ORGANOCATALYTIC ASYMMETRIC SUBSTITUTION REACTIONS OF MORITA–BAYLIS–HILLMAN CARBONATES

CHEN GUOYING

NATIONAL UNIVERSITY OF SINGAPORE

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ORGANOCATALYTIC ASYMMETRIC SUBSTITUTION REACTIONS OF MORITA–BAYLIS–HILLMAN CARBONATES

CHEN GUOYING
(*M.Sc., Dalian Institute of Chemical Physics)*

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Thesis Declaration

The work in this thesis is the original work of CHEN GUOYING, performed independently under the supervision of Prof. Lu Yixin, Chemistry Department, National University of Singapore, between 04/08/2008 and 04/08/2012.

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CHEN GUOYING		
Name	Signature	Date

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Table of Contents

Summary

The organocatalytic asymmetric reactions of Mortia-Baylis-Hillman (MBH) adducts have been received much attention. The asymmetric allylic substitution reactions of MBH carbonates were well studied in the presence of nucleophilic catalysts. In this thesis, two types of nucleophiles were used in the asymmetric substitution reaction of MBH carbonates.

Chapter 1 presented a brief summary of organocatalytic asymmetric reactions of MBH carbonates. Two types of reactions of MBH adducts were summarized. One was the asymmetric allylic substitution reactions while the other was asymmetric [3+2] annulation reactions. Several examples were given in both types of reactions.

In Chapter 2, a highly enantioselective substitution reaction of MBH carbonates with nitroalkanes using bifunctional tertiary amine–thiourea catalysts was described. The different regioselectivity was achieved and the plausible mechanism was proposed. The simple manipulation of the product could provide the useful α-alkylidene-γ-butyrolactam.

In Chapter 3, a highly enantioselective allylic substitution reactions of isatin-derived MBH carbonates with nitroalkane was described in the presence of Lewis base catalyst derived from cinchona alkaloid. The product could transform to interesting spiral oxindole structure by simple reducing reaction. The plausible mechanism was also discussed.

In Chapter 4, a highly enantioselective allylic substitution reaction of MBH carbonate with an azlactone using phosphine-thiourea catalyst was described. The azlactone as a masked formyl anion was used in the allylic substitution reaction. The product might transform to useful α-alkylidene-γ-butyrolactone.

List of Tables

List of Schemes

List of Figures

List of Abbreviations

Ac	Acetyl
Aq	Aqueous
Ar	Aromatic
Atm	Atmosphere
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bz	Benzoyl
Bu	Butyl
Cat.	Catalysts
Conc.	Concentrated
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethylene
DIAD	Diisopropylazodicarboxylate
DMAP	4-Dimethylaminopyridine
DME	Dimethyl ether
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
d.r.	Diastereomeric ratio
E^+	Electrophile
ee	Enantiomeric excess
Et	Ethyl
EWG	Electron-withdrawing group

HPLC	High performance liquid chromatography
IPA	*iso*-Propanol
LA	Lewis acid
Me	Methyl
Ms	Methyl sulfonyl
Naph (Np)	Naphthyl
NR	No reaction
Ph	Phenyl
Pr	Propyl
PTC	Phase transfer catalyst
Py (pyr)	Pyridine
R.T.	Room temperature
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	Triethylamine
TFA	Trifluoromethylacetic acid
THF	Tetrahydrofuran
TIPB	1,3,5-Triisopropylