-H group helps to control the stereoselectivity of the reaction, which is not observed in pyrrolidine-based catalysis.



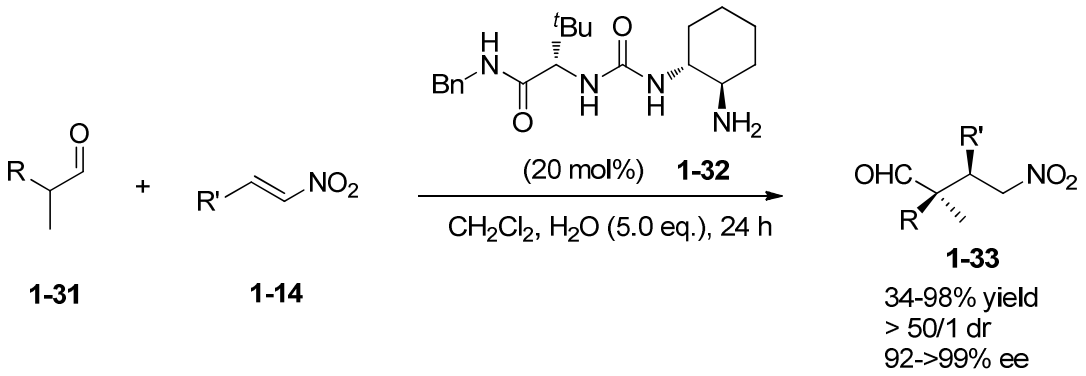
Scheme 1-9 Primary amines in iminium and enamine catalysis

The early example of application of primary amines in asymmetric reactions was reported by Pizzarello and Weber.[110] They discovered that primary amino acids, such as alanine and isovaline could catalyze the aldol reaction in water effectively. Subsequently, the simple primary amino acids and simple peptides were reported as catalysts in aldol reactions by Amedjkouh,[111] Córdova,[112] and Tsogoeva.[113] Since than, various primary amines have been developed and successfully used in asymmetric reactions. In the following section, the conjugate additions catalyzed by primary amines via enamine intermediates will be reviewed.[114]

1.3.4 Asymmetric Conjugate Addition Catalyzed by Primary Amines

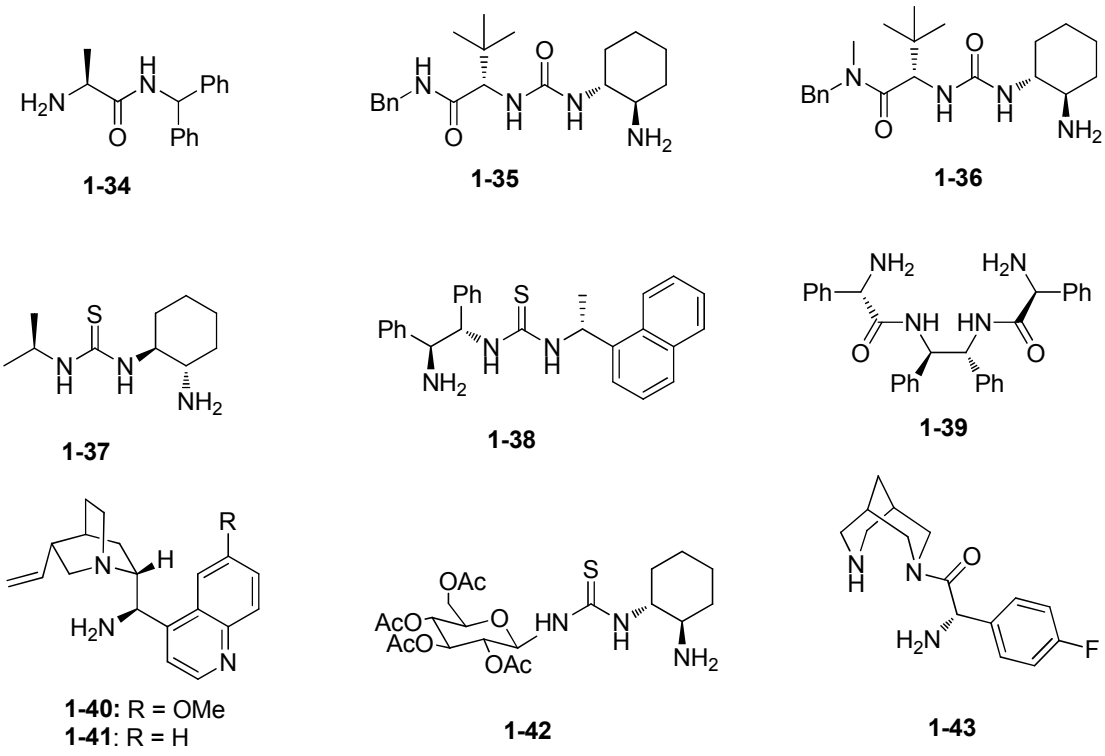
In 2006, Jacobsen reported the primary amine-thiourea **1-32** as a bifunctional catalyst for the conjugate addition of α,α-disubstituted aldehydes **1-31** to nitrostyrenes **1-14** (Scheme 1-10).[115] Excellent diastereoselectivities (up to > 50:1 dr) and high

enantioselectivities (up to 99% ee) were obtained. They also hypothesized that the stereocontrol was attributed to the simultaneous activation of nucleophiles via the enamine intermediates and electrophiles through the hydrogen bonding interaction between the thiourea function and the nitro moiety.



Scheme 1-10 Conjugate addition of aldehydes mediated by primary amine-thiourea

Subsequently, different primary amines have been developed to mediate the conjugate addition of aldehydes and ketones to different electrophiles. Some selected catalysts used in conjugate addition are shown in Scheme 1-11. For example, 9-amino derivative of cinchona alkaloid **1-41** developed by McCooey and Connon, was used to catalyze the conjugate addition of aldehydes to nitroolefins.[116] High yield and excellent enantioselectivity were attainable. With the same catalyst, Chen also reported the conjugate addition of aromatic ketones to alkylidenemalononitriles with moderate enantioselectivities.[117]



Scheme 1-11 Chiral primary amines used in asymmetric conjugate addition

1.4 Hydrogen-bond Containing Organocatalysts

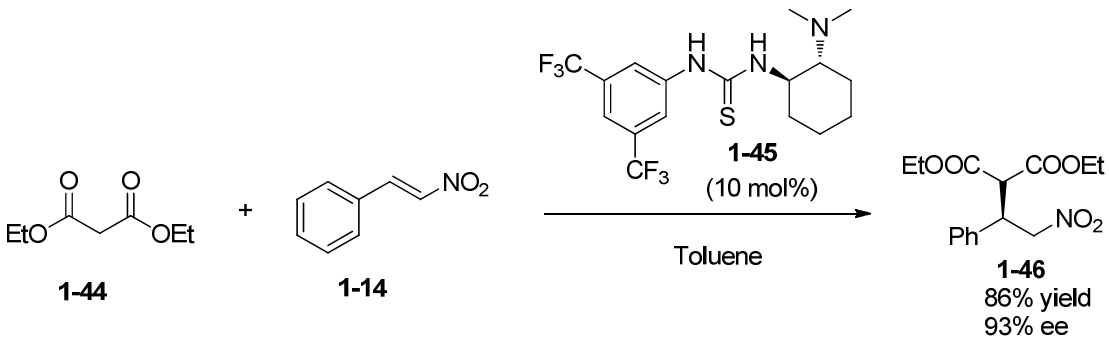
1.4.1 Introduction

Small-molecules containing chiral hydrogen-bonding donors as active centers have emerged as an active frontier of research of asymmetric catalysis. One of the earliest examples was reported by Wynberg in 1981.[118] They described that natural cinchona alkaloids catalyzed the enantioselective conjugate addition of substituted thiophenol to α,β-unsaturated ketones with moderate enantioselectivities. Subsequently, Inoue presented that diketopiperazine cyclo(L-phenylalanine-L-histidine) catalyzed effectively the hydrocyanation of benzaldehydes.[119] In 1984, Merck researchers reported the alkylation of indanone nucleophiles proceeding well

with chiral N-alkyl cinchona alkaloid derivatives.[120] Since then, there have been less and less reports on the application of chiral small molecules in hydrogen bonding catalysis. In 1998, Jacobsen reported highly enantioselective hydrocyanation of imines catalyzed by a thiourea catalyst derived from chiral cyclohexane-1,2-diamine with up to 91% ee.[121,122] In the following decade, the asymmetric catalysis via hydrogen bonding activation has become a flourishing area.[123-133] In this section, the development of the conjugate addition catalyzed by thiourea-based bifunctional catalysts will be reviewed.

1.4.2 Thiourea-Based Bifunctional Catalysts Used in Conjugate Additions

Among most hydrogen-bonding catalysts,[123-133] thiourea-based bifunctional organocatalysts definitely represent one of the most important classes.[134-139] The first example was introduced by Takemoto in 2003 (Scheme 1-12).[140,141] It was shown that conjugate addition of malonate esters **1-44** to nitroolefins **1-14** mediated by tertiary amine-thiourea **1-45** yielded adduct **1-46** in 86% yield and with up to 93% ee.



Scheme 1-12 Conjugate addition catalyzed by tertiary amine-containing thiourea

They also proposed the activation mode for the conjugate addition (Fig. 1-3).[141b] Bidentate hydrogen-bonding interaction between the nitro group and the thiourea function enhanced the electrophilic character of the reacting carbon centre. Another hydrogen-bonding interaction between the tertiary amine and the malonate in the activated enol form helped stabilize the transition state.

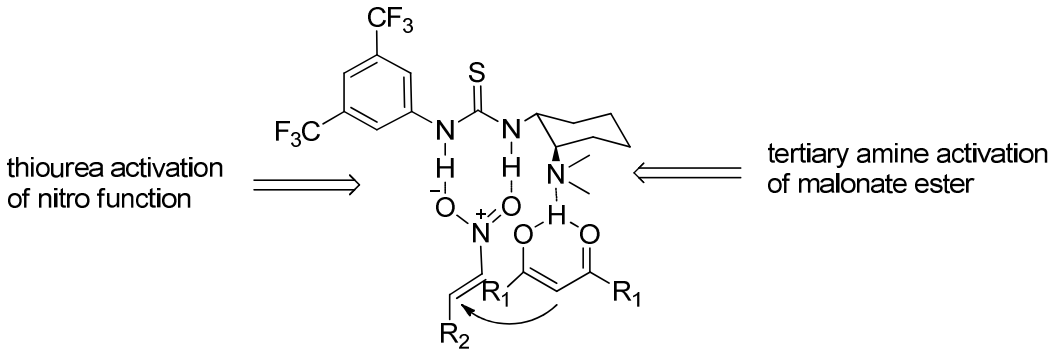
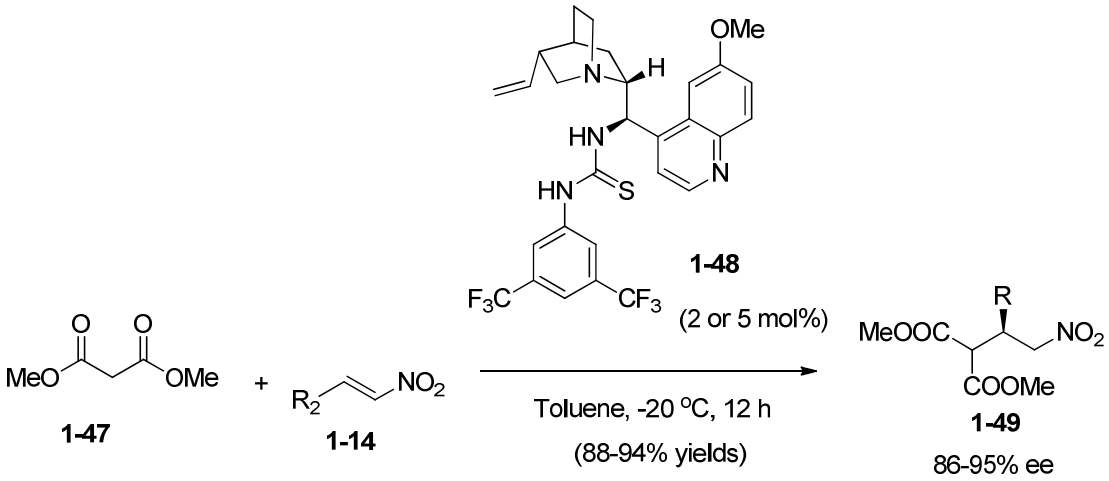


Figure 1-3 H-bonding interaction between thiourea-containing bifunctional catalyst and nitrostyrene

Based on tertiary amine-thiourea **1-45**, many types of reactions were reported including asymmetric conjugate addition of γ,δ-unsaturated β-ketoesters to nitro olefins,[142] aza-Henry reactions,[143] and other related reactions.[144,145]

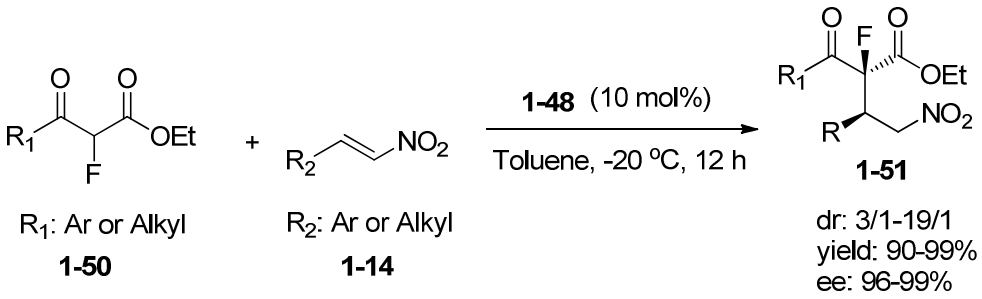
Subsequently, H-bonding donor catalyst **1-48** obtained by derivatizing the C-9 hydroxy group of cinchona alkaloids with a thiourea moiety was developed by Soós, Connon, and Dixon.[146-148] The presence of thiourea function and its relative stereochemistry at C-8/C-9 in bifunctional thiourea catalyst **1-48** were shown to be essential for asymmetric conjugate addition of malonate **1-47** to nitro-alkenes **1-14** (Scheme 1-13).[146,147,149] Interestingly, the analogous C-9 quinine-derived thiourea proved to be less enantioselective and reactive than **1-48**. The catalyst **1-48** was

remarkably active and could be used in loadings as low as 0.5 mol % without compromising the efficiency or selectivity of the transformations.



Scheme 1-13 Conjugate additions catalyzed by thiourea-cinchona alkaloid catalyst

In 2009, our group also demonstrated to use the bifunctional thiourea catalyst **1-48** to mediate the asymmetric conjugate addition of fluorinated ketoesters **1-50** to nitro-alkenes **1-14** (Scheme 1-14).[150] The reaction scope was very broad. When the aromatic or aliphatic substituted donors and acceptors were employed, good yields, high dr's and excellent enantioselectivities were attained in all cases.



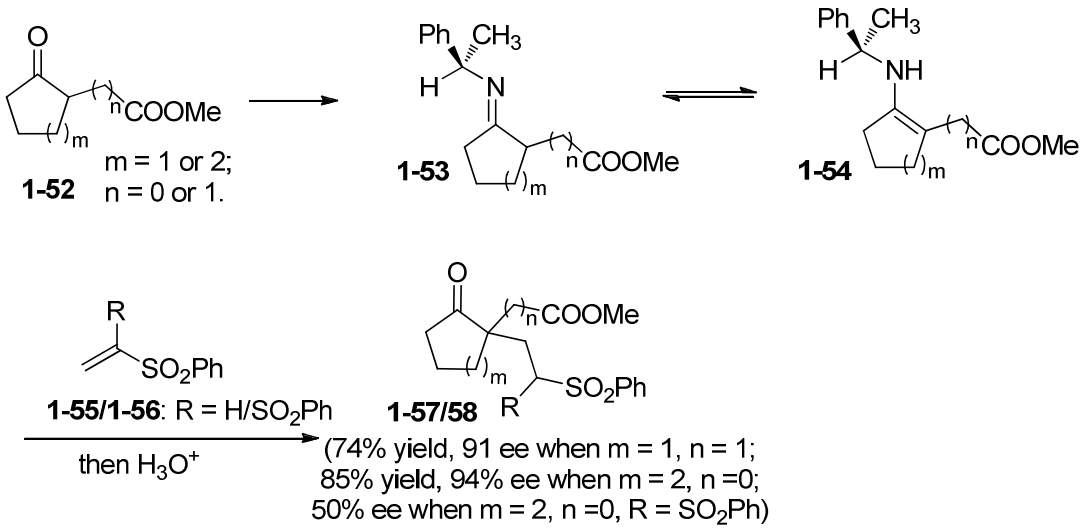
Scheme 1-14 Asymmetric conjugate addition with fluorinated ketoesters catalyzed thiourea-cinchona alkaloid catalyst

In the past few years, various reactions catalyzed by cinchona alkaloid-derived thiourea **1-48** were reported, including cyclization,[151] Friedel-Crafts addition,[152,153] conjugate additions,[154] and other reactions.[155-158] Exploration of new bifunctional thiourea catalysts in the conjugate additions was also reported.[159-168]

1.5 Asymmetric Conjugate Adddition to Vinyl Sulfones

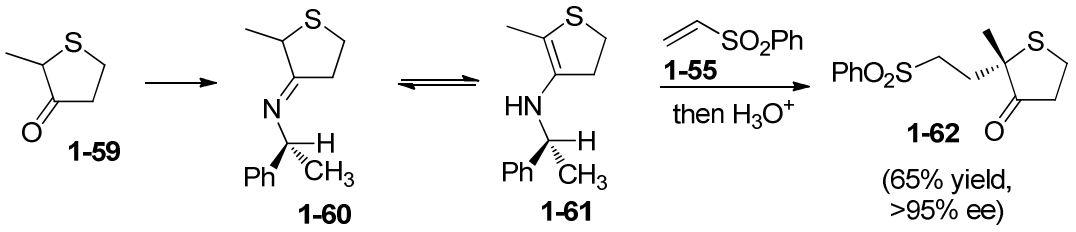
1.5.1 Enamine-Based Conjugate Additions to Vinyl Sulfones

Sulfones are very useful building blocks in organic synthesis.[169] Application of sulfone functions either as donors or acceptors in the conjugate additions has attracted much attention.[170a,170b] The first example involving vinyl sulfone as an acceptor was reported by d'Angelo (Scheme 1-15).[170b,170c] They developed highly regio- and stereoselective conjugate additions that made use of chiral imine/enamine intermediates derived from ketone substrates. Very shortly, they extended their methodology to the asymmetric conjugate additions to vinyl sulfones **1-55/56**.[170]



Scheme 1-15 Asymmetric conjugate additions involving chiral imines/enamines

As illustrated in Scheme 1-15, ketoesters **1-52** reacted with *R*(+)-1-phenylethyl-amine to yield chiral imines **1-53**, and their enamine tautomers **1-54** were added to phenyl vinyl sulfone **1-55** to yield sulfones **1-57** in good yield and with excellent enantioselectivity. The reactions were applicable to both five- and six-membered ring systems. However, conjugate addition to 1,1-bis(phenylsulfonyl)ethylene **1-56** was not very effective, affording the desired adducts **1-58** with only 50% ee.



Scheme 1-16 Asymmetric synthesis of 2,2-disubstituted tetrahydrothiophen-3-ones

Subsequently, Desmaele prepared a chiral imine **1-60** derived from 2-methyltetr-ahydrothiophen-3-one **1-59** and treated it with phenyl vinyl sulfone **1-55** to afford the adduct **1-62** in 65% yield and with >95% ee (Scheme 1-16).[171] The remarkable stereoselectivity was believed to result from a *syn* approach between enamine and sulfone electrophile and the related six-membered "aza-ene-synthesis-like" transition state (Fig. 1-4).

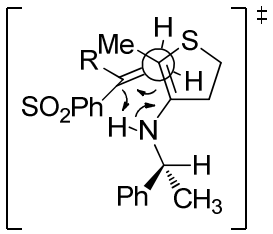
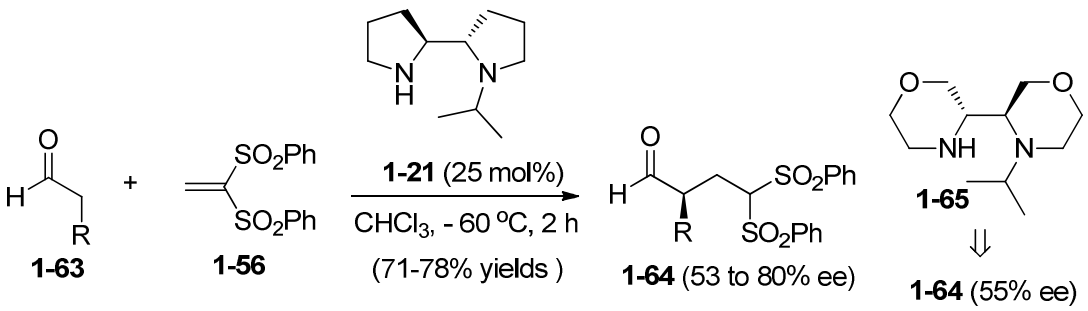


Figure 1-4 Proposed enamine formation between chiral primary amine and ketone

In a pioneering study,[172] Alexakis explored the conjugate additions of aldehydes **1-63** to vinyl sulfone **1-56** (Scheme 1-17). *N*-Isopropyl-2,2'-bipyrrolidine **1-21** was found to be effective, yielding the adducts **1-64** in good yields and with up to 80% ee. Better enantioselectivities were observed when more hindered aldehydes were used, and bimorpholine **1-65** was shown to be more effective than bipyrrolidine **1-21**.[173]



Scheme 1-17 Bipyrrolidine-promoted asymmetric conjugate addition of aldehydes to vinyl sulfone

They proposed an acyclic synclinal model involving a *trans* enamine described by Seebach to explain the conjugate addition of aldehydes to vinyl sulfone **1-56**. The *si*, *si* transition state is less hindered and thus favoured than the *re*, *re* transition state, leading to the formation of *R* adduct (Fig. 1-5).

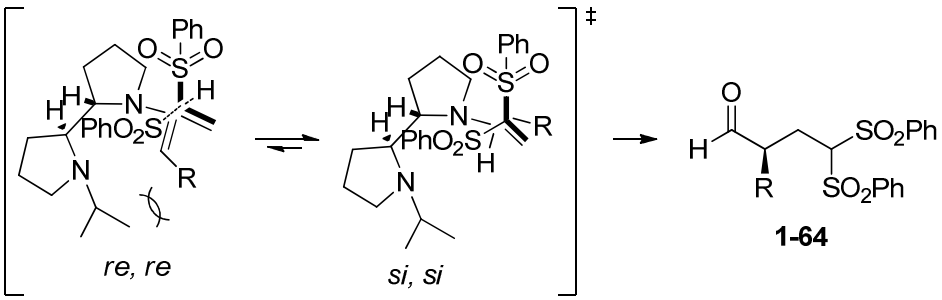
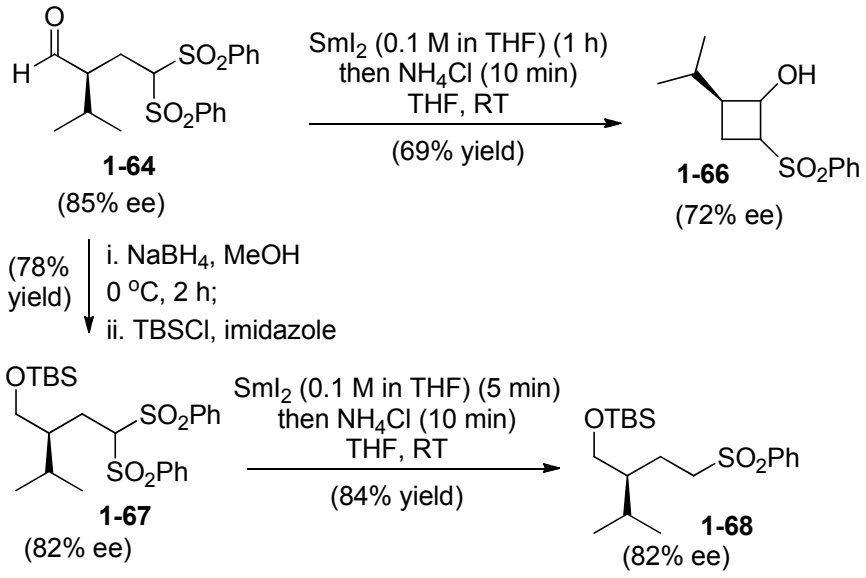


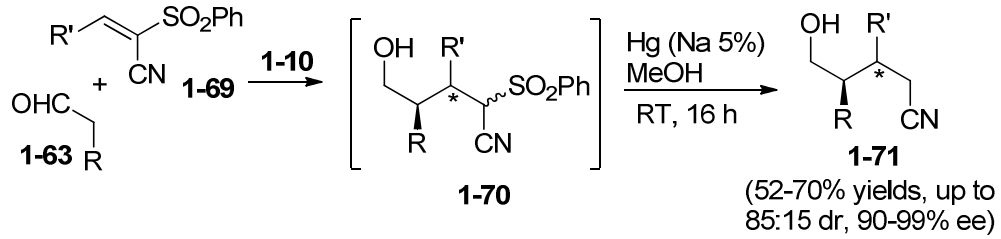
Figure 1-5 Proposed transition state between bipyrrolidine and aldehydes

In a later full study of organocatalytic conjugate addition of aldehydes to vinyl sulfone, they also found the catalyst **1-10** was much more effective than their previously reported bipyrrolidine **1-21**.[174] It was shown that freshly prepared samarium diiodide efficiently mediated reductive monodesulfonylation of the adduct **1-64** to give mono-sulfone **1-68**, which is potentially a nucleophilic agent and can be easily derivatized at the α-position. Moreover, an intramolecular samarium Barbier reaction afforded cyclobutanol **1-66** (Scheme 1-18).



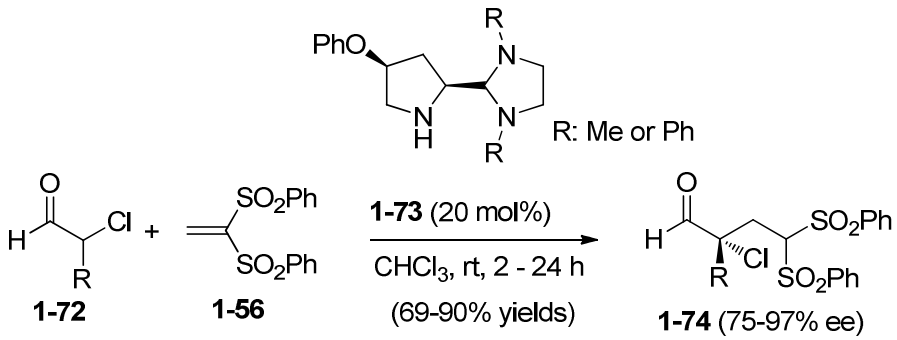
Scheme 1-18 Transformations to vinyl sulfone adduct

In 2009, Palomo reported highly enantioselective conjugate additions of aldehydes to vinyl sulfones, in which they utilized prolinol silyl ethers **1-10** as the catalysts of choice.[175] Interestingly, *E*-cyano vinyl sulfones **1-69** were examined as acceptors in their investigation. The reduction of intermediates **1-70** yielded cyano alcohols **1-71**, which might be difficult to access directly from the unsaturated nitriles (Scheme 1-19).



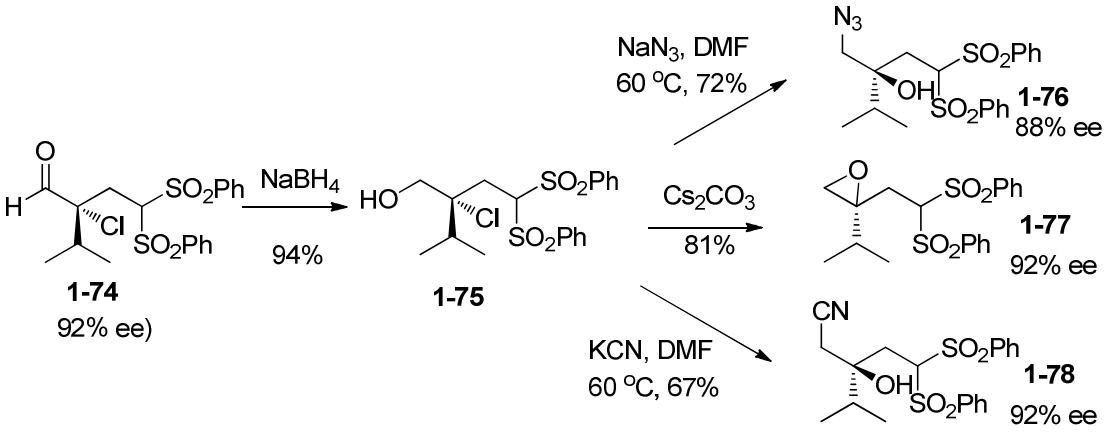
Scheme 1-19 Asymmetric conjugate additions involving α-cyano vinyl sulfones

Very recently, Alexakis explored highly enantioselective conjugate additions of α-chloro aldehydes **1-72** to vinyl sulfone **1-56** with their newly designed aminal pyrrolidine catalysts **1-73** (Scheme 1-20).[176] Good yields and high enantioselectivities (up to 97% ee) were obtained for the adducts **1-74** in all cases.



Scheme 1-20 Asymmetric conjugate additions of α-chloro aldehydes to vinyl sulfone

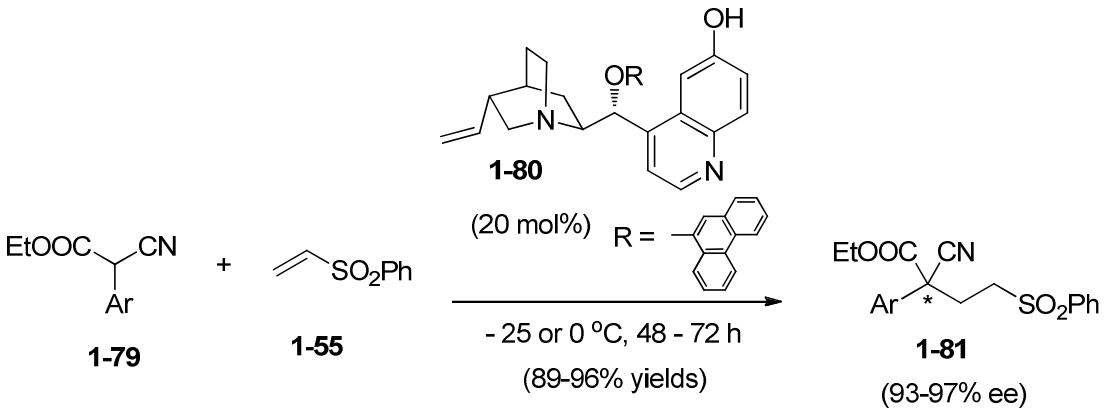
Interestingly, the products were very useful and could be converted into many useful building blocks (Scheme 1-21). After reduction of the desired adduct **1-74** into alcohol **1-75**, 2,2-disubstituted epoxide **1-77** could be obtained without losing enantiomeric purity using Cs_2CO_3 as base. In situ epoxide ring opening with KCN or NaN_3 could generate the corresponding products **1-76/78** with only a little loss of enantiopurity to 88% ee in the case of the sodium salt.



Scheme 1-21 Facile conversions of vinyl sulfone adduct

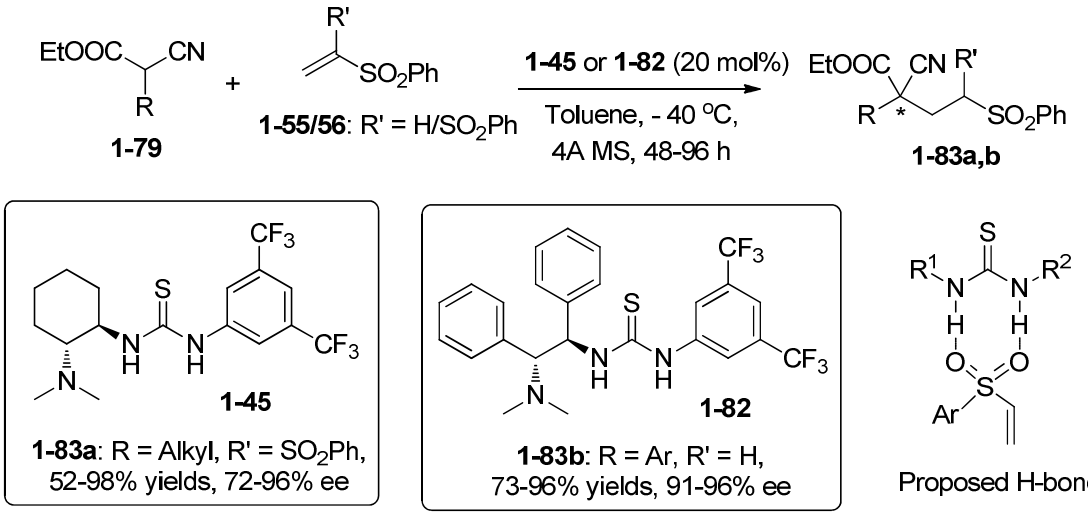
1.5.2 Conjugate Addition to Vinyl Sulfones Mediated by Bifunctional Catalysts

In 2005, Deng employed organocatalysts derived from cinchona alkaloids to catalyze enantioselective conjugate additions to vinyl sulfone.[177,178] C6'-OH quinine **1-80** could promote a highly enantioselective conjugate addition of α-substituted α-cyanoacetate **1-79** to vinyl sulfone **1-55**, affording the desired adduct **1-81** possessing highly functionalized all-carbon quaternary stereocenters in high yields and with excellent enantioselectivities (Scheme 1-22). However, to the aliphatic substituted cyano-esters, the reactions were not applicable.



Scheme 1-22 Conjugate additions to vinyl sulfone promoted by cinchona alkaloid-derived organocatalyst

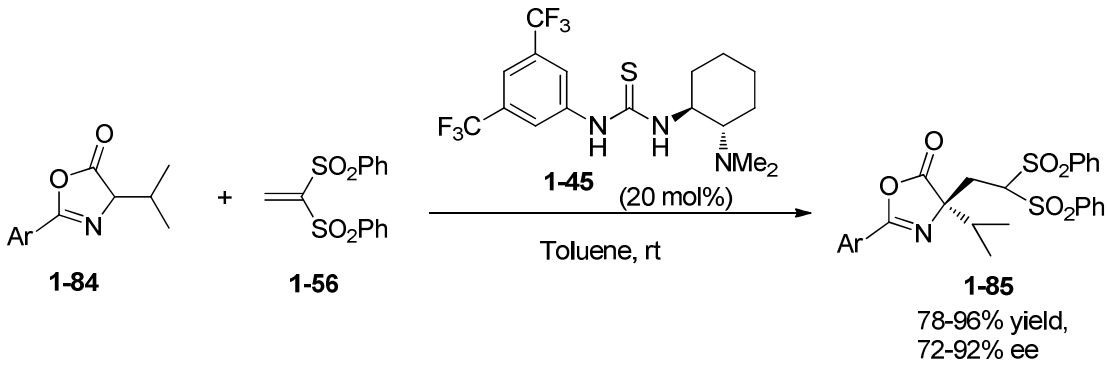
Subsequently, Chen reported the same conjugate addition of α-substituted α-cyanoacetates to vinyl sulfone catalyzed by new bifunctional catalysts (Scheme 1-23).[179] With the catalyst **1-45**, the addition of α-substituted α-cyanoacetates **1-79** to vinyl sulfone **1-55** proceeded well to provide the desired adducts **1-83a** in 96% yield and with 96% ee. When α-aliphatic substituted α-cyanoacetates were used, vinyl sulfone **1-56** was used in order to improve the activities of the acceptors. With the catalyst **1-82**, the addition of α-aliphatic substituted α-cyanoacetates **1-79** to vinyl sulfone **1-56**, yielded the desired adducts **1-83b** in 98% yield and with 96% ee. It was believed that double hydrogen-bonding interactions were involved between thiourea function in the catalyst and vinyl sulfone substrate (Scheme 1-23).



Scheme 1-23 Bifunctional thiourea-containing catalyst-mediated conjugate addition to vinyl sulfones

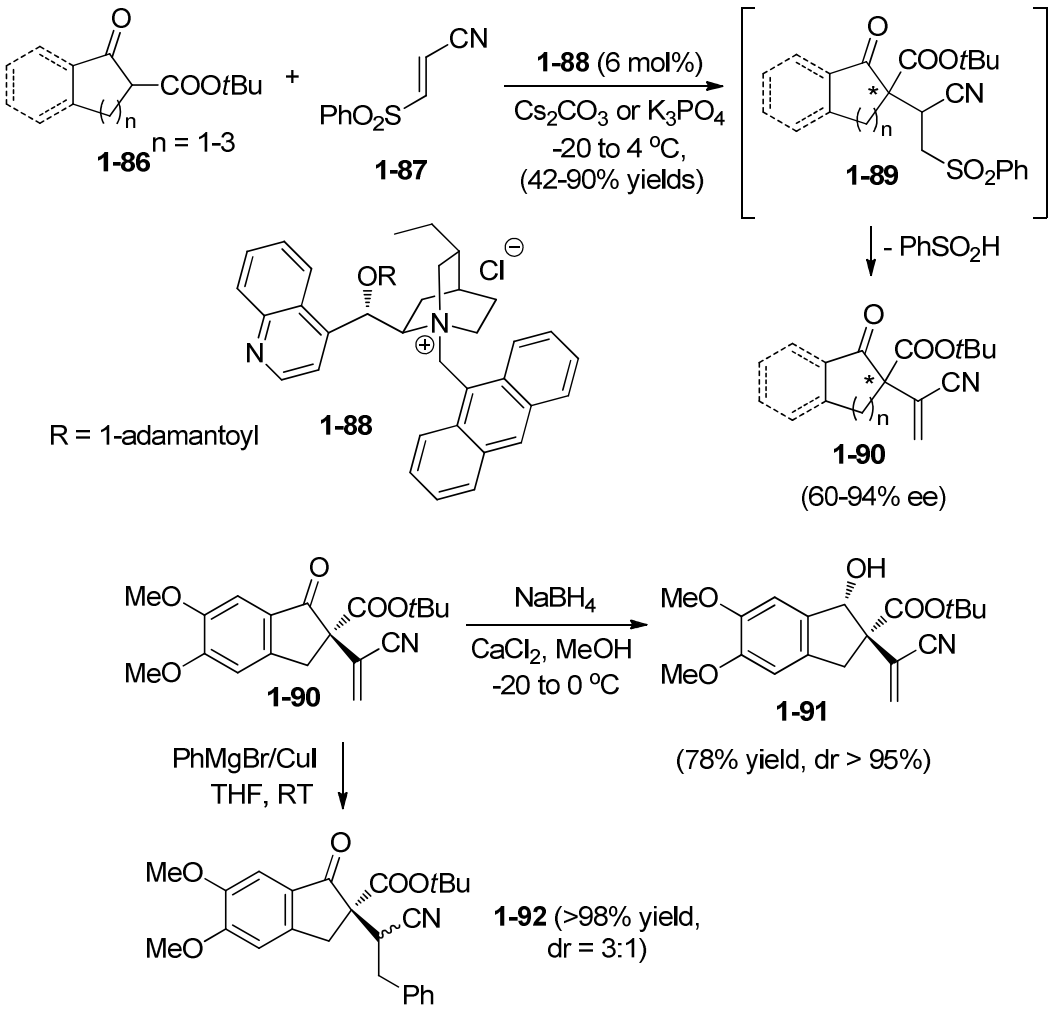
In 2010, Rios reported an organocatalytic enantioselective conjugate additions of oxazolones **1-84** to vinyl sulfone **1-56** to construct all quaternary carbon centers (Scheme 1-24).[180] When bifunctional organocatalyst **1-45** was employed, good yields

(up to 96%) and high enantioselectivities (up to 92% ee) were obtained. The adducts **1-85** were very useful and could be used to synthesize α,α-disubstituted amino acids.



Scheme 1-24 Asymmetric conjugate addition of oxazolones to vinyl sulfone catalyzed by bifunctional thiourea catalyst

Recently, Jorgensen described an interesting organocatalytic *anti*-conjugate reaction in which a sulfone group was employed both as a directing and leaving group (Scheme 1-25).[181] Ketoesters **1-86** were selected as nucleophiles to examine their conjugate additions to activated alkenes under phase-transfer catalytic conditions. In the presence of **1-88**, the addition to activated alkenes **1-87** containing both sulfone and cyano groups proceeded smoothly to generate intermediate **1-89**, the in situ elimination of the sulfone moiety then gave *anti*-conjugate product **1-90**. The resulting acrylonitrile **1-90** was chemoselectively transformed into reduced acryl nitrile **1-91** and saturated product **1-92**.



Scheme 1-25 Sulfone as a directing and removable group in conjugate additions

1.6 Objectives of Research

Up to now, uses of vinyl sulfones in conjugate additions are less-explored.[169-181] High enantioselectivities were only achieved in the conjugate addition of prepared enamines[170,171] and α-cyanoacetates[177-179] to vinyl sulfones. Although the additions of aldehydes to vinyl sulfone were reported, the enantioselectivities were not satisfactory.[172-174] Meanwhile, the additions of other nucleophiles to vinyl sulfone still remain unknown.

The purpose of this thesis is to design and synthesize different organocatalysts which can mediate highly stereoselective conjugate additions of various nucleophiles to vinyl sulfones. In particular, the following have been investigated in this thesis: (1) investigation of prolinol silyl ethers as catalysts to promote the conjugate addition of aldehydes to vinyl sulfones; (2) applications of cinchonidine-derived primary amines in the conjugate addition of ketones to vinyl sulfone; (3) design and synthesis of threonine-based *O*-TBS-*N*-sulfonamide for the conjugate addition of α,α-disubstituted aldehydes to vinyl sulfone; (4) examination of cinchona alkaloid-derived bifunctional and trifunctional thiourea catalysts in the asymmetric conjugate addition of nitroalkanes and oxindoles to vinyl sulfone. The details of these investigations will be elaborated in the remaining chapters of this thesis.

Chapter 2 Organocatalytic Conjugate Addition of Aldehydes to Vinyl Sulfones: Enantioselective α-Alkylations of Aldehydes and Their Derivatives

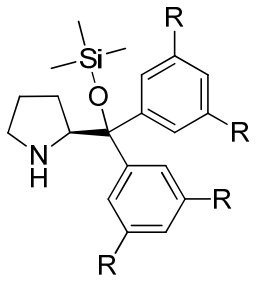
2.1 Introduction

Sulfones are widely employed as valuable intermediates in organic synthesis.[169] Asymmetric conjugate addition of carbon nucleophiles to vinyl sulfones represents an important carbon-carbon bond-forming reaction and provides an easy access to various optically pure sulfones.[170-181] In a number of early reports, enamines preformed from ketones were successfully added to vinyl sulfones; however, the additions were non-stereoselective. Subsequently, D'Angelo developed enantioselective additions of imines derived from cyclic ketones and chiral 1-phenyethylamine to vinyl sulfones.[170,171] Deng reported elegant cinchona alkaloid-mediated enantioselective conjugate additions to vinyl sulfones for the construction of all carbon-quaternary stereocenters.[177,178] Recently, Alexakis and his co-workers described an asymmetric organocatalytic conjugate addition of aldehydes to vinyl sulfone.[172-174] The reactions were promoted by their well-designed *N*-*i*Pr-2,2'-bipyrrolidine catalysts, and the adducts were obtained with modest to good enantioselectivity. Despite all the aforementioned excellent advances, highly enantioselective catalytic conjugate addition of carbonyl substrates to vinyl sulfones remains a challenging task, particularly with aldehyde substrates.

Recently, asymmetric aminocatalysis has attracted much attention. Particularly, proline and its various structural analogues have been shown to be efficient catalysts for a wide range of reactions.[104] In this chapter, we will discuss our studies of prolinol silyl ethers as catalysts for the conjugate addition of aldehydes to vinyl sulfones.

2.2 Diphenylprolinol Silyl Ethers Derived from Proline

Although Alexakis reported the conjugate addition of aldehydes to vinyl sulfone, only poor to moderate enantioselectivity was obtained (**Section 1.5.1**, Figure 1-5). We thought there was much space to improve the enantioselectivity of the reaction. The enamine formation from hindered secondary amines might be adequate to control the enantioselectivities of the reaction. Diphenylprolinol silyl ethers **1-10** and **2-6** (Fig. 2-1), independently developed by the groups of Hayashi and Jørgensen, were successfully used to promote the addition of aldehydes to nitrostyrene.[182-184] In this project, they were considered to be suitable for the conjugate additions. Thus, diphenylprolinol silyl ether **1-10** and **2-6** were prepared accordingly.[182-184]



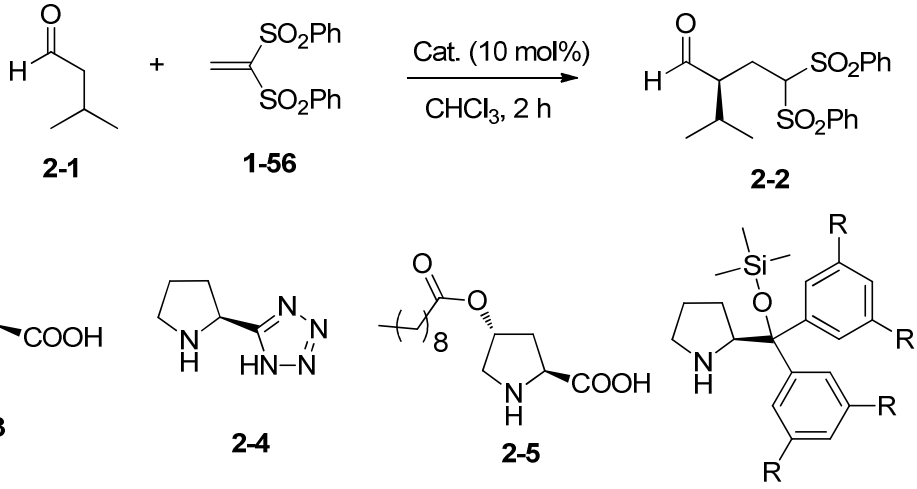
1-10 R = H; **2-6** R = CF_3

Figure 2-1 Diphenylprolinol silyl ethers

2.3 Preliminary Studies

2.3.1 Catalyst Screen

Table 2-1 Screening of organocatalysts for the asymmetric conjugate addition of isovaleraldehyde to vinyl sulfone[a]



Entry	Catalyst	Temp/(°C)	Yield[b]/(%)	*ee*[c]/(%)
1	**2-3**	RT	56	2
2	**2-4**	RT	41	31
3	**2-5**	RT	76	9
4	**1-10**	RT	92	89
5	**2-6**	RT	93	98

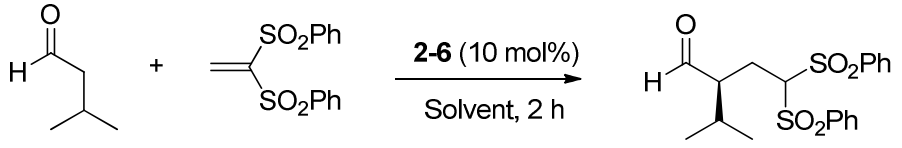
[a] The reactions were performed with isovaleraldehyde (0.5 mmol), vinyl sulfone (0.05 mmol) and catalyst (0.005 mmol) in anhydrous solvent (0.1 mL) at room temperature, unless otherwise specified. [b] Isolated yield. [c] The *ee* value was determined by chiral HPLC analysis.

The initial studies began from the conjugate addition of isovaleraldehyde **2-1** to vinyl sulfone **1-56**. A series of secondary amine catalysts derived from proline were tested and the results are summarized in Table 2-1. Not surprisingly, proline was less effective, promoting the reaction in moderate yields and with poor enantioselectivities

(entry 1). L-Proline-derived tetrazole **2-4** promoted the reaction not better than proline (entry 2). Substituted hydroxyl proline **2-5** could mediate the addition in good yield, but the enantioselectivity was very disappointing (entry 3). Prolinol silyl ether **1-10**, turned out to be a good catalyst, promoting the reaction in 92% yield and with 89% ee (entry 4). The trifluoromethylsubstituted silylated diphenylprolinol catalyst **2-6** was much more effective than diphenylprolinol silyl ether **1-10**, affording the desired adduct **2-2** in 93% yield and with up to 98% ee (entry 5).

2.3.2 Solvent Screen

Table 2-2 Screening of solvents for the asymmetric conjugate addition of isovaleraldehyde to vinyl sulfone[a]



2-1 **1-56** **2-2**

Entry	Solvent	Temp (^oC)	Yield[b] (%)	*ee*[c] (%)
1	$CHCl_3$	RT	93	98
2	CH_3CN	RT	87	79
3	CH_2Cl_2	RT	94	96
4	Toluene	RT	95	98
5	DMSO	RT	71	79
6	CH_3OH	RT	88	91
7	THF	RT	95	96
8	**$CHCl_3$**	**0**	**94**	**>99**

[a] The reactions were performed with isovaleraldehyde (0.5 mmol), vinyl sulfone (0.05 mmol) and catalyst (0.005 mmol) in indicated solvent (0.1 mL) at room temperature for 2 h, unless otherwise specified. [b] Isolated yield. [c] The *ee* value was determined by chiral HPLC analysis.

The effects of various common solvents were examined for the addition of isovaleraldehyde **2-1** to vinyl sulfone **1-56**, and the results are summarized in Table 2-2. Most organic solvents were effective except for polar solvents, such as DMSO and CH_3CN (entries 2 & 5). In DMSO, the reaction could proceed in 71% yield and with 79% ee (entries 5). The reason might be attributed to the less efficient enamine formation in DMSO and CH_3CN. Among the screened solvents, both toluene and chloroform were the best and provided us with 98% ee (entries 1 & 4). Chloroform was chosen for synthetic convenience. When the reaction was carried out at 0 ^oC, essentially enantiomerically pure adduct was obtained (entry 8).

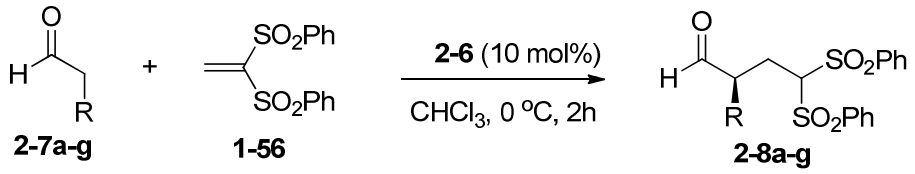
2.4 Generality of Reaction

2.4.1 Scope of Aldehydes

Having identified the optimal reaction condition, the generality of the reaction was then examined. The results of the conjugate addition with various aldehydes are summarized in Table 2-3. When propionaldehyde **2-7a** was employed, it proceeded well in 93% yield and with 97% ee (entry 1). Long chain aldehydes did not affect the yields and enantioselectivities (entries 2 to 5). For example, the addition of aldehyde **2-7e** containing 10 carbons to vinyl sulfone **1-56** proceeded with >99% ee (entry 5). When the aldehyde containing a big bulky group was employed, the reaction could proceed without losing enantioselectivity. For example, when 3,3-dimethylbutanal **2-7f** was used, 93% yield and 94% ee were obtained. Interestingly, when the catalyst

loading was lowered to 5%, the reaction was very efficient without losing the enantioselectivity and yield. For example, when **2-7a** was employed, same yield and enantioselectivity maintained with the completion of the reaction in 2 hours. These results indicated the enamine formation was very efficient with various aldehydes.

Table 2-3 Organocatalytic conjugate additions of various aldehydes to vinyl sulfone catalyzed by prolinol silyl ether **2-6**[a]



Entry	Product	Yield[b] (%)	*ee*[c] (%)
1	**2-8a** (R = CH_3)	93	97
2	**2-8b** (R = $CH_3(CH_2)_2$)	94	99
3	**2-8c** (R = $CH_3(CH_2)_3$)	95	99
4	**2-8d** (R = $CH_3(CH_2)_4$)	94	>99
5	**2-8e** (R = $CH_3(CH_2)_8$)	97	>99
6	**2-8f** (R = ^{t}Bu)	93	94
7	**2-8g** (R = Bn)	94	95

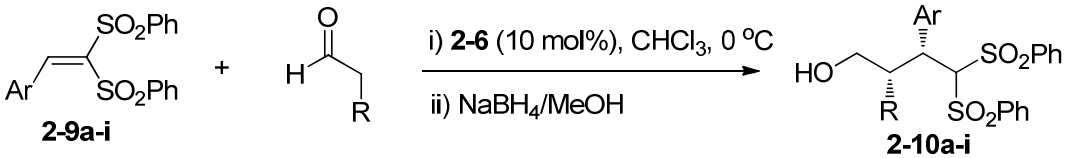
[a] The reactions were performed with aldehyde (0.5 mmol), vinyl sulfone (0.05 mmol) and catalyst (0.005 mmol) in anhydrous $CHCl_3$ (0.1 mL) at 0 ^{o}C. [b] Isolated yield. [c] The *ee* value was determined by chiral HPLC analysis.

2.4.2 Scope of Vinyl Sulfones

To make our methodology synthetically more useful, we extended the reaction scope to 2-aryl-substituted vinyl sulfones **2-9a-i** (Table 2-4). In all cases, *syn*-addition adducts were isolated in good yields and with excellent enantioselectivities. When

β-phenyl-substituted vinyl sulfone **2-9a** was employed, *syn*-addition adduct **2-10a** was obtained in 91% yield, with 15:1 dr and with 98% ee (entry 1). β-Furan or thiophene substituted vinyl sulfones **2-9d/e** also proved to be good, affording us the desired adducts in good yield and with high enantioselectivity (entries 4 & 5). Subsequently, the aldehydes were further explored. When different aldehydes were employed, the additions proceeded efficiently, yielding the desired adducts in good yield and with high diastereomeric ratio and perfect enantioselectivity (entries 8 & 9). However, there are some limitations herein. For example, the electron-withdrawing aryl-substituted vinyl sulfone is not applicable because it is too unstable to prepare, such as 4-NO_2-Phenyl subsitituted vinyl sulfone (**2-9j**) decomposed rapidly during column purification.

Table 2-4 Organocatalytic conjugate addition of aldehydes to 2-aryl-substituted vinyl sulfones[a]



Entry	Product	Catalyst	Time (h)	Yield[b] (%)	*Syn* /*anti*[c]	*ee*[d] (%)
1	**2-10a** (R = Me, Ar = Ph)	**2-6**	12	91	15:1	98
2	**2-10b** (R = Me, Ar = *p*-Me-Ph)	**2-6**	12	88	10:1	95
3	**2-10c** (R = Me, Ar = *p*-OMe-Ph)	**2-6**	20	94	10:1	>99
4	**2-10d** (R = Me, Ar = 2-furan)	**2-6**	14	86	4:1	98
5	**2-10e** (R = Me, Ar = 2-thiophene)	**2-6**	16	90	3:1	98
6	**2-10f** (R = Me, Ar = 2-naphylene)	**2-6**	24	82	10:1	99

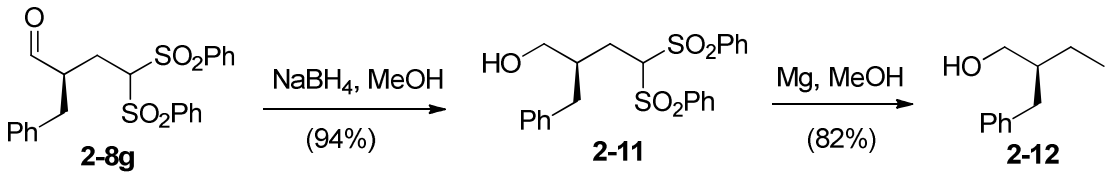
7	**2-10g** (R = Me, Ar = *p*-Br-Ph)	**2-6**	15	92	12:1	99
8	**2-10h** (R = Bn, Ar = *p*-OMe-Ph)	**1-10**	12	91	17:1	99
9	**2-10i** (R = $CH_3(CH_2)_2$, Ar = *p*-Ph)	**1-10**	16	94	6:1	99

[a] The reactions were performed with aldehyde (0.5 mmol), vinyl sulfone (0.05 mmol) and catalyst (0.005 mmol) in anhydrous $CHCl_3$ (0.1 mL) at 0 ^oC. [b] Isolated yield. [c] Determined by ^1H NMR analysis of the crude product. [d] The *ee* value of the *syn*-isomer was determined by chiral HPLC analysis.

2.5 Determination of Absolute Configuration and Conversions of Adducts into Chiral Building Blocks

Adduct of the addition of an aldehyde to vinyl sulfone is a versatile intermediate in organic synthesis. The facile conversion of aldehyde into a number of useful functional groups, in combination with well-established desulfonylation methods, offers a unique asymmetric entry to α-alkylated aldehydes and their derivatives.

2.5.1 Determination of Absolute Configuration of 2-8a-g

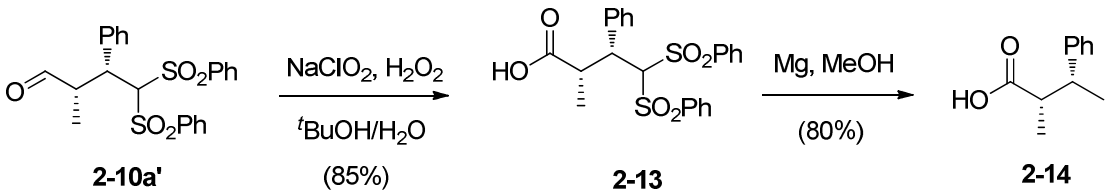


Scheme 2-1 Coversion of adduct **2-8g** into alcohol **2-12**

As shown in Scheme 2-1, the adduct **2-8g** was reduced with $NaBH_4$ into alcohol **2-11** in 94% yield. Removal of sulfone groups of compound **2-11** afforded the alcohol

2-12, the configuration of which was determined by comparison with literature data.[185] The absolute configuration of adduct **2-8g** was deduced accordingly, and the absolute configuration of products **2-8a-f** were assigned by analogy.

2.5.2 Determination of Absolute Configuration of 2-10a-i



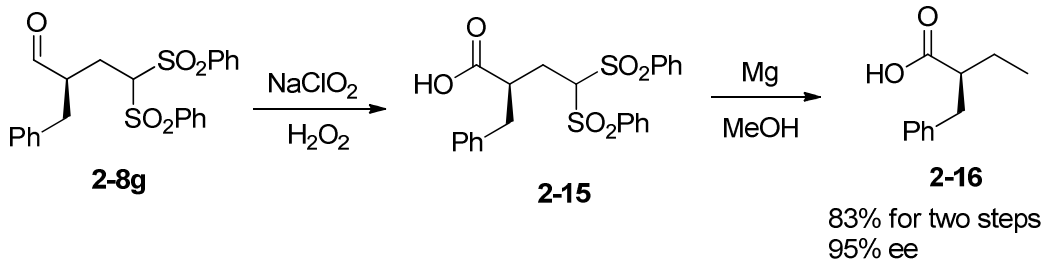
2-10a' **2-13** **2-14**

Scheme 2-2 Coversion of adduct **2-10a'** into acid **2-14**

As shown in Scheme 2-2, sulfone **2-13** was obtained from oxidation of crude product **2-10a'** with sodium chlorite. After removal of sulfone functions of **2-13**, acid **2-14** was obtained as a single diastereomer. The configuration of **2-14** was assigned by comparison with literature data.[186] The absolute configuration of **2-10a'** was deduced accordingly. Absolute configurations of **2-10b-i** were assigned by analogy.

2.5.3 Product Manipulation

Synthesis of Chiral Acid

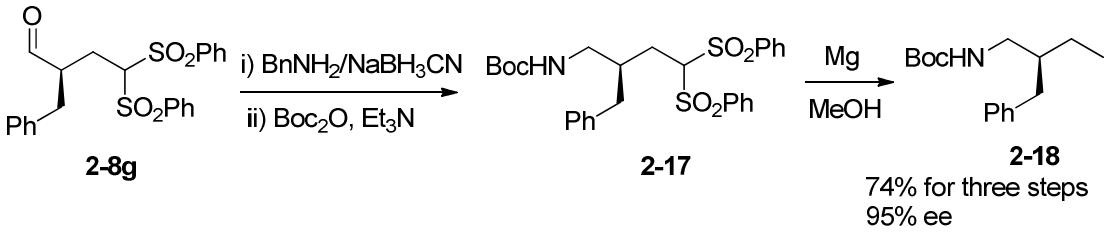


2-8g **2-15** **2-16**

Scheme 2-3 Conversion of adduct **2-8g** into acid **2-16**

Scheme 2-3 illustrates the synthetic route of conversion the addition adduct **2-8g** into chiral acid **2-16**. Oxidation of aldehyde **2-8g** with sodium chlorite and hydroperoxide afforded the corresponding acid **2-15**, which was subjected directly to the desulfonation step with Mg in methanol to generate the product **2-16** in 83% yield for two steps without losing any enantioselectivity.

Synthesis of Chiral Amine



Scheme 2-4 Coversion of adduct **2-8g** into chiral amine **2-18**

As illustrated in Scheme 2-4, the adduct **2-8g** was successfully converted into chiral amine **2-18**. Reductive-amination of aldehyde **2-8g** with benzyl amine and $NaBH_3CN$ afforded the amine intermediate. After protecting with Boc_2O, carbamate **2-17** was obtained and was used to synthesize chiral amine **2-18** with Mg in methanol. After three steps, 74% yield and 95% ee value were obtained.

2.6 Conclusion

In summary, we have reported for the first time that silylated diphenylprolinol **1-10** and **2-6** were used efficiently for the conjugate addition of aldehydes to vinyl

sulfones. Important features of the reaction are the following: (1) 2-aryl-substituted vinyl sulfones were applied as acceptors in the conjugate additions for the first time; (2) the reported reaction was general in scope: different types of aldehydes and aromatic substituted vinyl sulfones were applicable; (3) high enantioselectivities and good diastereoselectivities were attained.

2.7 Experimental Section

2.7.1 General Methods

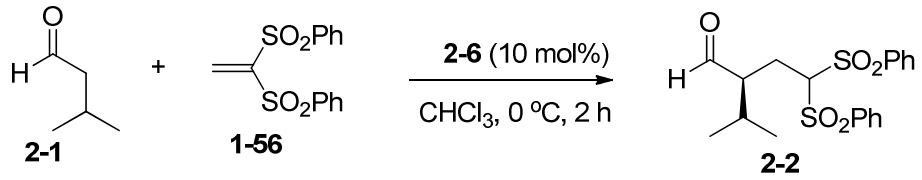
All the aldehydes and 1,2-bis(phenylsulfonyl)ethylene were purchased from Sigma-Aldrich. All 2-aryl-substituted vinyl sulfones (**2-9a-i**) were prepared according to literature procedure.[187] Chemicals and solvents were purchased from commercial suppliers and used as received.

^{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: 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). 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. For

thin-layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F_{254}) were used, and compounds were visualized under a UV light at 254 nm. Further visualization was achieved by staining with iodine, or ceric ammonium molybdate followed by heating on a hot plate. Flash chromatography separations were performed on Merck 60 (0.040 - 0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by chiral-phase HPLC analysis.

2.7.2 Representative Procedure for the Conjugate Additions

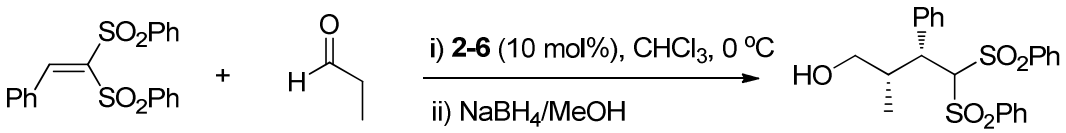
Addition of Unmodified Aldehydes to 1,1-Bis(benzenesulfonyl)ethylene (1-56) Catalyzed by Prolinol Silyl Ether 2-6



Isovaleraldehyde **2-1** (0.054 mL, 0.5 mmol) was added to a mixture of (*S*)-2-(bis(3,5-bis(trifluoromethyl)phenyl)(trimethylsilyloxy)methyl)pyrrolidine **2-6** (3.0 mg, 0.005 mmol) and 1,1-bis(benzenesulfonyl)ethylene **1-56** (15.4 mg, 0.05 mmol) in anhydrous chloroform (0.05 mL) in a sample vial at 0 ^{o}C. The vial was then capped and the reaction mixture was stirred at 0 ^{o}C for 2 h and quenched with the addition of aqueous HCl (1 N). The organic layer was extracted three times with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography

(ethyl acetate /hexanes = 1:5 to 1:2) afforded the desired product **2-2** as a pale yellow oil (18.5 mg, 94%). The enantiometric excess of product was determined by chiral HPLC analysis.

Addition of Aldehydes to 2-Aryl-Substituted Vinyl Sulfones Catalyzed by Prolinol Silyl Ether 2-6

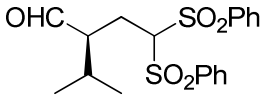


2-9a **2-7a** **2-10a**

Propionaldehyde **2-7a** (36 μL, 0.5 mmol) was added to a mixture of the catalyst **2-6** (3.0 mg, 0.005 mmol) and 2-phenyl-vinyl sulfone **2-9a** (19.2 mg, 0.05 mmol) in anhydrous chloroform (0.05 mL) in a sealed sample vial at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 12 h and then the reaction mixture was concentrated. The residue was diluted in methanol (5 mL), and the resulting mixture was cooled down to 0 ^{o}C. $NaBH_4$ (17 mg, 0.5 mmol) was added. After stirring at 0 ^{o}C for 15 minutes, aqueous HCl (1 M, 5 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate several times (3 x 5 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification by column chromatography (ethyl acetate /hexanes = 1:5 to 1:2) afforded the desired **2-10a** as colorless oil (20.2 mg, 91%).

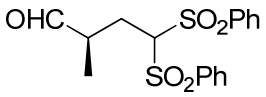
2.7.3 Characterizations of Intermediates and Adducts

(*S*)-2-Isopropyl-4,4-bis(phenylsulfonyl)butanal (**2-2**)



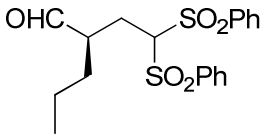
A white solid; $[\alpha]_D$ = + 57.31 (c = 1.83, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.94-0.96 (d, *J* = 4.2 Hz , 3H), 1.00-1.01 (d, *J* = 4.2 Hz, 3H), 2.13-2.17 (m, 1H), 2.49-2.54 (m, 1H), 2.92-2.94 (t, *J* = 3.0 Hz, 1H), 4.70-4.72 (m, 1H), 7.57-7.61 (m, 4H), 7.72-7.76 (m, 1H), 7.71-7.73 (m, 2H), 7.90-7.92 (m, 2H), 9.61 (s, 1H), which was in agreement with literature data;[172] The ee value of **2-2** was 99%, t_R (major) = 19.0 min, t_R (minor) = 23.1 min (Chiralcel AS-H, λ = 220 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*R*)-2-Methyl-4,4-bis(phenylsulfonyl)butanal (**2-8a**)



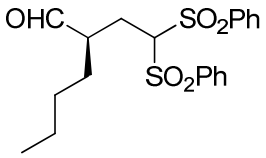
A pale yellow oil; $[\alpha]_D$ = + 52.3 (c = 1.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.15-1.17 (d, *J* = 7.4 Hz, 3H), 2.04-2.17 (m, 1H), 2.48-2.58 (m, 1H), 3.03-3.10 (m, 1H), 4.73-4.77 (m, 1H), 7.55-7.60 (m, 4H), 7.67-7.71 (m, 2H), 7.90-7.95 (m, 4H), 9.56 (s, 1H), which was in agreement with literature data;[172] The ee value of **2-8a** was 97%, t_R (major) = 29.9 min, t_R (minor) = 33.5 min (Chiralcel AS-H, λ = 220 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*R*)-2-(2,2-Bis(phenylsulfonyl)ethyl)pentanal (**2-8b**)



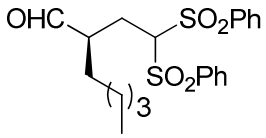
A colorless oil; $[\alpha]_D$ = + 40.2 (c = 1.31, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.90-0.94 (t, *J* = 7.3 Hz, 3H), 1.29-1.59 (m, 3H), 1.61-1.70 (m, 1H), 2.13-2.22 (m, 1H), 2.44-2.48 (m, 1H), 2.95-2.98 (m, 1H), 4.70-4.74 (m, 1H), 7.56-7.60 (m, 4H), 7.64-7.69 (m, 2H), 7.88-7.95 (m, 4H), 9.54 (s, 1H), which was in agreement with literature data;[176] The ee value of **2-8b** was 99%, t_R (major) = 21.4min, t_R (minor) = 24.2 min (Chiralcel AS-H, λ = 220 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*R*)-2-(2,2-Bis(phenylsulfonyl)ethyl)hexanal (**2-8c**)



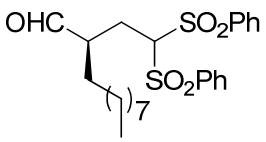
A pale yellow oil; $[\alpha]_D$ = + 42.11 (c = 1.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.93-0.97 (t, *J* = 7.2 Hz, 3H), 1.33-1.34 (m, 4H), 1.46-1.76 (m, 2H), 2.17-2.27 (m, 1H), 2.48-2.57 (m, 1H), 2.98-3.03 (m, 1H), 4.74-4.78 (m, 1H), 7.58-7.64 (m, 4H), 7.71-7.75 (m, 2H), 7.92-8.00 (m, 4H), 9.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.74, 22.61, 24.42, 28.55, 29.08, 48.86, 80.62, 129.12, 129.15, 129.38, 129.67, 34.56, 134.70, 137.73, 203.41; HRMS (ESI) *m/z* calcd for $C_{20}H_{22}O_5S_2$ $[M+Na]^+$ 431.0957, found 431.0966; The ee value of **2-8c** was 99%, t_R (major) = 19.1 min, t_R (minor) = 23.0 min (Chiralcel AS-H, λ = 220 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*R*)-2-(2,2-Bis(phenylsulfonyl)ethyl)heptanal (**2-8d**)



A white solid; $[\alpha]_D$ = + 26.4 (c = 0.91, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.86-0.90 (t, *J* = 7.0 Hz, 3H), 1.22-1.27 (m, 6H), 1.41-1.49 (m, 1H), 1.62-1.69 (m ,1H), 2.13-2.22 (m ,1H), 2.43-2.53 (m, 1H), 2.94-2.99 (m, 1H), 4.70-4.74 (m, 1H), 7.54-7.60 (m, 4H), 7.67-7.71 (m, 1H), 7.88-7.95 (m, 4H), 9.54 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.90, 22.31, 24.40, 26.12, 29.35, 31.65, 48.89, 80.60, 129.11, 129.14, 129.36, 129.67, 134.55, 134.69, 137.74, 203.41; HRMS (ESI) *m/z* calcd for $C_{20}H_{22}O_5S_2$ $[M+Na]^+$ 445.1114, found 445.1114; The ee value of **2-8d** was > 99%, t_R (major) = 17.3 min, t_R (minor) = 19.8 min (Chiralcel AS-H, λ = 220 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

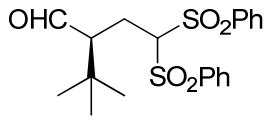
(*R*)-2-(2,2-Bis(phenylsulfonyl)ethyl)undecanal (**2-8e**)



A white solid; $[\alpha]_D$ = + 10.64 (c = 1.41, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.86-0.88 (t, *J* = 4.3 Hz, 3H), 1.20-1.26 (m, 14H), 1.44-1.48 (m, 1H), 1.64-1.69 (m, 1H), 2.12-2.22 (m, 1H), 2.43-2.53 (m, 1H), 2.93-2.98 (m,1H), 4.70-4.74 (m, 1H), 7.54-7.60 (m , 4H), 7.66-7.73 (m, 2H), 7.88-7.95 (m, 4H), 9.54 (s,1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.01, 22.57, 24.36, 26.41, 29.16, 29.23, 29.35, 29.37, 29.47, 31.77, 48.87, 80.56, 129.05, 129.10, 129.33, 129.63, 134.50, 134.64, 137.66, 137.71, 203.37; HRMS (ESI) *m/z* calcd for $C_{20}H_{22}O_5S_2$ $[M+Na]^+$ 501.1740, found 501.1748; The ee

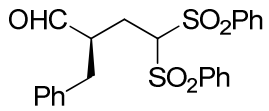
value of **2-8e** was >99%, t_R (major) = 39.3 min, t_R (minor) = 44.5 min (Chiralcel AS-H, λ = 220 nm, 15% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

(*S*)-2-(2,2-Bis(phenylsulfonyl)ethyl)-3,3-dimethylbutanal (**2-8f**)



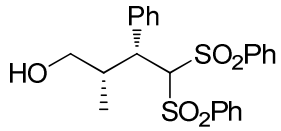
A white solid; $[\alpha]_D$ = + 61.33 (c = 1.81, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 9H), 2.23-2.29 (m, 1H), 2.49-2.59 (m, 1H), 2.75-2.79 (m, 1H), 4.53-4.57 (m, 1H), 7.56-7.70 (m, 6H), 7.85-7.95 (m, 1H), 9.71 (s, 1H), which was in agreement with the literature;[172] The ee value of **2-8f** was 94%, t_R (major) = 61.1 min, t_R (minor) = 64.4 min (Chiralcel AD-H, λ = 220 nm, 15% ^{i}PrOH/hexanes, flow rate = 1.0 mL/min).

(*R*)-2-Benzyl-4,4-bis(phenylsulfonyl)butanal (**2-8g**)



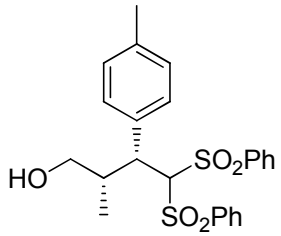
A white solid; $[\alpha]_D$ = + 18.7 (c = 0.91, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.02-2.11 (m, 1H), 2.47-2.67 (m, 2H), 3.13-3.19 (m, 1H), 3.38-3.48 (m, 1H), 4.68-4.72 (m, 1H), 7.18-7.20 (m, 2H), 7.26-7.47 (m, 5H), 7.53-7.58 (m, 2H), 7.62-7.67 (m, 4H), 7.85-7.87 (m, 2H), 9.67 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.21, 35.72, 50.34, 80.34, 127.05, 128.92, 129.11, 129.15, 129.25, 129.91, 134.49, 134.57, 137.02, 137.95, 202.57; HRMS (ESI) *m/z* calcd for $C_{20}H_{22}O_5S_2$ $[M+Na]^+$ 465.0801, found 465.0807; The ee value of **2-8g** was 95%, t_R (major) = 39.2 min, t_R (minor) = 43.1 min (Chiralcel AS-H, λ = 220 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(2*S*,3*R*)-2-Methyl-3-phenyl-4,4-bis(phenylsulfonyl)butan-1-ol (**2-10a**)



A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.73-0.76 (d, *J* = 7.0 Hz, 3H), 2.31 (s, 1H), 3.12-3.19 (m, 1H), 3.60-3.64 (m, 1H), 3.85-3.89 (d, *J* = 10.4 Hz, 1H), 4.14-4.18 (m, 1H), 5.77-5.78 (d, *J* = 1.7 Hz, 1H), 7.25-7.27 (m, 3H), 7.36-7.41 (m, 6H), 7.51-7.57 (m, 2H), 7.64-7.70 (m,. 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.42, 37.43, 48.67, 67.35, 85.08, 127.51, 128.14, 128.43, 128.77, 128.91, 128.98, 130.12, 133.81, 134.00, 138.22, 139.95); HRMS (ESI) *m/z* calcd for $C_{20}H_{22}O_5S_2$ $[M+Na]^+$ 467.0957, found 467.0966; The ee value of **2-10a** was 98%, t_R (major) = 13.5 min, t_R (minor) = 15.4 min (Chiralcel AD-H, λ = 220 nm, 20% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

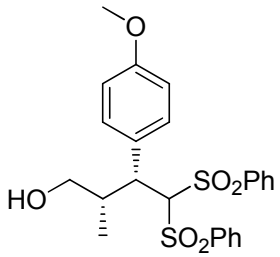
(2*S*,3*R*)-2-Methyl-4,4-bis(phenylsulfonyl)-3-*p*-tolylbutan-1-ol (**2-10b**)



A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77-0.80 (d, *J* = 6.9 Hz, 3H), 2.35 (s, 3H), 3.16-3.18 (m, 1H), 3.62-3.66 (m, 1H), 3.86-3.90 (m, 1H), 4.14-4.19 (m, 1H), 5.85-5.86 (d, *J* = 4.2 Hz, 1H), 7.10-7.13 (d, *J* = 8.0 Hz, 2H), 7.38-7.42 (m, 6H), 7.53-7.57 (m, 2H), 7.68-7.76 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 24.21, 35.72, 50.34, 80.34, 127.05, 128.92, 128.98, 129.11, 129.15, 129.25, 129.91, 134.49, 134.57, 137.02; HRMS (ESI) *m/z* calcd for $C_{24}H_{26}O_5S_2$ $[M+Na]^+$ 481.1114, found

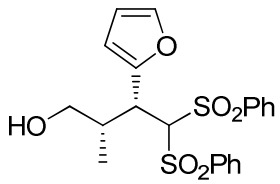
481.1112; The ee value of **2-10b** was 95%, t_R(minor) = 84.3 min, t_R (major) = 92.3 min (Chiralcel AD-H, λ = 220 nm, 10% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

(2*S*,3*R*)-3-(4-Methoxyphenyl)-2-methyl-4,4-bis(phenylsulfonyl)butan-1-ol (**2-10c**)



A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.73-0.75 (d, *J* = 4.1 Hz, 3H), 3.07-3.12 (m, 1H), 3.57-3.61 (m, 1H), 3.81 (s, 3H), 3.77-3.83 (m, 1H), 4.09-4.12 (m, 1H), 5.82-5.83 (d, *J* = 1.1 Hz, 1H), 6.79-6.80 (d, *J* = 5.3 Hz, 2H), 7.44-7.47 (m, 6H), 7.51-7.54 (m, 2H), 7.71-7.72 (m, 2H), 7.79-7.80 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 17.35, 37.75, 48.04, 55.05, 67.49, 84.7, 113.31, 128.40, 128.65, 128.86, 129.73, 131.39, 133.74, 133.83, 139.88, 140.22, 158.71; HRMS (ESI) *m/z* calcd for $C_{24}H_{26}O_6S_2$ $[M+Na]^+$ 497.1063, found 497.1063; The ee value of **2-10c** was >99%, t_R (minor) = 19.0 min, t_R (major) = 21.7 min (Chiralcel AD-H, λ = 220 nm, 20% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

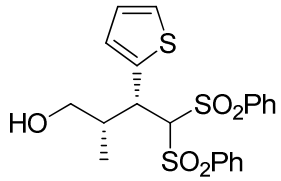
(2*S*,3*R*)-3-(Furan-2-yl)-2-methyl-4,4-bis(phenylsulfonyl)butan-1-ol (**2-10d**)



A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74-0.77 (d, *J* = 6.9 Hz, 3H), 2.96-

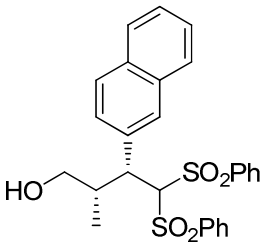
3.00 (m, 1H), 3.54-3.60 (m, 1H), 3.89-3.97 (m, 1H), 5.89-5.90 (d, *J* = 2.0 Hz, 1H), 6.16-6.23 (m, 1H), 6.39-6.40 (m, 1H), 7.12-7.17 (m, 1H), 7.39-7.60 (m, 6H), 7.80-7.91 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 16.62, 38.02, 42.75, 67.64, 83.39, 110.70, 128.72, 128.77, 128.87, 128.97, 129.05, 129.46, 129.86, 133.90, 133.98, 141.11; HRMS (ESI) *m/z* calcd for $C_{21}H_{22}O_6S_2$ $[M+Na]^+$ 457.0750, found 457.0760; The ee value of **2-10d** was 98%, t_R (minor) = 36.8 min, t_R (major) = 39.0 min (Chiralcel AD-H, λ = 220 nm, 15% *i*PrOH/hexanes, flow rate = 0.5 mL/min).

(2*S*,3*R*)-2-Methyl-4,4-bis(phenylsulfonyl)-3-(thiophen-2-yl)butan-1-ol (**2-10e**)



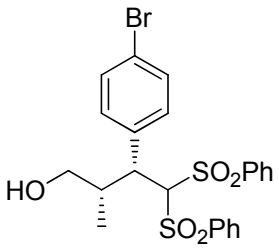
A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85-0.85 (d, *J* = 3.8 Hz, 3H), 3.05-3.07 (m, 1H), 3.52-3.55 (m, 1H), 4.06-4.15 (m, 1H), 5.83-5.84 (d, 1H), 6.92-6.93 (m, 1H), 7.07-7.08 (m, 1H), 7.22-7.23 (m, 1H), 7.42-7.49 (m, 4H), 7.50-7.59 (m, 2H), 7.77-7.84 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 17.11, 39.21, 43.8), 67.12, 84.64, 126.25, 128.63, 128.80, 128.82, 128.93, 129.00, 129.18, 133.98, 134.02, 139.36, 139.85, 140.22; HRMS (ESI) *m/z* calcd for $C_{21}H_{22}O_5S_3$ $[M+Na]^+$ 473.0522, found 473.0532; The ee value of **2-10e** was 98%, t_R (major) = 14.3 min, t_R (minor) = 15.7 min (Chiralcel AD-H, λ = 220 nm, 20% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(2*S*,3*R*)-2-Methyl-3-(naphthalen-2-yl)-4,4-bis(phenylsulfonyl)butan-1-ol (**2-10f**)



A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76-0.78 (d, *J* = 6.9 Hz, 3H), 2.15 (s, OH, 1H), 3.27-3.35 (m, 1H), 3.68-3.72 (m, 1H), 4.03-4.07 (m, 1H), 4.20-4.24 (m, 1H), 5.81-5.82 (d, *J* = 0.2 Hz, 1H), 7.32-7.34 (m, 3H), 7.45-7.54 (m, 4H), 7.68-7.75 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.52, 37.21, 48.64, 67.16, 85.47, 125.96, 126.02, 127.43, 127.48, 127.90, 128.47, 128.82, 128.89, 129.00, 132.63, 132.98, 133.87, 134.04, 136.07, 139.71, 140.19; HRMS (ESI) *m/z* calcd for $C_{27}H_{26}O_5S_2$ $[M+Na]^+$ 517.1114, found 517.1121; The ee value of **2-10f** was 99%, t_R (major) = 22.9 min, t_R (minor) = 25.0 min (Chiralcel AD-H, λ = 220 nm, 20% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

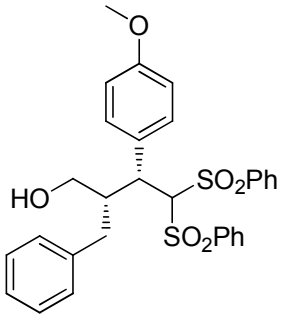
(2*S*,3*R*)-3-(4-Bromophenyl)-2-methyl-4,4-bis(phenylsulfonyl)butan-1-ol (**2-10g**)



A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72-0.74 (d, *J* = 6.9 Hz, 3H), 3.07-3.11 (m, 1H), 3.54-3.58 (m, 1H), 4.08-4.08 (d, *J* = 5.0 Hz, 1H), 4.11-4.12 (d, *J* = 1.8 Hz, 1H), 5.90-5.91 (d, *J* = 1.8 Hz, 1H), 7.26-7.37 (m, 7H), 7.50- 7.53 (m, 3H), 7.61-7.64 (m, 2H), 7.70-7.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.42, 37.60, 48.27, 67.55, 84.00, 121.02, 128.40, 128.66, 129.00, 131.17, 132.21, 133.93, 134.02,

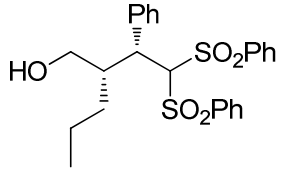
136.66; HRMS (ESI) *m/z* calcd for $C_{23}H_{23}O_5S_2$ $[M+Na]^+$ 545.0087, found 545.0081; The ee value of **2-10g** was 99%, t_R (minor) = 16.0 min, t_R (major) = 18.6 min (Chiralcel AD-H, λ = 220 nm, 20% ^{i}PrOH/hexanes, flow rate = 1.0 mL/min).

(2*S*,3*R*)-2-Benzyl-3-(4-methoxyphenyl)-4,4-bis(phenylsulfonyl)butan-1-ol (**2-10h**)



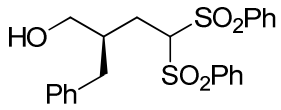
A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.49-2.54 (m, 1H), 2.60-2.64 (m, 1H), 3.34-3.35 (d, *J* = 3.0 Hz, 2H), 3.68-3.72 (m, 1H), 3.81 (s, 3H), 4.08-4.10 (m, 1H), 5.48-5.49 (d, *J* = 3.0 Hz, 1H), 6.72-6.74 (d, *J* = 5.1 Hz, 2H), 7.29-7.32 (m, 10H), 7.34-7.35 (m, 4H), 7.40-7.48 (m, 1H), 7.83-7.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.08, 43.44, 46.56, 55.18, 61.98, 86.37, 125.96, 113.51, 126.31, 128.10 , 128.28, 128.65, 128.84, 128.87, 128.94, 129.20, 131.77, 133.60, 134.06, 139.93, 140.43, 140.56, 158.94; HRMS (ESI) *m/z* calcd for $C_{27}H_{26}O_5S_2$ $[M-H]^-$ 549.1411, found 549.1411. The ee value of **2-10h** was 99%, t_R (major) = 32.8 min, t_R (minor) = 59.5 min (Chiralcel AD-H, λ = 220 nm, 20% ^{i}PrOH/hexanes, flow rate = 1.0 mL/min).

(*R*)-2-((*S*)-1-Phenyl-2,2-bis(phenylsulfonyl)ethyl)pentan-1-ol (**2-10i**)



A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75-0.77 (d, *J* = 6.4 Hz, 3H), 1.06-1.10 (m, 2H), 1.18-1.20 (m, 1H), 1.36-1.39 (m, 1H), 2.94-2.97 (m, 1H), 3.70-3.73 (m, 1H), 3.97-3.99 (d, *J* = 6.9 Hz, 1H), 4.22-4.25 (m, 1H), 5.81-5.82 (d, *J* = 0.8 Hz, 1H), 7.29-7.31 (m, 4H), 7.38-7.40 (m, 3H), 7.49-7.54(m, 4H), 7.64-7.66 (m, 2H), 7.72-7.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.14, 20.04, 32.35, 42.26, 47.57, 63.96, 84.86, 127.60, 128.10), 128.39, 128.82, 128.84, 128.89, 128.92, 128.97, 130.39, 133.81, 133.98, 137.79, 140.08, 140.22; HRMS (ESI) *m/z* calcd for $C_{27}H_{26}O_5S_2$ $[M-H]^-$ 471.1305, found 471.1317; The ee value of **2-10i** was 99%, t_R (major) = 68.6 min, t_R (minor) = 71.6 min (Chiralcel AD-H, λ = 220 nm, 10% *i*PrOH/Hexanes, flow rate = 0.5 mL/min).

(*R*)-2-Benzyl-4,4-bis(phenylsulfonyl)butan-1-ol (**2-11**)

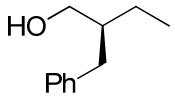


Crude (*R*)-2-benzyl-4,4-bis(phenylsulfonyl)butanal **2-8g** (133 mg, 0.3 mmol) from the conjugate addition to vinyl sulfone **1-56** was dissolved in MeOH (10 mL). The mixture was cooled to 0 °C, and $NaBH_4$ was added in one portion (25 mg, 0.66 mmol). After one hour, saturated aqueous NH_4Cl solution (9 mL) was added. The layers were separated, and the aqueous phase was extracted with ethyl acetate (2 x 3 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (ethyl acetate /hexanes = 1:3 to 1:1) afforded **2-11** as a pale yellow oil (120 mg, 90%).

$[\alpha]_D$ = - 24.6 (c = 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05-2.30 (m, 3H),

2.30-2.44 (m, 1H), 2.59-2.66 (m, 1H), 3.42-3.48 (m, 1H), 3.64-3.69 (m, 1H), 4.94-4.98 (m, 1H), 7.08-7.10 (m, 2H), 7.22-7.30 (m, 3H), 7.39-7.44 (m, 2H), 7.50-7.68 (m, 6H), 7.88-7.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.57, 38.21, 40.73, 65.25, 81.11, 126.35, 128.56, 128.92, 129.00, 129.23, 129.42, 129.80, 134.38, 134.47, 136.68, 137.79, 139.10; HRMS (ESI) *m/z* calcd for $C_{27}H_{26}O_5S_2$ $[M-H]^-$ 443.0992, found 443.0983.

(*S*)-2-Benzylbutan-1-ol (**2-12**)

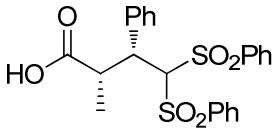


The activated magnesium metal (0.18 g, 7.5 mmol) was added to a solution of alcohol **2-11** (100 mg, 0.23 mmol) in anhydrous methanol (15 mL) with stirring. The mixture was heated to 50 ^{o}C to initiate continuous hydrogen generation, and then the heating was discontinued. After 40 min, the reaction mixture was brought to reflux for 2 h. After cooling down to room temperature, the mixture was poured into 2 N HCl solution (10 mL) and extracted with ether several times (3 x 10 mL). The organic extracts were combined, dried over Na_2SO_4 and filtered. Solvent was removed *in vacuo*, and the residue was purified by column chromatography (ethyl acetate /hexanes = 1:5) to afford the desired product as a yellow oil (31 mg, 82%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05-1.10 (t, *J* = 7.4 Hz, 3H), 1.49-1.55 (m, 1H), 1.84-1.89 (m, 1H), 2.76-2.78 (d, *J* = 7.2 Hz, 2H), 3.66-3.68 (d, *J* = 5.4 Hz, 2H), 7.30-7.44 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.24, 23.24, 37.23, 44.06, 64.42, 125.78, 128.22, 129.09, 140.78; The ee value was determined by chiral HPLC analysis using a

Chiralcel AS-H column, λ = 220 nm, 10% *i*PrOH/hexanes, flow rate = 0.5 mL/min, t_R (major) = 8.9 min, t_R (minor) = 10.4 min; $[\alpha]_D$ = + 6.49 (c = 1.71, $CHCl_3$) (*lit*:[185] $[\alpha]_D$ = - 3.8 (c = 4.3, CH_2Cl_2)).

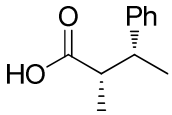
(2*S*,3*R*)-2-Methyl-3-phenyl-4,4-bis(phenylsulfonyl)butanoic acid (**2-13**)



To a stirred solution of crude (*R*)-2-benzyl-4,4-bis(phenylsulfonyl)butanal **2-10a'** (0.14 g, 0.30 mmol) in *tert*-butanol/water (3.0 mL, v/v = 1:1) was added sodium chlorite (39.0 mg, 0.45 mmol) and 30% aqueous solution of H_2O_2 (0.17 mL, 1.50 mmol). After stirring at rt for 3 h, the reaction mixture was then concentrated, and the residue was taken up in ethyl acetate (10 mL), washed with water (2 x 5 mL). Organic extract was dried over Na_2SO_4, concentrated and the residue was purified by column chromatography (ethyl acetate /hexanes = 1:2 to ethyl acetate) to afford the acid **2-13** as a white foam (114 mg, 82%).

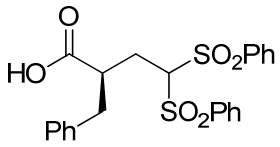
^{1}H NMR (300 MHz, CDCl3) δ 1.13 (d, *J* = 7.1 Hz, 3H), 3.95-4.02 (m, 1H), 4.06-4.21 (m, 1H), 5.70 (d, *J* = 2.8 Hz, 1H), 7.31-7.33 (m, 7H), 7.46-7.50 (m, 2H), 7.59-7.61 (m, 4H), 7.68-7.70 (m, 2H); ^{13}C NMR (75 MHz, CDCl3) δ 18.08, 42.38, 47.30, 83.77, 128.22, 128.44, 128.68, 128.78, 128.91, 130.88, 133.87, 134.42, 138.86, 140.49, 180.65; $[\alpha]_D$ = - 12.1 (c = 1.43, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{23}H_{22}O_6S_2$ $[M-H]^-$ = 457.0779, found = 457.0362.

(2*S*,3*R*)-2-Methyl-3-phenylbutanoic acid (**2-14**)



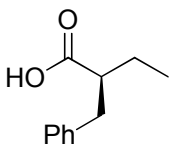
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (d, *J* = 7.0 Hz, 3H), 1.36 (d, *J* = 7.0 Hz, 3H), 2.64-2.68 (m, 1H), 2.94-2.97 (m, 1H), 7.21-7.27 (m, 3H), 7.28-7.31 (m, 2H), which was in agreement with literature data; $[\alpha]_D$ = + 10.5 (c = 0.31, $CHCl_3$), *lit*:[186] $[\alpha]_D$ = + 11.3 (c = 0.3, $CHCl_3$).

(*R*)-2-Benzyl-4,4-bis(phenylsulfonyl)butanoic acid (**2-15**)



^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22-2.24 (m, 1H), 2.49-2.51 (m, 1H), 2.73-2.76 (t, *J* = 1.9 Hz, 1H), 3.17-3.21 (m, 1H), 3.41-3.43 (t, *J* = 5.0 Hz, 1H), 4.79-4.81 (t, *J* = 1.9 Hz, 1H), 7.21-7.23 (d, *J* = 7.0 Hz, 2H), 7.36-7.37 (m, 3H), 7.47-7.55 (m, 4H), 7.66-7.71 (m, 4H), 7.86-7.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.71, 38.23, 44.37, 80.94, 127.04, 128.87, 129.06, 129.23, 129.29, 129.32, 129.96, 134.68, 137.47, 136.69, 137.74, 179.24; $[\alpha]_D$ = - 14.5 (c = 1.2, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{23}H_{22}O_6S_2$ $[M+Na]^+$ = 481.0750, found = 481.0756.

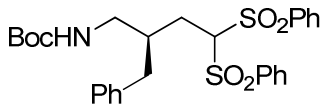
(*S*)-2-Benzylbutanoic acid (**2-16**)



^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94-0.99 (t, *J* = 7.3 Hz, 3H), 1.60-1.67 (m, 2H),

2.60-2.65 (m, 1H), 2.73-2.80 (m, 1H), 2.95-3.02 (m, 1H), 7.18-7.29 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.57, 24.73, 37.66, 48.81, 126.35, 128.39, 128.87, 139.13, 181.57; $[\alpha]_D$ = + 25.8 (c = 1.5, $CHCl_3$); For the enantiomeric excess determination, acid **2-16** was difficult to be resolved. **2-16** was reduced to alcohol **2-12**, and the ee value was determined accordingly: Chiralcel AS-H column, λ = 220 nm, 10% *i*PrOH/Hexanes, flow rate = 0.5 mL/min, t_R (major) = 8.9 min, t_R (minor) = 10.4 min.

(*R*)-*tert*-Butyl benzyl(2-benzyl-4,4-bis(phenylsulfonyl)butyl)carbamate (**2-17**)

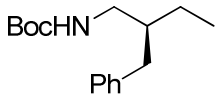


Benzyl amine (64 mg, 0.60 mmol) was added to a solution of (*R*)-2-benzyl-4,4-bis(phenylsulfonyl)butanal **2-8g** (133 mg, 0.30 mmol) in methanol (3 mL), and the mixture was brought to reflux for 1 h. After cooling down to 0 ^oC, $NaBH_3CN$ (76 mg, 1.2 mmol) was added to the reaction mixture, after which acetic acid was added to adjust the pH of solution to 6. After stirring at room temperature for 3 hours, triethylamine was added to the solution to adjust the pH to 8, and Boc_2O (190 mg, 0.9 mmol) was added. After stirring at room temperature overnight, the solution was concentrated and the residue was taken up in ethyl acetate (30 mL). The organic extracts were washed with aqueous HCl (1 N, 10 mL x 3), water (10 mL x 3) and brine (10 mL), respectively, and dried over anhydrous $MgSO_4$. After filtration, the mixture was concentrated and purified by column chromatography (ethyl acetate /hexanes = 1:5 to 1:2) to yield **2-17** as a colorless oil (0.16 g, 84%).

^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.12-2.14 (m, 2H), 2.42-2.45 (m, 1H),

2.69-2.72 (m, 2H), 2.99-3.12 (m, 2H), 4.30-4.52 (d, 2.5H), 5.00 (s, 0.5H), 7.12-7.17(m, 4H), 7.29-7.32 (m, 6H), 7.33-7.46 (m, 4H), 7.53-7.66 (m, 4H), 7.82-7.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.43, 28.36, 37.32, 37.94, 49.58, 50.78, 76.71, 80.23, 126.39, 127.28, 127.65, 128.56, 128.69, 128.84, 129.28, 129.84, 134.30, 136.84, 138.15, 139.36, 155.99; $[\alpha]_D$ = - 12.2 (c = 2.3, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{35}H_{39}NO_6S_2$ $[M+Na]^+$ = 656.2111, found = 656.2112.

(*S*)-*tert*-Butyl benzyl(2-benzylbutyl)carbamate (**2-18**)



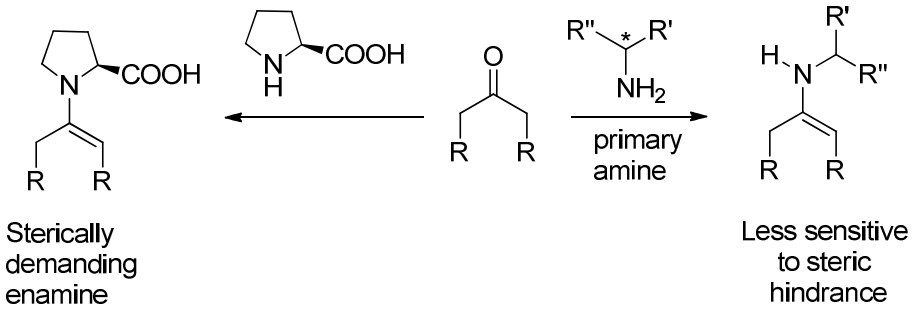
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85-0.90 (t, *J* = 7.7 Hz, 3H), 1.29-1.34 (m, 2H), 1.48 (s, 9H), 1.91-1.95 (t, *J* = 6.3 Hz, 1H), 2.53 (s, 2H), 3.05-3.20 (m, 2H), 4.32-4.49 (m, 2H), 7.11-7.29 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.77, 23.82, 28.43, 37.95, 39.92, 49.64, 50.26, 79.64, 125.74, 127.06, 127.37, 127.87, 128.22, 128.41, 129.00, 138.40, 140.94, 156.30; $[\alpha]_D$ = - 4.2 (c = 1.3, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{23}H_{31}NO_2$ $[M+Na]^+$ = 376.2247, found = 376.2255; The ee value was determined by HPLC analysis using Chiralcel OD-H column, λ = 220 nm, 5% *i*PrOH/Hexanes, flow rate = 0.5 mL/min, t_R (major) = 7.6 min, t_R (minor) = 9.0 min.

Chapter 3 Asymmetric Oganocatalytic Conjugate Addition of Ketones to Vinyl Sulfone

3.1 Ketones as Donors in Conjugate Addition to Vinyl Sulfone

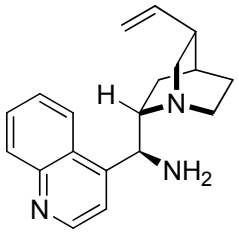
Having achieved highly enantioselective conjugate addition of aldehydes to vinyl sulfones mediated by silylated biarylprolinol, we were particularly interested to explore the conjugate addition of ketones to vinyl sulfones. Although the addition of ketones to other electrophiles, such as nitrostyrenes, imines, azodicarboxylate and nitrosobenzene has been reported,[104] a practical asymmetric organocatalytic conjugate addition of ketones to vinyl sulfones is still elusive.

Recently, chiral primary amines have been shown to be effective in asymmetric aminocatalysis.[114] Our group demonstrated for the first time that L-tryptophan was effective for the aldol reactions.[188] Subsequently, we showed that L-threonine-derived organocatalysts promoted highly enantioselective the asymmetric aldol and Mannich reactions.[189,190] In order to develop an organocatalytic conjugate addition of ketones to vinyl sulfone, a primary amine catalytic cycle of conjugate addition of ketones to vinyl sulfone was proposed (Scheme 3-1). The crucial enamine intermediate may be readily formed in the presence of a primary amine, whereas steric hindrance may hinder the efficient enamine formation when a secondary amine is employed as the catalyst. In this chapter, we will discuss our studies on cinchonidine-based primary amine to mediate the conjugate addition of ketones to vinyl sulfone.



Scheme 3-1 The enamine intermediates in the enamine catalysis

3.2 Catalyst Used in the Conjugate Addition of Ketones to Vinyl Sulfone



3-5

Cinchonidine-based primary amines have been used for the conjugate addition of aldehydes and ketones to nitrostyrenes.[116] In this project, it might be useful for the asymmetric conjugate addition of ketones to vinyl sulfone. The catalyst **3-5** was synthesized according to known procedure.[116]

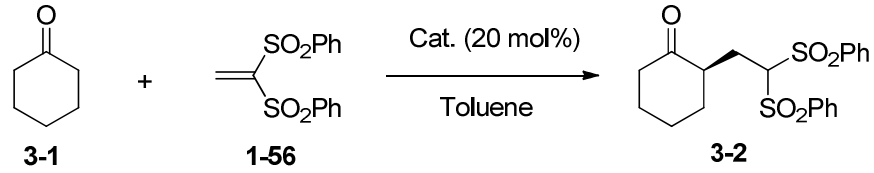
3.3 Preliminary Studies

3.3.1 Initial Screening with Primary Amines

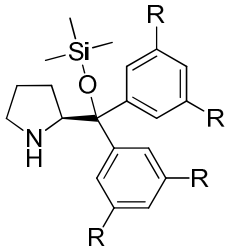
For the initial studies, we tested a few common secondary and primary amino catalysts in the addition of cyclohexanone **3-1** to vinyl sulfone **1-56** (Table 3-1). Not surprisingly, proline and silylated biarylprolinols **1-10 & 2-6** only afforded the desired adducts in very low yield (entries 1-3). Threonine-derived catalysts (**3-3a-c**),

catalyzed the reaction in high yield, but the enantioselectivity was very disappointing (entries 4-6). Serine-based catalysts (**3-4a-c**) were much more effective, mediating the addition reaction in excellent yield and with moderate enantioselectivity (entries 7-9). Cinchonidine-derived primary amine **3-5** turned out to be an excellent catalyst, giving the desired product in 86% yield and with 71% ee (entry 10).

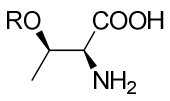
Table 3-1 Screening of organocatalysts for the asymmetric conjugate addition of cyclohexanone to vinyl sulfone[a]



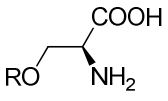
3-1 **1-56** **3-2**



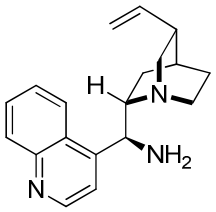
1-10: R = H; **2-6**: R = CF_3



3-3a: R = TBS;
3-3b: R = TBDPS;
3-3c: R = TIPS



3-4a: R = TBS;
3-4b: R = TBDPS;
3-4c: R = TIPS



3-5

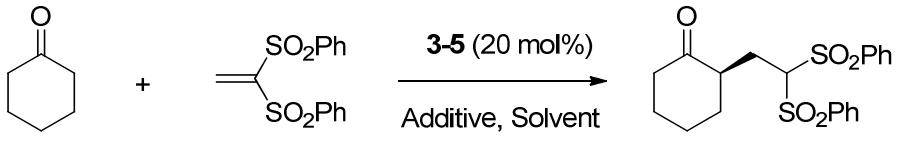
Entry	Catalyst	Temp/(°C)	Additive	Yield[b]/(%)	*ee*[c]/(%)
1	**proline**	RT	—	< 20	—
2	**1-10**	RT	—	31	48
3	**2-6**	RT	—	< 20	—
4	**3-3a**	RT	—	85	21
5	**3-3b**	RT	—	70	-2
6	**3-3c**	RT	—	83	7
7	**3-4a**	RT	—	96	60
8	**3-4b**	RT	—	95	44
9	**3-4c**	RT	—	95	46
10	**3-5**	RT	PhCOOH[d]	86	71

[a] The reaction were performed with cyclohexanone (0.5 mmol), vinyl sulfone (0.05 mmol) and catalyst (0.01 mmol) in anhydrous toluene (0.1 mL) at room temperature for 2 h, unless otherwise specified. [b] Isolated yield. [c] The *ee* value was determined by chiral HPLC analysis. [d] 20 mol% PhCOOH used.

3.3.2 Solvent, Additive and Temperature Screen

After identification of **3-5** as the best catalyst, a variety of solvents were screened (Table 3-2). Polar solvents, such as MeOH, DMSO and CH_3CN were not suitable, giving the desired adducts with disappointing enantioselectivity (entries 2, 4 & 5). Non-polar solvents, such as $CHCl_3$, THF and CH_2Cl_2 could provide us the desired product in good yield and with moderate enantioselectivity (entries 1, 3 & 6). After solvent screening, several acid additives were tested. Most additives could afford us good enantioselectivity (entry 6-8). Benzoic acid was the best, giving the conjugate adduct with 89% ee (entry 6). When the temperature was lowered to 0 ^oC, the conjugate adduct **3-2** was obtained in 94% yield and with 92% ee.

Table 3-2 Screening of solvents for the conjugate addition of cyclohexanone to vinyl sulfone[a]



3-1 **1-56** **3-2**

Entry	Solvent	Temp. (^oC)	Additive[b]	Yield[c] (%)	*ee*[d] (%)
1	THF	RT	PhCOOH	71	79
2	MeOH	RT	PhCOOH	95	27
3	CH_2Cl_2	RT	PhCOOH	94	78
4	DMSO	RT	PhCOOH	89	38
5	CH_3CN	RT	PhCOOH	95	49
6	$CHCl_3$	RT	PhCOOH	86	89
7	$CHCl_3$	RT	TFA	87	85
8	$CHCl_3$	RT	CSA	91	85

9	$CHCl_3$	-20	PhCOOH	45	90
10	$CHCl_3$	0	PhCOOH	94	92

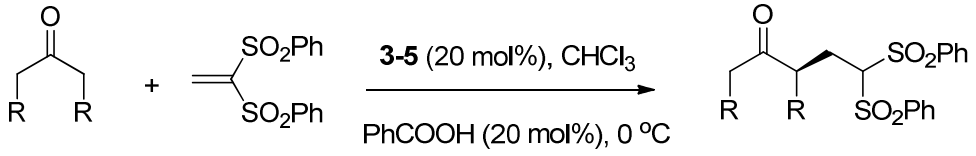
[a] The reaction were performed with cyclohexanone (0.5 mmol), vinyl sulfone (0.05 mmol) and catalyst (0.01 mmol) in indicated solvent (0.1 mL) at room temperature for 2 h, unless otherwise specified. [b] 20 mol% acid used. [c] Isolated yield. [d] The *ee* value was determined by chiral HPLC analysis.

3.4 Reaction Scope and Determination of Absolute Configuration

3.4.1 Scope of Ketones

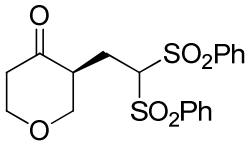
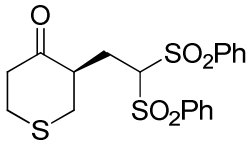
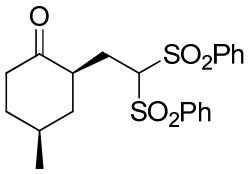
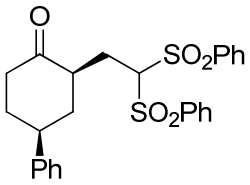
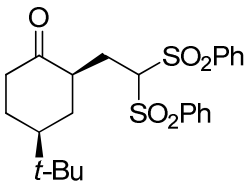
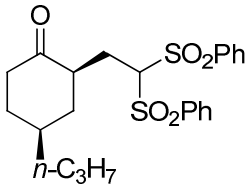
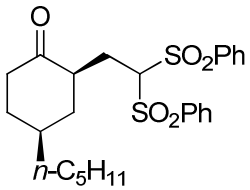
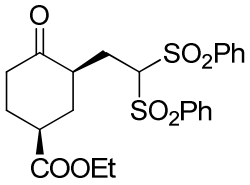
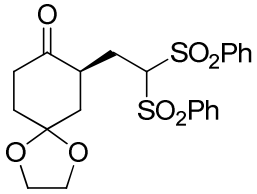
With the optimal condition, we examined various keones **3-6a-j** to establish the general utility of the reaction (Table 3-3). The additions with six-member ring cyclic ketones, such as **3-6a/b** and **3-6i** proceeded well with up to 95% ee (entries 1, 2 & 9). Substituted cyclic ketones **3-6c-h** were also applicable. In all cases, good results were obtained with up to 97% ee and up to 6:1 dr (entries 3-8). However, the acyclic ketones were not applicable. For example, when 3-pentanone was used, the yield was less than 30%. The conjugate addition of *O*-benzyl-hydroxyacetone to vinyl sulfone **1-56** gave the desired product with only 27% ee.

Table 3-3 Organocatalytic conjugate additions of various ketones to vinyl sulfone[a]



3-6a-j **1-56** **3-7a-j**

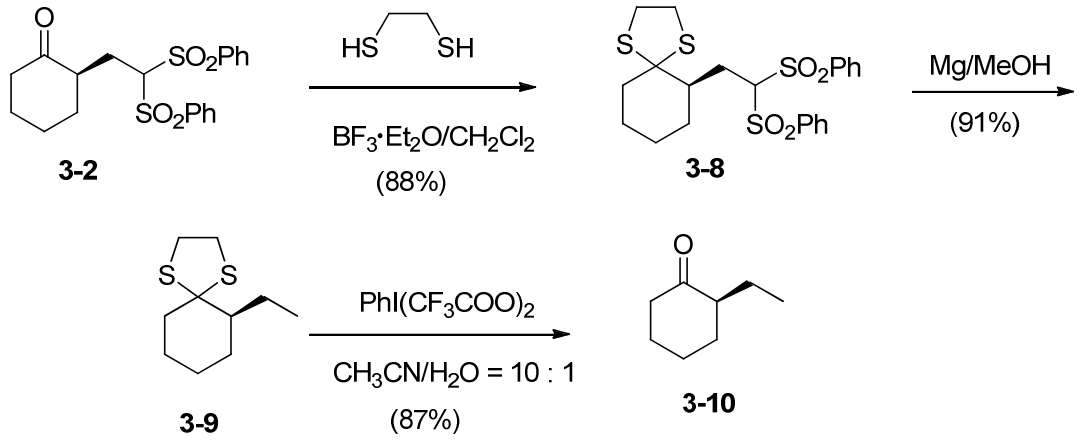
Entry	Product	Yield[b]/ (%)	dr[c]	*ee*[d]/ (%)

1	 **3-7a**	89	---	91
2	 **3-7b**	76	---	95
3	 **3-7c**	84	5 : 1	96
4	 **3-7d**	92	6 : 1	97
5	 **3-7e**	93	3 : 1	95
6	 **3-7f**	90	4 : 1	94
7	 **3-7g**	78	2.5 : 1	90
8	 **3-7h**	85	5 : 1	88
9	 **3-7i**	87	---	90

[a] The reactions were performed with ketone (0.05 mmol), vinyl sulfone (0.05 mmol), catalyst (0.01 mmol) and benzoic acid (0.01 mmol) in anhydrous $CHCl_3$ (0.1 mL) at 0 ^oC. [b] Isolated yield. [c] Determined by ^1H NMR analysis of the crude product. [d] The *ee* value was determined by chiral HPLC analysis.

3.4.2 Determination of Absolute Configuration of Adducts

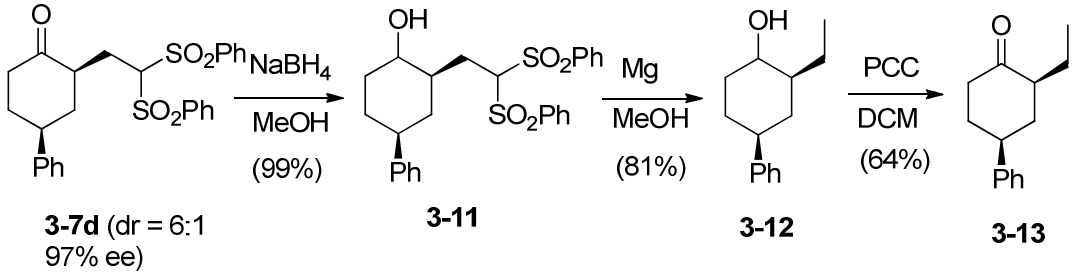
Following the sequence illustrated in Scheme 3-2, protection of the adduct **3-2** with ethanedithio afforded **3-8** in 88% yield. **3-8** was subjected to desulfonation step with Mg to yield the intermediate **3-9** in 91% yield. Removal of the protecting group of compound **3-9** afforded chiral cyclic ketone **3-10** in 87% yield. The absolute configuration of **3-10** was assigned by comparing its specific rotation with the literature data.[191] The absolute configuration of **3-2** was deduced accordingly, and configurations of conjugate adducts **3-7a-j** were assigned by analogy.



Scheme 3-2 Determination of absolute configuration of adduct **3-2**

3.4.3 Determination of Relative Configuration of Adducts

As shown in Scheme 3-3, the relative configuration of the adduct **3-7d** was determined. Adduct **3-7d** was reduced to alcohol **3-11** in quantitative yield. After removal of sulfone groups of **3-11**, alcohol **3-12** was obtained in 81% yield. Oxidation of alcohol **3-12** yielded cyclic ketone **3-13**. The two diastereoisomers of ketone **3-13** were separated by column chromatographic purification. The major diastereoisomer of **3-13** was subjected to a 2D-NOESY experiment to establish the relative configurations of the two chiral centers, and the relative configuration of **3-13** was determined accordingly. The relative configuration of **3-7d** was deduced, and relative configurations of the conjugate products **3-7c-h** were assigned by analogy.



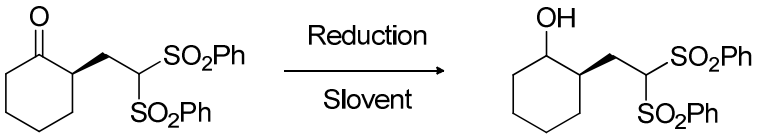
Scheme 3-3 Determination of relative configuration of adduct **3-7d**

3.5 A Synthesis of (1*S*, 2*S*)-Sodium Cyclamate

In order to illustrate the synthetic value of the reaction, the adduct **3-2** was subjected to synthesize sodium cyclamate, an important compound in the artificial sweeteners industry.[192] The first step was the reduction of ketone **3-2** to alcohol **3-14**. Herein we did a full study of the reaction. Various reducing reagents and temperature were examined (Table 3-4). The isomer with *cis*:*trans* ratio could be up to 8:1 with

$LiAlH_4$ at -78 °C. Interestingly, at -78 °C, opposite isomer with *cis*:*trans* ratio up to 1:6 was obtained when L-selectride was employed.

Table 3-4 Optimization of reduction of ketone **3-2** to alcohol **3-14**

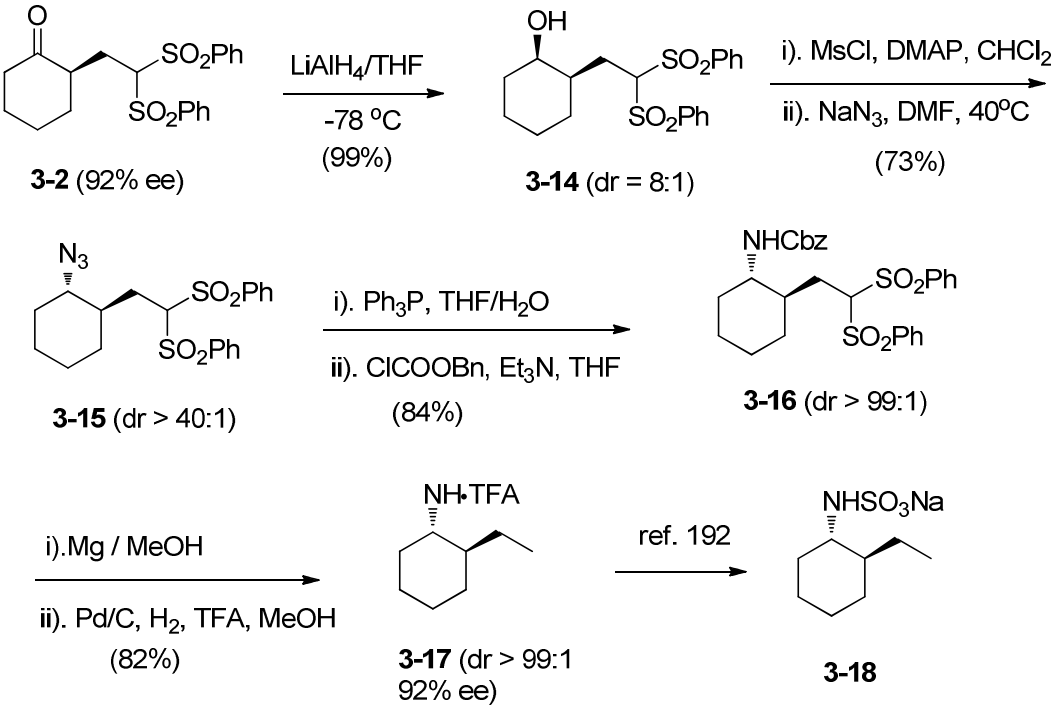


3-2 **3-14**

Reducing reagent	**Solvent**	**T/ °C**	**Yield/%**	***cis* : *trans***
$NaBH_4$	MeOH	0	> 95	1.2 : 1
	Et_2O	0	> 95	1.5 : 1
	MeOH	-78	> 95	3 : 1
	THF	0	> 95	1.5 : 1
$LiAlH_4$	THF	RT	> 95	3 : 1
	Et_2O	RT	> 95	3 : 1
	THF	0	> 95	4 : 1
	THF	**-78**	**> 95**	**8 : 1**
$Zn(BH_4)_2$	Et_2O	-78	> 95	5 : 1
$LiBH_4$	THF/EtOH	0	>95	3 : 1
L-Selectride	**THF**	**-78**	**> 95**	**1 : 6**

As shown in Scheme 3-4, subsequent reduction with $LiAlH_4$ of adduct **3-2** gave *cis*-**3-14** with 8:1 dr. Conversion of **3-14** into azide **3-15** proceeded well in 73% yield. Azide **3-15** was subjected to the reduction and protection steps to yield *trans*-**3-16** as a single diastereomer. Desulfonation with magnesium in methanol and removal of sulfone groups yielded chiral amine salt **3-17**, the transformation of which into sodium cyclamate **3-18** was well documented in literature.[192] It should be noted that the reduction of ketone **3-2** with L-selectride yielded *trans*-**3-14**, providing an easy

access to both *cis*- and *trans*-isomers of sodium cyclamate.



Scheme 3-4 A synthesis of (*S*, *S*)-sodium cyclamate

3.6 Conclusions

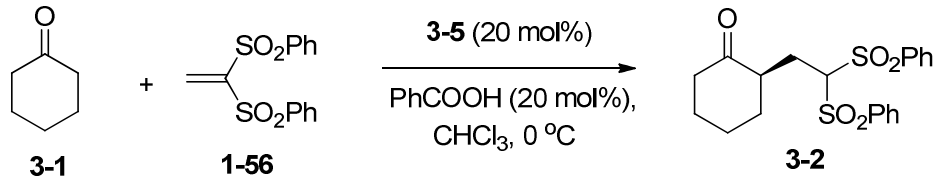
In conclusion, we have disclosed the first highly enantioselective organocatalytic conjugate addition of cyclic ketones to vinyl sulfone mediated by a cinchonidine-derived primary amine catalyst. The methodology described in this project provides an easy access to α-alkylated carbonyl compounds and their derivatives. More importantly, the product was very useful and could be used to synthesize sodium cyclamate.

3.7 Experimental Section

3.7.1 General Methods

The general methods of Chapter 2 were followed.

3.7.2 Representative Procedure for the Conjugate Addition of Cyclohexanone to 1,1-Bis(benzenesulfonyl)ethylene

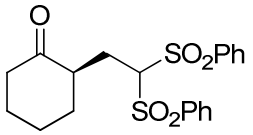


3-1 + 1-56 → 3-2

Cyclohexanone **3-1** (50 μL, 0.5 mmol) was added to a mixture of (*S*)-quinolin-4-yl((2*S*)-8-vinylquinuclidin-2-yl)methanamine **3-5** (3.0 mg, 0.01 mmol), benzoic acid (1.22 mg, 0.01 mmol) and 1,1-bis(benzenesulfonyl)ethylene **1-56** (15.4 mg, 0.05 mmol) in anhydrous chloroform (0.05 mL) in a vial at 0 ^{o}C. The vial was then capped, and the reaction mixture was stirred at 0 ^{o}C for 2 h. The reaction was quenched with the addition of 1N HCl (2 mL), and the mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (ethyl acetate /hexanes = 1:5 to 1:3) afforded the adduct **3-2** as a white solid (18.3 mg, 93%).

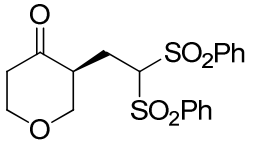
3.7.3 Characterizations of Intermediates and Adducts

(*R*)-2-(2,2-Bis(phenylsulfonyl)ethyl)cyclohexanone (**3-2**)



A white solid; $[\alpha]_D$ = + 17.2 (c = 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.25-1.31 (m, 2H), 1.56-1.84 (m, 2H), 1.96-2.11 (m, 3H), 2.29-2.34 (m, 2H), 2.49- 2.52 (m, 1H), 3.06-3.10 (m, 1H), 4.96-5.00 (m, 1H), 7.54-7.59 (m, 4H), 7.68-7.70 (m, 2H), 7.88-7.96 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.01, 26.52, 27.82, 34.81, 42.04, 47.37, 80.73, 128.49, 129.06, 129.29, 129.76, 130.17, 133.66, 134.44, 134.62, 138.01, 138.06, 212.39; HRMS (ESI) m/z calcd for $C_{20}H_{22}O_5S_2$ $[M+Na]^+$ 429.0801, found 429.0799; The ee value of **3-2** is 92%, t_R (major) = 23.6 min, t_R (minor) = 32.4 min (Chiralcel AS-H, λ = 220 nm, 30% ^{i}PrOH/hexanes, flow rate = 1.0 mL/min).

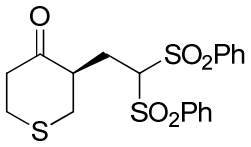
(*S*)-3-(2,2-Bis(phenylsulfonyl)ethyl)-tetrahydropyran-4-one (**3-7a**)



A colorless oil; $[\alpha]_D$ = + 23.3 (c = 1.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.84-1.92 (m, 1H), 2.31-2.36 (m, 1H), 2.56-2.62 (m, 2H), 3.66-3.69 (m, 1H),4.12-4.17 (m, 2H), 4.93-4.96 (m, 1H), 7.55-7.60 (m, 4H), 7.60-7.69 (m, 2H), 7.71-7.96 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.29, 42.30, 48.26, 68.58, 72.43, 80.34, 129.12, 129.16, 129.35, 129.67, 134.55, 134.73, 176.15; HRMS (ESI) m/z calcd for $C_{19}H_{20}O_6S_2$ $[M-H]^-$ 407.0629, found 407.0629; The ee value of **3-7a** is 91%, t_R (major) = 30.4 min,

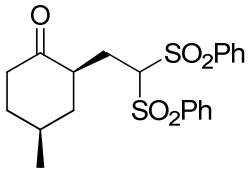
t_R (minor) = 45.3 min (Chiralcel AS-H, λ = 220 nm, 40% ^{i}PrOH/hexanes, flow rate = 1.0 mL/min).

(*R*)-3-(2,2-Bis(phenylsulfonyl)ethyl)-tetrahydrothiopyran-4-one (**3-7b**)



A colorless oil; $[\alpha]_D$ = + 34.3 (c = 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89-0.91 (m, 1H), 1.27-1.29 (m, 1H), 2.05-2.13 (m, 1H), 2.79-2.73 (m, 3H), 2.94- 2.96 (m, 2H), 3.43-3.46 (m, 1H), 4.86-4.90 (m, 1H), 7.60-7.63 (m, 4H), 7.73-7.75 (m, 2H), 7.92-8.00 (m, 4H); ^{13}C NMR (75 MHz, CDCl3) δ 26.17, 30.82, 36.23, 44.04, 49.82, 128.85, 128.90, 129.06, 129.11, 129.26, 129.54, 129.63, 134.47, 134.66, 137.75, 209.42; HRMS (ESI) m/z calcd for $C_{19}H_{20}O_5S_3$ $[M-H]^-$ 423.0400, found 423.0387; The ee value of **3-7b** is 95%, t_R (major) = 32.3 min, t_R (minor) = 47.8 min (Chiralcel AS-H, λ = 220 nm, 40% ^{i}PrOH/hexanes, flow rate = 1.0 mL/min.

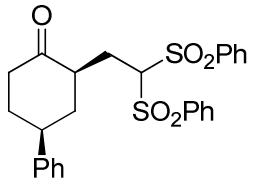
(2*R*,4*S*)-2-(2,2-Bis(phenylsulfonyl)ethyl)-4-methylcyclohexanone (**3-7c**)



A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12-1.15 (d, *J* = 6.9 Hz, 3H), 1.12-1.25 (m, 1H), 1.59-2.04 (m, 4H), 2.21-2.60 (m, 4H), 2.96-3.02 (m, 1H), 4.84-4.88 (m, 1H), 7.53-7.58 (m, 4H), 7.67-7.69 (m, 2H), 7.87-7.94 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 26.7, 33.3, 37.6, 40.0, 42.8, 43.9, 46.2, 80.8, 128.9, 129.2, 129.5,

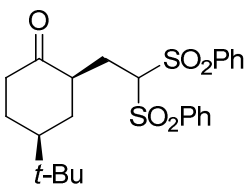
134.5, 212.9; HRMS (ESI) m/z calcd for $C_{21}H_{24}O_5S_2$ $[M+Na]^+$ 443.0957, found 443.0965; The ee value of **3-7c** is 96%, tr (major) = 58.3 min, tr (minor) = 85.0 min (Chiralcel AS-H, λ = 220 nm, 20% ^{i}PrOH/Hexanes, flow rate = 1.0 mL/min).

(2*R*,4*S*)-2-(2,2-Bis(phenylsulfonyl)ethyl)-4-phenylcyclohexanone (**3-7d**)



A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85-0.91 (m, 1H), 1.24-1.25 (m, 1H), 1.88-1.93 (m, 1H), 2.13-2.22 (m, 3H), 2.39-2.41 (m, 2H), 2.78-2.83 (m, 1H), 3.13-3.16 (m, 1H), 4.76-4.79 (m, 1H), 7.29-7.38 (m, 5H), 7.52-7.68 (m, 6H), 7.85-7.90 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.69, 31.72, 36.97, 38.19, 38.31, 45.54, 80.29, 126.64, 128.72, 129.10, 129.34, 129.40, 134.46, 134.51, 137.85, 143.29, 212.57; HRMS (ESI) m/z calcd for $C_{26}H_{26}O_5S_2$ $[M+Na]^+$ 505.1104, found 505.1102; The ee value of **3-7d** is 97%, tr (major) = 16.9 min, tr (minor) = 21.3 min (Chiralcel AD-H, λ = 220 nm, 30% ^{i}PrOH/Hexanes, flow rate = 1.0 mL/min).

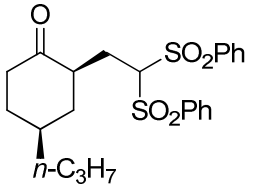
(2*R*,4*S*)-2-(2,2-Bis(phenylsulfonyl)ethyl)-4-*tert*-butylcyclohexanone (**3-7e**)



A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (m, 9H), 1.24-1.26 (m, 1H), 1.49-1.51 (m, 2H), 1.68-1.74 (m, 1H), 1.89-1.95 (m 2H), 2.25-2.35 (m, 3H), 2.60-2.80 (m,

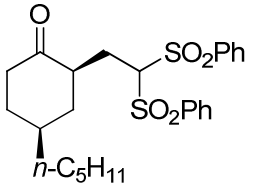
2H), 4.75-4.78 (m, 1H), 7.53-7.68 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.99, 26.85, 28.59, 31.25, 35.88, 38.55, 41.74, 46.36, 80.15, 129.00, 129.11, 129.26, 129.38, 129.67, 134.46, 134.52, 214.50; HRMS (ESI) m/z calcd for $C_{24}H_{30}O_5S_2$ $[M+Na]^+$ 485.1427, found 485.1430; Ee of **3-7e** is 95%, tr (major) = 12.2 min, tr (minor) = 35.6 min (Chiralcel AS-H, λ = 220 nm, 30% ^{i}PrOH/Hexanes, flow rate = 1.0 mL/min).

(2*R*,4*S*)-2-(2,2-Bis(phenylsulfonyl)ethyl)-4-propylcyclohexanone (**3-7f**)



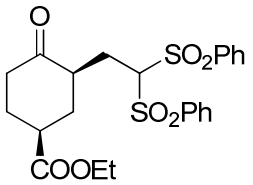
A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91-0.97 (m, 3H), 1.21-1.46 (m, 4H), 1.57-1.61 (m, 1H), 1.72-1.82 (m ,3H), 2.02-2.03 (m, 1H), 2.21-2.63 (m, 3H), 2.94-3.13 (m, 1H), 4.86-5.02 (m, 1H), 7.55-7.57 (m, 4H), 7.66 (m, 2H), 7.88-7.94 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.11, 20.20, 26.66, 31.60, 34.88, 36.28, 40.83, 43.89, 46.23, 80.53, 128.94, 129.02, 129.20, 129.28, 129.49, 129.66, 134.36, 134.50, 137.98, 213.07; HRMS (ESI) m/z calcd for $C_{23}H_{28}O_5S_2$ $[M+Na]^+$ 471.1270, found 471.1282; The ee value of **3-7f** is 94%, tr (major) = 39.2 min, tr (minor) = 48.8 min (Chiralcel AS-H, λ = 220 nm, 20% ^{i}PrOH/Hexanes, flow rate = 0.5 mL/min).

(2*R*,4*S*)-2-(2,2-Bis(phenylsulfonyl)ethyl)-4-pentylcyclohexanone (**3-7g**)



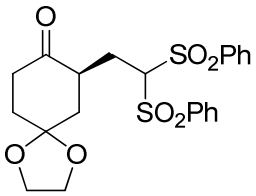
A colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88-0.97 (m, 3H), 1.25-1.45 (m, 10H), 1.79-2.04 (m, 4H), 2.16-2.32 (m, 2H), 2.94-3.15 (m, 1H), 4.85-5.03 (m, 1H), 7.55-7.58 (m, 4H), 7.67-7.88 (m, 2H), 7.91-7.94 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.94, 22.57, 27.24, 31.84, 32.67, 35.61, 36.57, 37.98，41.24, 43.92, 46.23, 80.53, 128.93, 129.01, 129.50, 129.66, 134.31, 134.35, 134.48, 137.93, 138.00, 213.08; HRMS (ESI) m/z calcd for $C_{25}H_{32}O_5S_2$ $[M+Na]^+$ 499.1583, found 499.1591; The ee value of **3-7g** is 90%, tr (major) = 29.0 min, tr (minor) = 31.6 min (Chiralcel AD-H, λ = 220 nm, 20% ^{i}PrOH/Hexanes, flow rate = 0.5 mL/min).

(1*S*,3*R*)-Ethyl 3-(2,2-bis(phenylsulfonyl)ethyl)-4-oxocyclohexanecarboxylate (**3-7h**)



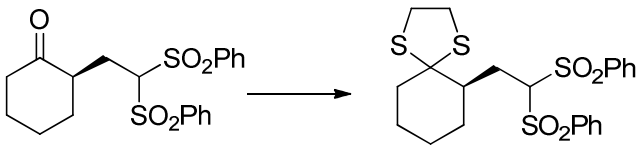
A yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26-1.34 (m, 4H), 1.52-1.58 (m, 1H), 1.84-1.94 (m, 2H), 2.26-2.30 (m, 1H), 2.38-2.60 (m, 3H), 2.63-2.64 (m, 1H), 2.82-3.24 (m, 1H), 4.10-4.28 (m, 2H), 4.88-5.01 (m , 1H), 7.56-7.60 (m, 4H), 7.67-7.70 (m, 2H), 7.89-7.97 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.20, 26.02, 28.24, 34.68, 32.67，38.40, 38.66, 44.04, 61.09, 80.66, 128.38, 128.98, 129.03, 129.07, 129.19, 129.23, 129.68, 129.82, 134.32, 134.54, 137.38, 138.22, 173.37, 211.14; HRMS (ESI) m/z calcd for $C_{23}H_{26}O_7S_2$ $[M+Na]^+$ 501.1012, found 501.1018; The ee value of **3-7h** is 88%, tr (major) = 28.1 min, tr (minor) = 35.1 min (Chiralcel AS-H, λ = 220 nm, 30% ^{i}PrOH/Hexanes, flow rate = 1.0 mL/min).

(*R*)-7-(2,2-Bis(phenylsulfonyl)ethyl)-1,4-dioxaspiro[4.5]decan-8-one (**3-7i**)



A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61-1.66 (m, 1H), 1.87-2.05 (m, 2H), 2.28-2.31 (m, 1H), 2.55-2.57 (m, 1H), 2.64-2.66 (m, 2H), 3.35-3.39 (m, 1H), 3.99-4.07 (m, 4H), 4.94-4.97 (m, 1H), 7.54-7.58 (m, 4H), 7.66-7.71 (m, 2H), 7.90-7.96 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.15, 34.52, 37.96, 41.04, 43.41, 64.61, 64.80, 80.67, 106.72, 129.02, 129.28, 129.63, 134.35, 134.51, 137.97, 210.81; HRMS (ESI) m/z calcd for $C_{22}H_{24}O_7S_2$ $[M+Na]^+$ 487.0856, found 487.0859; The ee value of **3-9i** is 90%, tr (major) = 28.2 min, tr (minor) = 45.1 min (Chiralcel AS-H, λ = 220 nm, 40% ^{i}PrOH/Hexanes, flow rate = 1.0 mL/min).

(*R*)-6-(2,2-Bis(phenylsulfonyl)ethyl)-1,4-dithiaspiro[4.5]decane (**3-8**)



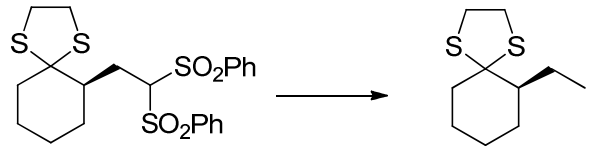
3-2 **3-8**

To a stirred solution of ketone **3-2** (406 mg, 1.0 mmol) and 1,2-ethanedithiol (0.17 mL, 2.0 mmol) in anhydrous dichloromethane (5 mL) at 0 ^{o}C, was added a catalytic amount of $BF_3{\cdot}Et_2O$, and the resultant was warmed up to room temperature and kept for 2 h. Aqueous NaOH (5%) (2 mL) was then added, and the resulting mixture was extracted with dichloromethane (3 x 6 mL). The combined organic layers were washed with brine (2 x 8 mL), dried over sodium sulfate and concentrated. The

residue was purified by flash chromatography (ethyl acetate /hexanes = 1:10 to 1:3) to furnish thioketal **3-8** (424 mg, 88%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88-0.92 (m, 1H), 1.16-1.25 (m, 1H), 1.47-1.67 (m, 4H), 1.81-18.6 (m, 1H), 2.02-2.15 (m, 3H), 2.80-2.83 (m, 1H), 3.11-3.21 (m, 4H), 4.81-4.83 (t, *J* = 5.1 Hz, 3H), 7.57-7.58 (m, 4H), 7.66-7.69 (m, 2H), 7.94-7.95 (m, 2H), 8.03-8.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.88, 25.36, 28.90. 31.45, 38.79, 39.14, 44.87, 45.64, 74.29, 82.34, 128.97, 129.14, 129.50, 129.59, 130.18, 134.52, 134.56, 137.49, 138.30; $[\alpha]_D$ = + 18.9 (c = 2.1, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{22}H_{26}O_4S_4$ $[M+Na]^+$ 505.0597, found 505.0593.

(*S*)-6-Ethyl-1,4-dithiaspiro[4.5]decane (**3-9**)

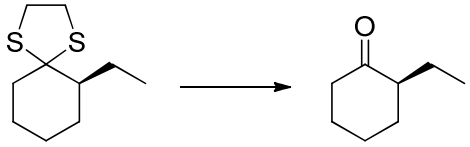


3-8 **3-9**

The activated magnesium metal (0.72 g, 30 mmol) was added to a solution of sulfone **3-8** (386 mg, 0.8 mmol) in anhydrous methanol (30 mL) with stirring. The mixture was heated to 50 ^{o}C to initiate continuous hydrogen generation, and then heating was discontinued. After 30 min, the reaction mixture was brought to gentle reflux for 2 h. After cooling down to room temperature, the mixture was poured into 2N HCl (10 mL) and extracted with ether (3 x 10 mL). The organic extracts were combined, dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo*, and the residue was purified by flash column chromatography (ethyl acetate /hexanes = 1:50 to 1:20) to afford the desired product **3-9** as a yellow oil (147 mg, 91%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89-0.92 (t, *J* = 7.5 Hz, 3H), 1.10-1.15 (m, 1H), 1.23-1.25 (m, 3H), 1.50-1.66 (m, 4H), 1.88-1.99 (m, 3H), 2.16-2.19 (d, *J* = 8.0 Hz, 1H), 3.20-3.27 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.30, 24.65, 26.08, 29.70, 30.38, 38.97, 39.08, 45.01, 50.02, 75.09; $[\alpha]_D$ = + 28.4 (c = 1.3, $CHCl_3$).

(*S*)-2-Ethylcyclohexanone (**3-10**)

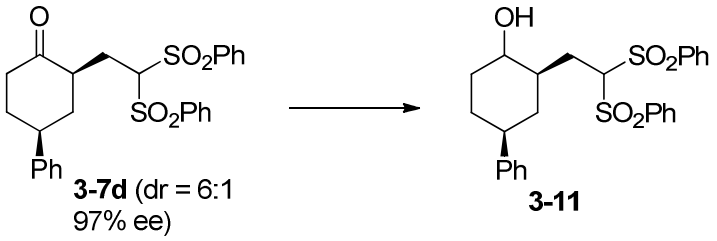


3-9 **3-10**

To a stirred solution of **3-9** (100 mg, 0.50 mmol) in CH_3CN/H_2O (9 mL/1 mL) was added $(CF_3CO_2)_2IPh$ (324 mg, 0.75 mmol). The mixture was stirred at room temperature for 10 min, and then quenched by the addition of saturated aqueous sodium carbonate (15 mL). The mixture was extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were dried with $MgSO_4$. The solvent was filtered and removed under reduced pressure. The residue was purified by flash chromatography (ethyl acetate /hexanes = 1:40 to 1:10) to afford ketone **3-10** (55 mg, 87 %) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88-0.91 (t, *J* = 7.6 Hz, 3H), 1.24-1.29 (m, 1H), 1.38-1.41 (m, 1H), 1.66-1.69 (m, 2H), 1.78-1.83 (m, 2H), 2.00-2.02 (m, 1H), 2.08- 2.12 (m, 1H), 2.18-2.20 (m, 1H), 2.25-2.32 (m, 1H), 2.36-2.37 (m, 1H); $[\alpha]_D$ = + 22.1 (c = 1.4, CH_3OH, *lit*[191] = + 24.1).

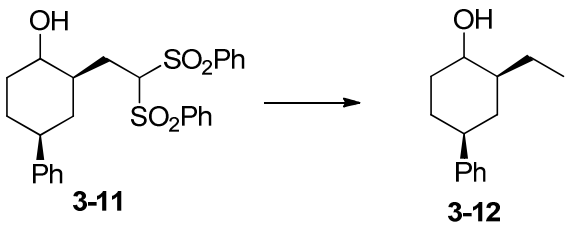
(2*R*,4*S*)-2-(2,2-Bis(phenylsulfonyl)ethyl)-4-phenylcyclohexanol (**3-11**)



$NaBH_4$ (76 mg, 2.0 mmol) was added to ketone **3-7d** (193 mg, 0.4 mmol) in methanol (20 mL) at 0 ^oC. After stirring for 1 h, aqueous HCl 1N (5 mL) was added to the mixture. The solution was extracted with ether (3 x 5 mL). The organic extracts were combined, dried over Na_2SO_4 and filtered to afford **3-11** as a colorless oil without further purification (190 mg, 97%).

^1H NMR (500 MHz, $CDCl_3$) δ 1.45-1.85 (m, 6H), 2.20-2.49 (m, 2H), 2.51-2.58 (m, 1.4H), 2.76-2.86 (m, 0.5H), 3.34-3.36 (m, 0.4H), 3.86-3.95 (m, 0.50H), 4.59-4.61 (m, 0.13H), 5.08-5.10 (m, 0.36H), 5.41-5.44 (m, 0.43H), 7.12-7.29 (m, 5H), 7.52-7.66 (m, 6H), 7.92-8.00 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.14, 20.99, 23.35, 29.30, 30.44, 31.56, 32.04, 35.96, 42.66, 43.22, 43.66, 60.34, 65.60, 71.99, 76.05, 81.57, 82.33, 126.62, 126.78, 128.39, 128.95, 129.04, 129.12, 129.45, 129.48, 129.64, 129.68, 134.40, 134.44, 134.48, 134.52, 137.59, 137.70, 137.76, 137.92, 145.43, 145. 60; HRMS (ESI) *m/z* calcd for $C_{26}H_{28}O_5S_2$ $[M+Na]^+$ 507.1260, found 507.1263.

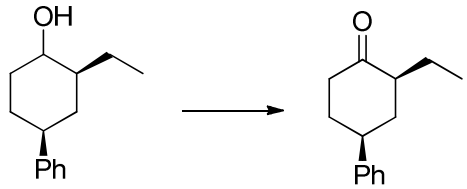
(2*S*,4*S*)-2-Ethyl-4-phenylcyclohexanol (**3-12**)



According to the procedure of preparation of **3-9**, intermediate **3-12** (33 mg, 81%) was obtained as a colorless oil from **3-11** (97 mg, 0.2 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94-0.99 (m, 3H), 1.43-1.67 (m, 6H), 1.76-1.77 (m, 1H), 1.84-1.86 (m , 1H), 1.94-1.98 (m , 1H), 2.55-2.60 (m , 0.15H, minor), 2.71-2.74 (m, 0.85H, major), 3.34-3.36 (m, 0.15H, minor), 3.89-3.90(m, 0.85H, major), 7.22-7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.09 (minor), 12.28 (major), 17.68 (major), 24.65 (minor), 30.03 (major), 31.69 (minor), 32.68 (minor), 34.31 (major), 36.01 (minor), 36.75 (major), 37.99 (minor), 41.83 (major), 43.73, 46.56, 72.56 (major), 74.17 (minor), 125.99, 126.94, 128.37, 146.39.

(2*S*,4*S*)-2-Ethyl-4-phenylcyclohexanone (**3-13**)



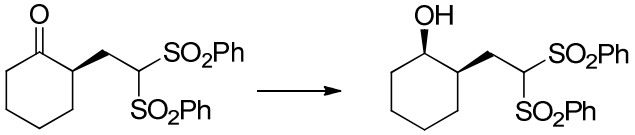
3-12 **3-13**

PCC (108 mg, 0.5 mmol) was added to the alcohol **3-12** (0.1 mmol) in anhydrous dichloromethane (5 mL). The whole mixture was stirred at rt for 2 h. Then additional dichloromethane (10 mL) was added to the mixture, which was filtered through the celite. The solvent was removed *in vacuo*, and the residue was purified by column chromatography (diethyl ether /hexanes = 1:20 to 1:5) to afford the major diastereoisomer **3-13** as a colorless oil (13 mg, 64%).

Major diastereoisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85-0.90 (t, J = 7.6 Hz, 3H), 1.14-1.18 (m, 1H), 1.52-1.58 (m, 1H), 1.76-1.83 (m, 1H), 1.95-2.09 (m, 4H), 2.32-

2.35 (m, 2H), 2.48-2.57 (m, 1H), 3.07-3.14 (m, 1H), 7.19-7.27 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.84, 24.55, 33.62, 37.43, 38.08, 38.31, 51.29, 126.46, 126.74, 128.56, 144.65, 214.37; For the major diastereoisomer, a 2D-NOESY experiment showed a correlation between the multiplet at 3.15–3.17 ppm (H-5′) and the doublet at 2.63-2.65 ppm (H-1′) which showed that these protons have a *syn* relationship.

(1*R*,2*R*)-2-(2,2-Bis(phenylsulfonyl)ethyl)cyclohexanol (**3-14**)

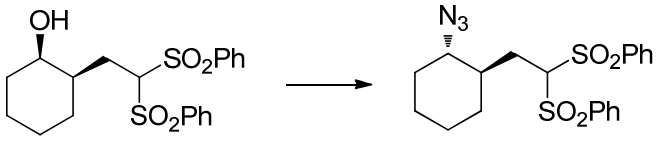


3-2 (92% ee) **3-14** (dr = 8:1)

Lithium aluminum hydride (380 mg, 10.0 mmol) was added to ketone **3-2** (406 mg, 1.0 mmol) in anhydrous tetrahydrofuran (20 mL) at -78 ^{o}C. After stirring at -78 ^{o}C for 1 h, water (10.0 mL), followed by 1N HCl (20 mL), was added carefully to destroy excess hydride. The mixture was extracted with ether several times (3 x 20 mL), and the organic extracts were combined, dried over sodium sulfate. After filtration, the filtrate was concentrated to give the desired product as a colorless oil (406 mg, 99%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80-0.91 (m, 1H), 1.09-1.23 (m, 3H), 1.60-1.96 (m, 6H), 2.01-2.50 (m, 1H), 3.19-3.25 (m, 1H), 5.35-5.39 (m, 1H), 7.53-7.58 (m, 4H), 7.55-7.56 (m, 2H), 7.70-7.97(m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.50, 25.23, 30.44, 31.48, 35.96, 42.82, 77.46, 81.71, 128.91, 129.00, 129.24, 129.42, 129.63, 134.37; HRMS (ESI) *m/z* calcd for $C_{20}H_{24}O_5S_2$ $[M+Na]^+$ 431.0957, found 431.0960.

1-(2-((1*R*,2*S*)-2-Azidocyclohexyl)-1-(phenylsulfonyl)ethylsulfonyl)benzene (**3-15**)



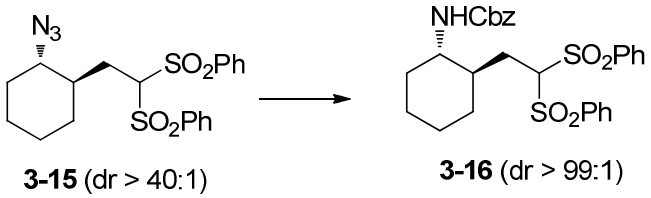
3-14 (dr = 8:1) **3-15** (dr > 40:1)

To the solution of DMAP (20 mg) and alcohol **3-14** (0.33 g, 0.8 mmol) in anhydrous dichloromethane (5 mL) at 0 °C was added methanesulfonyl chloride (114 mg, 1.0 mmol). After stirring at room temperature for 12 h, dichloromethane (20 mL) was added to the reaction mixture. The organic layer was washed with 1N HCl (3 x 10 mL), 1N NaOH (2 x 10 mL) and brine (3 x 10 mL), respectively, and the organic layer was dried over sodium sulfate. After filtration and concentration, the crude mesylate was used directly for the next step without further purification.

Sodium azide (0.65 g, 10 mmol) was added to the crude mesylate in anhydrous DMF (5 mL), and the solution was then stirred at 40 ^{o}C for 24 h. The reaction mixture was poured into ether (50 mL), and then washed with water (5 x 20 mL). The organic layer was separated, dried over Na_2SO_4 and filtered. Solvent was removed *in vacuo*, and the residue was purified by column chromatography (ethyl acetate /hexanes = 1:10 to 1:3) to afford the desired product as a colorless oil (253 mg, 73%).

$[\alpha]_D$ = - 42.1 (c = 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14-1.29 (m, 2H), 1.34-1.62 (m, 5H), 1.89-1.95 (m, 2H), 2.04-2.08 (m, 1H), 2.12-2.15 (m, 1H), 3.71 (d, *J* = 1.9 Hz, 1H), 4.49-4.51 (t, *J* = 6.3 Hz, 1H), 7.60-7.75 (m, 6H), 7.97-8.00 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.70, 24.37, 26.88, 28.69, 28.81, 37.98, 60.63, 81.08, 128.24, 129.05, 129.18, 129.57, 129.76, 134.71, 134.73, 137.72, 137.74; HRMS (ESI) *m/z* calcd for $C_{20}H_{23}N_3O_4S_2$ $[M+Na]^+$ 456.1029, found 456.1029.

Benzyl (1*S*,2*R*)-2-(2,2-bis(phenylsulfonyl)ethyl)cyclohexylcarbamate (**3-16**)



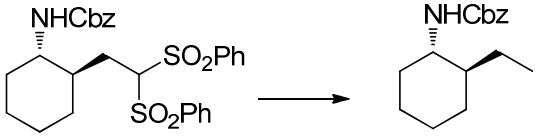
3-15 (dr > 40:1) **3-16** (dr > 99:1)

Triphenylphosphine (0.54 g, 2.0 mmol) was added to azide **3-15** (217 mg, 0.5 mmol) in THF (10 mL), followed by the addition of water (1.0 mL). The reaction mixture was stirred at room temperature for 12 h. The mixture was then concentrated, and the residue was dissolved in a mixture of diethyl ether (20 mL) and water (30 mL). The pH was adjusted to around 2 by the addition of aqueous HCl (1N). After vigorous stirring for 5 min, the organic layer was separated, and the aqueous layer was washed with diethyl ether (3 x 20 mL). The pH of the aqueous phase was adjusted to 13 by addition of aqueous 2N NaOH solution, and extracted with dichloromethane (3 x 15 mL). The organic extracts were combined, dried over Na_2SO_4 and filtered. Solvent was removed *in vacuo* to afford the crude amine, which was used directly for the next step.

To the crude amine in THF (10 mL), triethylamine (1 mmol, 0.14 mL) and benzyl carbonochloridate (120 mg, 0.7 mmol) were added, and the mixture was stirred at room temperature for 12 h. The solvent was then removed, and the residue was taken up in ethyl acetate (15 mL). The organic layer was washed with dilute HCl (3 x 10 mL), 1N aqueous NaOH (2 x 10 mL) and brine (2 x 10 mL), respectively, and dried over Na_2SO_4. After filtration, the solution was concentrated, and the residue was purified by flash column chromatography (ethyl acetate /hexanes = 1:5 to 1:3) to afford the desired product as a colorless oil (227 mg, 84%).

$[\alpha]_D$ = - 16.8 (c = 2.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.03-1.10 (m, 1H), 1.21-1.33 (m, 2H), 1.46-1.75 (m, 5H), 1.88-1.98 (m, 1H), 2.11-2.13 (m, 1H), 2.36-2.59 (m, 1H), 4.03-4.06 (m, 1H), 5.00-5.03 (d, *J* = 17.3 Hz, 1H), 5.12-5.25 (m, 2H), 5.26-5.28 (d, *J* = 12.1 Hz, 1H), 7.34-7.38 (m, 5H), 7.47-7.51 (m, 4H), 7.51-7.86 (m, 2H), 7.87-7.89 (m, 2H), 7.89-7.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.95, 24.65, 27.03, 28.37, 29.61, 30.74, 37.24, 47.19, 67.17, 77.39, 79.86, 128.17, 128.26, 128.53, 128.84, 128.93, 129.24, 129.44, 133.95, 134.32, 136.20, 137.71, 138.53, 156.34; HRMS (ESI) *m/z* calcd for $C_{28}H_{31}NO_6S_2$ $[M+Na]^+$ 564.1485, found 564.1482.

Benzyl (1*S*,2*S*)-2-ethylcyclohexylcarbamate (**3-17a**)



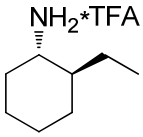
3-16 (dr > 99:1) **3-17a** (dr > 99:1 92% ee)

Following the procedure described as the compound **3-9**, compound **3-17a** (70 mg, 90%) was prepared from sulfone **3-16** (162 mg, 0.3 mmol), magnesium (270 mg, 12 mmol) and isolated as a colorless oil after flash column chromatography purification (ethyl acetate /hexanes = 1:15 to 1:8).

^1H NMR (500 MHz, $CDCl_3$) δ 0.88-0.91 (t, *J* = 7.6 Hz, 3H), 1.05-1.07 (m, 1H), 1.19-1.20 (m, 1H), 1.44-1.64 (m, 5H), 1.76-1.78 (m, 1H), 3.93-3.94 (m, 1H), 4.82 (s, 1H), 5.10 (s, 1H), 7.32-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.63, 21.50, 24.56, 24.66, 27.34, 30.89, 41.51, 49.43, 66.59, 128.10, 128.16, 128.54, 138.71, 155.96; HRMS (ESI) *m/z* calcd for $C_{16}H_{23}NO_2$ $[M+Na]^+$ 284.1621, found 284.1613.

The ee value of **3-17a** is 91%, t_R (major) = 18.8 min, t_R (minor) = 24.7 min (Chiralcel AS-H, λ = 220 nm, 5% ^{i}PrOH/hexanes, flow rate = 0.5 mL/min).

(1*S*,2*S*)-2-Ethylcyclohexanamine (**3-17**)

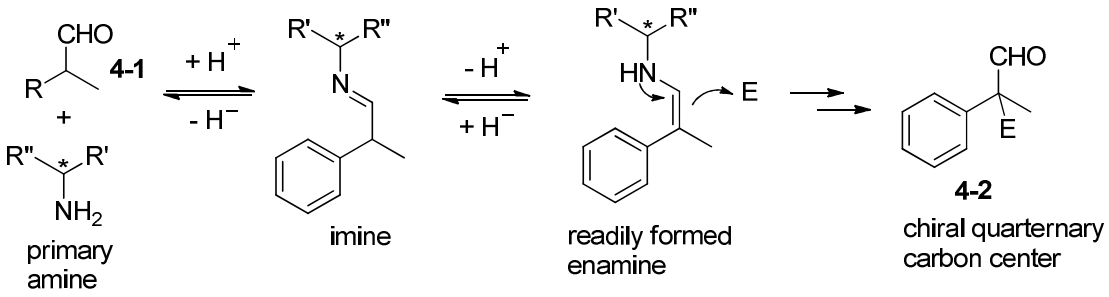


To a solution of carbamate **3-17a** (52 mg, 0.2mmol) and trifluoroacetic acid (0.1 mL) in methanol (3 mL) was added 10% Pd/C (10 mg). The resulting mixture was stirred under hydrogen gas. After one hour, the catalyst was removed by filtration through celite and concentrated *in vacuo* to yield **3-17** as a colorless oil (34 mg, 92%). ^{1}H NMR (500 MHz, CD_3OD) δ 0.98-1.01 (t, *J* = 7.6 Hz, 3H), 1.31-1.42 (m, 4H), 1.52-1.64 (m, 4H), 1.73-1.74 (m, 2H), 3.41-3.42 (m, 1H), which was in agreement with literature data.[192]

Chapter 4 Chiral Primary Amine Mediated Conjugate Addition of Branched Aldehydes to Vinyl Sulfone

4.1 Branched Aldehydes in Conjugate Addition

To further extend the scope of conjugate additions to vinyl sulfones, branched aldehydes were thought to be good donors. In order to promote the conjugate addition of the branched aldehydes to vinyl sulfone, primary amines might be a good choice. Compared with a secondary amine catalyst, a sterically less-hindered primary amine reacts readily with an α-branched aldehyde to yield an imine (Scheme 4-1). The presence of the phenyl ring makes the tautomerization to the crucial enamine intermediate favourable due to conjugation, and the subsequent reaction of the enamine intermediate with suitable electrophiles then generates a quaternary center.



Scheme 4-1 The enamine formation between 2-phenylpropanal and primary amine

Construction of quaternary stereogenic centers is one of the most challenging synthetic tasks, and has attracted much attention from organic chemists in the past decade.[193] The all-carbon quaternary chiral center with an adjacent functionality is a

useful structural scaffold, existing widely in many biologically and medicinally important molecules[194] (Fig. 4-1). However, there are only a few methods available which allows their efficient catalytic asymmetric synthesis.[195] To devise a synthetic method to access these structural units, we chose to focus on the potential activation of 2-aryl-substituted propanals via primary amine-induced enamine formation.[196] With a properly designed chiral primary amine catalyst, the conjugate addition of 2-aryl-substituted propanals to vinyl sulfones may proceed stereoselectively to create chiral quaternary carbon centers,[197] and the subsequent conversion of the sulfone groups to hydrogen atoms or alkyl groups[198] then generates all-carbon quaternary stereogenic centers with tunable alkyl chains. In this project, we show that a novel threonine-derived primary amine with an *N*-sulfonamide group efficiently promotes the asymmetric conjugate addition of α,α-disubstituted aldehydes to vinyl sulfone, generating all-carbon quaternary chiral centers.

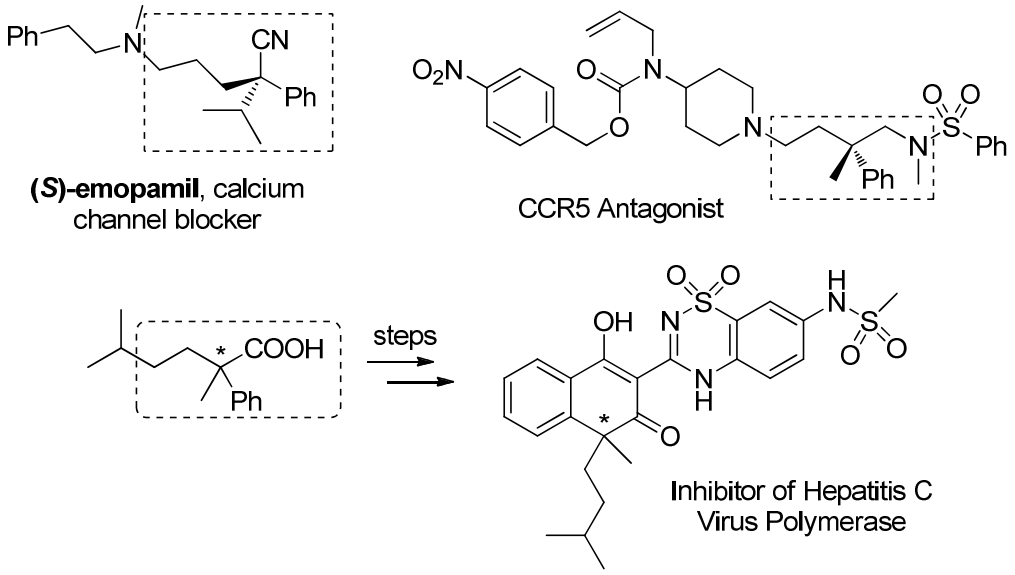
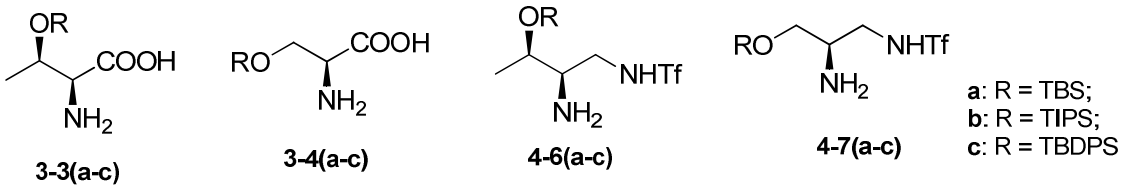


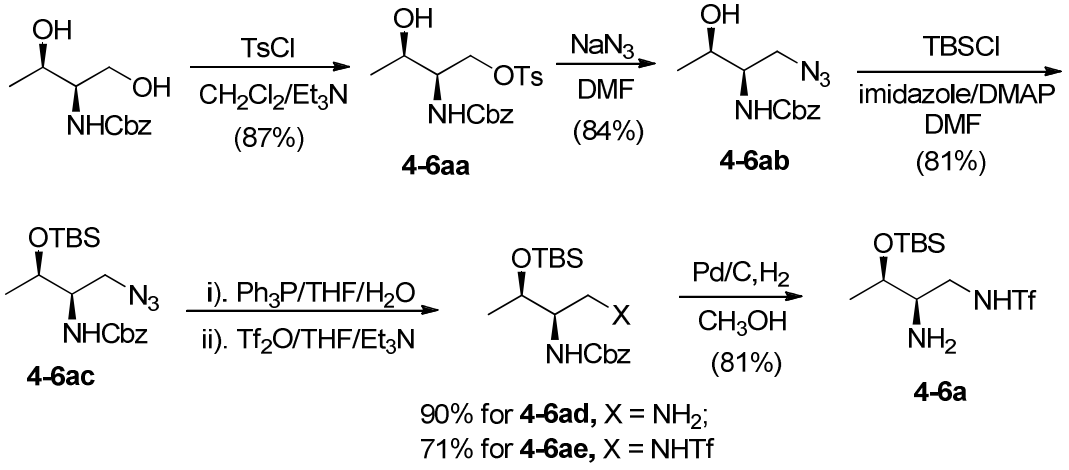
Figure 4-1 Examples showing the presence of all-carbon quaternary centers in biologically important compounds

4.2 Threonine- & Serine-Based Primary Amines Containing Sulfonamide



Scheme 4-2 Threonine-derived & serine-based primary amines

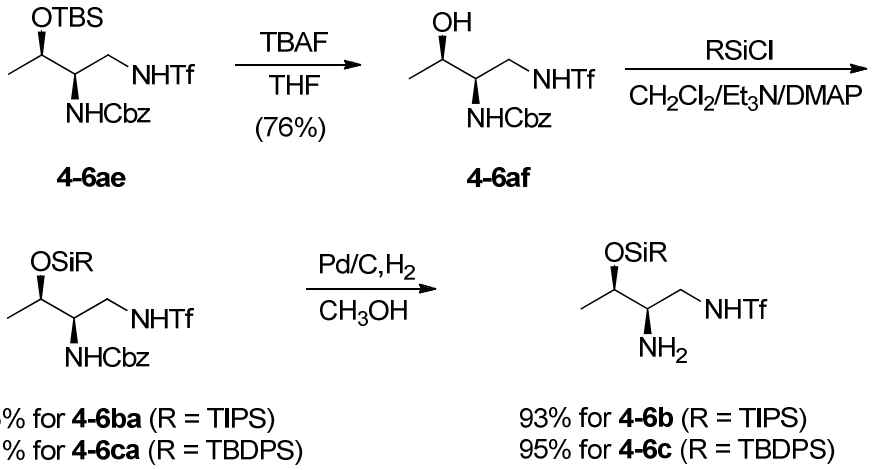
Based on our previous work, primary amines containing acid motifs are good catalysts for Aldol and Mannich reactions (Scheme 4-2). In this project, we wanted to introduce another functional group (NHTf) to increase the H-Bonding abilities. So primary amines **4-6a-c** & **4-7a-c** containing sulfonamide were synthesized.



Scheme 4-3 Synthetic scheme of threonine-based primary amine **4-6a**

Synthetic route for preparation of catalyst **4-6a** is outlined in Scheme 4-3. Benzyl ((2*R*,3*R*)-1,3-dihydroxybutan-2-yl)carbamate reacted with 4-toluene-1-sulfonyl chloride (TsCl) at 0 ^{o}C to yield the intermediate **4-6aa** in 87% yield. After subsequent

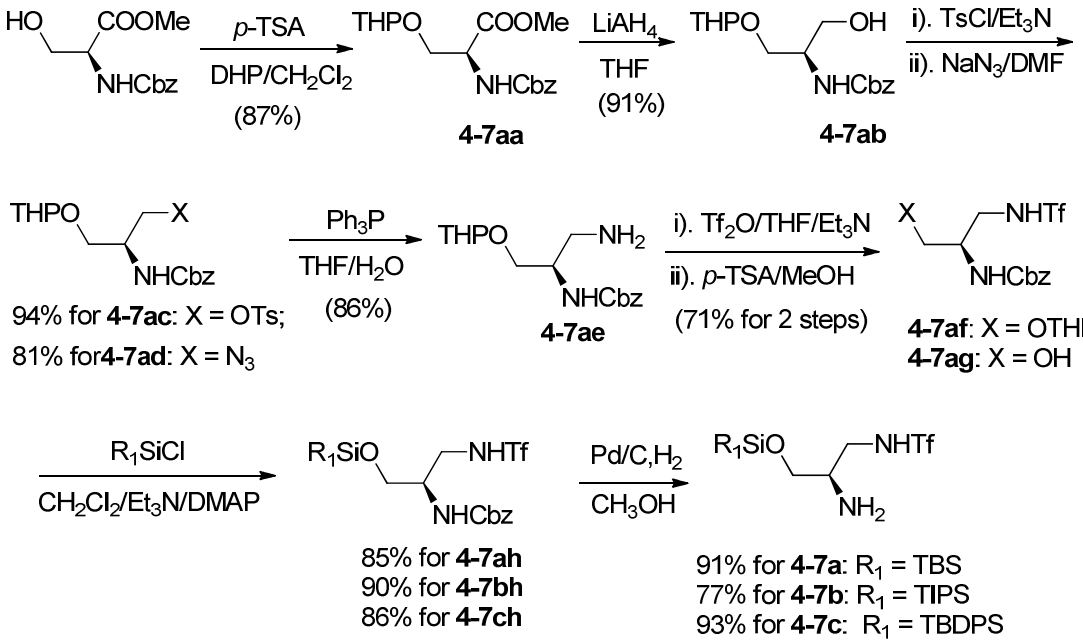
substitution with sodium azide, **4-6aa** could be converted into azide **4-6ab** in 84% yield. Silylation of the alcohol **4-6ab** with *tert*-butyldimethylsilyl chloride yielded azide **4-6ac** in 81% yield. The azide **4-6ac** was reduced with Ph_3P to amine **4-6ad** in good yield. The amine **4-6ad** reacted with Tf_2O to generate the sulfonamide **4-6ae** in 71% yield. After hydrogenation, the catalyst **4-6a** could be obtained in good yield. As shown in Scheme 4-4, another two catalysts **4-6b/c** were prepared. Removal of the silyl group in **4-6ae** with TBAF afforded alcohol **4-6af** in 76% yield. Silyation of the alcohol **4-6af** afforded the intermediates **4-6ba/ca** in good yields, and the catalysts **4-6b/c** could be obtained in > 90% yield after hydrogenation.



Scheme 4-4 Synthetic route of threonine-based primary amines **4-6b/c**

As shown in Scheme 4-5, primary amines **4-7a-c** were prepared. Protection of *N*-Cbz-serine methyl ester with dihydropyran afforded ester **4-7aa**. Reduction of the ester **4-7aa** with $LiAlH_4$ generated alcohol **4-7ab**. After subsequent three steps, the alcohol **4-7ab** could be converted into amine **4-7ae** in overall 60% yield. The amine **4-7ae** reacted with Tf_2O to yield sulfonamide **4-7af** and in situ removal of the

protecting group in **4-7af** yielded alcohol **4-7ag** in 71% yield. After silylation of the alcohol **4-7ag** and hydrogenation of **4-7ah-ch** with Pd/C, the catalysts **4-7a-c** were obtained in overall good yields.



Scheme 4-5 Synthetic route of serine-based primary amines **4-7a-c**

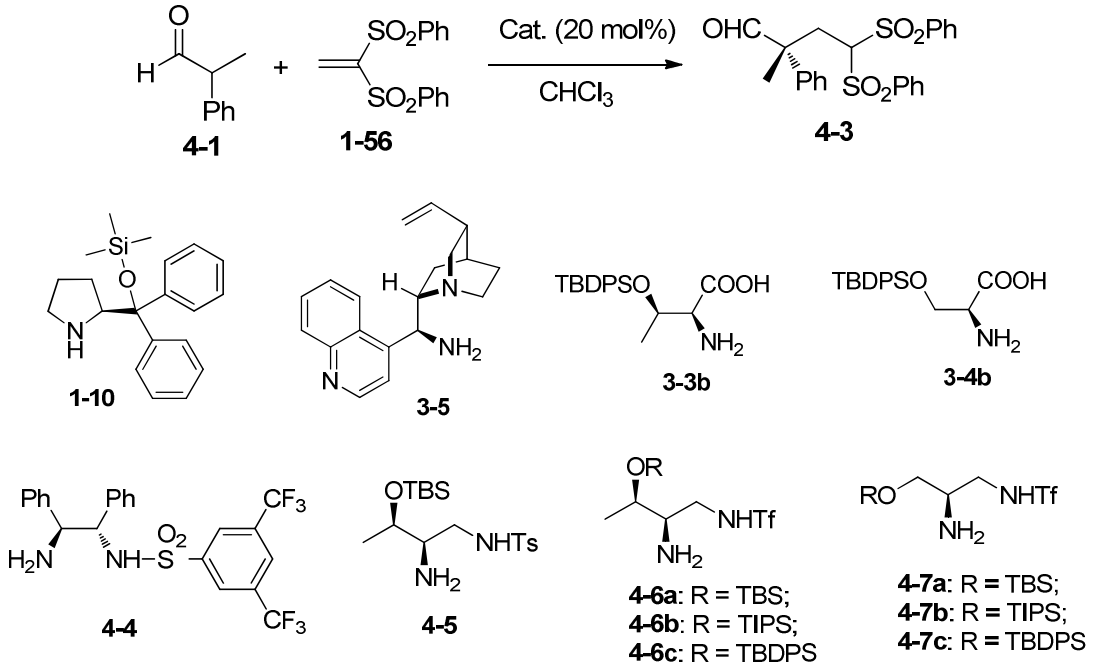
4.3 Results and Discussion

4.3.1 Catalyst Screen

We began our initial investigation by the addition of 2-phenylpropanal **4-1** to vinyl sulfone **1-56**. A wide range of amine catalysts were screened (Table 4-1). Not surprisingly, L-proline was ineffective, affording the desired product in moderate yield and with poor enantioselectivity (entry 1). Silylated biarylprolinol **1-10** also led to poor stereoselectivity (entry 2). Sulfonamide derivative of (*S*,*S*)-1,2-diphenylethylene-diamine (DPEN) **4-4** afforded the adduct in very poor yield (entry 6). Cinchonidine-

derived primary amine **3-5** turned out to be a good catalyst, yielding the desired adduct in high yield and with good enantioselectivity (entry 3). Threonine and serine-based catalysts **3-3b** and **3-4b**, yielded the product in high yield, but with low enantioselectivity (entries 4 & 5). Threonine-derived *N*-tosylsulfonamide **4-5** offered similar stereoselectivity as *O*-silylated threonine (entry 7). For various *N*-trifluoro-methanesulfonamide catalysts, threonine (**4-6a-c**) and serine-based (**4-7a-c**) structural motifs displayed similar catalytic efficiency (entries 8-13). Threonine-based *O*-TBS-*N*-sulfonamide **4-6a** was found to be the best catalyst, affording the desired adduct in 94% yield and with 74% ee (entry 8).

Table 4-1 Screening of catalysts for the conjugate addition of 2-phenylpropanal to vinyl sulfone[a]



Entry	Catalyst	Temp/ °C	Yield/[b] (%)	*ee*[c] (%)
1	**proline**	RT	60	25
2	**1-10**	RT	82	24

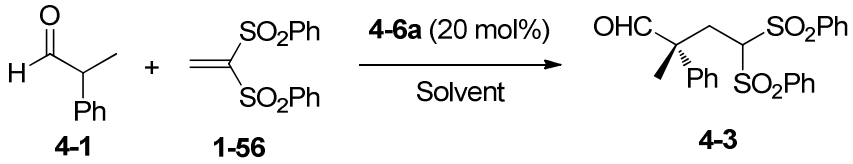
3	**3-5**	RT	75	70
4	**3-3b**	RT	85	44
5	**3-4b**	RT	90	45
6	**4-4**	RT	< 30	70
7	**4-5**	RT	74	44
8	**4-6a**	RT	94	74
9	**4-6b**	RT	93	56
10	**4-6c**	RT	93	55
11	**4-7a**	RT	91	72
12	**4-7b**	RT	87	56
13	**4-7c**	RT	71	61

[a] The reactions were performed with aldehyde (0.1 mmol), vinyl sulfone (0.05 mmol) and catalyst (0.01 mmol) in indicated solvent (0.1 mL) at room temperature for 4 h, unless otherwise specified. [b] Isolated yield. [c] The *ee* value was determined by chiral HPLC analysis.

4.3.2 Solvent & Temperature Screen

After identification of **4-6a** as the best catalyst, a series of solvents were further screened (Table 4-2). Polar solvents, such as DMF, were not suitable (entry 5). Non-polar solvents, such as CH_2Cl_2 and Et_2O, were suitable, mediating the reaction in good yields (81-94%), but the enantioselectivity were only moderate (entries 1, 3 & 4). Toluene was suitable, affording **4-3** in 93% yield and with 76% ee (entry 6). A series of substituted toluenes were tested (entries 7 & 8). *p*-Fluorotoluene was the best solvent, improving ee value to 79% while maintaining the excellent yield (entry 7). However, lowering the temperature did not give better enantioselectivity (entry 9). By performing the reaction with lower substrate concentration and lower catalyst loading (5 mol%), we were able to further improve the ee value to 83% (entry 10).

Table 4-2 Screening of solvents for the asymmetric conjugate addition of 2-phenyl-propanal to vinyl sulfone[a]



4-1 **1-56** **4-3**

Entry	Solvent	Temp/ °C	Yield/[b] (%)	*ee*[c] (%)
1	CH_2Cl_2	RT	88	62
2	MeOH	RT	81	40
3	THF	RT	94	57
4	Et_2O	RT	82	65
5	DMF	RT	67	8
6	toluene	RT	93	76
7	***p*-F-toluene**	**RT**	**92**	**79**
8	trifluorobenene	RT	91	76
9	*p*-F-toluene	0	72	72
10[d]	***p*-F-toluene**	**RT**	**93**	**83**

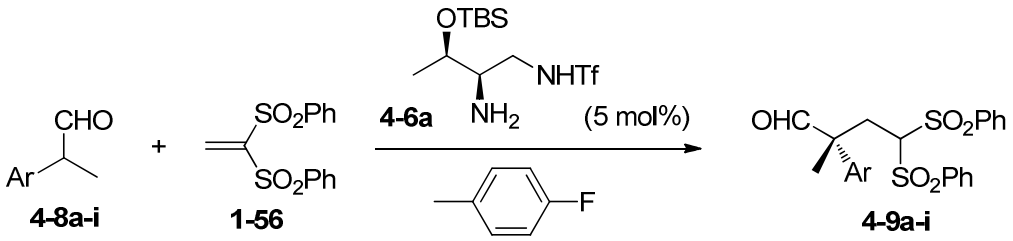
[a] The reactions were performed with aldehyde (0.1 mmol), vinyl sulfone (0.05 mmol) and catalyst (0.01 mmol) in indicated solvent (0.1 mL) at room temperature for 4 h, unless otherwise specified. [b] Isolated yield. [c] The ee value was determined by chiral HPLC analysis. [d] catalyst loading (0.0025mmol) and *p*-F-toluene (0.4 mL).

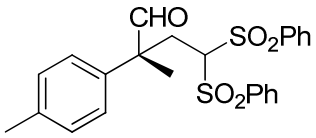
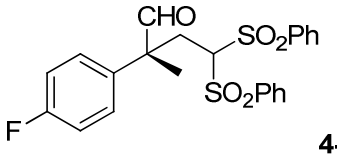
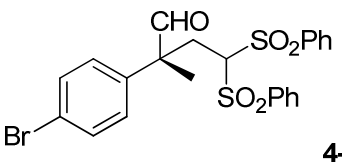
4.3.3 Scope of Branched Aldehydes

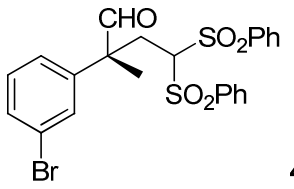
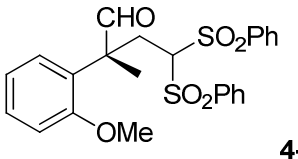
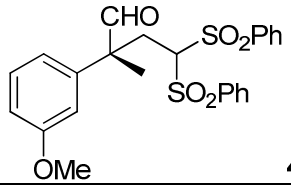
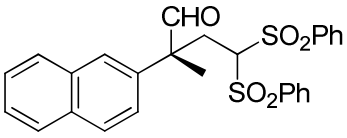
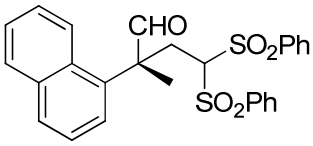
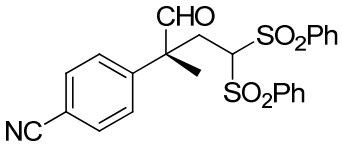
Having established the optimal conditions, we next examined the reaction scope (Table 4-3). Various 2-aryl-substituted propanals could be employed as donors, and the products were obtained in excellent yields and with good enantioselectivities (entries 1-8). For example, when 2-4'-Br-phenyl-substituted propanal was employed, 87% yield and 80% ee were obtained (entry 3). Although good results were obtained, there were still some problems unsolved. An electron-withdrawing group on the

aromatic ring was found to be detrimental, leading to a lower chemical yield and enantioselectivity (entry 9). When methyl group was changed to other alkyl group, the reaction could not proceed. For example, when 2-phenylbutanal was employed, 67% yield and 23% ee were obtained. When the aromatic ring was changed to aliphatic group, the reaction could not proceed. For example, when 2-ethylpentanal was utilized as a donor, no desired product was obtained. The reason could be that in the absence of an aromatic ring, tautomerization of imine to enamine might not occur readily, resulting in inefficient enamine catalysis.

Table 4-3 Asymmetric conjugate addition of 2-aryl-substituted propanals to vinyl sulfone catalyzed by chiral amine **4-6a**[a]



Entry	Product	T/(h)	Yield/[b] (%)	*ee*/[c] (%)
1	 **4-9a**	12	93	81
2	 **4-9b**	12	90	75
3	 **4-9c**	12	87	80

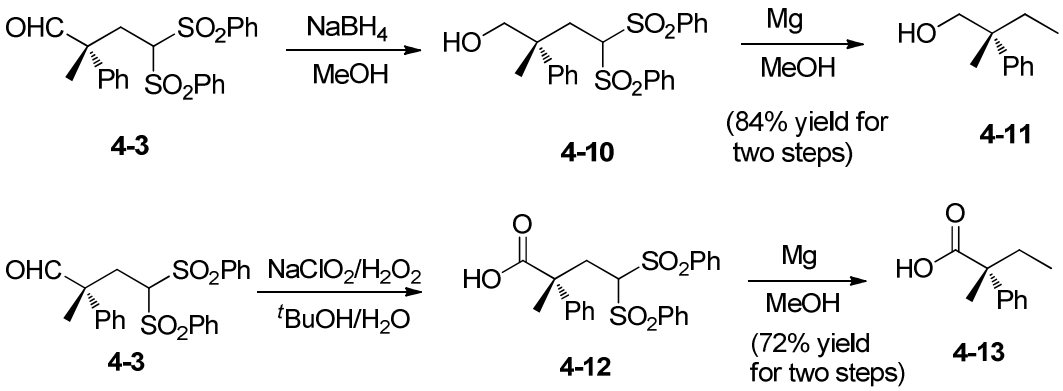
4	 **4-9d**	12	91	80
5	 **4-9e**	10	93	82
6	 **4-9f**	12	95	80
7	 **4-9g**	14	91	77
8	 **4-9h**	18	90	86
9	 **4-9i**	24	76	68

[a] The reactions were performed with aldehyde (0.1 mmol), vinyl sulfone (0.05 mmol) and catalyst (0.0025 mmol) in *para*-fluoro-toluene (0.8 mL) at room temperature for 12 h. [b] Isolated yield. [c] The ee value was determined by chiral HPLC analysis.

4.3.4 Determination of Absolute Configuration and Conversion of Adducts

The products were useful and could be readily converted into many different building blocks containing a chiral quaternary center and a neighboring functional group. As illustrated in Scheme 4-6, adduct **4-3** was reduced to alcohol **4-10** with $NaBH_4$. Removal of sulfone groups afforded branched alcohol **4-11** containing an

all-quaternary chiral center, the configuration of which was determined by comparison with literature data.[199] Oxidation of aldehyde **4-3** with sodium chlorite and hydroperoxide to the acid **4-12**, followed by removal of sulfone groups to generate the desired acid **4-13** containing an all-carbon quaternary chiral center.



Scheme 4-6 Conversion of adduct into chiral alcohol and acid

4.4 Conclusions

In conclusion, novel threonine-based *N*-sulfonamide organocatalysts were introduced for the first time, and such catalysts could efficiently promote enantioselective conjugate addition of 2-aryl-substituted propanals to 1,1-bis(benzenesulfonyl)ethylene in 91% yield and with up to 86% ee. The described method could be utilized to construct useful chiral building blocks containing all-carbon quaternary stereogenic centers and an adjacent common functional group. We anticipate that our method will find wide applications in the synthesis of medicinally important molecules.

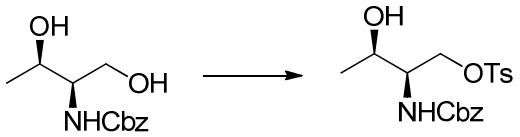
4.5 Experimental Section

4.5.1 General Methods

The general methods of Chapter 2 were followed.

4.5.2 Catalyst Synthesis and Characterization

(2*R*,3*R*)-2-(((benzyloxy)carbonyl)amino)-3-hydroxybutyl 4-methylbenzenesulfonate (**4-6aa**)



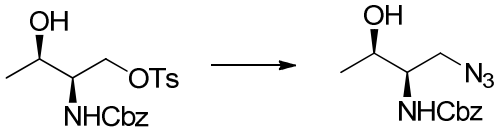
4-6aa

To an ice-cold solution of benzyl (2*R*,3*R*)-1,3-dihydroxybutan-2-ylcarbamate (2.39 g, 10.0 mmol) and triethylamine (15 mmol, 2.1 mL) in dichloromethane (50 mL) at 0 ^{o}C was added 4-toluenesulfonyl chloride (2.28 g, 12.0 mmol). The reaction mixture was stirred at room temperature for 6 h and then diluted with dichloromethane (50 mL). The organic phase was washed with aqueous $NaHCO_3$ (3 x 50 mL) and brine (2 x 50 mL), and dried over Na_2SO_4. The solution was filtered and concentrated under the reduced pressure to afford the crude product, which was subjected to flash chromatographic separation on silica gel (ethyl acetate /hexanes = 1:15 to 1:4) to afford **4-6aa** as a colorless oil (3.41 g, 87%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14-1.16 (d, *J* = 6.3 Hz, 3H), 2.41 (s, 3H), 3.00 (s, 1H), 3.71-3.78 (m, 1H), 4.00-4.07 (m, 2H), 4.11-4.14 (m, 1H), 5.06 (s, 2H), 5.51-5.52 (d, *J* = 8.9 Hz, 1H), 7.28-7.35 (m, 7H), 7.76-7.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.93, 21.63, 54.69, 65.38, 66.97, 68.90, 127.91, 127.93, 128.17, 128.55, 130.00,

132.52, 136.26, 145.15, 156.63; HRMS (ESI) m/z calcd for $C_{19}H_{23}NO_6S$ $[M+H]^+$ 416.1129, found 416.1118.

Benzyl (2*R*,3*R*)-1-azido-3-hydroxybutan-2-ylcarbamate (**4-6ab**)

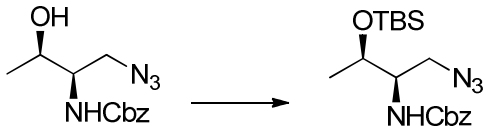


4-6aa **4-6ab**

Sodium azide (1.95 g, 30.0 mmol) was added to **4-6aa** (1.97 g, 5.0 mmol) in *N,N*-dimethylformamide (15 mL), and the resulting mixture was heated at 70 ^oC for 14 h. The reaction mixture was then allowed to cool to room temperature and diluted with ethyl acetate (75 mL). The organic phase was washed with H_2O (3 x 30 mL) and brine (3 x 30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to afford the crude product as a colorless oil (1.11 g, 84%), which was used in the next step.

^1H NMR (300 MHz, $CDCl_3$) δ 1.18-1.20 (d, J = 6.4 Hz, 3H), 2.82-2.83 (m, 1H), 3.42-3.45 (m, 2H), 3.62-3.67 (m, 1H), 3.97 (br, 1H), 5.11 (s, 2H), 5.50-5.53 (d, J = 8.7 Hz, 1H), 7.31-7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.23, 52.57, 55.13, 66.67, 67.03, 127.97, 128.18, 128.51, 136.13, 156.68; HRMS (ESI) m/z calcd for $C_{12}H_{16}N_4O_3$ $[M-H]^-$ 263.1150, found 263.1149.

Benzyl (2*R*,3*R*)-1-azido-3-(*tert*-butyldimethylsilyloxy)butan-2-ylcarbamate (**4-6ac**)

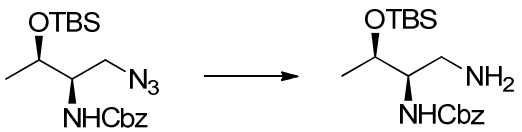


4-6ab **4-6ac**

To a stirred solution of azide **4-6ab** (1.27 g, 5 mmol) in freshly distilled *N,N*-dimethylformamide (5 mL) was added *tert*-butylchlorodimethylsilane (900 mg, 6.0 mmol), imidazole (680 mg, 10 mmol) and DMAP (120 mg, 1.0 mmol). After stirring at rt for 12 h, ethyl acetate (50 mL) was added to the reaction mixture and the mixture was washed with water (5 x 20 mL) and brine (2 x 20 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography (ethyl acetate /hexanes = 1:20 to 1:5) to afford the desired product as a colorless oil (1.53 g, 81%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.90 (s, 9H), 1.16-1.19 (d, J = 6.4 Hz, 3H), 3.27-3.31 (m, 1H), 3.41-3.44 (m, 1H), 3.68-3.71 (m, 1H), 4.01-4.05 (m, 1H), 5.10-5.15 (m, 3H), 7.31-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.11, -4.28, 17.90, 20.65, 25.76, 51.89, 55.62, 66.41, 66.95, 128.17, 128.51, 136.27, 156.27; HRMS (ESI) m/z calcd for $C_{18}H_{30}N_4O_3Si$ $[M+Na]^+$ 401.1979, found 401.1980.

Benzyl (2*R*,3*R*)-1-amino-3-(*tert*-butyldimethylsilyloxy)butan-2-ylcarbamate (**4-6ad**)



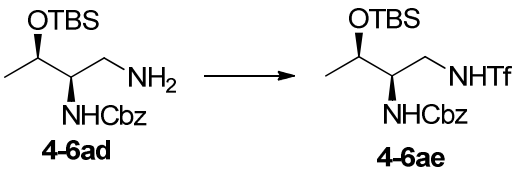
4-6ac **4-6ad**

Triphenylphosphine (629 mg, 2.4 mmol) was added to azide **4-6ac** (756 mg, 2.0 mmol) in tetrahedrofuran (15 mL) and H_2O (5.0 mL). The reaction mixture was

brought to reflux for 2 h. Solvent was removed under reduced pressure, and extra water (15 mL) was added. The aqueous layer was extracted with ethyl acetate several times (3 x 15 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (ethyl acetate/hexanes = 1:2 to triethylamine /ethyl acetate = 1:10) to afford the desired amine **4-6ad** as a colorless oil (634 mg, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02-0.03 (d, *J* = 2.3 Hz, 3H), 0.85 (s, 9H), 1.10-1.12 (d, *J* = 6.2 Hz, 3H), 1.19 (br, 2H), 2.69-2.71 (d, *J* = 6.9 Hz, 2H), 3.42-3.45 (m, 1H), 3.97-3.99 (m, 1H), 5.07-5.10 (s, 3H), 7.31-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.06, -4.30, 17.86, 20.89, 25.74, 44.31, 59.30, 66.66, 67.48, 128.02, 128.44, 131.92, 132.06, 136.51, 156.99; HRMS (ESI) m/z calcd for $C_{18}H_{32}N_2O_3Si$ $[M+H]^+$ 353.2264, found 353.2262.

Benzyl (2*R*,3*R*)-3-(*tert*-butyldimethylsilyloxy)-1-(trifluoromethylsulfonamido)butan-2-ylcarbamate (**4-6ae**)

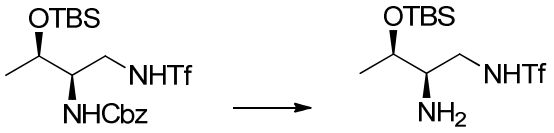


Trifluoromethanesulfonic anhydride (0.2 mL, 1.2 mmol) was added to amine **4-6ad** (0.35 g, 1.0 mmol) and triethylamine (0.42 mL, 3.0 mmol) in anhydrous dichloromethane (5 mL) at 0 ^{o}C, and the mixture was stirred at room temperature for 5 h. After diluting with dichloromethane (10 mL), the mixture was washed with aqueous $NaHCO_3$ (3 x 5 mL) and brine (2 x 5 mL). The organic layer was dried over

Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product, which was purified by flash column chromatography (ethyl acetate /hexanes = 1:10 to 1:2) to afford **4-6ae** as a white solid (344 mg, 71%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.13 (s, 6H), 0.93 (s, 9H), 1.21-1.23 (d, *J* = 6.2 Hz, 3H), 3.39-3.76 (m, 3H), 4.01-4.05 (m, 1H), 5.17 (s, 2H), 5.29-5.32 (d, *J* = 9.0 Hz, 1H), 7.39-7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.21, -4.24, 17.83, 20.87, 25.65, 25.79, 47.45, 55.95, 67.47, 67.68, 128.05, 128.29, 128.56, 135.79, 157.65; HRMS (ESI) m/z calcd for $C_{19}H_{31}F_3N_3O_5SSi$ $[M-H]^-$ 483.1602, found 483.1580.

N-((2*R*,3*R*)-2-Amino-3-(*tert*-butyldimethylsilyloxy)butyl)trifluoromethanesulfonamide (**4-6a**)

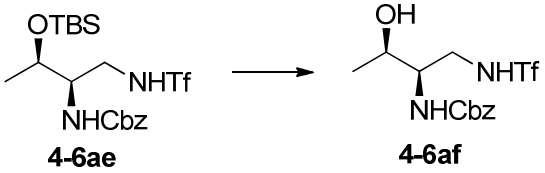


4-6ae **4-6a**

To the solution of **4-6ae** (194 mg, 0.4 mmol) in methanol (3 mL) was added 10% Pd/C (20 mg). The flask was then flushed with hydrogen, and a hydrogen balloon was connected. After stirring for 1 h, Pd/C was removed by filtration through Celite, the filtrate was concentrated *in vacuo* to yield **4-6a** as a white solid (113 mg, 81%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.15-1.17 (d, *J* = 6.2 Hz, 3H), 2.69-2.75 (m, 1H), 3.04-3.11 (m, 1H), 3.17 (s, 3H), 3.29-3.33 (m, 1H), 3.74-3.77 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.82, 20.04, 25.62, 29.59, 46.95, 56.57, 69.49, 117.68, 121.95; HRMS (ESI) m/z calcd for $C_{11}H_{25}F_3N_2O_3SSi$ $[M+H]^+$ 351.1375, found 351.1374.

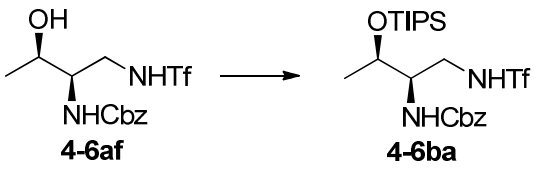
Benzyl (2*R*,3*R*)-3-hydroxy-1-(trifluoromethylsulfonamido)butan-2-ylcarbamate (**4-6af**)



To a stirred solution of **4-6ae** (484 mg, 1.0 mmol) in THF was added TBAF (1M in THF, 3 mL). After stirring at rt for 5 h, the solvent was removed. The residue was taken up in ethyl acetate (30 mL), and washed with water (3 x 15 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography (ethyl acetate /hexanes = 1:10 to 1:4) to yield **4-6af** as a white solid (281 mg, 76%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20-1.22 (d, *J* = 6.3 Hz 6H), 3.34-3.42 (m, 2H), 3.65-3.67 (m, 1H), 4.04-4.06 (m, 1H), 4.39 (br, 2H), 5.10 (s, 2H), 5.50-5.53 (d, *J* = 9.0 Hz, 1H), 7.30-7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.30, 46.24, 55.06, 66.55, 67.39, 117.55, 121.80, 127.87, 128.27, 128.54, 135.72, 157.37; HRMS (ESI) m/z calcd for $C_{13}H_{17}F_3N_2O_5S$ $[M-H]^-$ 369.0733, found 369.0729.

Benzyl(2*R*,3*R*)-1-(trifluoromethylsulfonamido)-3-(triisopropylsilyloxy)butan-2-ylcarbamate (**4-6ba**)

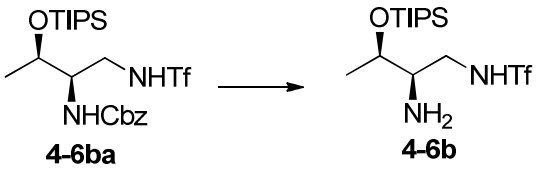


Chlorotriisopropylsilane (134 mg, 0.7 mmol) was added to a solution of alcohol

4-6af (178 mg, 0.5 mmol), triethylamine (0.14 mL, 1.0 mmol) and DMAP (12 mg, 0.1 mmol) in anhydrous dichloromethane (5 mL) at 0 ^{o}C. The mixture was then allowed to stir at room temperature for 5 h and diluted with dichloromethane (10 mL). The mixture was washed with water (3 x 10 mL) and brine (2 x 10 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product, which was purified by flash column chromatography (ethyl acetate /hexanes = 1:10 to 1:3) to afford **4-6ba** as a colorless oil (197 mg, 75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (m, 21H), 1.27-1.30 (m, 3H), 3.47-3.51 (m, 2H), 3.70-3.79 (m, 1H), 4.15-4.17 (m, 1H), 5.17 (s, 2H), 5.26-5.29 (d, *J* = 8.6 Hz, 1H), 7.39-7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.47, 17.95, 18.00, 20.81, 47.86, 56.00, 67.47, 68.62, 117.56, 121.82, 128.06, 128.30, 128.55, 135.79, 157.70; HRMS (ESI) m/z calcd for $C_{22}H_{37}F_3N_2O_5S$ Si $[M+Na]^+$ 549.2043, found 549.2041.

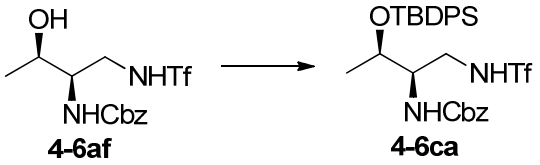
N-((2*R*,3*R*)-2-Amino-3-(triisopropylsilyloxy)butyl)trifluoromethanesulfonamide (**4-6b**)



Following the same procedure as described for the preparation of **4-6a**, **4-6b** was obtained as a white solid (73 mg, 93%) from the carbamate **4-6ba** (105 mg, 0.2mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (m, 21H), 1.21-1.23 (d, *J* = 8.4 Hz, 3H), 2.70-2.74 (m, 4H), 3.12-3.19 (m, 1H), 3.33-3.39 (m, 1H), 3.93-3.96 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.51, 17.97, 18.03，19.76，46.76, 56.47, 70.22, 117.65, 121.92;

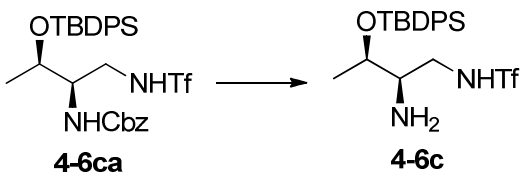
HRMS (ESI) m/z calcd for $C_{14}H_{31}F_3N_2O_3SSi$ $[M+H]^+$ 393.1838, found 393.1842.

Benzyl 3-(*tert*-butyldiphenylsilyloxy)-1-(trifluoromethylsulfonamido)butan-2-ylcarbamate (**4-6ca**)



Following the same procedure as described for the preparation of **4-6ba**, **4-6ca** was obtained as a colorless oil (278 mg, 91% yield) from **4-6af** (178 mg, 0.5mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08-1.12 (m, 12H), 3.10-3.12 (m, 1H), 3.40-3.43 (m, 1H), 3.64-3.65 (m, 1H), 3.88-3.89 (m, 1H), 5.14 (s, 2H), 5.29-5.31 (d, J = 8.8 Hz, 1H), 7.39-7.49 (m, 11H), 7.63-7.69 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.24, 20.83, 27.06, 47.43, 56.31, 67.56, 67.80, 80.49, 127.71, 128.11, 128.18, 128.40, 128.70, 130.05, 130.37, 132.34, 133.30, 135.87, 135.90, 157.75, 173.18; HRMS (ESI) m/z calcd for $C_{29}H_{35}F_3N_2O_5SSi$ $[M-H]^-$ 607.1915, found 607.1931.

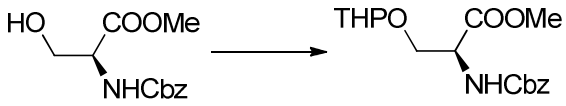
N-((2*R*,3*R*)-2-Amino-3-(*tert*-butyldiphenylsilyloxy)butyl)trifluoromethanesulfonamide (**4-6c**)



Following the procedure as described for the preparation of **4-6a**, the catalyst **4-6c** was obtained as a colorless oil (180 mg, 95% yield) from carbamate **4-6ca**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 12H), 2.65-2.71 (m, 1H), 3.04-3.16 (m, 5H), 3.72-3.75 (m, 1H), 7.39-7.45 (m, 6H), 7.63-7.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.21, 19.75, 27.01, 25.79, 46.63, 56.82, 70.62, 127.58, 127.89, 129.84, 130.08, 132.84, 133.61, 135.71, 135.79; HRMS (ESI) m/z calcd for $C_{21}H_{29}F_3N_2O_3SSi$ $[M+Na]^+$ 475.1702, found 475.1710.

(*S*)-Methyl 2-(benzyloxycarbonyl)-3-(tetrahydro-2H-pyran-2-yloxy)propanoate **(4-7aa)**



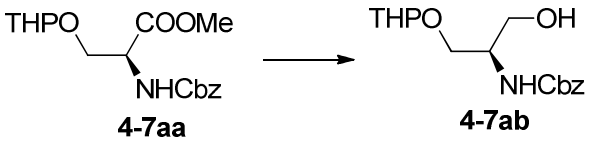
4-7aa

To a stirred solution of N-Cbz-(L)-serine-methyl ester (5.06 g, 20.0 mmol) and freshly distilled dihydropyran (10 mL) in dried dichloromethane (50 mL) was added *p*-toluenesulfonic acid monohydrate (95 mg, 0.5 mmol). After stirring at rt for 3 h, triethylamine (3 mmol, 0.42 mL) was added. The reaction mixture was concentrated, and the residue was taken up in EtOAc (100 mL). The organic extracts were washed with brine (3 x 50 mL), and dried over Na_2SO_4. After filtration and concentration, the residue was purified by column chromatography (ethyl acetate /hexanes = 1:15 to 1:5) to afford the desired product as a white solid (5.86 g, 87%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51-1.55 (m, 6H), 3.44-3.51 (m, 1H), 3.75-3.79 (m, 4.5H), 3.96-3.97 (m, 1H), 4.16-4.19 (m, 0.5H), 4.55-4.61 (m, 2H), 5.16 (s, 2H), 5.70-5.92 (m, 1H), 7.35-7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.83, 19.29, 25.08, 25.17, 30.03, 30.28, 52.35, 52.39, 54.14, 54.39, 61.65, 62.47, 66.89, 66.98,

67.09, 68.04, 98.43, 98.44, 128.00, 128.04, 128.11, 128.41, 128.44, 136.18, 155.95, 170.69, 170.82; HRMS (ESI) m/z calcd for $C_{17}H_{23}NO_6$ $[M+Na]^+$ 360.1418, found 360.1435.

Benzyl (*R*)-1-hydroxy-3-(tetrahydro-2H-pyran-2-yloxy)propan-2-ylcarbamate (**4-7ab**)

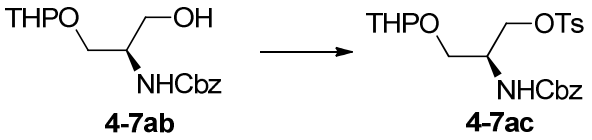


4-7aa **4-7ab**

$LiAlH_4$ (760 mg, 20.0 mmol) was added to ester **4-7aa** (3.37 g, 10.0 mmol) in anhydrous tetrahydrofuran (40 mL) at -20 ^oC. After stirring at -20 ^oC for 1 h, the excess hydride was destroyed by slow addition of water (10 mL). The reaction mixture was filtered through Celite, and the filtrate was concentrated *in vacuo*. Water (60 mL) was added to the residue, and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by flash column chromatography (ethyl acetate /hexanes = 1:5 to 1:2) afforded **4-7ab** as a colorless oil (2.81 g, 91%).

^1H NMR (300 MHz, $CDCl_3$) δ 1.48-1.51 (m, 4H), 1.72-1.81 (m, 2H), 3.13-3.15 (m, 1H), 3.51-3.71 (m, 3H), 3.80-3.94 (m, 4H), 4.55-4.57 (m, 1H), 5.13 (s, 2H), 5.52-5.63 (m, 1H), 7.35-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.64, 25.11, 30.39, 30.55, 52.06, 62.59, 62.83, 62.96, 63.19, 66.71, 66.77, 67.23, 67.46, 99.45, 99.86, 127.98, 128.02, 128.06, 128.41, 128.44, 136.32, 136.38, 156.37; HRMS (ESI) m/z calcd for $C_{16}H_{23}NO_5$ $[M+Na]^+$ 332.1468, found 332.1475.

(*S*)-2-(Benzyloxycarbonyl)-3-(tetrahydro-2H-pyran-2-yloxy)propyl-4-methylbenzene-sulfonate (**4-7ac**)

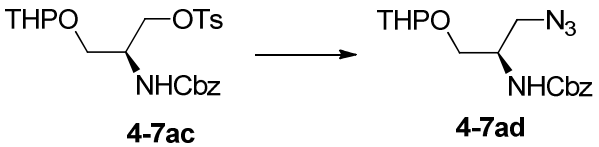


4-7ab **4-7ac**

Following the procedure as described for the preparation of **4-6aa**, tosylate **4-7ac** was obtained as a colorless oil (4.35 g, 94% yield) from **4-7ab** (3.09 g, 10.0 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39-1.51 (m, 6H), 2.39 (s, 3H), 3.35-3.52 (m, 2H), 3.67-3.80 (m, 2H), 4.06-4.18 (m, 3H), 4.40-4.46 (m, 1H), 5.03 (s, 2H), 5.16-5.34 (m, 1H), 7.28-7.37 (m, 7H), 7.73-7.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.16, 19.05, 19.52, 20.98, 21.58, 25.13, 25.18, 28.14, 30.17, 30.32, 49.50, 60.33, 61.99, 62.66, 65.16, 65.56, 66.90, 67.74, 68.18, 98.79, 99.51, 127.93, 128.03, 128.17, 128.51, 129.86, 132.63, 136.16, 144.93, 155.65; HRMS (ESI) m/z calcd for $C_{23}H_{29}NO_7S$ $[M+Na]^+$ 486.1557, found 486.1583.

Benzyl (*R*)-3-azido-1-(tetrahydro-2H-pyran-2-yloxy)propan-2-ylcarbamate (**4-7ad**)



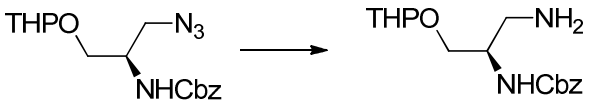
4-7ac **4-7ad**

Following the general procedure as described for the preparation of **4-6ab**, azide **4-7ad** was obtained as a colorless oil (1.35 g, 81% yield) from tosylate **4-7ac** (1.67 g, 5.0 mmol) and sodium azide (2.41 g, 37 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47-1.53 (m, 4H), 1.70-1.78 (m, 2H), 3.46-3.55 (m, 4H), 3.61-3.83 (m, 2H), 3.85-3.94 (m, 1H), 4.54-4.57 (m, 1H), 5.10 (s, 2H), 5.25-5.46

(m, 1H), 7.30-7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.24, 19.69, 25.12, 25.18, 30.27, 30.45, 50.29, 51.34, 51.62, 62.23, 62.88, 66.20, 66.76, 66.88, 98.91, 99.67, 128.03, 128.09, 128.14, 128.46, 128.48, 136.22, 136.30, 155.77; HRMS (ESI) m/z calcd for $C_{16}H_{22}N_4O_4$ $[M+Na]^+$ 357.1547, found 357.1542.

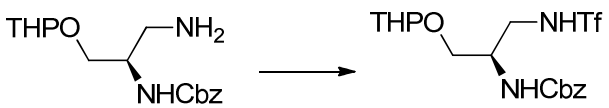
Benzyl (*R*)-1-amino-3-(tetrahydro-2H-pyran-2-yloxy)propan-2-ylcarbamate (**4-7ae**)



4-7ad **4-7ae**

Following the procedure described for the preparation of **4-6ad**, amine **4-7ae** was obtained as a colorless oil (1.06 g, 86% yield) from azide **4-7ad** (1.34 g, 4.0 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26-1.29 (m, 2H), 1.47-1.53 (m, 4H), 1.67-1.71 (m, 2H), 2.84-2.86 (d, *J* = 5.9 Hz, 2H), 3.41-3.84 (m, 5H), 4.52-4.54 (m, 1H), 5.10 (s, 2H), 5.48-5.63 (m, 1H), 7.30-7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.34, 19.69, 25.17, 25.22, 30.34, 30.51, 43.01, 43.31, 52.85, 62.22, 62.72, 66.20, 66.49, 66.57, 67.38, 67.66, 98.88, 99.51, 127.93, 127.99, 128.38, 128.40, 136.48, 136.56, 156.26; HRMS (ESI) m/z calcd for $C_{16}H_{24}N_2O_4$ $[M+H]^+$ 309.1809, found 309.1808.

Benzyl(*R*)-1-(tetrahydro-2H-pyran-2-yloxy)-3-(trifluoromethylsulfonamido)propan-2-ylcarbamate (**4-7af**)

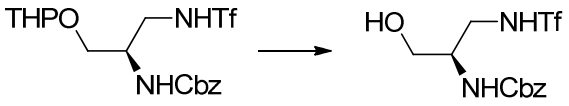


4-7ae **4-7af**

Following the procedure described for preparing **4-6ae**, curde sulfonamide **4-7af**

was obtained as a white solid from the amine **4-7ae** (310 mg, 1.0 mmol).

(*R*)-Benzyl 1-hydroxy-3-(trifluoromethylsulfonamido)propan-2-ylcarbamate (**4-7ag**)

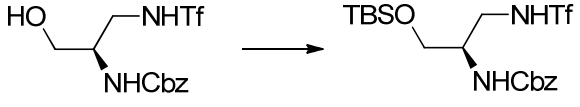


4-7af **4-7ag**

p-Toluenesulfonic acid monohydrate (38 mg, 0.2 mmol) was added to the crude sulfonamide **4-7af** in methanol (5 mL). After stirring at rt for 4 hours, the solvent was evaporated *in vacuo* to yield the crude product, which was purified by flash column chromatography (ethyl acetate /hexanes = 1:5 to 1:2) to afford **4-7ag** as a colorless oil (0.25 g, 71% for two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.33-3.39 (m, 2H), 3.64-3.71 (m, 2H), 3.81-3.82 (m, 1H), 5.09 (s, 2H), 5.75-5.77 (d, *J* = 4.9 Hz, 1H), 7.29-7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.88, 52.14, 61.81, 62.46, 118.47, 121.02, 127.93, 128.40, 128.64, 135.76, 157.20; HRMS (ESI) m/z calcd for $C_{12}H_{15}F_3N_2O_5S$ $[M-H]^-$ 355.0576, found 355.0564.

(*R*)-Benzyl-1-(*tert*-butyldimethylsilyloxy)-3-(trifluoromethylsulfonamido)propan-2-ylcarbamate (**4-7ah**)

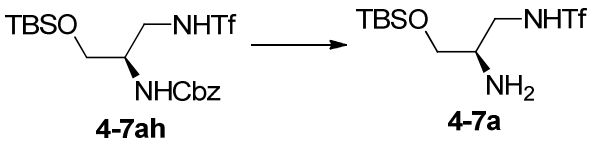


4-7ag **4-7ah**

Following the same procedure as described for the preparation of **4-6ba**, **4-7ah** was obtained as a colorless oil (0.8 g, 85% yield) from **4-7ag** (720 mg, 2.0 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.93 (s, 9H), 3.47-3.52 (m, 2H), 3.74-3.81 (m, 2H), 3.91-3.93 (m, 1H), 5.16 (s, 2H), 5.33-5.36 (d, *J* = 8.0 Hz, 1H), 6.53 (br, 1H), 7.35-7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.69, 18.09, 25.70, 29.66, 46.77, 51.27, 63.51, 67.41, 117.59, 121.85, 128.15, 128.35, 128.59, 135.82, 156.84; HRMS (ESI) m/z calcd for $C_{18}H_{29}F_3N_2O_5SSi$ $[M+Na]^+$ 493.1411, found 493.1418.

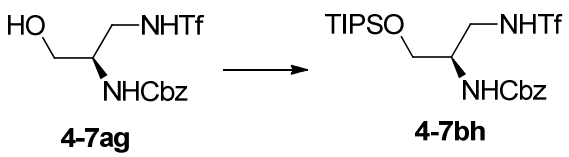
(*R*)-N-(2-Amino-3-(*tert*-butyldimethylsilyloxy)propyl)trifluoromethanesulfonamide (**4-7a**)



4-7ah **4-7a**

Following the procedure described for the preparation of **4-6a**, **4-7a** was obtained as a white solid (153 mg, 91% yield) from carbamate **4-7ah** (235 mg, 0.5 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 3.07-3.09 (m, 1H), 3.14-3.18 (m, 1H), 3.35-3.39 (m, 1H), 3.57-3.61 (m, 1H), 3.94 (br, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.63, -5.61, 18.15, 25.74, 46.74, 52.52, 65.541, 118.76, 1218.32; HRMS (ESI) m/z calcd for $C_{10}H_{23}F_3N_2O_3SSi$ $[M+H]^+$ 337.1230, found 337.1230.

(*R*)-Benzyl3-(trifluoromethylsulfonamido)-1-(triisopropylsilyloxy)propan-2-ylcarbamate (**4-7bh**)



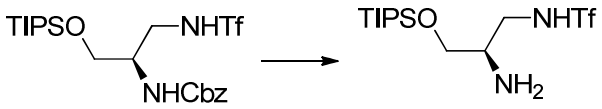
4-7ag **4-7bh**

Following the procedure described for the preparation of **4-6ba**, **4-7bh** was

obtained as a colorless oil (230 mg, 90% yield) from **4-7ag** (178 mg, 0.5mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05-1.11 (m, 21H), 3.47-3.51 (m, 2H), 3.80-3.88 (m, 3H), 5.12 (s, 2H), 5.36-5.39 (m, 1H), 7.34-7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.64, 17.76, 46.74, 51.46, 64.04, 67.30, 117.57, 121.83, 127.97, 128.22, 128.51, 135.84, 156.81; HRMS (ESI) m/z calcd for $C_{21}H_{35}F_3N_2O_5SSi$ $[M+Na]^+$ 535.1880, found 535.1868.

(*R*)-N-(2-Aamino-3-(triisopropylsilyloxy)propyl)trifluoromethanesulfonamide (**4-7b**)

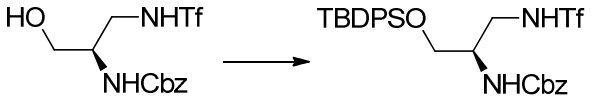


4-7bh **4-7b**

Following the general procedure as described for the preparation of **4-7a**, the catalyst **4-7b** was obtained as a colorless oil (116 mg, 77% yield) from the carbamate **4-7bh** (205 mg, 0.4mmol) and 10% Pd-C (25 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (m, 21H), 3.08-3.21 (m, 2H), 3.36-3.40 (m, 1H), 3.68-3.70 (m, 2H), 4.17 (br, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.70, 17.78, 46.88, 52.49, 66.15, 117.73, 122.00; HRMS (ESI) m/z calcd for $C_{13}H_{29}F_3N_2O_3SSi$ [M+H]+ 379.1702, found 379.1707.

(*R*)-Benzyl1-(*tert*-butyldiphenylsilyloxy)-3-(trifluoromethylsulfonamido)propan-2-yl-carbamate (**4-7ch**)

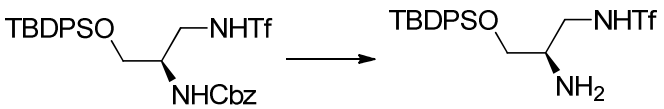


4-7ag **4-7ch**

Following the general procedure as described for the preparation of **4-6ba**, the carbamate **4-7ch** was obtained as a white solid (255 mg, 86% yield) from alcohol **4-7ag** (178 mg, 0.5mmol) and *tert*-butylchlorodiphenylsilane (181 mg, 0.7mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (s, 9H), 3.44-3.46 (m, 2H), 3.78-3.88 (m, 3H), 5.12-5.14 (d, *J* = 2.8 Hz, 2H), 5.28-5.31 (m, 1H), 6.53 (br, 1H), 7.40-7.47 (m, 11H), 7.64-7.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.10, 26.78, 46.46, 51.70, 63.71, 67.35, 117.59, 127.98, 128.00, 128.05, 128.26, 128.52, 130.16, 130.21, 132.10, 132.19, 135.39, 135.44, 135.80, 156.85; HRMS (ESI) m/z calcd for $C_{38}H_{33}F_3N_2O_5SSi$ $[M+Na]^+$ 617.1724, found 617.1716.

(*R*)-*N*-(2-Amino-3-(*tert*-butyldiphenylsilyloxy)propyl)trifluoromethanesulfonamide (**4-7c**)

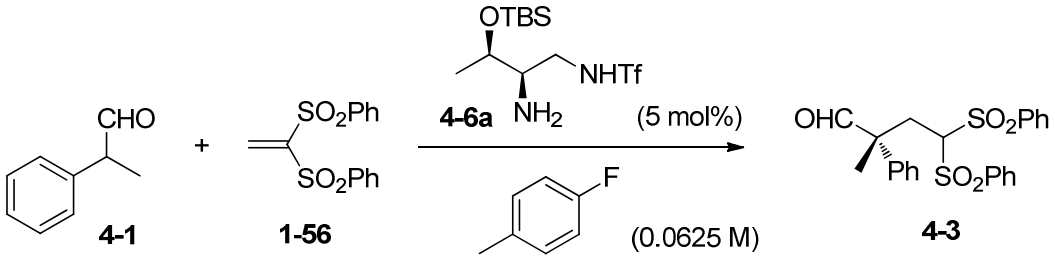


4-7ch **4-7c**

Following the general procedure as described for the preparation of **4-6a**, the catalyst **4-7c** was obtained as a colorless oil (171 mg, 93% yield) from the carbamate **4-7ch** (238 mg, 0.4mmol) and 10% Pd-C (30 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (s, 9H), 3.10-3.18 (m, 6H), 3.38-3.41 (m, 1H), 3.61-3.63 (m, 2H), 7.42-7.50 (m, 6H), 7.66-7.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.11, 26.74, 46.72, 52.25, 66.53, 127.84, 129.99, 132.60, 135.43; HRMS (ESI) m/z calcd for $C_{20}H_{27}F_3N_2O_3SSi$ $[M+H]^+$ 461.1537, found 461.1544.

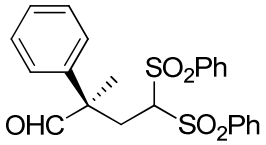
4.5.3 Representative Procedure for the Conjugate Addition



1,1-Bis(benzenesulfonyl)ethylene **1-56** (15.4 mg, 0.05 mmol) was added to a mixture of 2-phenylpropanal **4-1** (14 mg, 0.10 mmol) and *N*-((2*R*,3*R*)-2-amino-3-(*tert*-butyldimethylsilyloxy)butyl)-trifluoromethanesulfonamide **4-6a** (0.9 mg, 0.0025 mmol) in *para*-fluorotoluene (0.8 mL) in a sample vial at room temperature. The vial was then sealed, and the reaction mixture was stirred for 4 h and then quenched by addition of 1N aqueous HCl (2 mL). The mixture was extracted with ethyl acetate (3 x 3 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (ethyl acetate /hexanes = 1:5 to 1:2) to afford **4-3** as a white solid (20 mg, 93%). The enantiometric excess of **4-3** was determined by chiral HPLC analysis.

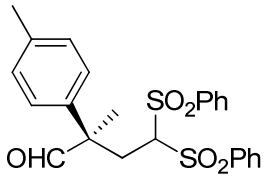
4.5.4 Characterizations of Intermediates & Adducts

(*R*)-2-Methyl-2-phenyl-4,4-bis(phenylsulfonyl)butanal (**4-3**)



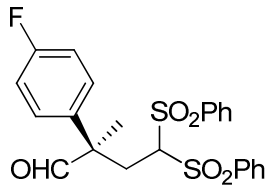
A white solid; $[\alpha]_D$ = - 1.78 (c = 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 3H), 2.79-3.00 (m, 2H), 4.41-4.44 (m, 1H), 7.24-7.27 (m, 2H), 7.40-7.56 (m, 7H), 7.64-7.67 (m, 4H), 7.85-7.87 (m, 2H), 9.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.54, 30.84, 53.03, 80.14, 127.55, 128.06, 129.03, 129.04, 129.22, 129.63, 129.71, 134.51, 134.54, 137.34, 137.80, 138.27, 201.26; HRMS (ESI) m/z calcd for $C_{23}H_{22}O_5S_2$ $[M+Na]^+$ 465.0801, found 465.0808; The ee value of **4-3** is 83%, t_R (major) = 22.3 min, t_R (minor) = 27.2 min (Chiralcel AS-H, λ = 220 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*R*)-2-Methyl-4,4-bis(phenylsulfonyl)-2-p-tolylbutanal (**4-9a**)



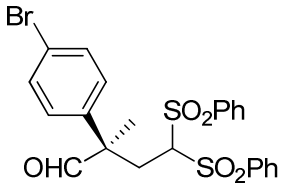
A white solid; $[\alpha]_D$ = + 31.0 (c = 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 3H), 2.39 (s, 3H), 2.75-2.96 (m, 2H), 4.40-4.43 (m, 1H), 7.12-7.15 (m, 2H), 7.21-7.24 (m, 2H), 7.26-7.58 (m, 4H), 7.64-7.6 (m, 4H), 7.86-7.89 (m, 2H), 9.56 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.51, 20.92, 30.80, 52.75, 80.31, 127.44, 128.96, 129.71, 129.76, 129.85, 134.43, 135.11, 137.42, 137.84, 137.91, 201.26; HRMS (ESI) m/z calcd for $C_{24}H_{24}O_5S_2$ $[M+Na]^+$ 479.0948, found 79.0942; The ee value of **4-9a** is 81%, t_R (major) = 21.7 min, t_R (minor) = 30.6 min (Chiralcel AS-H, λ = 220 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*R*)-2-(4-Fluorophenyl)-2-methyl-4,4-bis(phenylsulfonyl)butanal (**4-9b**)



A white solid; $[\alpha]_D$ = + 18.8 (c = 1.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 3H), 2.80-2.98 (m, 2H), 4.41-4.44 (m, 1H), 7.15-7.18 (m, 2H), 7.27-7.29 (m, 2H), 7.54-7.62 (m, 4H), 7.72-7.75 (m, 4H), 7.89-7.92 (m, 2H), 9.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.72, 31.15, 52.55, 80.14, 115.95, 116.24, 129.04, 129.26, 129.37, 129.66, 129.71, 134.07, 134.56, 137.30, 137.73, 200.84; HRMS (ESI) m/z calcd for $C_{23}H_{21}FO_5S_2$ $[M+Na]^+$ 483.0707, found 483.0710; The ee value of **4-9b** is 75%, t_R (major) = 26.3 min, t_R (minor) = 33.1 min (Chiralcel AS-H, λ = 220 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

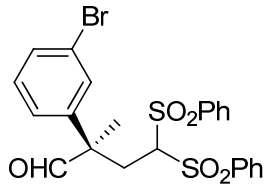
(*R*)-2-(4-Bromophenyl)-2-methyl-4,4-bis(phenylsulfonyl)butanal (**4-9c**)



A white solid; $[\alpha]_D$ = - 125.4 (c = 1.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 3H), 2.80-2.97 (m, 2H), 4.40-4.43 (m, 1H), 7.16-7.19 (m, 2H), 7.54-7.70 (m, 6H), 7.70-7.73 (m, 4H), 7.88-7.91 (m, 2H), 9.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.55, 31.03, 52.76, 80.11, 122.40, 129.04, 129.07, 129.24, 129.63, 129.73, 134.57, 137.28, 137.34, 137.68, 200.55; HRMS (ESI) m/z calcd for $C_{23}H_{21}BrO_5S_2$ $[M+Na]^+$ 542.9906, found 542.9906; The ee value of **4-9c** is 80%, t_R (major) = 25.5 min, t_R (minor) = 34.6 min (Chiralcel AS-H, λ = 220 nm, 30% *i*PrOH/hexanes, flow rate =

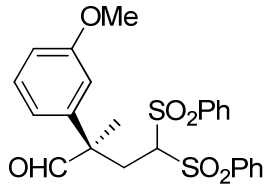
1.0 mL/min).

(*R*)-2-(3-Bromophenyl)-2-methyl-4,4-bis(phenylsulfonyl)butanal (**4-9d**)



A white solid; $[\alpha]_D$ = - 67.0 (c = 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 3H), 2.87-2.90 (m, 2H), 4.42-4.45 (m, 1H), 7.29-7.44 (m, 3H), 7.54-7.63 (m, 5H), 7.71-7.76 (m, 4H), 7.89-7.93 (m, 2H), 9.63 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.53, 31.15, 52.88, 79.98, 123.42, 126.36, 129.05, 129.10, 129.66, 129.71, 130.43, 130.68, 131.26, 134.56, 134.63, 137.24, 137.66, 140.91, 200.51; HRMS (ESI) m/z calcd for $C_{23}H_{21}BrO_5S_2$ $[M+Na]^+$ 542.9906, found 542.9927; The ee value of **4-9d** is 80%, t_R (major) = 45.2 min, t_R (minor) = 55.9 min (Chiralcel AS-H, λ = 220 nm, 20% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

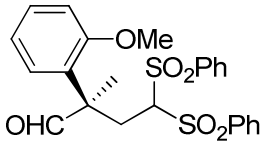
(*R*)-2-(3-Methoxyphenyl)-2-methyl-4,4-bis(phenylsulfonyl)butanal (**4-9e**)



A colorless oil; $[\alpha]_D$ = + 2.86 (c = 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 3H), 2.74-2.98 (m, 2H), 3.83 (s, 3H), 4.41-4.44 (m, 1H), 6.79-6.92 (m, 3H), 7.31-7.34 (m, 1H), 7.46-7.69 (m, 8H), 7.87-7.89 (m, 2H), 9.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.60, 30.77, 53.10, 55.30, 80.27, 113.23, 113.80, 119.70, 129.02, 129.70,

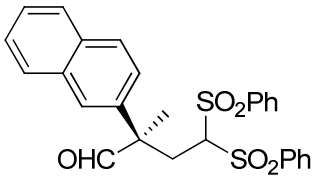
129.80, 130.22, 134.50, 201.07; HRMS (ESI) m/z calcd for $C_{24}H_{24}O_6S_2$ $[M+Na]^+$ 495.0907, found 495.0906; Ee is 80%, t_R (major) = 25.4 min, t_R (minor) = 35.2 min (Chiralcel AD-H, λ = 220 nm, 20% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*R*)-2-(2-Methoxyphenyl)-2-methyl-4,4-bis(phenylsulfonyl)butanal (**4-9f**)



A colorless oil; $[\alpha]_D$ = - 78.5 (c = 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 3H), 2.71-2.78 (m, 1H), 3.17-3.24 (m, 1H), 3.82 (s, 3H), 4.37-4.40 (m, 1H), 6.96-6.99 (m, 1H), 7.12-7.14 (m, 1H), 7.33-7.34 (m, 1H), 7.45-7.73 (m, 9H), 7.97-8.00 (m, 2H), 9.48 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.61, 27.56, 51.11, 55.17, 80.75, 111.25, 120.84, 127.42,127.93, 128.72, 128.84, 129.41, 129.86, 130.27, 134.08, 134.40, 137.42, 138.23, 157.30, 201.27; HRMS (ESI) m/z calcd for $C_{24}H_{24}O_6S_2$ $[M+Na]^+$ 497.0907, found 497.0918; The ee value of **4-9f** is 82%, t_R (major) = 18.6 min, t_R (minor) = 25.5 min (Chiralcel AD-H, λ = 220 nm, 20% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

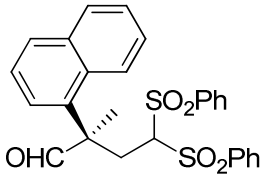
(*R*)-2-Methyl-2-(naphthalen-2-yl)-4,4-bis(phenylsulfonyl)butanal (**4-9g**)



A white solid; $[\alpha]_D$ = + 64.2 (c = 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.63 (s, 3H), 2.96-3.09 (m, 2H), 4.48-4.51 (m, 1H), 7.35-7.38 (m, 3H), 7.55-7.61 (m, 7H),

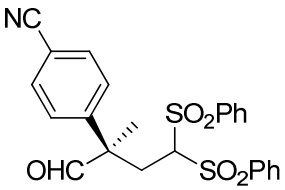
7.74-7.77 (m, 2H), 7.89-7.94 (m, 5H), 9.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.64, 30.83, 53.29, 80.42, 125.20, 126.71, 126.78, 127.54, 128.12, 128.88, 128.95, 128.99, 129.47, 129.82, 132.62, 133.27, 134.35, 134.47, 135.47, 137.46, 137.75, 201.05; HRMS (ESI) m/z calcd for $C_{27}H_{24}O_5S_2$ $[M+Na]^+$ 515.0957, found 515.0948; The ee value of **4-9g** is 77%, t_R (major) = 23.5 min, t_R (minor) = 28.5 min (Chiralcel AS-H, λ = 220 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*R*)-2-Methyl-2-(naphthalen-1-yl)-4,4-bis(phenylsulfonyl)butanal (**4-9h**)



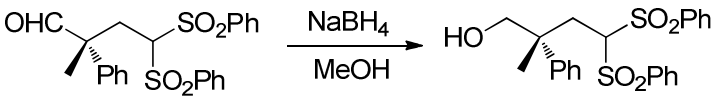
A white solid; $[\alpha]_D$ = - 12.5 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (s, 3H), 3.19-3.24 (m, 2H), 4.68-4.71 (m, 1H), 7.35-7.40 (m, 2H), 7.49-7.62 (m, 9H), 7.69-7.77 (m, 2H), 7.95-7.98 (m, 4H), 9.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.46, 29.93, 53.14, 80.57, 123.92, 125.21, 125.89, 125.97, 127.02, 128.70, 128.89, 129.53, 129.60, 129.78, 129.85, 134.24, 134.36, 134.47, 134.51, 134.78, 137.10, 138.06, 203.53; HRMS (ESI) m/z calcd for $C_{27}H_{24}O_5S_2$ $[M+Na]^+$ 515.0981, found 515.0981; The ee value of **4-9h** is 86%, t_R (major) = 18.6 min, t_R (minor) = 24.0 min (Chiralcel AD-H, λ = 220 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*R*)-4-(2-Methyl-1-oxo-4,4-bis(phenylsulfonyl)butan-2-yl)benzonitrile (**4-9i**)



A colorless oil; $[\alpha]_D$ = + 14.6 (c = 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 3H), 2.88-2.94 (m, 2H), 4.43-4.44 (m, 1H), 7.45-7.47 (m, 2H), 7.53-7.58 (m, 4H), 7.73-7.75 (m, 6H), 7.85-7.87 (m, 2H), 9.65 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.64, 31.47, 53.24, 79.73, 112.27, 118.11, 126.58, 128.36, 129.22, 129.25, 129.68, 129.78, 132.59, 132.88, 134.75, 134.88, 137.06, 137.62, 144.26, 200.38; MS (ESI) m/z calcd for $C_{24}H_{21}NO_5S_2$ $[M-H]^-$ 467.1, found 466.1; The ee value of **4-9i** is 68%, t_R (minor) = 44.4 min, t_R (major) = 52.8 min (Chiralcel AD-H, λ = 220 nm, 30% *i*PrOH/hexanes, flow rate = 1.0 mL/min).

(*R*)-2-Methyl-2-phenyl-4,4-bis(phenylsulfonyl)butan-1-ol (**4-10**)



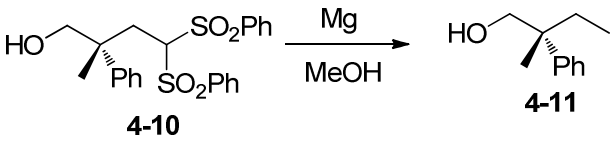
4-3 **4-10**

$NaBH_4$ (24 mg, 0.5 mmol) was added to aldehyde **4-3** (133 mg, 0.3 mmol) in methanol (3 mL) at 0 °C. After 1 h, the methanol was removed and saturated NH_4Cl solution (4 mL) was added. The aqueous phase was extracted with EtOAc (3 x 5 mL), and the organic extracts were combined and dried over Na_2SO_4. After filtration and concentration, the residue was purified by flash column chromatography (ethyl acetate /Hexanes = 1:5 to 1:3) to afford **4-10** as a colorless oil (128 mg, 96%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 3H), 2.65-2.72 (m, 3H), 3.72-3.74 (d, *J* = 12.0 Hz, 1H), 4.07-4.09 (d, *J* = 12.0 Hz, 1H), 4.74-4.76 (m, 1H), 7.27-7.29 (m, 1H),

7.35-7.39 (m, 4H), 7.47-7.52 (m, 4H), 7.62-7.68 (m, 4H), 7.78-7.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.79, 32.43, 42.94, 68.77, 81.27, 126.83, 126.99, 128.66, 128.97, 129.03, 129.65, 129.91, 134.56, 137.69, 137.85, 143.78; $[\alpha]_D$ = - 0.78 (c = 0.4, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{23}H_{24}O_5S_2$ $[M+Na]^+$ 467.0957, found 467.0963.

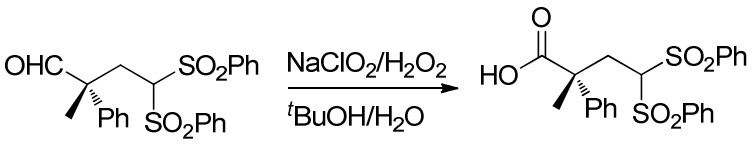
(*R*)-2-Methyl-2-phenylbutan-1-ol (**4-11**)



4-10 **4-11**

The activated magnesium metal (108 mg, 4.5 mmol) was added into a solution of silfone **4-10** (85 mg, 0.15 mmol) in anhydrous methanol (10 mL) with stirring. After 30 minutes, the reaction mixture was brought to gentle reflux for 2 h. After cooling down to rt, the mixture was poured into 2 N HCl (10 mL), and extracted with ether (3 x 10 mL). The organic extracts were combined, dried over Na_2SO_4 and filtered. Solvent was removed *in vacuo*. The residue was purified by column chromatography (ethyl acetate /hexanes = 1:15 to 1:5) to afford **4-11** as a colorless oil (35 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74-0.79 (t, *J* = 7.4 Hz, 3H), 1.38 (s, 3H), 1.58-1.65 (m, 1H), 1.81-1.89 (m, 1H), 3.57-3.61 (d, *J* = 10.8 Hz, 1H), 3.76-3.79 (d, *J* = 10.8 Hz, 1H), 7.19-7.24 (m, 1H), 7.29-7.42 (m, 4H); $[\alpha]_D$ = - 3.6 (c = 0.8, $CHCl_3$, lit^{199}_{neat} = - 1.77); The ee value of **4-11** is 83%, t_R (major) = 53.1 min, t_R (minor) = 58.2 min (Chiralcel OD-H, λ = 220 nm, 2% *i*PrOH/hexanes, flow rate = 0.2 mL/min).

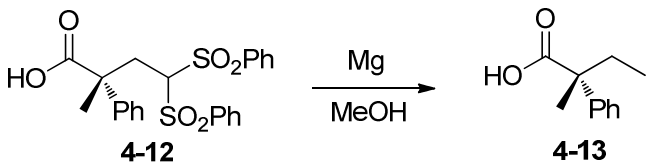
(*R*)-2-Methyl-2-phenyl-4,4-bis(phenylsulfonyl)butanoic acid (**4-12**)



4-3 **4-12**

To a stirred solution of conjugate adduct **4-3** (133 mg, 0.30 mmol) in a mixture of *tert*-butanol/water (4.0 mL, v/v = 1:1) were added sodium chlorite (78 mg, 0.90 mmol) and 30% aqueous solution of H_2O_2 (0.17 mL, 1.50 mmol), and the resulting mixture was stirred at room temperature for 3 h. The reaction mixture was then concentrated, and the residue was taken up in ethyl acetate (10 mL), washed with water (2 x 5 mL). The organic extract was dried over Na_2SO_4 and concentrated, and the residue was purified by column chromatography (ethyl acetate /hexanes = 1:2 to ethyl acetate) to afford the desired acid product **4-12** as a white foam (120 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77 (s, 3H), 2.83-2.91 (m, 1H), 3.17-3.24 (m, 1H), 4.52-4.54 (m, 1H), 7.27-7.29 (m, 5H), 7.46-7.69 (m, 8H), 7.94-7.97 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.94, 32.64, 49.67, 80.77, 127.07, 127.70, 128.60, 128.91, 129.33, 130.15, 134.24, 134.52, 137.34, 138.02, 140.06, 180.68; $[\alpha]_D$ = - 26.3 (c = 1.7, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{23}H_{22}O_6S_2$ $[M+Na]^+$ = 481.0750, found = 481.0756.

(*R*)-2-Methyl-2-phenylbutanoic acid (**4-13**)



4-12 **4-13**

Following the procedure of preparation of alcohol **4-11**, acid **4-13** (85% yield)

was obtained as a colorless oil from sulfone **4-12**.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83-0.88 (t, *J* = 7.4 Hz, 3H), 1.56 (s, 3H), 2.00-2.10 (m, 2H), 7.34-7.37 (m, 5H); $[\alpha]_D$ = - 17.4 (c = 2.7, $CHCl_3$). For the enantiomeric excess determination, Acid **4-13** was difficult to be resolved by chiral HPLC analysis. Acid **4-13** was reduced to corresponding alcohol **4-11** with $LiAH_4$, and the ee value was determined accordingly. The ee value of **4-11** is 82%, t_R (major) = 53.1 min, t_R (minor) = 58.2 min (Chiralcel OD-H, λ = 220 nm, 2% *i*PrOH/hexanes, flow rate = 0.2 mL/min).

Chapter 5 Enantioselective Conjugate Addition of Nitroalkanes to Vinyl Sulfones: An Organocatalytic Access to Chiral Amines

5.1 Background

After establishing the conjugate additions of aldehydes, ketones and branched aldehydes to vinyl sulfone via enamine activation in **Chapter 2-4**, we are particularly interested in developing new nucleophiles in conjugate addition to vinyl sulfones via other activation methods. Nitroalkanes are versatile donors, and their conjugate adducts have been demonstrated to be valuable intermediates in organic synthesis. The conjugate additions of nitroalkanes to imines,[200] nitrostyrenes,[201] and α,β-unsaturated carbonyl compounds[202] have been shown to be extremly useful in accessing a wide range of chiral structural scaffolds.

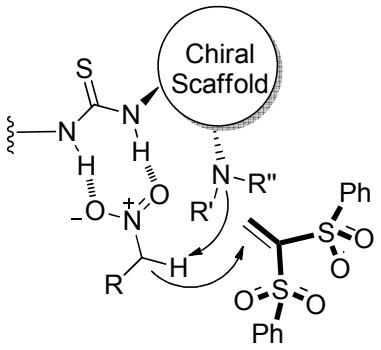
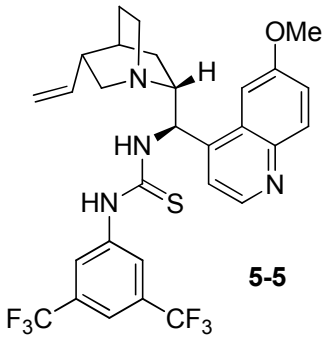


Figure 5-1 Working hypothesis of the conjugate addition of nitroalkanes to vinyl sulfone mediated by bifunctional thiourea catalyst

To the best of our knowledge, the asymmetric conjugate addition of nitroalkanes to vinyl sulfone is unknown in literature. It is hypothesized that bifunctional catalysts containing suitable hydrogen bond donor and tertiary amine moiety should be able to activate nitroalkane and facilitate their conjugate addition to vinyl sulfone, and

enantioselective addition may be feasible with the careful selection of chiral structural scaffolds (Figure 5-1). In this chapter, we will discuss in detail our studies on the asymmetric conjugate addition of nitroalkanes to vinyl sulfone catalyzed by quinidine-derived bifunctional thiourea catalyst.

5.2 Quinidine-Derived Thiourea-Containing Bifunctional Catalyst



5-5

Recently, the utilization of hydrogen bonding interactions represents an important approach in asymmetric catalysis.[123-133] In particular, thiourea-based organocatalysts have found wide applications in a huge number of organic reactions.[134-139] quinidine-derived bifunctional thiourea **5-5**, which was very useful for various reactions, was prepared according to the known procedure.[146]

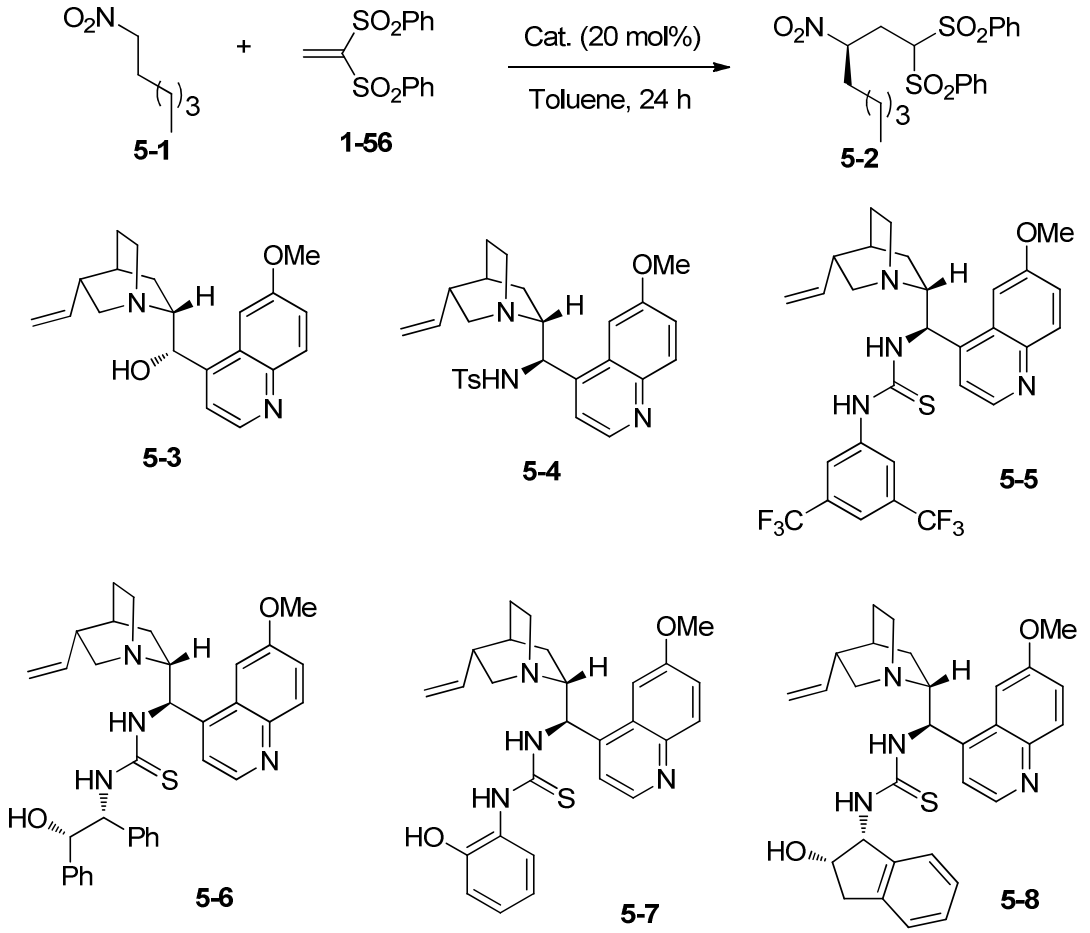
5.3 Results and Discussion

5.3.1 Catalyst Screen

For the initial exploration, we examined the catalyic effects of a number of cinchona alkaloid-based bifunctional catalysts for the addition of nitrohexane **5-1** to vinyl sulfone **1-56** (Table 5-1). Quinidine **5-3** catalyzed the reaction with low

enantioselectivity (entry 1). Quinidine-derived sulfonamide **5-4**, which promoted enantioselective conjugate addition of bicyclic α-substituted β-ketoesters to nitroolefins,[203] was found to be completely ineffective (entry 2). Quinidine-derived thiourea-containing bifunctional catalyst **5-5** was found to be effective with the yield up to 92% and enantioselectivity up to 76% (entry 3). Herein we thought multi-functional catalysts might be suitable for the reaction. A variety of multi-functional catalysts **5-6**, **5-7** & **5-8** derived from quinidine were chosen to screen in this reaction. Although good yields were obtained, only moderate enantioselectivities were observed (entries 4-6).

Table 5-1 Screening of organocatalysts for the asymmetric conjugate addition of nitrohexane to vinyl sulfone[a]



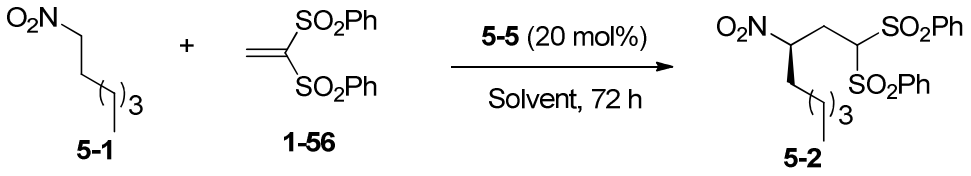
Entry	Catalyst	Yield[b] (%)	*ee*[c] (%)
1	**5-3**	91	40
2	**5-4**	< 10	-
3	**5-5**	92	76
4	**5-6**	85	70
5	**5-7**	87	54
6	**5-8**	85	47

[a] The reactions were performed with nitrohexane (0.3 mmol), vinyl sulfone (0.05 mmol) and catalyst (0.01 mmol) in toluene (0.5 mL) at room temperature, unless otherwise specified. [b] Isolated yield. [c] The ee value was determined by chiral HPLC analysis.

5.3.2 Solvent, Additive and Temperature Screen

After **5-5** was identified as the best catalyst, some common solvents were further screened (Table 5-2). Most solvents could provide us the desired adduct in good yields and with moderate enantioselectivities. For example, 81% yield and 70% ee was obtained when chloroform was used (entry 1). When toluene was used at -10 ^{o}C, 87% yield and 86% ee were obtained (entry 9).

Table 5-2 Screening of solvents for the asymmetric conjugate addition of nitrohexane to vinyl sulfone[a]



Entry	Solvent	Temp. (^{o}C)	Yield/[b] (%)	*ee*/[c] (%)
1	$CHCl_3$	rt	81	70

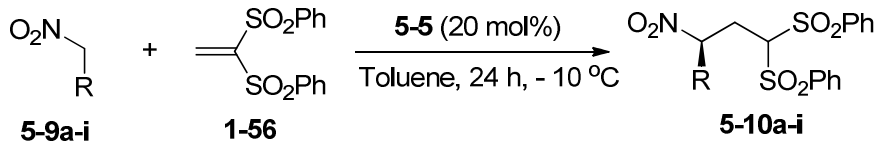
2	CH_2Cl_2	rt	83	61
3	CH_3CN	rt	86	40
4	THF	rt	61	43
5	MeOH	rt	73	44
6	Dioxane	rt	<30	---
7	Et_2O	rt	82	63
8	Acetone	rt	75	45
9	**Toluene**	**-10**	**87**	**86**

[a] The reactions were performed with nitrohexane (0.3 mmol), vinyl sulfone (0.05 mmol) and catalyst (0.01 mmol) in anhydrous solvent (0.5 mL) at indicated temperature, unless otherwise specified. [b] Isolated yield. [c] The *ee* value was determined by chiral HPLC analysis.

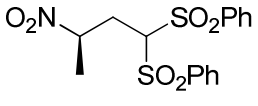
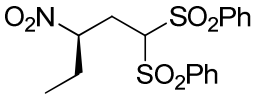
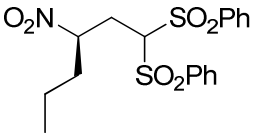
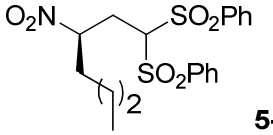
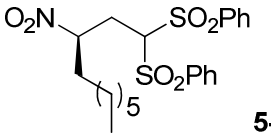
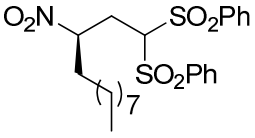
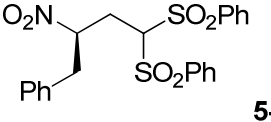
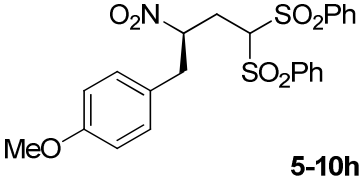
5.3.3 Scope of Nitroalkanes

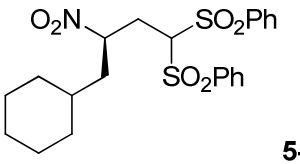
With the optimal condition, the scope of nitroalkanes was examined (Table 5-3). When different nitroalkanes were used, the reactions proceeded well. For example, when nitroethane was employed, 82% yield and 84% ee were obtained (entry 1). Nitroalkanes with long carbon chain did not negtively affect the enantioselectivity (entries 2 to 6). For example, the addition of nitroalkane containing 10 carbons to vinyl sulfone provided us the desired adduct with 80% ee (entry 6). For nitroalkane containing aromatic group or steric hindering group, the reaction still proceeded well (entries 7-9). For example, when (2-nitroethyl)-benzene was used, 87% yield and 74% ee were obtained. These results indicated the hydrogen bond formation was very efficient with various nitroalkanes.

Table 5-3 Asymmetric conjugate addition of various nitroalkanes to vinyl sulfone[a]



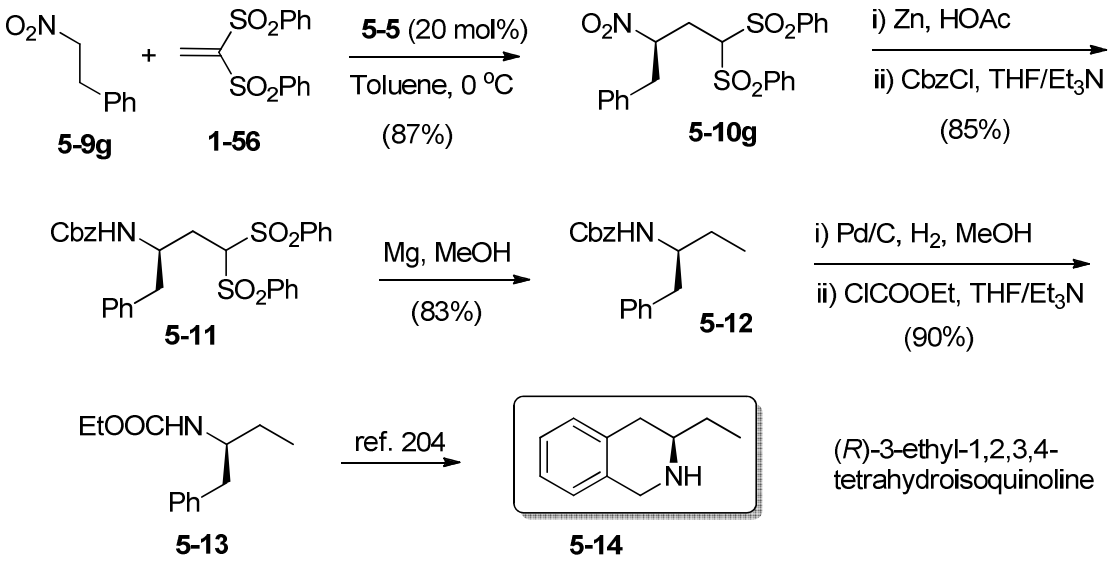
5-9a-i **1-56** **5-10a-i**

Entry	Product	T/(h)	Yield[b]/ (%)	*ee*[c]/ (%)
1	 **5-10a**	48	82	84
2	 **5-10b**	48	86	78
3	 **5-10c**	48	82	80
4	 **5-10d**	48	71	84
5	 **5-10e**	72	81	74
6	 **5-10f**	72	82	80
7	 **5-10g**	72	87	74
8	 **5-10h**	48	82	72

9	 **5-10i**	48	75	78

[a] The reactions were performed with nitroalkane (0.3 mmol), vinyl sulfone (0.05 mmol) and catalyst (0.01 mmol) in anhydrous toluene (0.5 mL) at -10 °C. [b] Isolated yield. [c] The ee value was determined by chiral HPLC analysis.

5.3.4 Synthesis of (*R*)-3-ethyl-1,2,3,4-tetrahydroisoquinoline

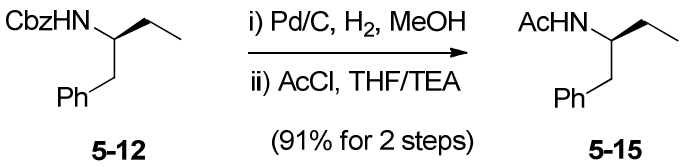


Scheme 5-1 A small synthesis of (*R*)-1,2,3,4-tetrahydroisoquinoline

The adducts from the addition of nitroalkanes to vinyl sulfone are very useful intermediates in organic synthesis. In particular, the reduction of nitro group to amino function, in combination with ready desulfonation, provides an easy access to chiral amines. To demonstrate the synthetic application of our methodology, we prepared (*R*)-3-ethyl-1,2,3,4-tetrahydroisoquinoline, which is an inhibitor of phenylethanolamine *N*-methyltransferase.[204] As shown in Scheme 5-1, the conjugate product **5-10g** was reduced *in situ* with zinc in acetic acid to the amine, followed by

protection with Cbz group to generate **5-11** in 85% yield for two steps. Removal of sulfone groups of the compound **5-11** afforded carbamate **5-12**. Hydrogenation of the carbamate **5-12** generated crude amine, which reacted with ethyl chloroformate to yield the intermediate **5-13** in 90% yield. Following the known procedure,[205] tetrahydroisoquinolin **5-14** could be obtained.

5.3.5 Determination of Absolute Configuration of Adducts



5-12 (91% for 2 steps) **5-15**

Scheme 5-2 Determination of absolute configuration of **5-10**

Compound **5-12** which was prepared following the procedure in Section 5.4.2. Hydrogenation of **5-12** afforded the crude amine, which reacted with acyl chloride to yield the known compound **5-15** in 91% yield for two steps. The configuration of **5-15** was determined by comparison with the literature data.[205] The configurations of the adducts **5-10a-i** were assigned by analogy.

5.4 Conclusions

In summary, we have disclosed the first organocatalytic enantioselective conjugate addition of nitroalkanes to vinyl sulfone promoted by a bifunctional

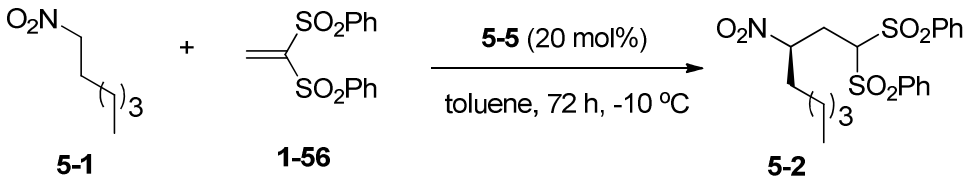
quinidine-derived thiourea catalyst. With the catalyst **5-5**, the reaction could proceed in up to 87% yield and with up to 86% ee. The described asymmetric conjugate addition, together with facile reduction and desulfonation, represents a novel approach to access α-branched chiral amines. The conjugate product was very useful and could be used to synthesize (*R*)-3-ethyl-1,2,3,4-tetrahydroisoquinoline.

5.5 Experimental Section

5.5.1 General Methods

The general methods of Chapter 2 were followed.

5.5.2 Representative Procedure for Addition of Nitrohexane to Vinyl Sulfone



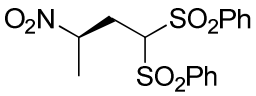
5-1 **1-56** **5-2**

Nitrohexane **5-1** (33 mg, 0.25 mmol) was added to a mixture of thiourea **5-5** (6.0 mg, 0.01 mmol) and 1,1-bis(benzenesulfonyl)ethylene **1-56** (15.4 mg, 0.05 mmol) in anhydrous toluene (0.2 mL) in a sealed sample vial at -10 ^{o}C. The reaction mixture was stirred at -10 ^{o}C for 72 h and then quenched with the addition of HCl 1N (2 mL). The organic layer was extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (ethyl acetate /hexanes = 1:5 to 1:2)

afforded the desired product as a white solid (19.1 mg, 87%).

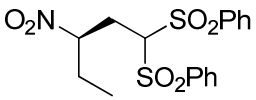
5.5.3 Characterizations of Intermediates and Adducts

(*R*)-1-(3-Nitro-1-(phenylsulfonyl)butylsulfonyl)benzene (**5-10a**)



A pale yellow oil; The ee value is 84%, t_R (major) = 126.40 min, t_R (minor) = 150.30 min (Chiralcel AS-H, λ = 254 nm, 10% ^{i}PrOH/hexanes, flow rate = 1.0 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59-1.61 (d, *J* = 7.0 Hz, 3H), 2.55-2.61 (m, 1H), 2.75-2.81 (m, 1H), 4.59-4.61 (m, 1H), 4.71-4.74 (m, 1H), 5.12-5.16 (m, 1H), 7.55-7.62 (m, 4H), 7.71-7.74 (m, 2H), 7.82-7.84 (m, 2H), 7.96-7.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.53, 30.86, 79.57, 80.62, 129.34, 129.40, 129.44, 129.57, 135.01, 136.80, 137.83; $[\alpha]_D$ = + 9.5 (c = 0.1, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{16}H_{17}NO_6S_2$ $[M+Na]^+$ 406.0414, found 482.0407.

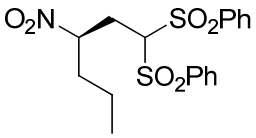
(*R*)-1-(3-Nitro-1-(phenylsulfonyl)pentylsulfonyl)benzene (**5-10b**)



A pale yellow oil; The ee value is 78%, t_R (major) = 43.74 min, t_R (minor) = 52.77 min (Chiralcel AS-H, λ = 254 nm, 10% ^{i}PrOH/hexanes, flow rate = 1.0 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98-1.01 (d, *J* = 7.6 Hz, 3H), 1.87-1.89 (m, 1H), 1.94-1.99 (m, 1H), 2.63-2.66 (m, 1H), 2.72-2.75 (m, 1H), 4.44-4.47 (m, 1H), 4.98-5.00 (m, 1H), 7.57-7.62 (m, 4H), 7.71-7.74 (m, 2H), 7.81-7.83 (m, 2H), 7.96-7.98 (m, 2H); ^{13}C

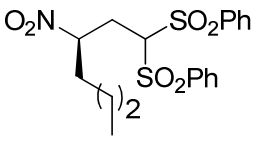
NMR (75 MHz, $CDCl_3$) δ 9.82, 27.26, 29.24, 79.57, 87.12, 128.49, 129.33, 129.38, 129.45, 129.57, 135.00, 136.77, 137.94, 140.39; $[\alpha]_D$ = - 6.1 (c = 0.21, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{17}H_{19}NO_6S_2$ $[M+Na]^+$ 420.0570, found 420.0562.

(*R*)-1-(3-Nitro-1-(phenylsulfonyl)hexylsulfonyl)benzene (**5-10c**)



A pale yellow oil; Ee is 80%, t_R (major) = 94.0 min, t_R (minor) = 102.8 min (Chiralcel (AS+AS)-H, λ = 254 nm, 30% ^{i}PrOH/hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92-0.97 (t, *J* = 7.4 Hz, 3H), 1.26-1.39 (m, 2H), 1.67-1.77 (m, 1H), 1.90-1.97 (m, 1H), 2.57-2.79 (m, 2H), 4.42-4.46 (m, 1H), 5.00-5.09 (m, 1H), 7.54-7.67 (m, 4H), 7.68-7.74 (m, 2H), 7.76-7.83 (m, 2H), 7.95-7.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.24, 18.70, 29.49, 35.75, 79.40, 85.64, 129.26, 129.29, 129.38, 129.45, 134.93, 136.62, 137.87; $[\alpha]_D$ = + 2.5 (c = 1.3, CH_2Cl_3); HRMS (ESI) m/z calcd for $C_{18}H_{21}NO_6S_2$ $[M+Na]^+$ 434.0703, found 434.0711.

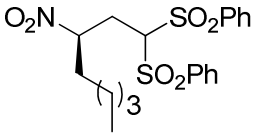
(*R*)-1-(3-Nitro-1-(phenylsulfonyl)heptylsulfonyl)benzene (**5-10d**)



A white solid; Ee is 83%, t_R (major) = 84.20 min, t_R (minor) = 98.69 min (Chiralcel (2AS)-H, λ = 254 nm, 30% ^{i}PrOH/hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87-0.92 (t, *J* = 6.7 Hz, 3H), 1.26-1.35 (m, 4H), 1.70-1.74 (m, 1H),

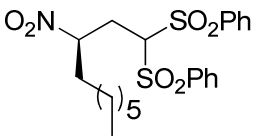
1.82-1.98 (m, 1H), 2.57-2.79 (m, 2H), 4.42-4.46 (m, 1H), 4.99-5.08 (m, 1H), 7.54-7.69 (m, 4H), 7.68-7.74 (m, 2H), 7.80-7.83 (m, 2H), 7.95-7.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.58, 21.89, 27.34, 29.49, 33.52, 79.41, 85.87, 129.25, 129.29, 129.37, 129.44, 134.92, 136.63, 137.87; $[\alpha]_D$ = + 2.2 (c = 0.3, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{19}H_{23}NO_6S_2$ $[M+Na]^+$ 434.0703, found 434.0711.

(*R*)-1-(3-Nitro-1-(phenylsulfonyl)octylsulfonyl)benzene (**5-2**)



A white solid; The ee value is 87%, t_R (major) = 55.04 min, t_R (minor) = 58.90 min (Chiralcel AD-H, λ = 254 nm, 7% ^{i}PrOH/hexanes, flow rate = 0.5 mL/min); ^1H NMR (300 MHz, $CDCl_3$) δ 0.86-0.89 (t, *J* = 6.6 Hz, 3H), 1.26-1.29 (m, 6H), 1.74-1.78 (m, 1H), 1.90-1.97 (m, 1H), 2.62-2.80 (m, 2H), 4.43-4.47 (m, 1H), 5.01-5.04 (m, 1H), 7.55-7.60 (m, 4H), 7.68-7.73 (m, 2H), 7.80-7.83 (m, 2H), 7.96-7.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.74, 22.13, 24.94, 29.50, 30.85, 33.78, 79.45, 85.88, 129.24, 129.29, 129.36, 129.44, 134.90, 136.68, 137.89; $[\alpha]_D$ = + 7.2 (c = 0.3, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{20}H_{25}NO_6S_2$ $[M+Na]^+$ 462.1040, found 462.1035.

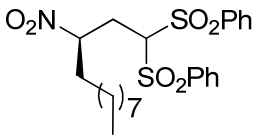
(*R*)-1-(3-Nitro-1-(phenylsulfonyl)hexylsulfonyl)benzene (**5-10e**)



A white solid; The ee value is 74%, t_R (major) = 71.12 min, t_R (minor) = 83.37 min

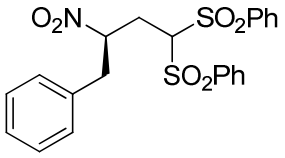
(Chiralcel AS-H, λ = 254 nm, 10% ^{i}PrOH/hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86-0.89 (t, *J* = 7.6 Hz, 3H), 1.25-1.29 (m, 10H), 1.73-1.77 (m, 1H), 1.90-1.97 (m, 1H), 2.62-2.80 (m, 2H), 4.42-4.45 (m, 1H), 5.02-5.05 (m, 1H), 7.55-7.62 (m, 4H), 7.70-7.75 (m, 2H), 7.81-7.82 (m, 2H), 7.96-7.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.96, 22.47, 25.28, 28.70, 28.75, 29.49, 31.49, 33.83, 79.41, 85.89, 129.25, 129.29, 129.36, 129.45, 134.91, 136.63, 137.87; $[\alpha]_D$ = + 3.2 (c = 1.2, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{22}H_{29}NO_6S_2$ $[M+Na]^+$ 490.1319, found 490.1321.

(*R*)-1-(3-Nitro-1-(phenylsulfonyl)hexylsulfonyl)benzene (**5-10f**)



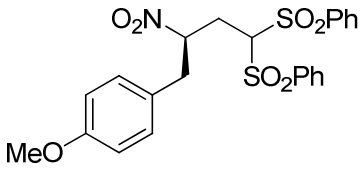
A white solid; The ee value is 80%, t_R (major) = 65.09 min, t_R (minor) = 77.51 min (Chiralcel AS-H, λ = 254 nm, 10% ^{i}PrOH/hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86-0.90 (t, *J* = 7.1 Hz, 3H), 1.25-1.27 (m, 15H), 1.74-1.76 (m, 1H), 1.90-1.95 (m, 1H), 2.62-2.80 (m, 2H), 4.41-4.45 (m, 1H), 5.01-5.02 (m, 1H), 7.55-7.60 (m, 4H), 7.68-7.73 (m, 2H), 7.80-7.83 (m, 2H), 7.96-7.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.00, 22.56, 25.28, 28.74, 29.08, 29.11, 29.25, 29.50, 31.72, 33.83, 79.45, 85.89, 129.23, 129.29, 129.36, 129.45, 134.90, 136.67, 137.90; $[\alpha]_D$ = + 3.1 (c = 0.32, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{24}H_{33}NO_6S_2$ $[M+Na]^+$ 518.1642, found 518.1645.

(*R*)-1-(2-Nitro-4,4-bis(phenylsulfonyl)butyl)benzene (**5-10g**)



A colorless oil; The ee value is 75%, t_R (major) = 60.19 min, t_R (minor) = 73.48 min (Chiralcel AD-H, λ = 254 nm, 20% ^{i}PrOH/hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.55-2.59 (m, 1H), 2.74-2.78 (m, 1H), 3.03-3.10 (m, 1H), 3.34-3.39 (m, 1H), 4.47-4.50 (m, 1H), 5.29-5.37 (m, 1H), 7.19 (m, 2H), 7.34-7.37 (m, 3H), 7.50-7.69 (m, 4H), 7.71-7.74 (m, 4H), 7.80-7.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.81, 39.97, 79.40, 86.21, 127.84, 129.11, 129.24, 129.40, 129.78, 134.04, 134.93, 136.94; $[\alpha]_D$ = + 12.8 (c = 0.9, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{22}H_{21}NO_6S_2$ $[M+Na]^+$ 482.0703, found 482.0705.

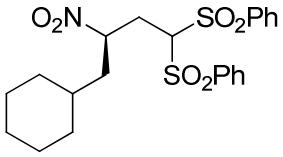
(*R*)-1-Methoxy-4-(2-nitro-4,4-bis(phenylsulfonyl)butyl)benzene (**5-10i**)



A colorless oil; The ee value is 72%, t_R (minor) = 37.69 min, t_R (major) = 80.32 min (Chiralcel AS-H, λ = 254 nm, 40% ^{i}PrOH/hexanes, flow rate = 1.0 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57-2.60 (m, 1H), 2.76-2.79 (m, 1H), 3.02-3.06 (m, 1H), 3.29-3.34 (m, 1H), 3.85 (s, 3H), 4.49-4.50 (m, 1H), 5.29-5.32 (m, 1H), 6.90-6.91 (d, *J* = 8.9 Hz, 2H), 7.10-7.12 (d, *J* = 8.9 Hz, 2H), 7.54-7.61 (m, 4H), 7.72-7.78 (m, 4H), 7.83-7.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.72, 39.28, 55.34, 79.50, 86.40, 114.52, 125.97,128.49, 129.17, 129.30, 129.42, 129.85, 129.87,130.03, 134.94,

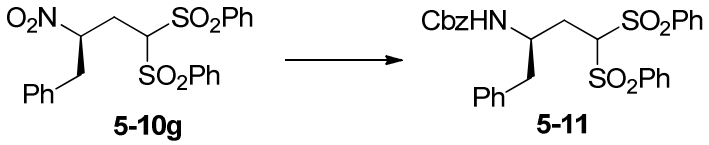
137.00; $[\alpha]_D$ = - 3.4 (c = 0.31, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{23}H_{23}NO_6S_2$ $[M+Na]^+$ 512.0808, found 512.0811.

(*R*)-1-(4-Cyclohexyl-3-nitro-1-(phenylsulfonyl)butylsulfonyl)benzene (**5-10i**)



A colorless oil; The ee value is 78%, t_R (major) = 25.77 min, t_R (minor) = 30.94 min (Chiralcel AS-H, λ = 254 nm, 20% ^{i}PrOH/hexanes, flow rate = 1.0 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90-0.92 (m, 2H), 1.17-1.20 (m, 4H), 1.65-1.70 (m, 6H), 2.64-2.71 (m, 2H), 4.40-4.43 (m, 1H), 5.12-5.13 (m, 1H), 7.57-7.81 (m, 8H), 7.95-7.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.71, 26.05, 30.00, 32.39, 32.97, 34.28, 41.40, 79.36, 83.88, 129.24, 129.31, 129.36, 129.43, 134.88, 136.65, 137.93; $[\alpha]_D$ = + 9.5 (c = 0.4, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{22}H_{27}NO_6S_2$ $[M+Na]^+$ 418.1172, found 418.1179.

(*R*)-Benzyl 1-phenyl-4,4-bis(phenylsulfonyl)butan-2-ylcarbamate (**5-11**)



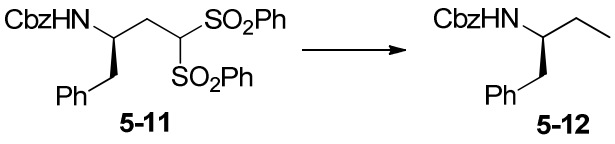
5-10g **5-11**

To a solution of compound **5-10g** (112 mg, 0.20 mmol) in THF (2.0 mL) containing acetic acid (1.5 mL) was added zinc powder (406 mg, 7.0 mmol). After stirring at room temperature for 24 h, the mixture was filtered, and the filtrate was concentrated and partitioned between aqueous $NaHCO_3$ and ethyl acetate. The organic

layer was washed with brine and dried with Na_2SO_4. The solvent was removed to afford the crude product, which was directly used for the next step. To a solution of crude amine in THF (5 mL) was added triethylamine (0.14 mL, 1.0 mmol) and CbzCl (41 mg, 0.24 mmol). The reaction mixture was stirred at room temperature for 3 h and concentrated. The residue was taken up in ethyl acetate (10 mL), washed with water (2 x 5 mL), and dried over Na_2SO_4. After filtration, the filtrate was concentrated, and the residue was purified by column chromatography (ethyl acetate /hexanes = 1:5 to 2:5) to afford **5-11** as a yellow oil (96 mg, 85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.07-2.28 (m, 1H), 2.37-2.39 (m, 1H), 2.72-2.76 (m, 1H), 2.89-2.93 (m, 1H), 3.85 (s, 3H), 4.08 (m, 1H), 4.71-4.74 (m, 2H), 5.07-5.13 (m, 2H), 7.11-7.13 (m, 2H), 7.31-7.38 (m, 8H), 7.45-7.49 (m, 4H), 7.65-7.66 (m, 2H), 7.79-7.80 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.10, 41.53, 51.40, 66.71, 77.38, 79.92, 126.86, 127.90, 128.15, 128.51, 128.69, 129.02, 129.31, 129.45, 134.30, 134.43, 136.35, 137.44, 137.54, 156.30; $[\alpha]_D$ = - 19.5 (c = 0.4, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{30}H_{29}NO_6S_2$ $[M+Na]^+$ 586.1329, found 586.1326.

(*S*)-Benzyl 1-phenylbutan-2-ylcarbamate (**5-12**)

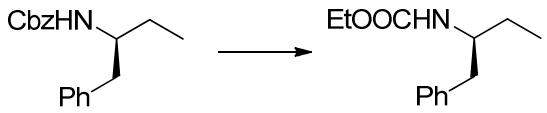


The activated magnesium metal (108 mg, 4.5 mmol) was added into a solution of (*R*)-benzyl 1-phenyl-4,4-bis(phenylsulfonyl)butan-2-ylcarbamate **5-11** (85 mg, 0.15 mmol) in anhydrous methanol (10 mL) with stirring. After 30 min, the reaction

mixture was brought to reflux for 2 h. Upon cooling down to room temperature, the mixture was poured into 2 N HCl solution (10 mL) and extracted with ether (3 x 10 mL). The organic extracts were combined, dried over Na_2SO_4 and filtered. Solvent was removed *in vacuo*, and the residue was purified by column chromatography (ethyl acetate /hexanes = 1:15 to 1:5) to afford the desired product as a white solid (35 mg, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89-0.94 (t, *J* = 7.4 Hz, 3H), 1.26-1.37 (m, 1H), 1.50-1.59 (m, 1H), 2.75-2.77 (d, *J* = 6.2 Hz, 2H), 3.80 (s, 1H), 4.48-4.51 (m, 1H), 5.05 (s, 2H), 7.14-7.32 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.27, 26.92, 40.74, 53.56, 66.42, 126.28, 127.90, 127.95, 128.28, 128.42, 129.39, 136.64, 137.95, 141.15; $[\alpha]_D$ = - 3.6 (c = 0.6, $CHCl_3$).

(*S*)-Ethyl 1-phenylbutan-2-ylcarbamate (**5-13**)



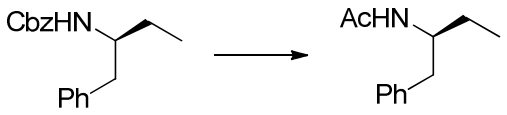
5-12 **5-13**

To a solution of carbamate **5-12** (15 mg, 0.053 mmol) in methanol (2 mL) was added 10% activated Pd/C (5 mg). The suspension was allowed to stir under a balloon of hydrogen gas. After 2 h, the reaction mixture was filtered through Celite, and the filtrate was concentrated *in vacuo*. To the residue in THF (2 mL) at 0 ^oC was added triethylamine (42 μL, 0.3 mmol) and ethyl chloroformate (22 mg, 0.2 mmol). After stirring at room temperature for 30 min, the reaction mixture was concentrated and taken up in ethyl acetate (10 mL). The organic extracts were washed with brine, dried

over Na_2SO_4 and filtered. The solvent was removed *in vacuo*, and the residue was purified by column chromatography (ethyl acetate /hexanes = 1:20 to 1:6) to afford the desired **5-13** as a colorless oil (10.6 mg, 90%).

$[\alpha]_D$ = - 3.1 (c = 0.32, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.88-0.93 (t, *J* = 7.4 Hz, 3H), 1.16-1.20 (t, *J* = 7.1 Hz, 3H), 1.30-1.33 (m, 1H), 1.50-1.53 (m, 1H), 2.73-2.76 (d, *J* = 6.2 Hz, 3H), 3.76 (s, 1H), 4.01-4.08 (m, 2H), 4.39 (s, 1H), 7.14-7.26 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.25, 14.52, 26.88, 40.83, 53.35, 60.51, 126.24, 128.50, 129.38, 138.07; The ee value is 74%, t_R (major) = 22.61 min, t_R (minor) = 29.89 min (Chiralcel AD-H, λ = 254 nm, 3% *i*PrOH/hexanes, flow rate = 0.4 mL/min).

(*S*)-N-(1-Phenylbutan-2-yl)acetamide (**5-15**)



5-12 **5-15**

Hydrogenation of the carbamate **5-12** followed the procedure described for preparation of **5-13**. To the residue in THF (2 mL) at 0 °C was added triethylamine (42 μL, 0.3 mmol) and acyl chloride (16 mg, 0.2 mmol). After stirring at room temperature for 30 min, the reaction mixture was concentrated and taken up in ethyl acetate (10 mL). The organic extracts were washed with 1N HCl (3 x 5 mL), 1N NaOH (3 x 5 mL) and brine, and dried over Na_2SO_4. After filtration, the filtrate was concentrated to afford the desired product as a colorless oil (9.2 mg, 91%).

^1H NMR (500 MHz, $CDCl_3$) δ 0.91-0.94 (t, *J* = 7.6 Hz, 3H), 1.31-1.37 (m, 1H), 1.53-1.58 (m, 1H), 1.92 (s, 3H), 2.77-2.79 (d, *J* = 6.3 Hz, 2H), 4.09-4.15 (m, 1H),

5.28-5.29 (m, 1H), 7.16-7.22 (m, 2H), 7.26-7.17 (m, 1H), 7.28-7.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.40, 23.44, 26.76, 40.38, 51.52, 126.38, 129.45, 138.05, 169.64; $[\alpha]_D$ = - 1.7 (c = 0.2, CH_3OH, *lit*[205] = - 1.9).

Chapter 6 Stereocontrolled Creation of All-Carbon Quaternary Stereocenters by Organocatalytic Conjugate Addition of Oxindoles to Vinyl Sulfones

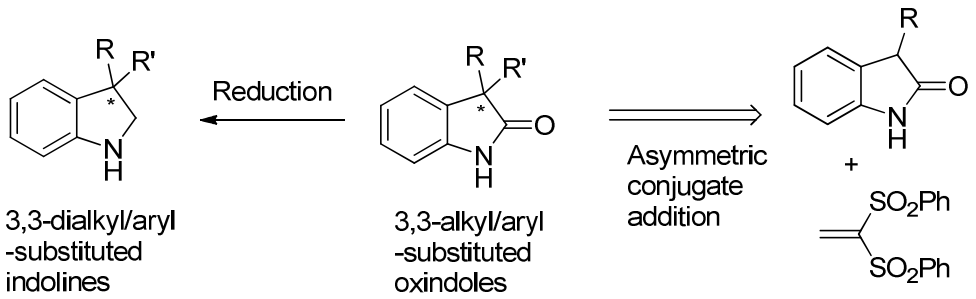
6.1 Introduction

In **Chapter 5**, we have established the conjugate addition of nitroalkanes to vinyl sulfone **1-56** mediated by quinidine-derived bifunctional thiourea **5-5**. In order to develop new donors in the conjugate additions to vinyl sulfones catalyzed by bi- or tri-functional thiourea catalysts, we were interested to explore the conjugate addition of oxindoles as donors to vinyl sulfones.

Oxindoles are widely present in natural products and bioactive molecules.[206] In particular, oxindoles bearing a quaternary stereogenic center[207] at the 3-position are extremely important and have been used in natural product synthesis and development of pharmaceutical agents. Various synthetic strategies have been devised in recent years for the asymmetric synthesis of 3,3-disubstituted oxindoles. Most approaches employ 3-substituted oxindoles as nucleophiles, including fluorination,[208] hydroxylation,[209] amination,[210] aldol and Mannich reactions,[211] allylic alkylation,[212] and conjugate addition.[213] By utilizing chiral nucleophilic catalyst-mediated rearrangement, the groups of Fu and Vedejs achieved efficient synthesis of 3-acylated oxindoles[214] bearing a quaternary stereocenter. In spite of the aforementioned great achievements in stereoselective synthesis of oxindoles with a quaternary center at the

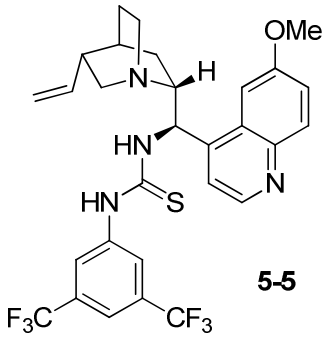
3-position, organocatalytic approaches to access chiral 3,3-dialkyl/aryl-substituted oxindoles are very limited.[215] It is thus highly desirable to develop asymmetric synthetic methods for the preparation of such medicinally useful and synthetically challenging molecules.

We envisioned that an organocatalytic conjugate addition of 3-aryl or 3-alkyl-substituted oxindoles to 1,1-bis(benzenesulfonyl)ethylene **1-56**, followed by desulfonation, might provide a viable approach for the construction of optically enriched 3,3-alky/aryl-substituted oxindoles. Moreover, facile reduction of the carbonyl moiety of oxindoles allows an easy access to 3,3-disubstituted indolines, which are known to be extremely important structural elements in many biologically active compounds and natural products (Scheme 6-1).[216] In this chapter, we will discuss our recent studies on the conjugate addition of 3-aryl or 3-alkyl-substituted oxindoles to 1,1-bis(benzenesulfonyl)ethylene, leading to enantioselective preparation of 3,3-alkyl/ aryl-substituted oxindoles and indolines bearing an all-carbon quaternary stereogenic center.



Scheme 6-1 Construction of 3,3-alkyl/aryl-substituted oxindoles and indolines

6.2 Quinidine-Derived Bifunctional Thiourea



5-5

To affect a stereoselective conjugate addition of oxindoles to vinyl sulfone, a bifunctional tertiary amine-thiourea catalyst with a properly installed Brønsted acid moiety is an obvious choice. Upon abstraction of a proton from oxindole, the non-covalent interaction between Brønsted acid moiety of the catalyst and oxindoles is expected to generate a structurally defined enolate, which may add to vinyl sulfone in a stereoselective manner. The enantioselective addition may be feasible with the careful selection of chiral structural scaffolds.

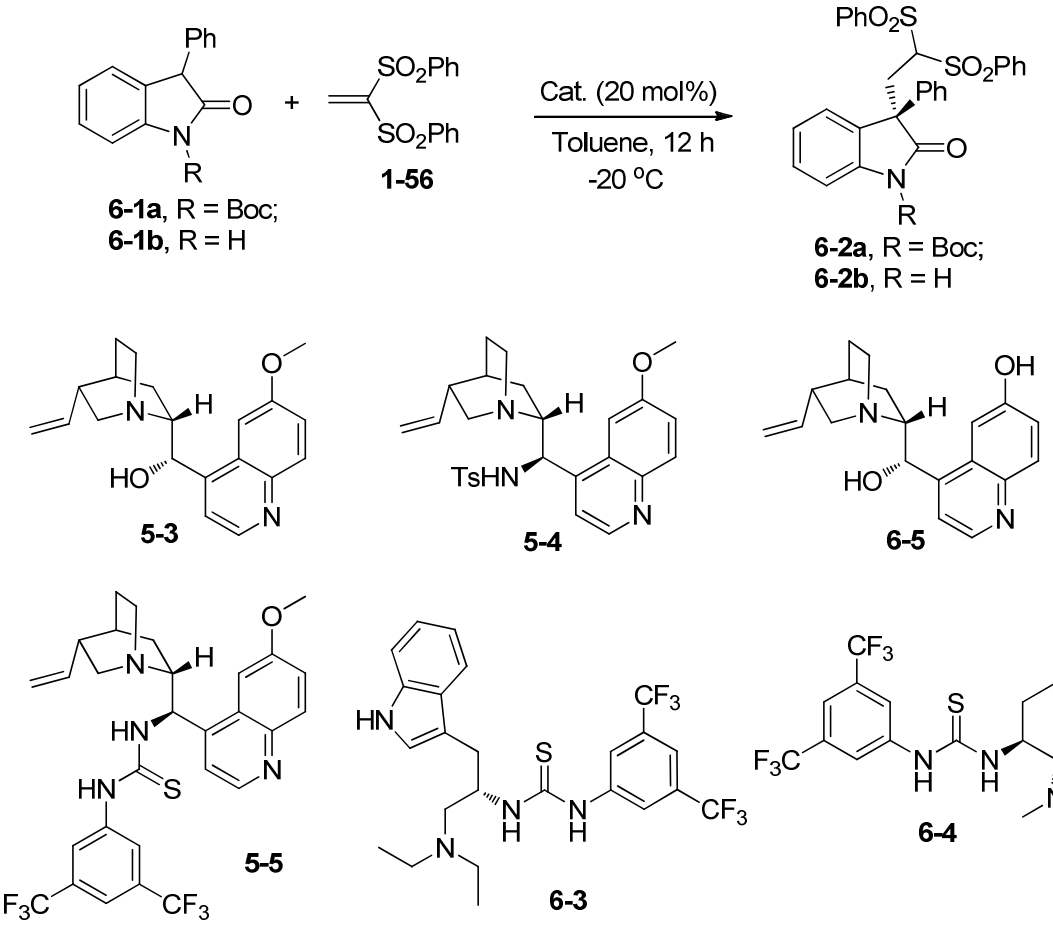
6.3 Conjugate Addition of 3-Aryl-Oxindoles to Vinyl Sulfone

6.3.1 Catalyst Screen

We began our initial studies from the addition of 3-phenyl-oxindole **6-1a** to vinyl sulfone **1-56**, and some bifunctional organocatalysts were screened (Table 6-1). Quinidine **5-3** catalyzed the reaction at -20 ^{o}C in good yield, but the enantioselectivity was very disappointing (entry 1). Quinidine-derived sulfonamide **5-4** mediated the reaction in 88% yield and with 12% ee (entry 2). Various thiourea-containing

bifunctional catalysts were further screened (entries 3-6). Quinidine-derived thiourea catalyst **5-5** was very efficient, yielding the desired adduct with 81% ee. L-Tryptophan-derived thiourea catalyst **6-3** could mediate the addition reaction, but only 28% ee was obtained (entry 4). Takemoto's catalyst **6-4** was ineffective, affording us the desired adduct with only 38% ee (entry 5). Bifunctional catalyst **6-5** could catalyze the reaction affording us the racemic product (entry 6). It should be noted that the Boc protection on nitrogen is crucial for the observed enantioselectivity, since the same **5-5**-catalyzed reaction employing oxindole **6-1b** gave racemic product, suggesting the important role of *N*-Boc group in asymmetric induction.

Table 6-1 Screening of catalysts in the conjugate addition of 3-phenyl-oxindole **6-1a** to vinyl sulfone **1-56**[a]



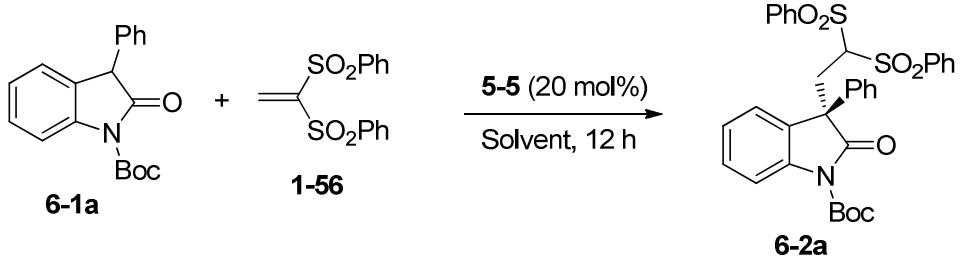
Entry	Catalyst	Yield[b] (%)	*ee*[c] (%)
1	**5-3**	91	20
2	**5-4**	88	12
3	**5-5**	95	81
4	**6-3**	92	28
5	**6-4**	88	38
6	**6-5**	90	2

[a] The reactions were performed with 3-phenyl-oxindole **6-1a** (0.06 mmol), vinyl sulfone (0.05 mmol) and the catalyst (0.01 mmol) in toluene (0.4 mL) at -20 ^{o}C, unless otherwise specified. [b] Isolated yield. [c] The *ee* value was determined by chiral HPLC analysis.

6.3.2 Solvent Screen

After identificaiton of **5-5** as the best catalyst, a series of common solvents were screened (Table 6-2). Polar solvents were not suitable. For example, when acetone was employed, only 26% ee was obtained (entry 5). Common solvents, such as $CHCl_3$, THF and CH_2Cl_2, could afford us good results (entries 1-4 & 6, 7). For example, when ether was employed, 92% yield and 79% ee were obtained (entry 3). When the temperature was lowered to -78 ^{o}C, 97% yield and 94% ee were obtained (entry 9).

Table 6-2 Screening of solvents for the asymmetric conjugate addition of 3-phenyl-oxindole to vinyl sulfone[a]



Entry	Solvent	Temp (^oC)	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	-20	91	57
2	$CHCl_3$	-20	94	78
3	Et_2O	-20	92	79
4	THF	-20	90	43
5	Acetone	-20	88	26
6	*p*-F-toluene	-20	93	73
7	*p*-CF_3-toluene	-20	92	58
8	Toluene	-60	93	89
9	Toluene	-78	97	94

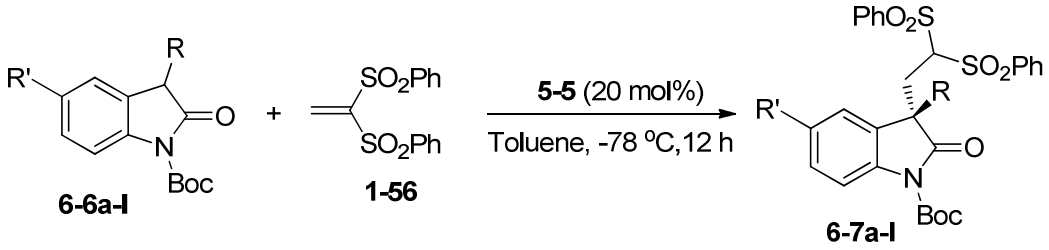
[a] The reactions were performed with 3-phenyl-oxindole (0.06 mmol), vinyl sulfone (0.05 mmol) and the catalyst (0.01 mmol) in indicated solvent (0.4 mL), unless otherwise specified. [b] Isolated yield. [c] The *ee* value was determined by chiral HPLC analysis.

6.3.3 Scope of 3-Aryl-Oxindoles

The generality of the conjugate addition of 3-aryl-oxindoles to vinyl sulfone was subsequently investigated (Table 6-3). A wide range of 3-aryl-substituted oxindoles **6-6a-l** could be employed as acceptors in the conjugate addition. Significant structural variation in the oxindole system was accommodated in the reaction. For example, *para*-methoxy group on the aromatic ring was tolerated and the sterically demanding product was obtained in 95% yield and with 91% ee (entry 4). The method was also compatible with electron-rich aryl groups (entries 7 & 9) and aryl fluoride substituents (entry 6). In all the examples examined, high yields and excellent enantioselectivities

were attainable (entries 1–11). However, when 3-benzyl-oxindole **6-6l** was used in the reaction, the desired product **6-7l** was obtained in 76% yield, but only with 28% ee (entry 12).

Table 6-3 Conjugate additions of various 3-aryl-oxindoles **6-6a-i** to vinyl sulfone **1-56** catalyzed by thiourea **5-5**[a]



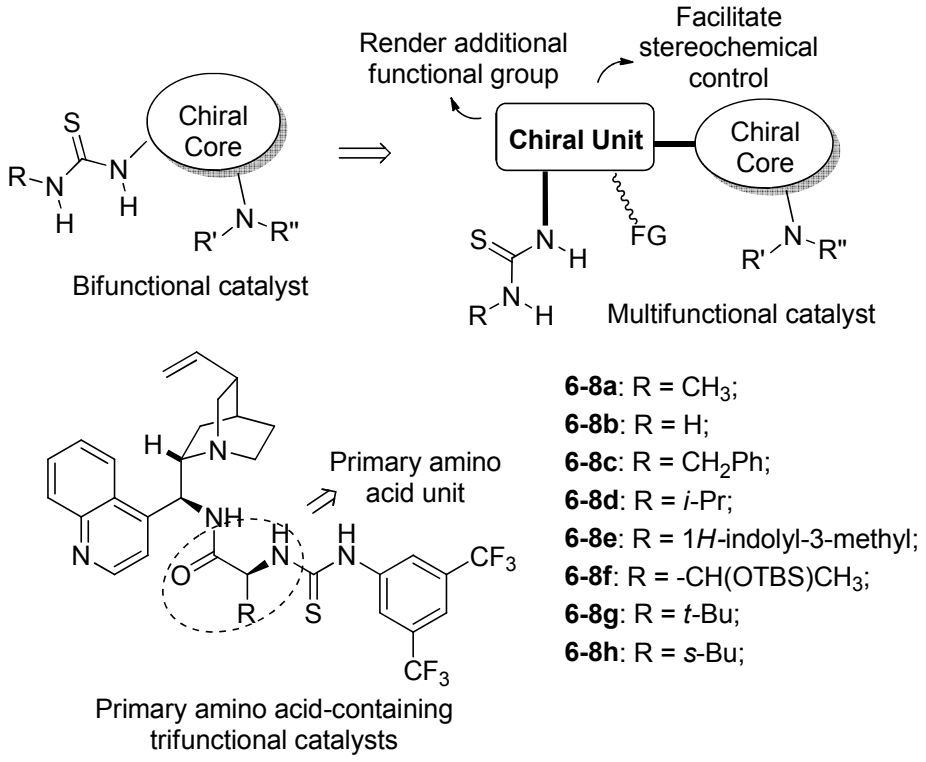
Entry	R/R'	Yield[b] (%)	*ee*[c] (%)
1	*p*-Me-C_6H_4/H (**6-7a**)	92	90
2	*m*-Me-C_6H_4/H (**6-7b**)	97	90
3	*o*-Me-C_6H_4/H (**6-7c**)	93	91
4	*p*-OMe-C_6H_4/H (**6-7d**)	95	91
5	*o*-OMe-C_6H_4/H (**6-7e**)	94	99
6	*p*-F-C_6H_4/H (**6-7f**)	97	94
7	*p*-Ph-C_6H_4/H (**6-7g**)	98	96
8	*p*-^{t}Bu-C_6H_4/H (**6-7h**)	96	84
9	2-naphthyl/H (**6-7i**)	95	93
10	Ph/CH_3 (**6-7j**)	95	90
11	Ph/F (**6-7k**)	94	93
12	Bn/H (**6-7l**)	76	28

[a] Reactions were performed with oxindole **6-6** (0.5 mmol), **1-56** (0.05 mmol) and the catalyst **5-5** (0.01 mmol) in anhydrous toluene (0.4 mL) at -78 °C for 12 h. [b] Isolated yield. [c] The *ee* value was determined by chiral HPLC analysis.

6.4 Conjugate Addition of 3-Alkyl-Oxindoles to Vinyl Sulfone

6.4.1 Cinchonidine-Derived Trifunctional Thiourea Catalysts

It is not surprising that **5-5**-catalyzed conjugate addition was not applicable to 3-alkyl substrates. In fact, all the examples reported in the literature only worked well either for 3-aryl or 3-alkyl-substituted oxindoles.[208-214] In order to achieve high enantioselectivity in the projected conjugate addition, it is essential for the catalyst to interact with oxindole and vinyl sulfone simultaneously in a cooperative manner, and we reasoned multifunctional catalysts may be a solution. Utilizing the existing bifunctional catalyst scaffolds, simple insertion of a chiral building block can result in novel trifunctional catalysts (Scheme 6-2).

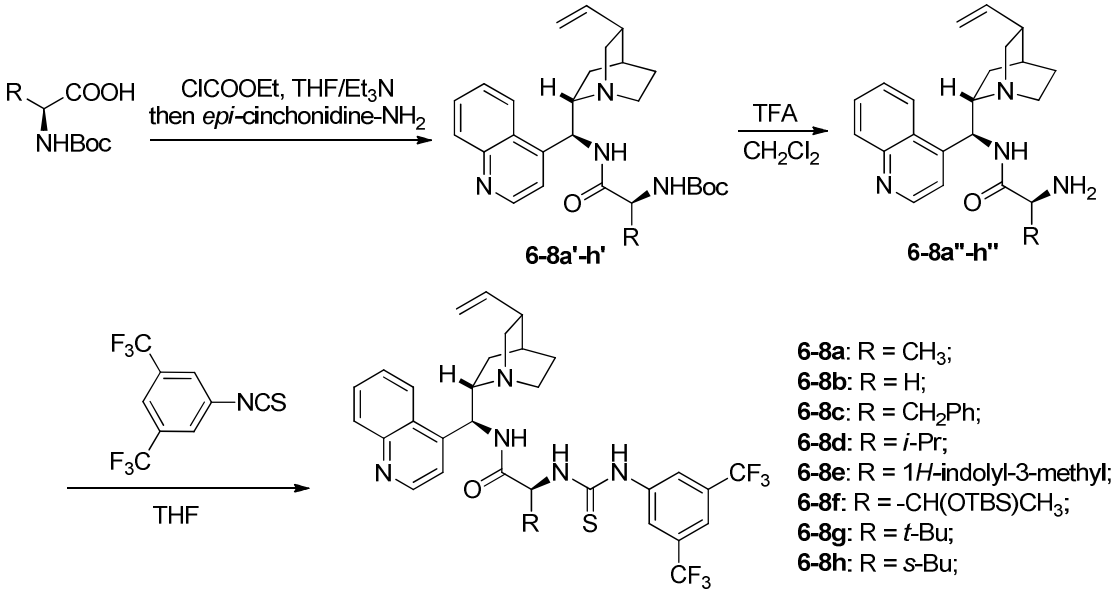


Scheme 6-2 Novel amino acid-containing trifunctional thiourea catalysts

Recently, primary amino acid-based synthetic methods have found wide applications in asymmetric synthesis.[114] To further expand the uses of primary amino acids in asymmetric catalysis, we decided to derive novel trifunctional catalysts by incorporating primary amino acid moieties into the bifunctional cinchona alkaloids, and a number of cinchonidine-derived trifunctional catalysts **6-8** were prepared.

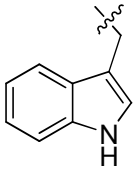
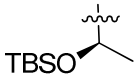
6.4.2 Synthesis of Cinchonidine-Derived Thiourea Catalysts 6-8a-h

The synthesis of catalysts **6-8a-h** is shown in Scheme 6-3. Different Boc-L-primary amino acids coupled with *epi*-cinchonidine-NH_2 to afford the amides **6-8a'-h'** in good yields (72-94%). After removal of the Boc group in **6-8a'-h'**, amines **6-8a"-h"** were obtained without further purification and used directly to react with 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene to afford **6-8a-h** in 81-95% yields.



Scheme 6-3 Preparation of amino acid-containing trifunctional thiourea **6-8a-h**

Chemical Yields

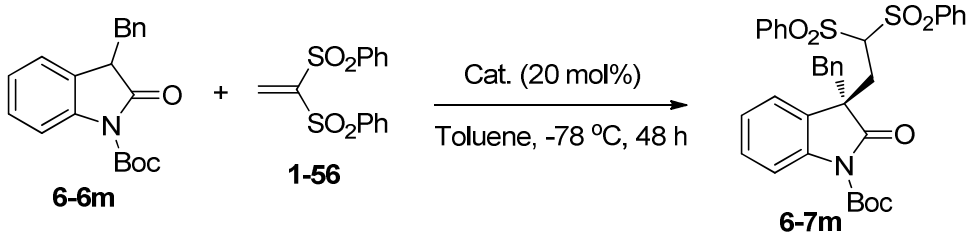
R	Compound	Yield (%)	Compound	Yield (%)
CH_3	**6-8a'**	81	**6-8a**	92
H	**6-8b'**	76	**6-8b**	90
CH_2Ph	**6-8c'**	88	**6-8c**	85
*i*Pr	**6-8d'**	94	**6-8d**	91
	**6-8e'**	91	**6-8e**	87
	**6-8f'**	89	**6-8f**	93
	**6-8g'**	72	**6-8g**	80
	**6-8h'**	84	**6-8h**	81

6.4.3 Catalyst Screen

Catalytic effects of trifunctional catalysts **6-8** for the conjugate addition of 3-benzyl-oxindole **6-6m** to vinyl sulfone **1-56** were examined (Table 6-4, entries 6-13). Catalysts with small substituents were not very effective (entries 6–7), however, good enantioselectivity was achieved with a phenylalanine-incorporating catalyst **6-8c** (entry 8). We were gratified to find that **6-8d** with a valine moiety incorporated afforded the desired adduct in 81% yield and 90% ee (entry 9). Tryptophan-containing catalyst **6-8e** was better than the catalyst with a phenylalanine moiety (entry 10). Further tuning of the steric hindrance at the amino acid side chain did not yield better catalysts (entries 11–13). These results suggested that the steric hindrance

at the R site in **6-8** may be important to facilitate thiourea moiety to adopt a relatively constraint conformation, however, a sterically too hindered group could be detrimental as the chiral pocket in **6-8** is rather crowded.

Table 6-4 Conjugate addition of 3-benzyl-oxindole **6-6m** to vinyl sulfone **1-56** mediated by novel trifunctional catalysts[a]



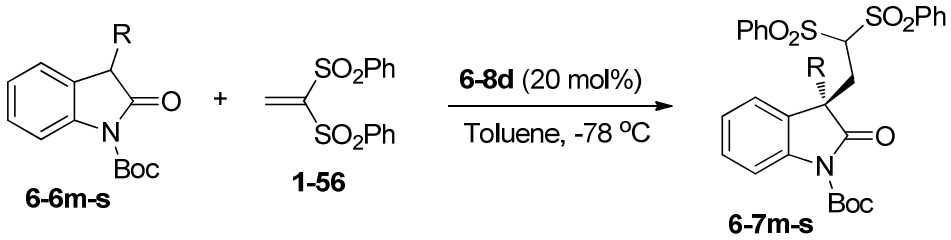
Entry	Catalyst	Yield[b] (%)	*ee*[c] (%)
1	**5-4**	72	30
2	**5-5**	76	28
3	**6-3**	74	37
4	**6-4**	76	41
5	**6-5**	67	40
6	**6-8a**	76	41
7	**6-8b**	72	37
8	**6-8c**	77	70
9	**6-8d**	81	90
10	**6-8e**	67	81
11	**6-8f**	54	37
12	**6-8g**	67	87
13	**6-8h**	64	75

[a] Reactions were performed with 3-benzyl-oxindole **6-6m** (0.06 mmol), **1-56** (0.05 mmol) and the catalyst (0.01 mmol) in toluene (0.4 mL) at -78 °C for 48 h. [b] Isolated yield. [c] The *ee* value was determined by chiral HPLC analysis.

6.4.4 Scope of 3-Alkyl-Oxindoles

After identification of **6-8d** as the best catalyst, the substrate scope was explored. The results are summarized in Table 6-5. Different 2-alkyl-oxindoles were screened. In all the examples examined, up to 88% yield and 91% ee were obtained. For example, when 3-4'-methoxyphenyloxindole **6-7o** was used, 88% yield and 90% ee were obtained (entry 3). When long chain alkyl substituted oxindoles were used, good yields were attained (entries 5-7). For example, when 2-alkyl-oxindole **6-7s** was used, up to 72% yield and up to 80% ee were obtained (entry 7).

Table 6-5 Asymmetric conjugate additions with various 3-alkyl-oxindoles[a]

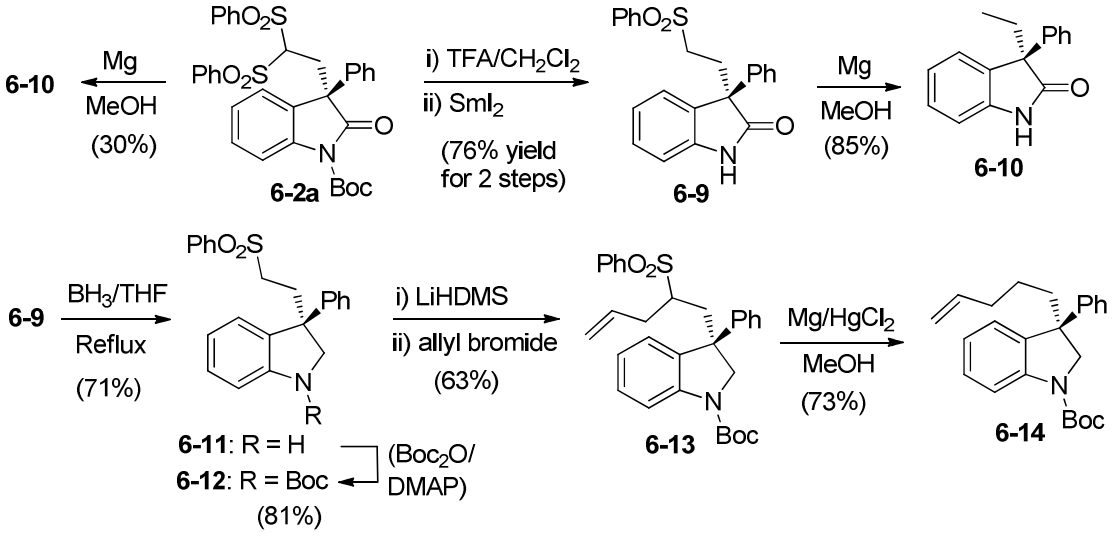


Entry	R	T (%)	Yield[b] (%)	*ee*[c] (%)
1	$C_6H_5CH_2$ (**6-7m**)	48	81	90
2	4-F-$C_6H_4CH_2$(**6-7n**)	60	85	91
3	4-OMe-$C_6H_4CH_2$(**6-7o**)	48	88	90
4	*n*-C_3H_7 (**6-7p**)	60	84	77
5	*n*-C_4H_9 (**6-7q**)	60	76	80
6	*n*-C_6H_{13} (**6-7r**)	72	80	77
7	*n*-$C_{11}H_{23}$ (**6-7s**)	96	72	80

[a] Reactions were performed with oxindole **6-6** (0.06 mmol), **1-48** (0.05 mmol) and **6-8d** (0.01 mmol) in anhydrous toluene (0.4 mL) at -78 °C. [b] Isolated yield. [c] The *ee* value was determined by chiral HPLC analysis.

6.5 Synthesis of 3-Alkyl-3-Aryl Oxindole and Indoline

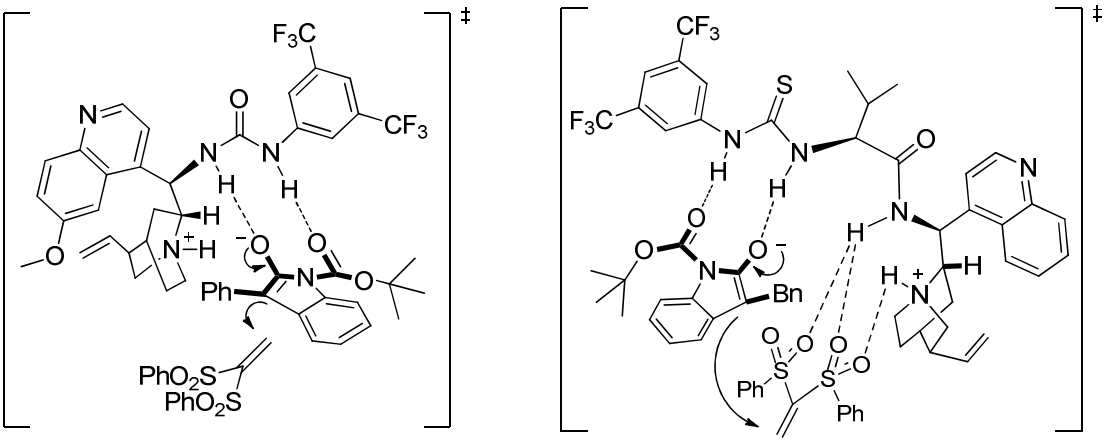
3,3-Alkyl/aryl-substituted oxindoles and indolines are important in biological sciences and medicinal chemistry.[217] The methodology described here represents an efficient approach to synthesize such very challenging scaffolds (Scheme 6-4). Treatment of adduct **6-2b** with magnesium/methanol only gave desired desulfonated product **6-10** in low yield, together with retro-Michael side products. To provide a practical solution, a two-step synthetic sequence was then devised. Selective removal of only one aryl sulfone was achieved by using samarium diiodide, and the subsequent desulfonation with magnesium yielded 3-alkyl-3-aryl-substituted oxindole **6-10**. Reduction of oxindole **6-9** afforded the corresponding indoline **6-11**. Compound **6-11** is an excellent intermediate for further structural elaboration. For example, allylation of **6-11**, followed by desulfonation created indoline **6-14** with an all-carbon quaternary center at the 3-position, which represents an important class of compounds in the development of therapeutic agents for CNS disease.[218]



Scheme 6-4 Synthesis of 3-alkyl-3-aryl oxindole and indoline

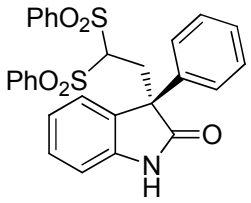
6.6 Proposed Transition States

Although the mechanisms of reactions reported herein remain to be clarified, plausible transition state models are proposed (Scheme 6-5). For 3-aryl-substituted oxindoles, tertiary amine-thiourea **5-5** catalyzes the reaction in a bifunctional mode, and it appears that aromatic interactions may be involved when vinyl sulfone approaches the oxindole. In the conjugate addition of 3-alkyl-oxindoles, It is hypothesized that the amide NH in **6-8d** facilitates the orientation of vinyl sulfone **1-56**, most likely through multi-hydrogen bonding interactions.



Scheme 6-5 Plausible mechanisms

6.7 X-Ray Crystallographic Analysis and Determination of Absolute Configurations of Adducts



6-2b

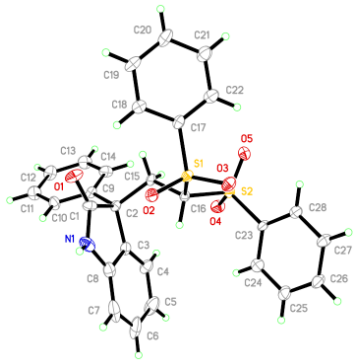


Figure 6-1 ORTEP Structure of Oxindole **6-2b**

The absolute configuration of **6-2b** (*R*) was assigned based on the X-ray crystallographic analysis of a single crystal of **6-2b**, and the configurations of **6-7a-l** were assigned by analogy. The specific rotation of adduct **6-7m** (90% ee, $[\alpha]_D$ = + 16.4 (c = 1.8, $CHCl_3$)) was opposite to that of **6-7l** (28% ee, $[\alpha]_D$ = - 6.2 (c = 1.1, $CHCl_3$)), thus the configuration of **6-7m** was assigned as (*R*), and the configurations of **6-7n-s** were assigned by analogy.

6.8 Conclusions

In conclusion, we have disclosed highly enantioselective organocatalytic conjugate additions of both 3-aryl and 3-alkyl-substituted oxindoles to 1,1-bis(benzenesulfonyl)- ethylene **1-56**. In particular, we introduced a novel class of trifunctional thiourea catalysts containing natural amino acid residues for the first time, which offered excellent stereocontrol in the reactions of 3-alkyl-oxindole substrates. Using the synthetic method developed as a key step, enantioselective synthesis of medicinally important 3,3-alkyl/aryl-substituted oxindoles and indolines with an all-carbon quaternary stereogenic center were realized.

6.9 Experimental Section

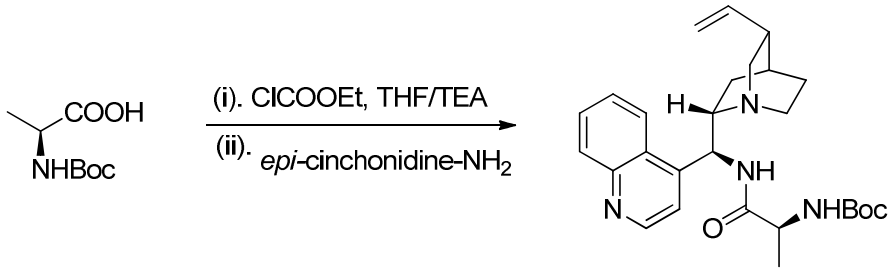
6.9.1 General Methods

The general methods of Chapter 2 were followed.

6.9.2 Catalyst Synthesis & Characterization

Preparation of catalyst 6-8a from (*S*)-2-((*tert*-butoxycarbonyl)amino) propanoic acid and CD-NH_2

tert-Butyl((*S*)-1-oxo-1-(((*S*)-quinolin-4-yl((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)-propan-2-yl)carbamate (**6-8a'**)



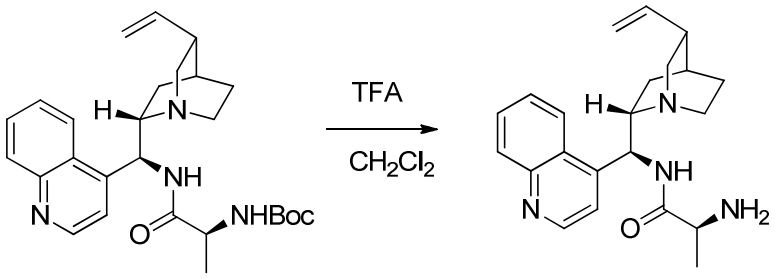
6-8a'

To a stirred solution of (*S*)-2-((*tert*-butoxycarbonyl)amino)propanoic acid (38 mg, 0.2 mmol) in anhydrous tetrahydrofuran (5 mL) and triethylamine (70 μL, 0.5 mmol) was added ethyl chloroformate (24 mg, 0.22 mmol) under N_2 at 0 ^oC. After stirring for 1 h, (*S*)-quinolin-4-yl ((2*S*)-8-vinylquinuclidin-2-yl)methanamine (*epi*-cinchonidine-NH_2, 58.6 mg, 0.2 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 2 h. After concentration, water (10 mL) was added to the residue, and the resulting mixture was extracted with dichloromethane (15 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column

chromatography (ethyl acetate /hexanes = 1:2 to ethyl acetate to ethyl acetate /methanol = 20:1) to afford **6-8a'** (75.2 mg, 81% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86-0.92 (m, 1H), 1.23-1.25 (m, 1H), 1.31-1.36 (m, 1H), 1.39 (s, 9H), 1.59-1.62 (m, 3H), 2.25 (m, 1H), 2.65-2.70 (m, 2H), 3.04 (br, 2H), 3.18-3.21 (m, 1H), 4.13- 4.15 (m, 1H), 4.89-4.95 (m, 2H), 5.20-5.24 (br, 2H), 5.57-5.68 (m, 2H), 7.37 (s, 1H), 7.57- 7.69 (m, 3H), 8.10-8.11 (d, *J* = 8.2 Hz, 1H), 8.35-8.37 (m, 1H), 8.81-8.82 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.16, 18.08, 25.90, 27.31, 27.78, 28.29, 39.47, 55.85, 56.62, 59.75, 64.47, 79.73, 114.53, 123.25, 126.67, 129.08, 129.22, 130.40, 141.20, 148.49, 149.98, 155.33, 172.61; HRMS (ESI) m/z calcd for $C_{27}H_{36}N_4O_3$ $[M+H]^+$ 465.2836, found 465.2846.

(*S*)-2-Amino-*N*-((*S*)-quinolin-4-yl((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)propanamide (**6-8a"**)

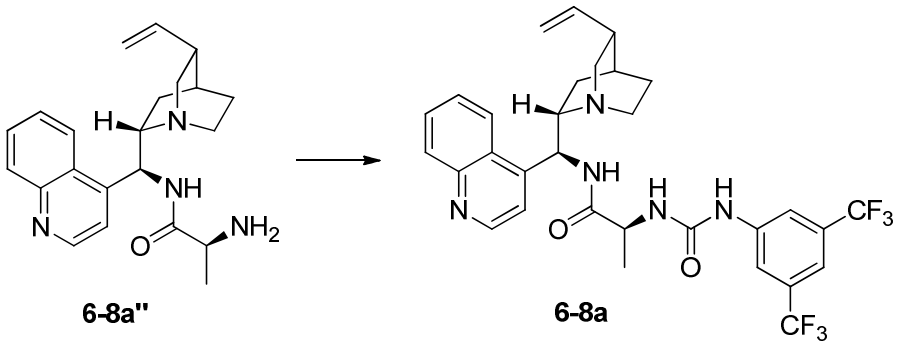


6-8a' **6-8a"**

To a stirred solution of **6-8a'** (46 mg, 0.10 mmol) in dichloromethane (4.0 mL) was added trifluoroacetic acid (0.4 mL). After stirring at room temperature for 12 h, aqueous $NaHCO_3$ (15 mL) was added. The resulting mixture was then extracted with dichloromethane (10 mL x 3), and the organic extracts were combined, dried over Na_2SO_4, filtered and concentrated. The crude product was used directly in the next

step without further purification.

(*S*)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)-*N*-((*S*)-quinolin-4-yl((1*S*,2*S*,4*S*,5*R*)-5-vinyl-quinuclidin-2-yl)methyl)propanamide (**6-8a**)



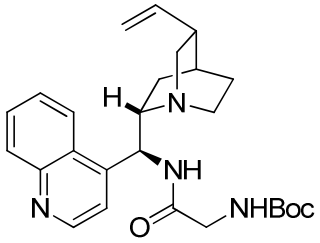
To a stirred solution of crude **6-8a"** in tetrahydrofuran (5.0 mL) at room temperature was added 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (27 mg, 0.10 mmol). After stirring for 2 h, the reaction mixture was concentrated under reduced pressure to afford the crude product, which was subjected to flash chromatographic separation (ethyl acetate /hexanes = 1:2 to ethyl acetate) to afford product **6-8a** (58.4 mg, 92% for two steps) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77-0.80 (m, 1H), 0.87-1.00 (m, 1H), 1.25-1.27 (m, 2H), 1.48- 1.49 (d, *J* = 7.6 Hz, 3H), 1.62 (s, 3H), 2.29 (s, 1H), 2.71-2.79 (m, 2H), 3.06 (br, 1H), 3.22-3.26 (m, 1H), 4.91-4.97 (m, 3H), 5.33 (br, 1H), 5.64-5.67 (m, 1H), 7.18 (s, 2H), 7.34-7.41 (m, 4H), 7.58 (s, 1H), 7.91 (s, 1H), 8.22-8.31 (m, 2H), 8.47-8.48 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.95, 14.16, 18.25, 24.34, 25.61, 27.13, 27.54, 27.68, 29.68, 39.31, 39.71, 40.81, 42.57, 46.05, 53.45, 55.69, 56.66, 59.82, 64.56, 114.80, 118.47, 119.74, 121.91, 122.42, 123.24, 124.08, 125.62, 126.25, 126.55, 128.76, 130.05, 130.37, 130.64, 138.85, 140.83, 141.63, 145.22, 147.72,

149.88, 150.04, 154.58, 175.40, 182.08; HRMS (ESI) m/z calcd for $C_{31}H_{31}F_6N_5OS$ $[M+H]^+$ 636.2204, found 636.2244.

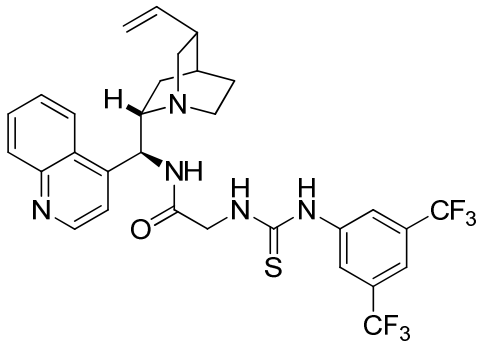
All the other catalysts (6-8b-h) were prepared following the same procedures described for the preparation of 6-8a

tert-Butyl 2-oxo-2-((*S*)-quinolin-4-yl((2*S*)-8-vinylquinuclidin-2-yl)methylamino)ethyl carbamate (**6-8b'**)



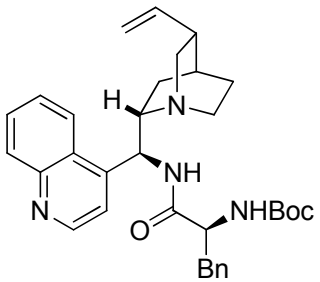
A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85-0.87 (m, 1H), 1.36 (s, 9H), 1.35-1.43 (m, 1H), 1.58-1.61 (m, 10H), 1.59 (s, 9H),1.86-1.90 (m, 1H), 2.65-2.70 (m, 2H), 3.08 (br, 2H), 3.18-3.23 (m, 1H), 3.70-3.72 (m, 2H), 4.91-4.97 (m, 2H), 5.37 (br, 1H), 5.57 (br, 1H), 5.66-5.68 (m, 1H), 7.36 (s, 1H), 7.58-7.69 (m, 3H), 8.09-8.12 (d, J = 8.2 Hz, 1H), 8.35-8.36 (m, 1H), 8.81-8.82 (d, J = 4.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.79, 26.00, 27.30, 27.72, 28.30, 34.38, 39.44, 40.84, 44.03, 55.82, 79.73, 114.60, 123.31, 126.79, 127.23, 129.18, 130.37, 141.20, 148.50, 150.01, 155.95, 169.46; HRMS (ESI) m/z calcd for $C_{26}H_{34}N_4O_3$ $[M+H]^+$ 451.2720, found 451.2715.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-(2-oxo-2-((*S*)-quinolin-4-yl((2*S*)-8-vinylquinuclidin-2-yl)-methylamino)ethyl)thiourea (**6-8b**)



A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87-0.89 (m, 1H), 0.99-1.07 (m, 1H), 1.02 (s, 9H), 1.32-1.37 (m, 1H), 1.62-1.89 (m, 2H), 2.32 (s, 1H), 2.70-2.76 (m, 2H), 3.17-3.22 (m, 1H), 3.68- 3.72 (m, 1H), 4.30-4.34 (m, 1H), 4.94-4.97 (m, 2H), 5.45 (br, 1H), 5.65-5.68 (m, 1H), 7.41-7.49 (m, 2H), 7.55 (br, 1H), 7.90-8.10 (m, 4H), 8.20-8.22 (d, J = 8.8 Hz, 2H), 8.71 (br, 1H), 9.47 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.42, 14.64, 27.13, 27.43, 39.21, 40.83, 45.99, 47.05, 55.64, 114.90, 117.43, 119.89, 122.06, 122.37, 122.82, 124.23, 126.40, 126.92, 129.43, 130.32, 130.80, 131.06, 131.33, 131.59, 140.43, 140.74, 148.37, 149.93, 170.38, 171.05, 181.65; HRMS (ESI) m/z calcd for $C_{30}H_{29}F_6N_5OS$ $[M+H]^+$ 622.2064, found 622.2042.

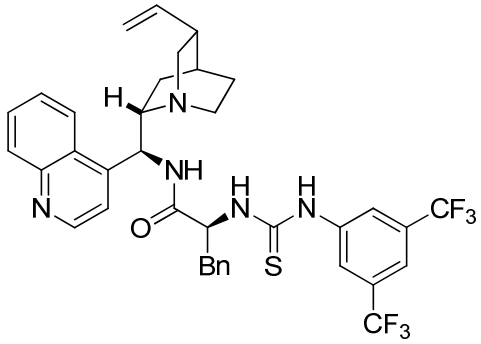
tert-Butyl (*S*)-1-oxo-3-phenyl-1-((*S*)-quinolin-4-yl((2*S*)-8-vinylquinuclidin-2-yl)methylamino)propan-2-yl-carbamate (**6-8c'**)



A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88-0.91 (m, 1H), 1.24-1.29 (m, 1H), 1.39 (s, 9H), 1.53-1.60 (m, 3H), 2.22 (br, 1H), 2.51 (br, 1H), 2.57-2.61 (br, 1H), 2.85

(br, 1H), 2.90-2.93 (m, 2H), 3.03-3.14 (m, 2H), 4.37-4.39 (m, 1H), 4.87-4.93 (m, 3H), 5.18 (br, 1H), 5.59-5.66 (m, 1H), 7.08 (br, 1H), 7.22-7.26 (m, 3H), 7.28-7.30 (m, 4H), 7.48-7.50 (m, 1H), 7.57-7.59 (m, 1H), 7.68-7.72 (m, 1H), 8.11-8.13 (d, J = 8.7 Hz, 1H), 8.33 (br, 1H), 8.84-8.85 (d, J = 4.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.11, 25.72, 27.23, 27.69, 28.18, 37.81, 39.40, 40.53, 55.27, 55.67, 60.11, 79.90, 114.44, 123.16, 126.62, 126.78, 128.52, 128.99, 129.32, 130.38, 136.37, 141.11, 148.47, 149.85, 155.11, 171.22; HRMS (ESI) m/z calcd for $C_{33}H_{40}N_4O_3$ $[M+H]^+$ 541.3176, found 541.3175.

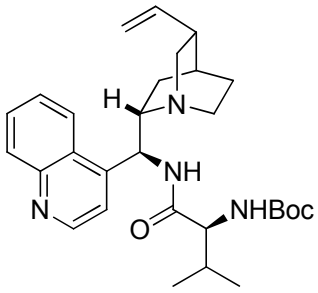
3,5-Bis(trifluoromethyl)phenyl (*S*)-1-oxo-3-phenyl-1-((*S*)-quinolin-4-yl((2*S*)-8-vinyl-quinuclidin-2-yl)methylamino)propan-2-ylcarbamodithioate (**6-8c**)



A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.72 (br, 1H), 1.26-1.28 (m, 2H), 1.58-1.60 (m, 3H), 2.27 (br, 1H), 2.58-2.72 (m, 3H), 2.95 (br, 1H), 3.08-3.10 (d, J = 7.6 Hz, 2H), 3.16-3.20 (m, 1H), 4.91-4.98 (m, 2H), 5.20 (br, 1H), 5.62-5.66 (m, 1H), 7.24-7.25 (br, 1H), 7.28-7.30 (m, 3H), 7.37-7.44 (m, 5H), 7.57-7.58 (m, 1H), 7.62 (br, 1H), 8.11-8.13 (d, J = 8.2 Hz, 1H), 8.29-8.33 (m, 1H), 8.45 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.52, 25.60, 27.13, 27.83, 38.54, 39.37, 40.80, 55.74, 59.04, 67.97, 114.77, 118.47, 119.71, 121.88, 124.05, 125.18, 126.61, 127.39, 128.11, 128.20,

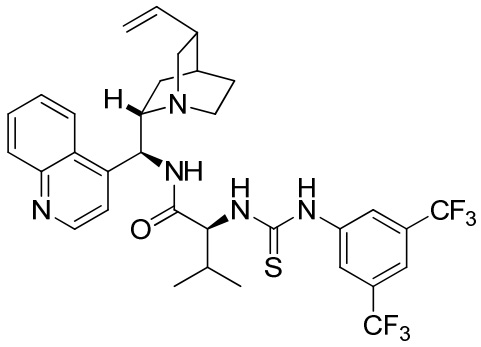
128.92, 130.18, 130.30, 130.58, 130.85, 131.11, 135.94, 138.78, 140.93, 147.79, 149.89, 166.96, 173.53, 181.76; HRMS (ESI) m/z calcd for $C_{37}H_{35}F_6N_5OS$ $[M+H]^+$ 712.2569, found 712.2565.

tert-Butyl (*S*)-3-methyl-1-oxo-1-((*S*)-quinolin-4-yl((2*S*)-8-vinylquinuclidin-2-yl)methylamino)butan-2-ylcarbamate (**6-8d'**)



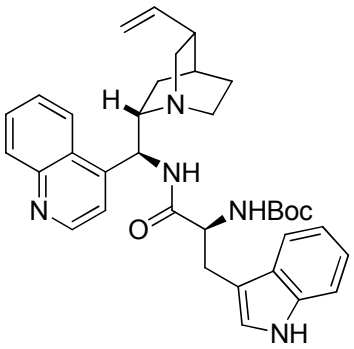
A colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87-0.89 (d, *J* = 6.3 Hz, 3H), 0.94-0.95 (d, *J* = 6.9 Hz, 4H), 1.40 (s, 10H), 1.55-2.67 (m, 3H), 2.02-2.05 (m, 1H), 2.28 (br, 1H), 2.68-2.71 (m, 2H), 3.03 (br, 2H), 3.21-3.25 (m, 1H), 3.89-3.92 (m, 1H), 4.92-4.97 (m, 2H), 5.26 (br, 1H), 5.63- 5.69 (m, 1H), 7.41-7.42 (d, *J* = 4.4 Hz, 1H), 7.53-7.63 (m, 2H), 7.68-7.72 (m, 1H), 8.12-8.13 (d, *J* = 6.3 Hz, 1H), 8.37-8.38 (d, *J* = 8.2 Hz, 1H), 8.84-8.85 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.78, 19.16, 25.78, 27.24, 27.74, 28.18, 30.69, 39.44, 40.65, 55.75, 59.81, 77.20, 79.52, 114.50, 123.12, 126.56, 127.07, 128.96, 130.38, 141.10, 148.46, 149.90, 155.60, 171.58; HRMS (ESI) m/z calcd for $C_{29}H_{40}N_4O_3$ $[M+H]^+$ 493.3173, found 493.3169.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-3-methyl-1-oxo-1-((*S*)-quinolin-4-yl((2*S*)-8-vinylquinuclidin-2-yl)methylamino)butan-2-yl)thiourea (**6-8d**)



A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (br, 1H), 0.85-1.01 (m, 1H), 1.06-1.11(m, 6H), 1.28 (br, 2H), 1.98-2.00 (m, 1H), 2.29 (br, 1H), 2.75 (m, 2H), 3.03 (br, 2H), 3.22-3.25 (m, 1H), 4.64 (br, 1H), 4.92-4.96 (m, 2H), 5.35 (br, 1H), 5.63-5.67 (m, 1H), 7.12 (s, 2H), 7.29 (s, 1H), 7.43-7.45 (m, 3H), 7.59-7.62 (m, 2H), 8.23-8.28 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.54, 19.67, 25.54, 27.14, 27.78, 29.69, 30.97, 39.42, 40.94, 55.79, 64.25, 114.82, 118.64, 121.92, 122.26, 124.09, 125.91, 126.26, 126.50, 128.90, 130.30, 130.61, 138.62, 140.93, 149.92, 174.01, 182.29; HRMS (ESI) m/z calcd for $C_{33}H_{35}F_6N_5OS$ $[M+Na]^+$ 664.2541, found 664.2567.

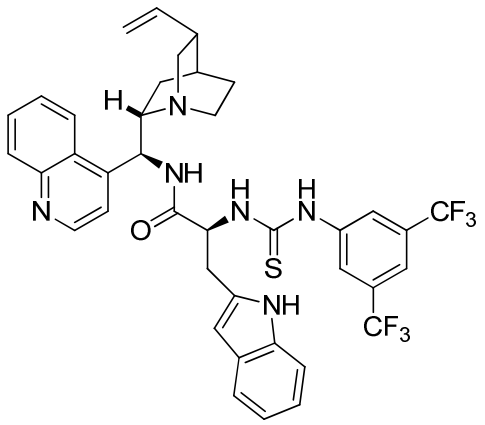
tert-Butyl (*S*)-3-(1*H*-indol-3-yl)-1-oxo-1-((*S*)-quinolin-4-yl((2*S*)-8-vinylquinuclidin-2-yl)methylamino)propan-2-ylcarbamate (**6-8e'**)



A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86-0.90 (m, 1H), 1.26-1.30(m, 1H), 1.44 (s, 9H), 1.56 (br, 2H), 2.21 (br, 1H), 2.40 (br, 1H), 2.54-2.58 (m, 1H), 2.65 (br,

1H), 2.92 (br, 1H), 3.04-3.14 (m, 2H), 3.22-3.27 (m, 1H), 4.54 (br, 1H), 4.89-4.94 (m, 2H), 5.24 (br, 1H), 5.59-5.65 (m, 1H), 6.65 (s, 1H), 6.65 (s, 1H), 7.10 (s, 1H), 7.17-7.19 (m, 1H), 7.21 (s, 1H), 7.30-7.32 (m, 1H), 7.58-7.60 (m, 2H), 7.70-7.73 (m, 2H), 8.17-8.19 (d, J = 8.2 Hz, 1H), 8.34 (br, 1H), 8.82- 8.83 (d, J = 4.5 Hz, 1H), 8.95 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.21, 21.06, 25.81, 27.33, 27.79, 28.03, 28.34, 39.49, 40.31, 55.42, 55.68, 60.42, 79.87, 109.97, 111.30, 114.47, 118.75, 119.50, 121.93, 123.39, 123.54, 126.69, 127.64, 129.16, 130.24, 136.36, 141.27, 148.42, 149.93, 155.45, 172.07; HRMS (ESI) m/z calcd for $C_{35}H_{41}N_5O_3$ $[M+H]^+$ 580.3282, found 580.3304.

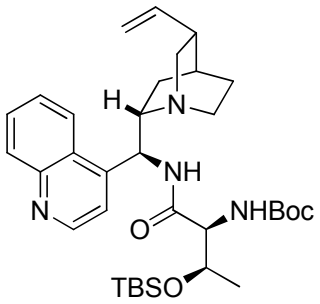
1-((*R*)-3-(1*H*-indol-3-yl)-1-oxo-1-((*S*)-quinolin-4-yl((2*S*)-8-vinylquinuclidin-2-yl)methylamino)-propan-2-yl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (**6-8e**)



A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.65-0.70 (m, 1H), 0.88-0.90 (m, 1H), 1.20-1.21(m, 1H), 1.44-1.47 (m, 2H), 1.56 (s, 1H), 2.21 (br, 1H), 2.41 (br, 1H), 2.50 (br, 1H), 2.59-2.61 (d, J = 10.7 Hz, 1H), 2.91 (br, 1H), 3.05-3.08 (m, 1H), 3.28-3.33 (m, 2H), 4.89-4.92 (m, 2H), 5.15 (br, 1H), 5.31 (br, 1H), 5.58-5.61 (m, 1H), 6.84 (s, 1H), 7.15-7.20 (m, 2H), 7.27-7.29 (m, 1H), 7.30- 7.47 (m, 5H), 7.60-7.71 (m, 2H),

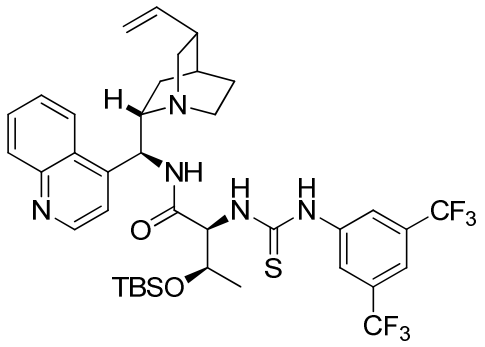
7.81 (s, 1H), 8.10-8.12 (m, 1H), 8.25 (br, 1H), 8.40 (s, 1H), 8.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.19, 25.55, 25.69, 27.10, 27.72, 28.20, 39.40, 40.30, 55.64, 59.04, 60.45, 109.92, 111.57, 114.68, 118.06, 118.37, 118.56, 119.70, 121.90, 122.37, 122.72, 123.07, 124.07, 125.10, 126.24, 124.57, 127.39, 129.02, 129.86, 130.75, 131.02, 131.28, 136.36, 139.00, 141.01, 147.75, 149.77, 173.68; HRMS (ESI) m/z calcd for $C_{39}H_{36}F_6N_6OS$ $[M+H]^+$ 751.2650, found 751.2652.

tert-Butyl (2*S*,3*R*)-3-(*tert*-butyldimethylsilyloxy)-1-oxo-1-((*S*)-quinolin-4-yl((2*S*)-8-vinylquinuclidin-2-yl)methylamino)butan-2-ylcarbamate (**6-8f'**)



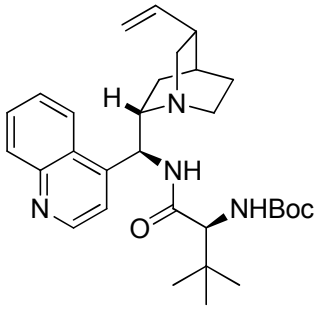
A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.11 (s, 3H), 0.86-0.92 (m, 1H), 0.94 (s, 9H), 1.12-1.13 (d, *J* = 6.3 Hz, 3H), 1.39 (s, 9H), 1.55-1.60 (m, 3H), 2.28 (br, 1H), 2.65-2.71 (m, 2H), 3.08 (br, 1H), 3.20-3.25 (m, 1H), 4.08 (s, 1H), 4.23 (s, 1H), 4.94-4.98 (m, 2H), 5.46 (s, 1H), 5.67-5.71 (m, 1H), 7.39-7.40 (d, *J* = 3.8 Hz, 3H), 7.61 (s, 1H), 7.70-7.73 (m, 1H), 8.13-8.15 (d, *J* = 8.2 Hz, 1H), 8.16 (br, 1H), 8.40 (s, 1H), 8.88-8.89 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.00. -4.86, 17.94, 18.05, 25.74, 27.46, 27.86, 28.29, 39.57, 40.78, 56.03, 58.97, 68.40, 79.40, 114.48, 123.15, 126.75, 129.08, 130.45, 141.32, 149.98, 155.46, 170.13; HRMS (ESI) m/z calcd for $C_{34}H_{52}N_4O_4Si$ $[M+H]^+$ 609.3831, found 609.3819.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((2*S*,3*R*)-3-(^{t}butyldimethylsilyloxy)-1-oxo-1-((*S*)-quinolin-4-yl((2*S*)-8-vinylquinuclidin-2-yl)methylamino)butan-2-yl)thiourea (**6-8f**)



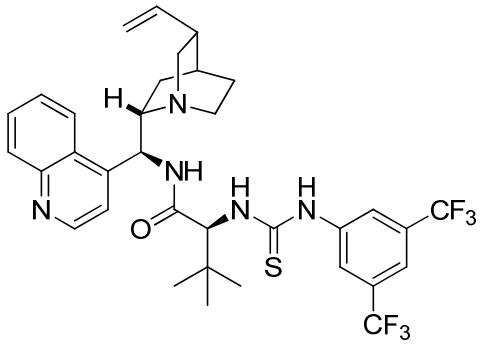
A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.23 (s, 3H), 0.26 (s, 3H), 0.88 (m, 1H), 1.00 (s, 9H), 1.00-1.02 (d, *J* = 11.4 Hz, 3H), 1.20-1.22 (m, 2H), 1.60-1.63 (m, 3H), 2.31 (s, 1H), 2.68- 2.74 (m, 2H), 3.08 (br, 2H), 3.22-3.25 (m, 1H), 4.44 (s, 1H), 4.96-5.00 (m, 2H), 5.09 (s, 1H), 5.51 (br, 1H), 5.68-5.72 (m, 1H), 7.29-7.33 (m, 1H), 7.46-7.48 (m, 1H), 7.55-7.62 (m, 4H), 7.98 -8.00 (d, *J* = 8.2 Hz, 1H), 8.22-8.24 (d, *J* = 8.2 Hz, 1H), 8.50 (br, 1H), 8.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.72. -4.67, 17.89, 18.00, 25.77, 27.33, 27.83, 39.46 40.91, 56.04, 61.98, 68.12, 114.67, 118.52, 121.81, 122.57, 123.48, 123.98, 126.64, 129.14, 130.56, 131.73, 131.99, 139.31, 141.10, 149.96, 170.67, 180.96; HRMS (ESI) m/z calcd for $C_{38}H_{47}F_6N_5O_2SSi$ $[M+H]^+$ 780.3198, found 780.3225.

tert-Butyl(*S*)-3,3-dimethyl-1-oxo-1-((*S*)-quinolin-4-yl((2*S*)-8-vinylquinuclidin-2-yl)methylamino)butan-2-ylcarbamate (**6-8g'**)



A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (s, 9H), 0.96-0.98 (m, 1H), 1.36 (s, 9H), 1.35- 1.37 (m, 1H), 1.58-1.61 (m, 1H), 2.27 (br, 1H), 2.68-2.71 (m, 2H), 3.02 (br, 2H), 3.20-3.23 (t, *J* = 10.7 Hz, 1H), 3.86-3.88 (d, *J* = 9.5 Hz, 1H), 4.90-4.98 (m, 3H), 5.33 (br, 1H), 5.63-5.69 (m, 1H), 7.40-7.42 (m, 1H), 7.57 (s, 1H), 7.66-7.69 (m, 1H), 8.11-8.12 (d, *J* = 8.2 Hz, 1H), 8.35-8.36 (d, *J* = 8.2 Hz, 1H), 8.82-8.83 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.47, 27.33, 27.86, 28.24, 34.27, 39.57, 40.78, 55.82, 62.25, 79.50, 114.59, 123.19, 126.62, 128.98, 130.47, 141.20, 148.53, 149.92, 150.00, 155.81, 170.89; HRMS (ESI) m/z calcd for $C_{30}H_{42}N_4O_3$ $[M+H]^+$ 506.3332, found 507.3344.

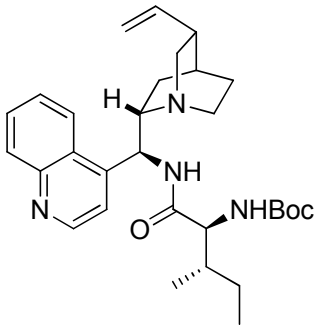
1-(3,5-Bis(trifluoromethyl)phenyl)-3-((*S*)-3,3-dimethyl-1-oxo-1-((*S*)-quinolin-4-yl((2*S*)-8-vinyl-quinuclidin-2-yl)methylamino)butan-2-yl)thiourea (**6-8g**)



A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.72-0.74 (m, 1H), 0.86-0.92 (m, 1H), 1.02 (s, 9H), 1.22-1.24 (m, 2H), 1.58 (s, 2H), 2.24 (s, 1H), 2.68-2.71 (m, 2H),

2.90-2.98 (m, 2H), 3.18-3.22 (m, 1H), 4.89-4.92 (m, 2H), 5.06 (br, 1H), 5.35 (br, 1H), 5.60 (br, 1H), 7.20-7.26 (m, 1H), 7.40-7.71 (m, 6H), 8.22 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.39, 27.31, 27.80, 29.66, 34.47, 39.41, 40.96, 50.97, 55.76, 60.85, 65.90, 114.73, 118.21, 119.78, 121.95, 122.25, 124.12, 125.28, 126.29, 126.71, 129.08, 130.14, 130.35, 130.40, 130.67, 130.94, 138.93, 140.98, 146.60, 147.66, 149.81, 172.56, 182.29; HRMS (ESI) m/z calcd for $C_{34}H_{37}F_6N_5OS$ $[M+H]^+$ 678.2696, found 678.2694.

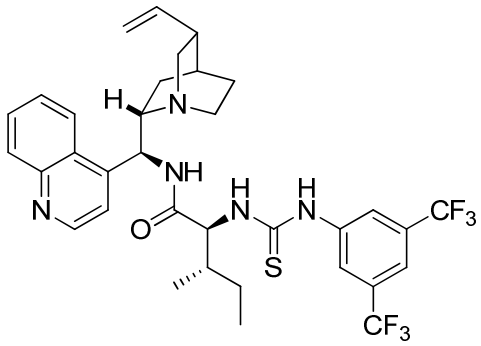
tert-Butyl (2*S*,3*S*)-3-methyl-1-oxo-1-((*S*)-quinolin-4-yl((2*S*)-8-vinylquinuclidin-2-yl) methylamino)pentan-2-ylcarbamate (**6-8h'**)



A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84-0.85 (t, *J* = 7.0 Hz, 3H), 0.91-0.92 (d, *J* = 6.9 Hz, 3H), 1.10-1.17 (m, 1H), 1.29-1.33 (m, 1H), 1.36-1.39 (m, 2H), 1.38 (s, 9H), 1.55-1.64 (m, 3H), 1.76-1.79 (m, 1H), 2.27-2.28 (m, 1H), 2.67-2.71 (m, 2H), 3.03 (br, 2H), 3.20-3.25 (m, 1H), 3.94-3.96 (m, 1H), 4.91-4.97 (m, 3H), 5.35 (br, 1H), 5.64-5.69 (m, 1H), 7.40-7.41 (m, 1H), 7.55- 7.65 (m, 2H), 7.68-7.70 (m, 1H), 8.11-8.13 (d, *J* = 8.2 Hz, 1H), 8.36-8.38 (d, *J* = 8.2 Hz, 1H), 8.83-8.84 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.32, 15.55, 24.71, 25.80, 27.31, 27.80, 28.25, 30.01, 37.25, 39.50, 40.70, 55.81, 59.02, 60.18, 114.58, 123.22, 126.63, 129.04,

130.42, 141.16, 149.96, 155.63, 171.63; HRMS (ESI) m/z calcd for $C_{30}H_{42}N_4O_3$ $[M+H]^+$ 507.3332, found 506.3340.

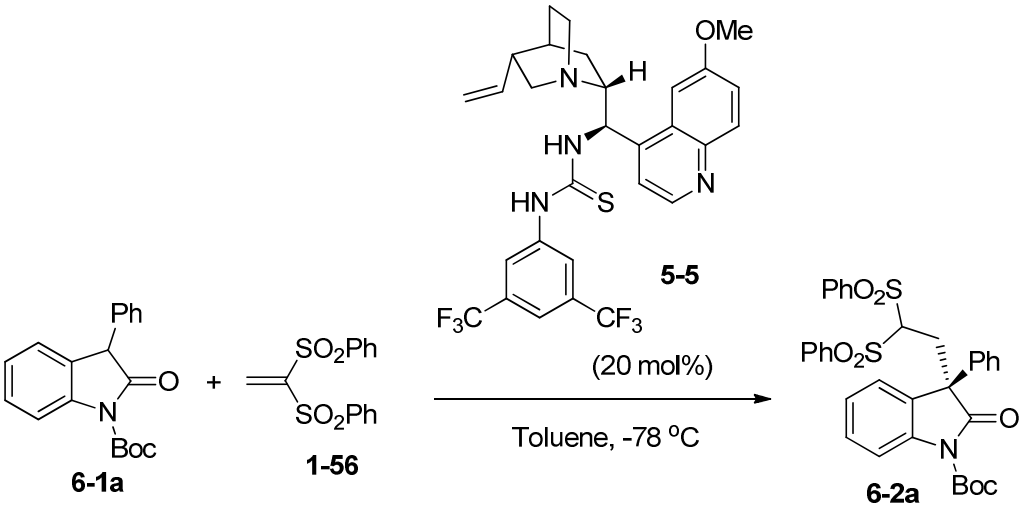
1-(3,5-Bis(trifluoromethyl)phenyl)-3-((2*S*,3*S*)-3-methyl-1-oxo-1-((*S*)-quinolin-4-yl((2*S*)-8-vinyl-quinuclidin-2-yl)methylamino)pentan-2-yl)thiourea (**6-8h**)



A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.71-0.75 (m, 1H), 0.91-0.95 (m, 3H), 1.00-1.03 (m, 3H), 1.23-1.25 (m, 3H), 1.60 (s, 3H), 1.74-1.77 (m, 1H), 2.27 (s, 1H), 2.73 (s, 2H), 3.01 (br, 2H), 3.20-3.25 (m, 1H), 4.69 (s, 1H), 4.91-4.95 (m, 2H), 5.33 (br, 1H), 5.64-5.66 (m, 1H), 7.17 (s, 1H), 7.30-7.72 (m, 6H), 8.21-8.39 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.20, 15.89, 22.66, 25.46, 25.99, 27.11, 27.75, 29.66, 37.15, 39.36, 40.89, 55.77, 60.46, 62.81, 114.82, 118.31, 119.75, 121.91, 122.29, 124.09, 125.32, 126.26, 126.51, 128.92, 130.28, 130.40, 130.65, 138.88, 140.93, 145.63, 147.81, 149.94, 174.00, 182.06, 182.13; HRMS (ESI) m/z calcd for $C_{34}H_{37}F_6N_5OS$ $[M+Na]^+$ 678.2697, found 678.2708.

6.9.3 Representative Procedure for the Conjugate Addition

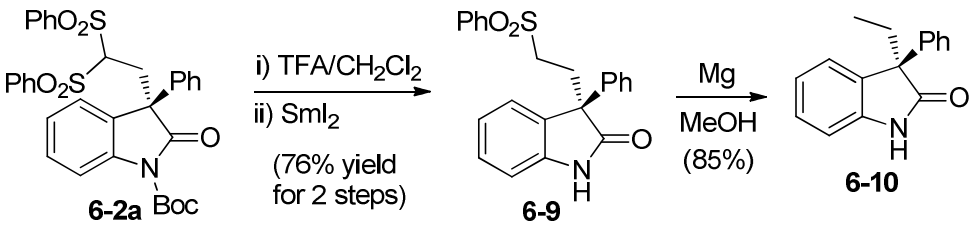
Addition of oxindole 6-1a to 1,1-bis(benzenesulfonyl-ethylene 1-56 catalyzed by 5-5



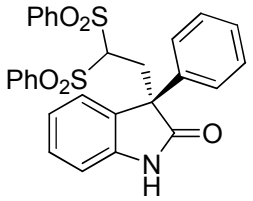
1,1-Bis(benzenesulfonyl)ethylene **1-56** (15.4 mg, 0.05 mmol) was added to a mixture of *tert*-butyl 2-oxo-3-phenylindoline-1-carboxylate **6-1a** (18.6 mg, 0.06 mmol) and **5-5** (6.0 mg, 0.01 mmol) in anhydrous toluene (0.4 mL) in a sealed sample vial at -78 ^{o}C. After stirring at -78 ^{o}C for 12 h, the reaction mixture was concentrated *in vacuo* to yield the crude product, which was purified by flash column chromatography (ethyl acetate/hexanes = 1:5 to 1:1) to afford the desired adduct **6-2a** as a white solid (29.9 mg, 97%).

6.9.4 Synthesis of 3-Alkyl-3-Aryl Oxindole and Indoline

Preparation of Oxindole 6-10



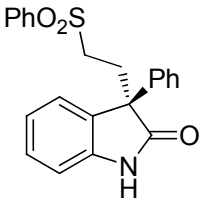
(*R*)-3-(2,2-Bis(phenylsulfonyl)ethyl)-3-phenylindolin-2-one (**6-2b**)



To a stirred solution of **6-2a** (62 mg, 0.1 mmol) in dichloromethane (4.0 mL) at room temperature was added trifluoroacetic acid (0.4 mL). After stirring for 2 h, aqueous $NaHCO_3$ (10 mL) was added. The resulting mixture was extracted with dichloromethane several times (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*, and the residue was purified by column chromatography (ethyl acetate /hexanes = 1:3 to 1:1) to afford the **6-2b** as a white solid (51 mg, 99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.44-3.48 (m, 2H), 4.54-4.57 (m, 1H), 7.03-7.06 (m, 1H), 7.26- 7.47 (m, 6H), 7.53-7.79 (m, 10H), 8.11-8.13 (m, 2H), 8.98 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.97, 55.65, 80.70, 110.93, 122.44, 126.48, 126.67, 127.77, 128.75, 128.89, 129.18, 129.23, 129.31, 129.55, 129.66, 130.83, 134.26, 134.69, 135.93, 138.15, 140.26, 142.14, 179.03; $[\alpha]_D$ = + 14.2 (c = 1.4, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{28}H_{23}NO_5S_2$ $[M+Na]^+$ 540.0887, found 540.0890.

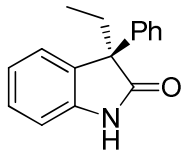
(*R*)-3-Phenyl-3-(2-(phenylsulfonyl)ethyl)indolin-2-one (**6-9**)



To a stirred solution of **6-2b** (52 mg, 0.1 mmol) in anhydrous tetrahydrofuran (2 mL) at 0 ^{o}C under N_2 was added SmI_2 (0.1 M in THF, 10 mL, 1 mmol). After 5 min, the color of the reaction mixture changed from green to yellow, water (2 mL) was then added. The resulting mixture was extracted with dichloromethane (10 mL x 3), and the organic extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (ethyl acetate/hexanes = 1:5 to 1:2) to afford desired product **6-9** as a white solid (28.7 mg, 76%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.53-2.59 (m, 1H), 2.73-2.79 (m, 1H), 2.90-2.95 (m, 1H), 3.08- 3.14 (m, 1H), 6.92-6.93 (d, *J* = 7.6 Hz, 1H), 7.04-7.06 (m, 2H), 7.25-7.27 (m, 6H), 7.50-7.53 (m, 2H), 7.61-7.64 (m, 1H), 7.83-7.84 (d, *J* = 8.2 Hz, 2H), 9.02 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.93, 51.82, 55.42, 110.81, 123.14, 124.69, 126.70, 127.89, 128.06, 128.96, 129.42, 131.23, 133.92, 138.15, 138.59, 140.80, 179.83; $[\alpha]_D$ = + 10.7 (c = 1.0, $CHCl_3$); MS (ESI) m/z calcd for $C_{22}H_{19}NO_3S$ $[M+Na]^+$ 400.2, found 400.1.

(*R*)-3-Ethyl-3-phenylindolin-2-one (**6-10**)

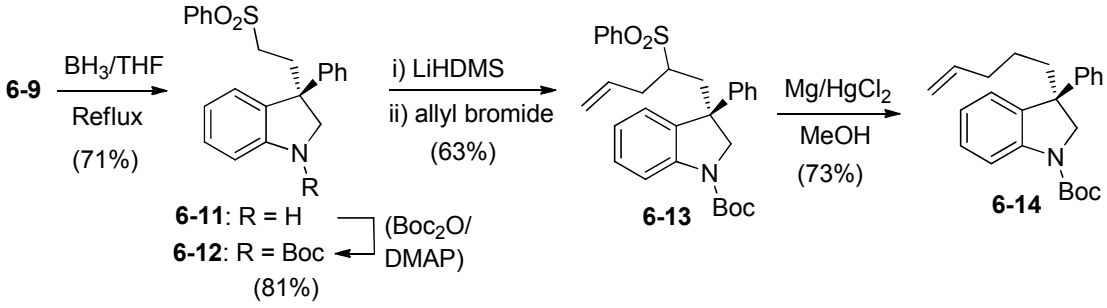


The activated magnesium metal (48 mg, 2.0 mmol) was added to a stirred solution of oxindole **6-9** (19 mg, 0.05 mmol) in anhydrous methanol (2 mL). After 30 minutes, the reaction mixture was brought to reflux for 2 h. Then the reaction mixture was poured into 2 N HCl (aq.) (3 mL) and extracted with ether (3 x 5 mL). The

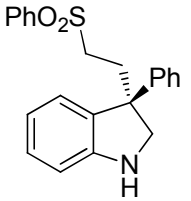
combined organic extracts were dried over Na_2SO_4 and filtered. Solvent was removed *in vacuo*, and the residue was purified by column chromatography (ethyl acetate/hexanes = 1:15 to 1:5) to afford **6-10** as a colorless oil (10.1 mg, 85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.75-0.77 (t, *J* = 7.4 Hz, 9H), 2.22-2.25 (m, 1H), 2.43-2.48 (m, 2H), 6.93-6.94 (d, *J* = 7.6 Hz, 1H), 7.09-7.10 (d, *J* = 1.3 Hz, 1H), 7.10-7.11 (d, *J* = 1.3 Hz, 1H), 7.18-7.29 (m, 2H), 7.30-7.32 (m, 2H), 7.36-7.38 (m, 2H), 7.61 (s, 1H), which was in agreement with literature data;[219] The ee value of **12** was 90%, t_R (major) = 13.55 min, t_R (minor) = 16.07 min (Chiralcel IA-H, λ = 254 nm, 15% ^{i}PrOH/hexanes, flow rate = 0.5 mL/min).

Preparation of Indoline 6-14



(*R*)-3-Phenyl-3-(2-(phenylsulfonyl)ethyl)indoline (**6-11**)

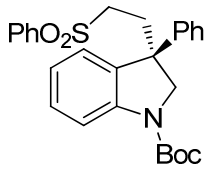


Borane-methyl sulfide complex (0.3 mL, 2M in THF, 0.6 mmol) was added to a stirred solution of sulfone **6-9** (75 mg, 0.2 mmol) in anhydrous THF (3 mL) at 0 ^{o}C, the mixture was warmed up slowly to room temperature, and then brought to reflux

for 3 h. After cooling down to room temperature, a pre-cooled solution of 5% aqueous $NaHCO_3$ (5 mL) was added and the resulting mixture was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography (ethyl acetate /hexanes = 1:5 to 1:1) afforded indoline **6-11** (51 mg, 71% yield) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52-2.62 (m, 2H), 2.95-3.04 (m, 1H), 3.16-3.27 (m, 1H), 3.55-3.68 (m, 3H), 6.72-6.78 (m, 2H), 6.86-6.88 (m, 1H), 7.09-7.12 (m, 1H), 7.25-7.33 (m, 5H), 7.57-7.68 (m, 3H), 7.86-7.89 (m, 2H);^{13}C NMR (75 MHz, $CDCl_3$) δ 30.92, 52.55, 52.68, 61.58, 110.32, 118.92, 124.72, 126.60, 126.72, 127.93, 128.40, 129.24, 132.05, 133.62, 138.88, 144.41, 151.07; MS (ESI) m/z calcd for $C_{22}H_{21}NO_2S$ $[M+H]^+$ 363.1, found 364.1.

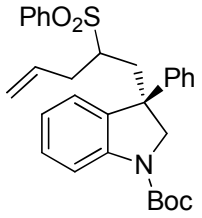
(*R*)-*tert*-Butyl 3-phenyl-3-(2-(phenylsulfonyl)ethyl)indoline-1-carboxylate (**6-12**)



To a stirred solution of indoline **6-11** (50.8 mg, 0.14 mmol) in anhydrous CH_3CN (20 mL) under N_2 was added DMAP (50 mg, 0.4 mmol) and Boc anhydride (100 mg, 0.44 mmol). After stirring at room temperature for 3 h, the reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (ethyl acetate /hexanes = 1:15 to 1:3) to afford **6-12** (52.2 mg, 81% yield) as a white foam.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (s, 9H), 2.53-2.58 (m, 2H), 2.86-2.93 (m, 1H), 3.03-3.11 (m, 1H), 4.00 (m, 2H), 6.89-6.99 (m, 2H), 7.22-7.37 (m, 7H), 7.59-7.63 (m, 2H), 7.68-7.71 (m, 1H), 7.87-7.89 (m, 2H);^{13}C NMR (75 MHz, $CDCl_3$) δ 28.33, 31.70, 49.96, 52.34, 61.94, 77.17, 115.16, 122.54, 124.62, 126.43, 126.73, 127.04, 127.93, 128.74, 128.78, 129.31, 133.76, 139.75, 144.08, 152.02; MS (ESI) m/z calcd for $C_{27}H_{29}NO_4S$ $[M+Na]^+$ 486.2, found 486.1.

(3*R*)-*tert*-Butyl 3-phenyl-3-(2-(phenylsulfonyl)pent-4-en-1-yl)indoline-1-carboxylate **(6-13)**

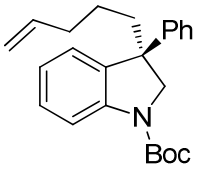


A solution of lithium bis(trimethylsilyl)amide (0.25 mL, 1.0 M, 0.25 mmol) in toluene was added to a solution of **6-12** (23 mg, 0.05 mmol) in THF (2 mL) at 0 ^{o}C. After stirring at 0 ^{o}C for 30 minutes, allyl bromide (60 mg, 0.5 mmol) was added. The mixture was warmed up slowly to room temperature and stirred for 1 h. The reaction mixture was partitioned between saturated aqueous NH_4Cl (2 mL) and CH_2Cl_2 (5 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexanes = 1:15 to 1:5) to afford **6-13** (15.8 mg, 63% yield) as a white foam.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (s, 5H), 1.31 (s, 4H), 2.86-2.89 (m, 1H), 3.04-3.10

(m, 1H), 3.30-3.33 (d, *J* = 9.4 Hz, 1H), 3.49-3.54 (m, 1H), 3.70-3.88 (m, 3H), 5.20-5.26 (m, 2H), 5.86- 5.89 (m, 1H), 6.56-6.73 (m, 2H), 6.75-6.90 (m, 1H), 7.00-7.40 (m, 7H), 7.53-7.70 (m, 3H), 7.76- 7.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.38, 27.50, 28.34, 29.62, 33.40, 35.35, 51.43, 51.65, 51.81, 65.90, 66.23, 67.89, 68.68, 83.12, 108.17, 108.26, 117.63, 117.76, 118.37, 124.73, 125.01, 126.51, 126.59, 126.68, 126.88, 128.38, 128.41, 128.65, 128.83, 128.88, 129.03, 129.20, 132.48, 133.37, 133.53, 133.76, 133.82, 137.87, 144.63; MS (ESI) m/z calcd for $C_{30}H_{33}NO_4S$ $[M+Na]^+$ 526.0, found 526.0.

(*R*)-*tert*-Butyl 3-(pent-4-en-1-yl)-3-phenylindoline-1-carboxylate (**6-14**)



Following the same procedure described for the preparation of **6-10**, indoline **6-14** (7.6 mg, 0.023 mmol) was obtained as a colorless oil from **6-13** (15 mg, 0.03 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.10-2.17 (m, 1H), 2.23-2.27 (m, 1H), 2.38-2.46 (m, 2H), 3.45-3.52 (m, 2H), 3.73-3.78 (m, 3H), 5.21-5.32 (m, 2H), 5.89-5.95 (m, 1H), 6.58-6.60 (m, 1H), 6.73-6.76 (m, 1H), 7.02- 7.04 (m, 1H), 7.14-7.17 (m, 1H), 7.22-7.24 (m, 1H), 7.31-7.34 (m, 2H), 7.39-7.41 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.01, 31.40, 33.59, 51.54, 67.01, 77.12, 80.11, 107.80, 117.45, 117.68, 124.87, 126.23, 126.74, 127.94, 128.30, 133.76, 134.33, 145.50, 151.61, 172.95; MS (ESI) m/z calcd for $C_{24}H_{29}NO_2$ $[M+H]^+$ 364.1, found 364.1.

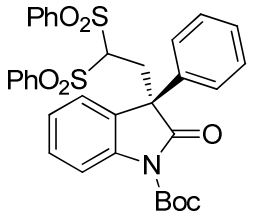
6.9.5 Characterizations of Intermediates & Adducts

Determination of enantiomeric excesses of conjugate adducts:

The racemic mixtures of **6-2a**, **6-7f**, **6-7l**, **6-7m**, **6-7n**, **6-7o** and **6-7q** could be resolved in HPLC chromatogram, and ee was determined by HPLC chromatogram.

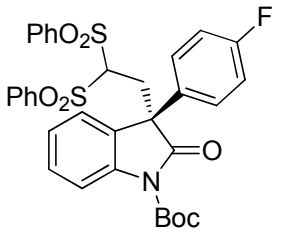
For all the other adducts, i.e. **6-7(a-e)**, **6-7(g-l)**, **6-7p** & **6-7(r-s)**, they could not be well-resolved in HPLC chromatogram, the ee was determined by analyzing the corresponding de-Boc products, denoted as **6-7(a'-e')**, **6-7(g'-l')**, **6-7p' & 6-7(r'-s')**.

(*R*)-*tert*-Butyl 3-(2,2-bis(phenylsulfonyl)ethyl)-2-oxo-3-phenylindoline-1-carboxylate **(6-2a)**



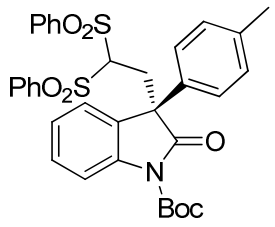
A white solid; The ee value was 94%, t_R (major) = 19.74 min, t_R (minor) = 24.68 min (Chiralcel OD-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 9H), 3.30-3.34 (m, 2H), 4.41-4.43 (m, 1H), 7.20-7.26 (m, 7H), 7.49-7.76 (m, 9H), 8.00 -8.06 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.02, 32.04, 55.25, 80.60, 84.36, 116.28, 124.56, 125.76, 126.74, 128.01, 128.80, 128.91, 129.35, 129.67, 131.03, 134.43, 134.76, 135.74, 137.98, 140.77, 141.24, 149.22, 175.17; $[\alpha]_D$ = + 22.7 (c = 1.1, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{33}H_{31}NO_7S_2$ $[M+Na]^+$ 640.1434, found 640.1439.

(*R*)-*tert*-Butyl-3-(2,2-bis(phenylsulfonyl)ethyl)-3-(4-fluorophenyl)-2-oxoindoline-1-carboxylate (**6-7f**)



A white solid; The ee value was 94%, t_R (major) = 60.03 min, t_R (minor) = 77.44 min (Chiralcel IC-H, λ = 254 nm, 10% *i*PrOH/hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (s, 9H), 3.26-3.29 (m, 1H), 4.40-4.42 (m, 1H), 6.96-7.39 (m, 6H), 7.52-7.77 (m, 9H), 7.99-8.11 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.06, 32.32, 54.72, 80.59, 84.56, 115.62, 115.79, 116.45, 124.69, 125.73, 127.85, 128.63, 128.69, 128.98, 129.03, 129.39, 129.89, 131.06, 134.51, 134.84, 135.75, 136.53, 136.55, 137.98, 141.25, 149.18, 161.42, 163.39, 175.13; $[\alpha]_D$ = + 54.5 (c = 2, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{33}H_{30}FNO_7S_2$ $[M+Na]^+$ 658.1340, found 658.1337.

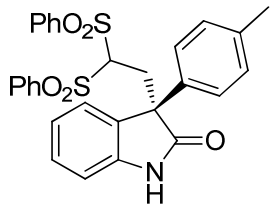
(*R*)-*tert*-Butyl 3-(2,2-bis(phenylsulfonyl)ethyl)-2-oxo-3-*p*-tolylindoline-1-carboxylate (**6-7a**)



A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (s, 9H), 2.29 (s, 3H), 3.27-3.32 (m, 1H), 4.42- 4.44 (m, 1H), 6.97-6.99 (m, 1H), 7.13-7.16 (m, 1H), 7.25-7.29 (m, 3H), 7.33-7.37 (m, 2H), 7.41- 7.44 (m, 2H), 7.07 (s, 4H), 7.29-7.31 (m, 1H), 7.32-7.34 (m,

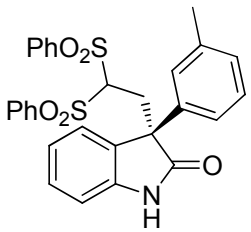
1H), 7.50-7.53 (m, 3H), 7.59-7.62 (m, 2H), 7.64-7.66 (m, 1H), 7.75-7.76 (m, 1H), 7.76-7.78 (m, 2H), 8.00-8.06 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.93, 28.08, 32.08, 55.01, 80.67, 116.27, 124.57, 125.73, 126.64, 128.39, 128.93, 128.99, 129.43, 129.52, 129.60, 131.06, 134.44, 134.74, 135.91, 137.88, 137.92, 138.09, 141.25, 149.32, 175.34; $[\alpha]_D$ = + 5.5 (c = 2.6, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{34}H_{33}NO_7S_2$ $[M+Na]^+$ 654.1591, found 654.1598.

(*R*)-3-(2,2-Bis(phenylsulfonyl)ethyl)-3-*p*-tolylindolin-2-one (**6-7a'**)



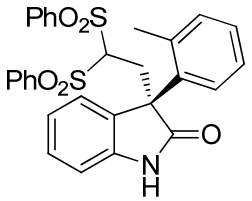
A white solid; The ee value was 90%, t_R (major) = 28.99 min, t_R (minor) = 64.14 min (Chiralcel AD-H, λ = 254 nm, 35% *i*PrOH/hexanes, flow rate = 1.0 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.25 (s, 3H), 3.21-3.28 (m, 2H), 4.37-4.40 (m, 1H), 6.90-7.22 (m, 6H), 7.27-7.64 (m, 9H), 7.96 -7.98 (m, 2H), 8.21 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.93, 31.03, 55.33, 80.78, 110.76, 122.55, 126.56, 128.92, 129.29, 129.50, 129.92, 131.03, 134.28, 134.68, 135.96, 137.33, 137.63, 138.33, 141.97, 178.92; HRMS (ESI) m/z calcd for $C_{29}H_{25}NO_5S_2$ $[M+Na]^+$ 554.1066, found 554.1066.

(*R*)-3-(2,2-Bis(phenylsulfonyl)ethyl)-3-*m*-tolylindolin-2-one (**6-7b'**)



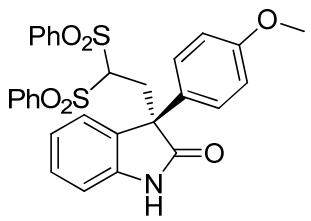
A white solid; The ee value was 90%, t_R (major) = 23.78 min, t_R (minor) = 43.67 min (Chiralcel AD-H, λ = 254 nm, 40% *i*PrOH/hexanes, flow rate = 1.0 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.24-3.39 (m, 2H), 4.40-4.42 (m, 1H), 6.95-6.97 (m, 1H), 7.06-7.17 (m, 5H), 7.26 -7.35 (m, 2H), 7.43-7.64 (m, 8H), 7.99-8.03 (m, 2H), 8.33 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.62, 30.90, 55.62, 80.80, 110.81, 122.56, 123.77, 126.61, 127.31, 128.64, 128.68, 128.92, 128.93, 129.27, 129.31, 129.89, 131.05, 134.28, 134.71, 135.93, 138.31, 138.48, 140.21, 142.01, 178.92; $[\alpha]_D$ = + 48.6 (c = 1.8, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{29}H_{25}NO_5S_2$ $[M+Na]^+$ 554.1066, found 554.1068.

(*R*)-3-(2,2-Bis(phenylsulfonyl)ethyl)-3-*o*-tolylindolin-2-one (**6-7c'**)



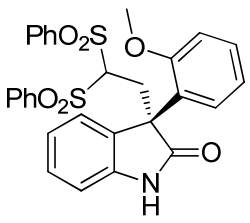
A white solid; The ee value was 91%, t_R (major) = 16.09 min, t_R (minor) = 103.35 min (Chiralcel AD-H, λ = 254 nm, 40% *i*PrOH/hexanes, flow rate = 1.0 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.78 (s, 3H), 3.06-3.10 (m, 1H), 3.69-3.73 (m, 1H), 4.05-4.07 (m, 1H), 6.94-6.95 (m, 1H), 7.07 -7.08 (m, 5H), 7.10-7.627 (m, 5H), 7.45-7.62 (m, 5H), 8.05-8.06 (m, 2H), 9.11 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.98, 29.97, 55.28, 79.93, 110.18, 122.94, 126.23, 126.75, 127.16, 128.11, 128.66, 128.73,128.98, 129.06, 130.12, 131.29, 131.40, 132.65, 133.86, 134.75, 135.78, 136.98, 137.46, 138.70, 142.24, 179.09; $[\alpha]_D$ = + 14.5 (c = 2.3, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{29}H_{25}NO_5S_2$ $[M+Na]^+$ 554.1043, found 554.1040.

(*R*)-3-(2,2-Bis(phenylsulfonyl)ethyl)-3-(4-methoxyphenyl)indolin-2-one (**6-7d'**)



A white solid; The ee value was 91%, t_R (major) = 34.95 min, t_R (minor) = 64.06 min (Chiralcel AD-H, λ = 254 nm, 35% *i*PrOH/hexanes, flow rate = 1.0 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.22-3.30 (m, 2H), 3.76 (s, 3H), 4.43-4.46 (m, 1H), 6.79-6.81 (m, 2H), 6.94-6.96 (m, 1H), 7.18-7.26 (m, 3H), 7.34-7.36 (m, 2H), 7.46-7.50 (m, 2H), 7.53-7.55 (m, 2H), 7.56-7.58 (m, 1H), 7.63-7.70 (m, 3H), 8.02-8.11 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.16, 54.76, 55.19, 80.69, 110.59, 114.08, 122.50, 126.44, 127.77, 128.84, 129.23, 129.87, 130.96, 132.24, 134.22, 134.62, 135.82, 138.26, 141.74, 159.06, 178.73; $[\alpha]_D$ = + 39.3 (c = 1.8, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{29}H_{25}NO_6S_2$ $[M+Na]^+$ 570.1040, found 570.1031.

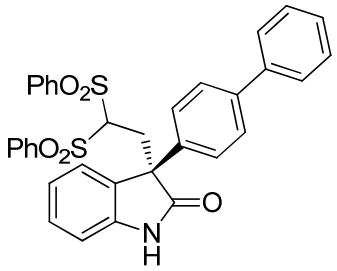
(*S*)-3-(2,2-Bis(phenylsulfonyl)ethyl)-3-(2-methoxyphenyl)indolin-2-one (**6-7e'**)



A white solid; The ee value was 99%, t_R (major) = 21.76 min, t_R (minor) = 123.70 min (Chiralcel AD-H, λ = 254 nm, 40% *i*PrOH/hexanes, flow rate = 1.0 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.98-3.02 (m, 1H), 3.60 (s, 3H), 3.68-3.72 (m, 1H), 4.28-4.30 (m, 1H), 6.83-7.03 (m, 4H), 7.23-7.62 (m, 11H), 7.99-8.00 (m, 2H), 8.25 (s, 1H);

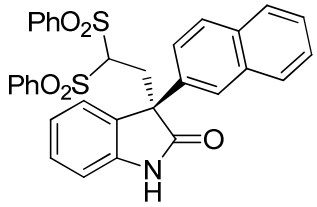
^{13}C NMR (75 MHz, $CDCl_3$) δ 28.26, 53.57, 55.50, 80.20, 109.47, 112.56, 120.97, 122.29, 126.30, 127.43, 128.12, 128.47, 128.74, 128.87, 129.01, 129.31, 131.16, 133.91, 134.58, 136.09, 138.80, 142.03, 157.36, 179.64; $[\alpha]_D$ = -10.9 (c = 0.9, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{29}H_{25}NO_6S_2$ $[M+Na]^+$ 570.1040, found 570.1034.

(*R*)-3-([1,1'-Biphenyl]-4-yl)-3-(2,2-bis(phenylsulfonyl)ethyl)indolin-2-one (**6-7g'**)



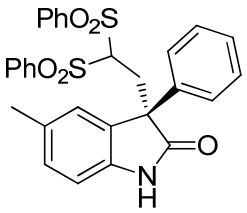
A white solid; The ee value was 96%, t_R (major) = 34.20 min, t_R (minor) = 55.04 min (Chiralcel AD-H, λ = 254 nm, 35% *i*PrOH/hexanes, flow rate = 1.0 mL/min); ^{1}H NMR (500 MHz, *d6*-DMSO) δ 3.07-3.09 (m, 1H), 3.26-3.28 (m, 1H), 4.91-4.93 (m, 1H), 6.97-6.99 (m, 1H), 7.13- 7.16 (m, 1H), 7.25-7.29 (m, 3H), 7.33-7.37 (m, 2H), 7.41-7.44 (m, 2H), 7.53-7.58 (m, 2H), 7.59-7.60 (m, 3H), 7.62-7.69 (m, 2H), 7.72-7.76 (m, 2H), 7.77-7.80 (m, 4H), 10.76 (s, 1H); ^{13}C NMR (75 MHz, *d6*-DMSO) δ 31.36, 54.37, 79.63, 110.90, 122.64, 127.09, 127.44, 127.48, 128.09, 129.30, 129.44, 129.73, 129.84, 129.97, 129.98, 131.13, 135.45, 135.56, 136.68, 138.14, 139.78, 139.82, 140.22, 142.87, 178.48; $[\alpha]_D$ = + 66.7 (c = 0.9, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{34}H_{27}NO_5S_2$ $[M+Na]^+$ 616.1213, found 616.1212.

(*R*)-3-(2,2-Bis(phenylsulfonyl)ethyl)-3-(naphthalen-2-yl)indolin-2-one (**6-7i'**)



A white solid; The ee value was 93%, t_R (major) = 30.92 min, t_R (minor) = 68.66 min (Chiralcel AD-H, λ = 254 nm, 40% ^{i}PrOH/hexanes, flow rate = 1.0 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.40-3.45 (m, 2H), 4.55-4.57 (m, 1H), 6.99-7.01 (m, 1H), 7.18-7.26 (m, 2H), 7.33-7.50 (m, 8H), 7.59-7.76 (m, 8H), 7.99-8.02 (m, 2H), 8.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.03, 55.67, 80.66, 110.95, 122.69, 124.60, 125.65, 126.34, 126.45, 126.54, 127.42, 128.32, 128.80, 128.93, 128.97, 129.33, 129.44, 129.97, 130.87, 132.66, 133.08, 134.33, 134.68, 136.05, 137.36, 138.28, 141.97, 178.82; $[\alpha]_D$ = + 26.3 (c = 2.4, THF); HRMS (ESI) m/z calcd for $C_{32}H_{25}NO_5S_2$ $[M+Na]^+$ 590.1066, found 590.1066.

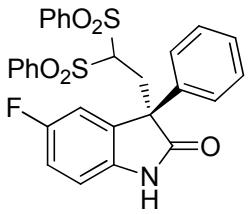
(*R*)-3-(2,2-Bis(phenylsulfonyl)ethyl)-5-methyl-3-phenylindolin-2-one (**6-7j'**)



A white solid; The ee value was 90%, t_R (major) = 26.05 min, t_R (minor) = 55.32 min (Chiralcel AD-H, λ = 254 nm, 35% *i*PrOH/hexanes, flow rate = 1.0 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.24-3.44 (m, 2H), 4.50-4.53 (m, 1H), 6.86-6.89 (m, 1H), 7.16-7.21 (m, 2H), 7.30-7.36 (m, 3H), 7.49-7.54 (m, 2H), 7.57-7.75 (m, 6H), 8.08-8.11 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.12, 30.90, 55.56, 80.80, 84.14, 110.45, 126.96, 127.70, 128.70, 128.83, 129.12, 129.64, 129.78,

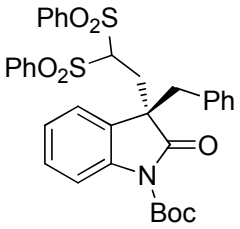
131.07, 132.04, 134.20, 134.66, 135.76, 138.49, 139.39, 140.41, 159.22, 178.; $[\alpha]_D$ = + 42.9 (c = 1.8, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{29}H_{25}NO_5S_2$ $[M+Na]^+$ 554.1066, found 554.1064.

(*R*)-3-(2,2-Bis(phenylsulfonyl)ethyl)-5-fluoro-3-phenylindolin-2-one (**6-7k'**)



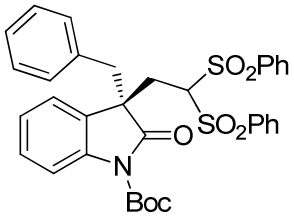
A white solid; The ee value was 93%, t_R (major) = 25.90 min, t_R (minor) = 41.54 min (Chiralcel AD-H, λ = 254 nm, 35% *i*PrOH/hexanes, flow rate = 1.0 mL/min); ^1H NMR (300 MHz, $CDCl_3$) δ 3.32-3.36 (m, 2H), 4.46-4.49 (m, 1H), 6.91-6.93 (m, 1H), 7.04-7.09 (m, 2H), 7.29-7.33 (m, 4H), 7.54-7.81 (m, 8H), 8.08-8.11 (m, 2H), 8.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.03, 55.91, 80.66, 111.34, 111.44, 113.84, 114.16, 115.65, 115.97, 126.48, 127.99, 128.86, 128.93, 128.99, 129.23, 130.99, 131.28, 131.39, 134.41, 134.79, 135.62, 137.73, 138.12, 139.63, 157.23, 160.44, 178.62; $[\alpha]_D$ = + 59.3 (c = 0.8, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{28}H_{22}NFO_5S_2$ $[M+Na]^+$ 558.0804, found 558.0794.

(S)-*tert*-Butyl 3-benzyl-3-(2,2-bis(phenylsulfonyl)ethyl)-2-oxoindoline-1-carboxylate **(6-7l)**



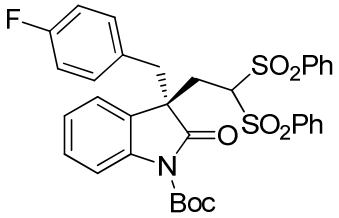
A colorless oil; The ee value was 28%, t_R (major) = 25.49 min, t_R (minor) = 29.01 min (Chiralcel IA-H, λ = 254 nm, 15% *i*PrOH/hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 9H), 2.93-3.04 (m, 3H), 3.19-3.24 (m, 1H), 4.87-4.91 (m, 1H), 6.79-6.81 (d, *J* = 6.8 Hz, 2H), 7.08-7.33 (m, 6H), 7.55-7.61 (m, 7H), 7.87-7.90 (d, *J* = 7.6 Hz, 2H), 8.00-8.03 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.94, 30.66, 45.64, 52.47, 79.23, 83.89, 115.63, 123.69, 124.06, 126.95, 127.70, 128.16, 128.90, 128.92, 129.02, 129.39, 130.03, 130.64, 134.03, 134.28, 134.67, 136.19, 138.06, 140.30, 148.47, 176.28; $[\alpha]_D$ = - 6.2 (c = 1.1, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{34}H_{33}NO_7S_2$ $[M+Na]^+$ 654.1611, found 654.1605.

(*R*)-*tert*-Butyl 3-benzyl-3-(2,2-bis(phenylsulfonyl)ethyl)-2-oxoindoline-1-carboxylate (**6-7m**)



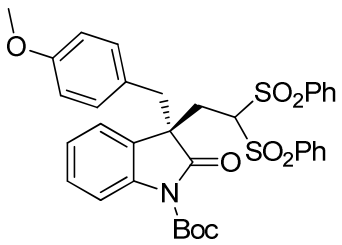
A colorless oil; The ee value was 90%, t_R (minor) = 25.49 min, t_R (major) = 29.01 min (Chiralcel IA-H, λ = 254 nm, 15% ^{i}PrOH/hexanes, flow rate = 0.5 mL/min); ^{1}H NMR, ^{13}C NMR & HRMS are the same as those of **6-7l**; $[\alpha]_D$ = + 16.4 (c = 1.8, $CHCl_3$).

(*R*)-*tert*-Butyl 3-(2,2-bis(phenylsulfonyl)ethyl)-3-(4-fluorobenzyl)-2-oxoindoline-1-carboxylate (**6-7n**)



A colorless oil; The ee value was 91%, t_R (minor) = 39.73 min, t_R (major) = 43.94 min (Chiralcel AD-H, λ = 254 nm, 15% *i*PrOH/hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (s, 5H), 1.61 (s, 4H), 2.90-3.00 (m, 3H), 3.18-3.22 (m, 1H), 4.50-4.88 (m, 1H), 6.73-6.75 (m, 4H), 7.21-7.37 (m, 3H), 7.54-7.79 (m, 7H), 7.86-7.87 (d, *J* = 7.6 Hz, 2H), 7.99-8.00 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.42, 28.01, 30.64, 44.89, 52.66, 79.22, 84.20, 114.58, 114.74, 114.95, 115.84, 117.24, 123.63, 123.75, 124.29, 128.06, 129.00, 129.03, 129.15, 129.29, 129.35, 129.46, 129.68, 129.89, 130.67, 130.76, 131.47, 131.56, 131.62, 134.43, 134.81, 136.10, 138.08, 140.38; $[\alpha]_D$ = +11.9 (c = 3.0, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{34}H_{32}FNO_7S_2$ $[M+Na]^+$ 672.1521, found 672.1524.

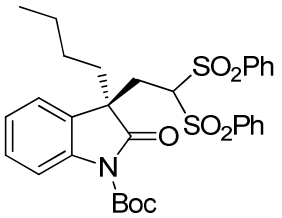
(*R*)-*tert*-Butyl 3-(2,2-bis(phenylsulfonyl)ethyl)-3-(4-methoxybenzyl)-2-oxoindoline-1-carboxylate (**6-7o**)



A colorless oil; The ee value was 90%, t_R (minor) = 45.27 min, t_R (major) = 58.13 min

(Chiralcel AD-H, λ = 254 nm, 15% *i*PrOH/hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (s, 9H), 2.88-2.97 (m, 3H), 3.11-3.16 (m, 1H), 3.72 (s, 3H), 4.82-4.84 (m, 1H), 6.59-6.61 (d, *J* = 8.9 Hz, 1H), 6.69-6.70 (d, *J* = 8.9 Hz, 1H), 7.12-7.14 (d, *J* = 7.6 Hz, 1H), 7.22-7.24 (m, 1H), 7.29-7.35 (m, 1H), 7.52-7.61 (m, 4H), 7.67-7.73 (m, 3H), 7.86-7.87 (d, *J* = 7.6 Hz, 2H), 7.99-8.00 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.03, 30.56, 44.97, 52.69, 55.08, 83.99, 113.19, 115.79, 123.77, 124.13, 126.15, 128.33, 128.98, 129.49, 130.75, 131.19, 134.38, 134.76, 138.13, 140.43, 148.59, 158.57, 176.55; $[\alpha]_D$ = + 17.8 (c = 1.1, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{35}H_{35}NO_8S_2$ $[M+Na]^+$ 684.1687, found 684.1681.

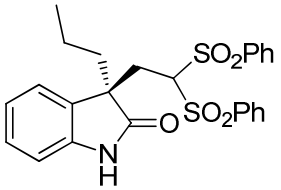
(*R*)-*tert*-Butyl 3-(2,2-bis(phenylsulfonyl)ethyl)-3-butyl-2-oxoindoline-1-carboxylate **(6-7q)**



A colorless oil; The ee value was 80%, t_R (minor) = 24.04 min, t_R (major) = 26.44 min (Chiralcel AD-H, λ = 220 nm, 10% *i*PrOH/hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.74-0.77 (t, *J* = 7.6 Hz, 3H), 0.98-1.01 (m, 1H), 1.11-1.17 (m, 2H), 1.58-1.61 (m, 2H), 1.65 (s, 9H), 1.81-1.90 (m, 1H), 2.65-2.69 (m, 1H), 2.83-2.87 (m, 1H), 4.82-4.84 (m, 1H), 7.18-7.24 (m, 2H), 7.35-7.40 (m, 1H), 7.52-7.59 (m, 4H), 7.67- 7.70 (m, 2H), 7.81-7.98 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.66, 22.63, 26.21, 28.11, 31.90, 38.64, 50.79, 78.87, 84.27, 115.84, 124.59, 128.91, 128.95,

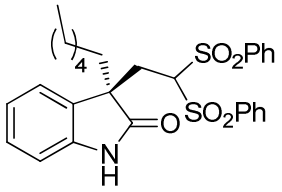
129.00, 129.50, 129.57, 130.66, 134.27, 134.70, 136.38, 138.55, 140.31, 149.13, 156.88, 177.23; $[\alpha]_D$ = + 8.0 (c = 1.0, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{31}H_{35}NO_7S_2$ $[M+Na]^+$ 620.1712, found 620.1721.

(*R*)-3-(2,2-Bis(phenylsulfonyl)ethyl)-3-propylindolin-2-one (**6-7p'**)



A colorless oil; The ee value was 77%, t_R (minor) = 69.58 min, t_R (major) = 91.99 min (Chiralcel AS-H, λ = 254 nm, 20% *i*PrOH/hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.72-0.75 (t, *J* = 7.0 Hz, 3H), 0.83-0.86 (m, 1H), 1.06-1.09 (m, 1H), 1.59-1.61 (m, 1H), 1.77-1.83 (m, 1H), 2.68-2.84 (m, 2H), 4.94-4.96 (m, 1H), 6.87-6.88 (d, *J* = 7.7 Hz, 1H), 7.08-7.25 (m, 3H), 7.47-7.69 (m, 6H), 7.82-7.83 (d, *J* = 7.6 Hz, 1H), 7.92 (s, 1H), 7.97-7.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.90, 17.37, 30.65, 39.98, 50.69, 78.78, 110.05, 122.51, 123.74, 128.57, 128.83, 128.91, 129.26, 130.57, 134.10, 134.58, 138.49, 141.00, 179.97; $[\alpha]_D$ = + 15.2 (c = 0.9, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{25}H_{25}NO_7S_2$ $[M+Na]^+$ 506.1066, found 506.1073.

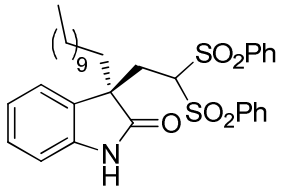
(*R*)-3-(2,2-Bis(phenylsulfonyl)ethyl)-3-hexylindolin-2-one (**6-7r'**)



A colorless oil; The ee value was 76%, t_R (minor) = 11.94 min, t_R (major) = 28.66 min

(Chiralcel OD-H, λ = 254 nm, 20% *i*PrOH/hexanes, flow rate = 1.0 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79-0.82 (t, *J* = 7.0 Hz, 3H), 1.09-1.18 (m, 8H), 1.59-1.65 (m, 1H), 1.78-1.84 (m, 1H), 2.67- 2.84 (m, 2H), 4.94-4.97 (m, 1H), 6.87-6.89 (d, *J* = 7.6 Hz, 1H), 7.11-7.28 (m, 3H), 7.47-7.69 (m, 7H), 7.81-7.83 (m, 2H), 7.96-7.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.95, 22.48, 24.02, 29.20, 30.78, 31.41, 37.96, 50.69, 78.85, 110.09, 122.64, 123.82, 128.66, 128.91, 129.00, 129.36, 130.66, 131.10, 134.18, 134.65, 136.50, 138.61, 141.01, 179.9; $[\alpha]_D$ = + 26.4 (c = 0.5, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{28}H_{31}NO_7S_2$ $[M+Na]^+$ 548.1529, found 548.1521.

(*R*)-3-(2,2-Bis(phenylsulfonyl)ethyl)-3-undecylindolin-2-one (**6-7s'**)



A colorless oil; The ee value was 80%, t_R (minor) = 19.96 min, t_R (major) = 46.85 min (Chiralcel OD-H, λ = 254 nm, 20% *i*PrOH/hexanes, flow rate = 0.5 mL/min); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77-0.78 (br, 1H), 0.86-0.89 (t, *J* = 7.0 Hz, 3H), 1.10-1.28 (m, 17H), 1.59-1.61 (m, 1H), 1.78-1.83 (m, 1H), 2.68-2.84 (m, 2H), 4.95-4.97 (m, 1H), 6.87-6.89 (d, *J* = 7.6 Hz, 1H), 7.10-7.25 (m, 3H), 7.47-7.69 (m, 6H), 7.82-7.98 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.01, 22.58, 23.98, 29.15, 29.22, 29.39, 29.46, 30.69, 31.80, 37.85, 50.61, 78.77, 110.05, 122.51, 123.71, 128.56, 128.83, 128.91, 129.28, 130.56, 131.02, 134.09, 134.56, 136.42, 138.51, 140.99, 179.93; $[\alpha]_D$ = + 7.3 (c = 1.9, $CHCl_3$); HRMS (ESI) m/z calcd for $C_{33}H_{41}NO_5S_2$ $[M+Na]^+$ 618.2345, found 618.2332.

Chapter 7 References

1. Gardner, M. The New Ambidextrous; 3rd Rev. Ed; W. H. Freeman & Co: New York, 1990.
2. Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726.
3. Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138.
4. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds. *Comprehensive Asymmetric Catalysis*, 1st Ed, Springer: Berlin, **1999**.
5. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, Wiley: New York, **1994**.
6. Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd Ed. Wiley-VCH: New York, **2000**.
7. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
8. Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.
9. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
10. Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1995**, *34*, 1059.
11. Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.
12. Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3174.
13. Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.;

Kasahara, I.; Noyori, R. *J. Am. Chem. Soc*. **1987**, *109*, 1596.

14. Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629.
15. Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.
16. Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801.
17. (a) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328.
18. La, D. S.; Alexander, J. B.; Cefalo, D. R.; Graf, D. D.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 9720.
19. El-Qisairi, A.; Hamed, O.; Henry, P. M. *J. Org. Chem.* **1998**, *63*, 2790.
20. Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669.
21. Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 496.
22. Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.
23. Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446.
24. Bhattacharya, A.; Dolling, U. H.; Grabowski, E. J. J.; Karady, S.; Ryan, K. M.; Weinstock, L. M. *Angew. Chem., Int. Ed.* **1986**, *25*, 476.
25. Odonnell, M. J.; Bennett, W. D.; Wu, S. D. *J. Am. Chem. Soc.* **1989**, *111*, 2353.
26. Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446.

27. Denmark, S. E.; Fu, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 12021.

28. Denmark, S. E.; Fu, J. P. *Org. Lett.* **2002**, *4*, 1951.

29. Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432.

30. Denmark, S. E.; Stavenger, R. A.; Wong, K. T.; Su, X. P. *J. Am. Chem. Soc.* **1999**, *121*, 4982.

31. Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279.

32. Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012.

33. Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867.

34. List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.

35. List, B. *Synlett* **2001**, 1675.

36. List, B. *Tetrahedron* **2002**, *58*, 5573.

37. List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656.

38. List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395.

39. Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450.

40. Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

41. Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.

42. Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894.

43. Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519.

44. Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139.

45. Ooi, T.; Takeuchi, M.; Maruoka, K. *Synthesis* **2001**, 1716.

46. Ooi, T.; Tayama, E.; Doda, K.; Takeuchi, M.; Maruoka, K. *Synlett* **2000**, 1500.

47. Ooi, T.; Uematsu, Y.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 1551.

48. Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.

49. (a) Chen, Y.-C; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542. (b) Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2002**, *124*, 2870 and references therein. (c) Singh, R. P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 2422.

50. McCooey, S.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599.

51. Mizuta, S.; Shibata, N.; Goto, Y.; Furukawa, T.; Nakamura, S. and Toru, T. *J. Am. Chem. Soc.* **2007**, *129*, 6394.

52. (a) Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794; (b) Tao, B. T.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091; (c) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412.

53. Murugan, R.; Scriven, E. F. V. *Aldrichimica Acta* **2003**, *36*, 21.

54. Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157.

55. Xu, J.-Y; Guan, Y.; Yang, S.; Ng, Y.; Peh, G.; Tan, C.-H. *Chem. Asian J.* **2006**, *1*, 724.

56. For proline derivatives: (a) Priem, G.; Anson, M. S.; Macdonald, S. J. F.; Pelotier, B.; Campbell, I. B. *Tetrahedron Lett.* **2002**, *43*, 6001. (b) Priem, G.; Pelotier, B. Campbell, I. B.; Macdonald, S. J. F.; Anson, M. S. *Synlett* **2003**, *5*, 679. (c) Priem, G.; Pelotier, B.; Macdonald, S. J. F.; Anson, M. S.; Campbell, I. B. *J. Org. Chem.* **2003**, *68*, 3844. (d) Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**,

125, 13368. (e) Rabalakos, C.; Wulff, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 13524. (f) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262. (g) Hartikka, A.; Arvidsson, P. I. *Eur. J. Org. Chem.* **2005**, *20*, 4287. (h) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2006**, *128*, 734. (i) Zhu, Q.; Lu, Y. *Org. Lett.* **2008**, *10*, 4803.

57. (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (b) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198.
58. Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589.
59. Dove, A. P.; Pratt, R. C.; Lohmeijer, B. G. G.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 13798.
60. Hashimoto, T.; Maruoka, K. *Chem. Rev*. **2007,** *107*, 5656.
61. Westermann, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151.
62. List, B. *Synlett* **2001**, 1675.
63. List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395.
64. List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.
65. List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656.
66. Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bogevig, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254.
67. (a) Enders, D.; Seki, A. *Synlett* **2002**, 26. (b) Mielgo, A.; Velilla, I.; Bengoa, E. G.; Palomo, C. *Chem. Eur. J.* **2010**, DOI: 10.1002/ chem.201000376.

68. Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III *Tetrahedron Lett*er **2001**, *42*, 4441.

69. Pikho, P. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 544.

70. Steiner, D. D.; Mase, N.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706.

71. Marigo, M.; Fielenbach, D.; Braunton, A.; Kjaersgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703.

72. Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

73. Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.

74. Wilson, R. M.; Jen, W. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616.

75. Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.

76. Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.

77. Marigo, M.; Franzen, J.; Poulsen, T. B.; Zhuang, W.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964.

78. Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240.

79. Yang, J.-W.; Fonseca, M. T. H.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 6660.

80. Yang, J.-W.; Fonseca, M. T. H.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 108.

81. Berkessel, A.; Gro¨ger, H. *Asymmetric Organocatalysis: From Biomimetic*

Concepts to Application in Asymmetric Synthesis; Wiley-VCH: Weinheim, 2005.

82. Mukherjee, S.; Yang, J.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.
83. Córdova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun.* **2005**, 3586.
84. Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.
85. Blarer, S. J.; Seebach, D. *Chem. Ber.* **1983**, *116*, 2250.
86. Seebach, D.; Missbach, M.; Calderari, G.; Eberle, M. *J. Am. Chem. Soc.* **1990**, *112*, 7625.
87. Blarer, S. J.; Schweizer, W. B.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 1637.
88. Yamada, S.; Hiroi, K.; Achiwa, K. *Tetrahedron Lett.* **1969**, *10*, 4233.
89. Yamada, S.; Otani, G. *Tetrahedron Lett.* **1969**, *10*, 4237.
90. List, B. *Acc. Chem. Res.* **2004**, *37*, 548.
91. List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.
92. Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260.
93. Enders, D.; Seki, A. *Synlett* **2002**, 26.
94. Kotrusz, P.; Toma, S.; Schmalz, H.-G.; Adler, A. *Eur. J. Org. Chem.***2004**, 1577.
95. Rasalkar, M. S.; Potdar, M. K.; Mohile, S. S.; Salunkhe, M. M. *J.Mol. Catal. A* **2005**, *235*, 267.
96. Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611.
97. Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559.

98. Andrey, O.; Alexakis, A.; Tomassini, A.; Bernarddinelli, G. *Ad*v. *Synth. Catal.* **2004**, *346*, 1147.

99. Mosse, S.; Andrey, O.; Alexakis, A. *Chimia* **2006**, *60*, 216.

100. Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966.

101. Wang, J.; Li, H.; Lou, B.; Zu, L.; Guo, H.; Wang, W. *Chem. Eur. J.* **2006**, *12*, 4321.

102. Aslanian, R.; Lee, G.; Iyer, R. V.; Shih, N.-Y.; Piwinski, J. J.; Draper, R. W.; McPhail, A. T. *Tetrahedron: Asymmetry* **2000**, *11*, 3867.

103. Zu, L.; Wang, J.; Li, H.; Wang, W. *Org. Lett.* **2006**, *8*, 3077.

104. (a) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369. (b) Ting, Y.-F.; Chang, C.; Reddy, R. J.; Magar, D. R.; Chen, K. *Chem. Eur. J*. **2010**, DOI: 10.1002/chem.201000483. (c) Wu, X.-Y.; Dai, X.-Y.; Nie, L.-L.; Fang, H.-H.; Chen, J.; Ren, Z.-J.; Cao, W.-G.; Zhao, G. *Chem. Commun*. **2010**, *46*, 2733. (d) Chen, J.-R.; Cao, Y.-J.; Zou, Y.-Q.; Tan, F.; Fu, L.; Zhu X.-Y.; Xiao, W.-J. *Org. Biomol. Chem.* **2010**, *8*, 1275. (e) Benfatti, F.; Capdevila, M. G.; Zoli, L.; Benedetto, E.; Cozzi, P. G. *Chem. Commun*. **2009**, 5919. (f) Um, J. M.; Gutierrez, O.; Schoenebeck, F.; Houk, K. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 6001. (g) Gotoh, H.; Okamura, D.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2009**, *11*, 4056. (h) McGarraugh, P. G.; Brenner, S. E. *Org. Lett.* **2009***, 11*, 5654. (i) Westermann, B.; Ayaz, M.; Berkel, S. S. *Angew. Chem., Int. Ed*. **2010**, *49*, 846. (j) Mager, I.; Zeitler, K. *Org. Lett.* **2009***, 12*, 1480. (k) Terrasson, V.; Figueiredo, R.

M.; Campagne, J. M. *Eur. J. Org. Chem.* **2010**, 2635. (l) Li, Z.-B.; Luo, S.-P.; Guo, Y.; Xia, A.-B.; Xu, D.-Q. *Org. Biomol. Chem.* **2010**, DOI: 10.1039/ c002197k.

105. Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int.Ed.* **2005**, *44*, 4212.

106. Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794.

107. Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876.

108. Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.

109. List, B.; Lerner R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

110. Pizzarello, S.; Weber, A. L. *Science* **2004**, *303*, 1151.

111. Amedjkouh, M. *Tetrahedron: Asymmetry* **2005**, *16*, 1411.

112. (a) Córdova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun.* **2005**, 3586. (b) Córdova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem. Eur. J.* **2006**, *12*, 5383. (c) Bassan, A.; Zou, W.; Reyes, E.; Himo, F.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7028. (d) Zou, W.; Ibrahem, I.; Dziedzic, P.; Sunden, H.; Córdova, A. *Chem. Commun.* **2005**, 4946.

113. Tsogoeva, S. B.; Wei, S. *Tetrahedron: Asymmetry* **2005**, *16*, 1947.

114. For recent reviews on primary amine catalysis, see (a) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun*. **2009**, 1807. (b) Xu, L.-W.; Lu, Y. *Org. Biomol. Chem*. **2008**, *6*, 2047. (c) Peng, F.; Shao, Z. *J. Mol. Catal. A: Chem*. **2008**, *285*, 1. (d) Chen, Y.-C. *Synlett* **2008**, 1919. For recent work on primary amine in Michael reactions, see (e) Liu, C.; Lu, Y. *Org. Lett.* **2010**, *12*, 2278. (f) Peng, L.; Xu, X.-Y.; Wang, L.-L.;

Huang, J.; Bai, J.-F.; Huang, Q.-C.; Wang, L.-X. *Eur. J. Org. Chem.* **2010**, 1849. (g) Yoshida, M.; Sato, A.; Hara, S. *Org. Biomol. Chem*. **2010**, DOI: 10.1039/ c003940c. (h) Yang, T.-Q.; Chen, X.-K.; Xiao, H.; Liu, W.; Zhao, G. *Chem. Commun*. **2010**, DOI: 10.1039/c002552f. (i) Li, P.-F.; Yamamoto, H. *Chem. Commun*. **2009**, 5412. (j) Wang, J.-F.; Qi, C.; Ge, Z.-M.; Cheng, T.-M.; Li, R.-T. *Chem. Commun*. **2010**, *46*, 2124.

115. Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.*, **2006**, *45*, 6366.

116. McCooey, S. H.; Connon, S. J. *Org. Lett.*, **2007**, *9*, 599.

117. Yue, L.; Du, W.; Liu, Y.-K; Chen, Y.-C. *Tetrahedron Lett.* **2008**, *49*, 3881.

118. (a) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417. (b) Wynberg, H. *Top. Stereochem.* **1986**, *16*, 97.

119. (a) Oku, J. I.; Inoue, S. *J. Chem. Soc.*, *Chem. Commun.* **1981**, 229. (b) Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181. (c) Jackson, W. R.; Jayatilake, G. S.; Matthews, B. R.; Wilshire, C. *Aust. J. Chem.* **1988**, *41*, 203.

120. (a) Dolling, U.-H.; Davis, P.; Grabowski, E. J. *J. Am. Chem. Soc.***1984**, *106*, 446. (b) Conn, R. S. E.; Lovell, A. V.; Karady, S.;Weinstock, L. M. *J. Org. Chem.* **1986**, *51*, 4710.

121. Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.

122. Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012.

123. Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289.

124. Hammet, L. P. *Physical Organic Chemistry: Reaction rates, equilibria and mechanisms*, 2nd Edition, McGraw-Hill Book Company Inc. **1970**.

125. McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094.

126. Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424.

127. Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120.

128. Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed*. **2005**, *44*, 1924.

129. Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999.

130. Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed*. **2006**, *45*, 1520.

131. Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.

132. Yu, X.; Wang, W. *Chem. Asian J*. **2008**, *3*, 516.

133. (a) Konishi, H.; Lam, T. Y.; Malerich, J.; Rawa, V. *Org. Lett.* **2010**, *12*, 2028. (b) Xu, D.-Q.; Wang, Y.-F.; Zhang, W.; Luo, S.-P.; Zhong, A.-G.; Xia, A.-B.; Xu, Z.-Y. *Chem. Eur. J.* **2010**, *16*, 4177.

134. Steinhagen, H.; Helmchen, G. *Angew. Chem., Int. Ed.* **1996**, *35*, 2339.

135. Wuest, J. D. *Acc. Chem. Res.* **1999**, *32*, 81.

136. Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187.

137. Ma, J.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566.

138. Muniz, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6622.

139. Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924.

140. Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

141. (a) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.-N.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (b) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151.

142. Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H.; Takemoto, Y. *Tetrahedron Letter*

2006, *62*, 365.

143. Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2006**, *12*, 466.
144. Inokuma, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 9413.
145. Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 807.
146. McCooey, S. H.; Connon, S. *J. Angew. Chem., Int. Ed.* **2005**, *44*, 6367.
147. Murtagh, J. E.; McCooey, S. H.; Connon, S. *J. Chem. Commun.* **2005**, 227.
148. Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967.
149. Faltin, C.; Fleming, E. M.; Connon, S. J. *J. Org. Chem.* **2004**, *69*, 6496.
150. Han, X.; Luo, J.; Liu, C.; Lu, Y. *Chem. Commun.* **2009**, 2044.
151. McCooey, S.; McCabe, T.; Connon, S. J. *J. Org. Chem.* **2006**, *71*, 7494.
152. Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360.
153. Yu, P.; He, J.; Guo, C. *Chem. Commun*. **2008**, 2355.
154. (a) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048. (b) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191.
155. Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481.
156. Bassas, O.; Huuskonen, J.; Rissanen, K.; Koskinen, A. P. *Eur. J. Org. Chem*. **2009**, 1340.
157. Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc*. **2006**, *128*, 4932.
158. Zhu, Q.; Lu, Y. *Org. Lett.* **2009**, *11*, 1721.

159. Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293.

160. Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732.

161. Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964.

162. Steele, R. M.; Monti, C.; Gennari, C.; Piarulli, U.; Andreoli, F.; Vanthuyne, N.; Roussel, C. *Tetrahedron: Asymmetry* **2006**, *17*, 999.

163. Li, P.; Chai, Z.; Zhao, S.-L.; Yang, Y.-Q.; Wang, H.-F.; Zheng, C.-W.; Cai, Y.-P.; Zhao,-G.; Zhu, S.-Z. *Chem. Commun.* **2009**, 7369.

164. Li, X.; Xi, Z.-G.; Luo. S.-Z.; Cheng, J.-P. *Org. Biomol. Chem.* **2010**, *8*, 77.

165. Konishi, H.; Lam, T. Y.; Malerich, J.; Rawal, V. *Org. Lett.* **2010**, *12*, 2029.

166. Magnus, R.; Alexander, K. Roland, F. *Chem. Eur. J*. **2010**, *16*, 4173.

167. Liao, Y.-H.; Chen, W.-B.; Wu, Z.-J.; Du, X. L.; Cun, L. F.; Zhang, X.-M.; Yuana, W.-C. *Adv. Synth. Catal*. **2010**, *352*, 827.

168. (a) Zhang, Y.-N.; Yu, C.-G.; Ji, Y.-F.; Wang, W. *Chem. Asian J.* **2010**, DOI: 10.1002/ asia.201000014. (b) Zhang, H. L.; Syed, S.; Barbas, C. F., III. *Org. Lett.* **2010**, *12*, 708. (c) Zea, A.; Valero, G.; Alba, A.; Moyano, A.; Rios, R. *Adv. Synth. Catal.* **2010**, *352,* 1102.

169. (a) Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951. (b) Simpkins, N. S. *Sulfones in Organic Synthesis*, Pergamon Press, Oxford, **1993**.

170. (a) Nielsen, M.; Jacobsen, C. B.; Holub, N.; Paixao, W. B.; Jógensen, K. A. *Angew. Chem., Int. Ed*. **2010**, *49*, 2668. (b) Zhu, Q.; Lu, Y. *Aust. J. Chem*. **2009**, *62*, 951. (c) Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273. (d) For a review on asymmetric Michael additions using chiral

imines, see: d'Angelo, J.; Desmaele, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459.

171. (a) d'Angelo, J.; Revial, G. *Tetrahedron: Asymmetry* **1991**, *2*, 199. (b) Pinheiro, S.; Guingant, A.; Desmaele, D.; d'Angelo, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1003.
172. Mosse, S.; Alexakis, A. *Org. Lett.* **2005**, *7*, 4361.
173. Mosse, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559.
174. Mosse, S.; Alexakis, A.; Mareda, J.; Bollot, G.; Bernardinelli, G.; Filinchuk, Y. *Chem. Eur. J.* **2009**, *15*, 3204.
175. Lanad, A.; Maestro, M.; Masdeu, C.; Puente, A.; Vera, S.; Oiarbide, M.; Palomo, C. *Chem. Eur. J.* **2009**, *15*, 1562.
176. Quintard, A.; Alexakis, A. *Chem. Commun.* **2010**, DOI: 10.1039/ c000326c.
177. Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948.
178. Li, H.; Song, J.; Deng, L. *Tetrahedron* **2009**, *65*, 3139.
179. Liu, T.-Y; Long, J.; Li, B.-J; Jiang, L.; Li, R.; Wu, Y.; Ding, L.; Chen, Y-C. *Org. Biomol. Chem.* **2006**, *4*, 2097.
180. Alba, A. R.; Company, X.; Valero, G.; Moyano, A.; Rios, R. *Chem. Eur. J.* **2010**, DOI: 10.1002/chem.200903025.
181. Aleman, J.; Reyes, E.; Richter, B.; Overgaard, J.; Jorgensen, K. A. *Chem. Commun.* **2007**, 3921.
182. Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.
183. Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int.*

Ed. **2005**, *44*, 794.

184. Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876.

185. Kondakov, D. Y.; Negishi, E. *J. Am. Chem. Soc.* **1996**, *118*, 1577.

186. Sharma, G. V. M.; Reddy, K. L.; Lakshimi, P. S.; Ravi, R.; Kunwar, A. C. *J. Org. Chem.* **2006**, *71*, 3967.

187. Ziegler, E,; Ruef, W.; Zwainz, J. G. *Anorganische Chemie, Organische Chemie,* **1975**, *30*, 755.

188. Jiang, Z.-Q; Liang, Z.; Wu, X.-Y.; Lu, Y. *Chem. Commun*. **2006**, 2801.

189. Cheng, L.-L.; Wu, X.-Y.; Lu, Y. *Org. Biomol. Chem.* **2007**, *5*, 1018.

190. Cheng, L.-L.; Han, X.; Huang, H.; Wong, M. W.; Lu, Y. *Chem. Commun*. **2007**, 4143.

191. Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081.

192. Wiley, R. A.; Pearson, D. A.; Schmidt, V.; Wesche, S. B.; Roxoniig, J. J. *J. Med. Chem.* **1983***, 26,* 1077.

193. (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (c) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (d) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (e) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873. (f) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (g) Christoffers, J.; Baro, A. Eds. *Quaternary Stereocenters*, Wiley-VCH, Weinheim, **2005**.

194. Teodori, E.; Baldi, E.; Dei, S.; Gualtieri, F.; Romanelli, M. N.; Scapecchi, S.; Bellucci, C.; Ghelardini, C.; Matucci, R. *J. Med. Chem.* **2004**, *47*, 6070.

195. For earlier reports on the use of chiral auxiliary for the construction of a quaternay center, see: (a) Paquette, L. A.; Gilday, J. P.; Ra, C. S. *J. Am. Chem. Soc.* **1987**, *109*, 6858. (b) Nishimura, N.; Mitsunobu, O. *Tetrahedron Letter* **2000**, *41*, 2945. For a recent example, see: (c) Hashimoto, T.; Sakata, K.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 5014.

196. For primary amine-promoted conjugate addition of branched aldehydes to nitroolefins, see: (a) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366. (b) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599.

197. Mosse, S.; Alexakis, A.; Mareda, J.; Bollot, G.; Bernardinelli, G.; Filinchuk, Y. *Chem. Eur. J.* **2009**, *15*, 3204. One example of addition of 2-naphthyl propanal to vinyl sulfone catalyzed by diphenylprolinol silyl ether with 91% ee was described, the other two related examples did not preceed well (0% ee and 47% ee).

198. (a) Backvall, J.-E.; Chinchilla, R.; Najera, C.; Yus, M. *Chem. Rev.* **1998**, *98*, 2291. (b) Najera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547.

199. Paquette, L. A.; Gilday, J. P.; Ra, C. S. *J. Am. Chem.Soc.* **1987**, *109*, 6858.

200. (a) Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110. (b) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466. (c) Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; Lopez, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 117. (d) Wang, C.; Zhou, Z.; Tang, C. *Org. Lett.* **2008**, *10*, 1707. (e) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625. (f) Xu, X.;

Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2006**, *12*, 466.

201. Lu, S.-F.; Du, D.-M.; Xu, J.; Zhang, S.-W. *J. Am. Chem. Soc.* **2006**, *128*, 7418.

202. For the enantioselective addition of nitroalkanes to α,β-unsaturated ketones, see: (a) Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Letter* **1994**, *35*, 8233. (b) Yamaguchi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M.; *Tetrahedron* **1997**, *53*, 11223. (c) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975. (d) Halland, N.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331. (e) Prieto, A.; Halland, N.; Jorgenson, K. A. *Org. Lett.* **2005**, *7*, 3897. For the enantioselective addition of nitroalkanes to α,β-unsaturated aldehydes, see: (f) Hojabri, L.; Hartikka, A.; Moghaddam, F. M.; Arvidsson, P. I. *Adv. Synth. Catal.* **2007**, *349*, 740. (g) Wang. Y.; Li, P.; Liang, X.; Zhang, T.-Y.; Ye, J. *Chem. Commun*. **2008**, 1232.

203. Luo, J.; Xu, L.-W.; Hay, A. S. Robyn; Lu, Y. *Org. Lett.* **2009**, *11*, 437.

204. Grunewald, G. L.; Sall, D. J.; Monn, J. A. *J. Med. Chem.* **1988**, *31*, 824.

205. Campbell, M. J.; Johnson, J. S. *Org. Lett*. **2007**, *9*, 1521.

206. For selected reviews, see: a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. c) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. d) Trost, B. M.; Brennan, M. K. *Synthesis*, **2009**, 3003.

207. a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. c) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. d) Christoffers, J.; Baro, A. *Adv. Synth.*

Catal. **2005**, *347*, 1473. e) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873. f) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. g) Christoffers, J.; Baro, A. Eds. *Quaternary Stereocenters*, Wiley-VCH, Weinheim, 2005.

208. a) Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001. b) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sedeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164. c) Ishimaru, T.; Shibata, N.; Horikawa, T.; Yasuda, N.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4157.

209. a) Ishimaru, T.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *J. Am. Chem. Soc.* **2006**, *128*, 16488. b) Sano, D.; Nagata, K.; Itoh, T. *Org. Lett.* **2008**, *10*, 1593. c) Bui, T.; Candeias, N. R.; Barbas, C. F. III *J. Am. Chem. Soc.* **2010**, *132*, 5574.

210. a) Jiang, K.; Peng, J.; Cui, H.-L.; Chen, Y.-C. *Chem. Commun.* **2009**, 3955. b) Qian, Z.-Q.; Zhou, F.; Du, T.-P.; Wang, B.-L.; Ding, M.; Zhao, X.-L.; Zhou, J. *Chem. Commun.* **2009**, 6753. c) Cheng, L.; Liu, L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2009**, *11*, 3874.

211. a) Ogawa, S.; Shibata, N.; Inagaki, J.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem,. Int. Ed.* **2007**, *46*, 8666. b) Nakamura, S.; Hara, N.; Nakashima, H.; Kubo, K.; Shibata, N.; Toru, T. *Chem. Eur. J.* **2008**, *14*, 8079. c) Luppi, G.; Cozzi, P. G.; Monari, M.; Kaptein, B.; Broxterman, Q. B.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 7418. d) Tian, X.; Jiang, K.; Peng, J.; Du, W.; Chen, Y.-C. *Org. Lett.* **2008**, *10*, 3583. e) Cheng, L.; Liu, L.; Jia, H.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2009**, *74*,

4650.

212. a) Trost, B. M.; Frederiksen, M. U. *Angew. Chem., Int. Ed.* **2005***, 44,* 308. b) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2007**, *129*, 14548.

213. a) Bui, T.; Syed, S.; Barbas, C. F., III *J. Am. Chem. Soc.* **2009**, *131*, 8758. b) He, R.; Ding, C.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 4559. c) Kato, Y.; Furutachi, M.; Chen, Z.; Mitsunuma, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9168. d) Galzerano, P.; Bencivenni, G.; Pesciaioli, F.; Mazzanti, A.; Giannichi, B.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem. Eur. J.* **2009**, *15*, 7846. e) He, R.; Shirakawa, S.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 16620; f) Li, X.; Xi, Z.-G.; Luo, S.; Cheng, J.-P. *Org. Biomol. Chem*. **2010**, *8*, 77.

214. a) Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368. b) Hills, I. D.; Fu, G. C. *Angew. Chem. Int. Ed.* **2003**, *42*, 3921. c) Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925.

215. For a recent asymmetric synthesis via hetero-Claisen rearrangement, see: a) Duguet, ; Slawin, A. M. Z.; Smith, A. D. *Org. Lett.* **2009**, *11*, 3858. For pharmacological acitivities of 3-alkyl-3-aryloxindoles, see: b) Goehring, R. R.; Sachdeva, Y. P.; Pisipati, J. S.; Sleevi, M. C.; Wolfe, J. F. *J. Am. Chem. Soc.* **1985**, *107*, 435.

216. a) Liu, D.; Zhao, G.; Xiang, L. *Eur. J. Org. Chem.* **2010**, DOI : 10.1002/ejoc. 201000323. b) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A.

Chem. Rev. **1997**, *97*, 787. c) Liu, K. G.; Robichaud, A. J. *Drug. Dev. Res.* **2009**, *70*, 145.

217. Brown R. T. in *The Chemistry of Heterocyclic Compounds*; J. E. Saxton, Ed.; Part 4. Indoles: The Monoterpenoid Indole Alkaloid; John Wiley and Sons: New York, 1983, Vol. 25, pp 85-97.
218. Vu, A. T.; Cohn, S. T.; Zhang, P.; Kim, C. Y.; Mahaney, P. E.; Bray, J. A.; Johnston, G. H.; Koury, E. J.; Cosmi, S. A.; Deecher, D. C.; Smith, V. A.; Harrison, J. E.; Leventhal, L.; Whiteside, G. T.; Kennedy, J. D.; Trybulski, E. J. *J. Med. Chem.* **2010**, *53*, 2051.
219. Duguet, N.; Slawin, A. M. Z.; Smith, A. D. *Org. Lett.* **2009**, *11*, 1721.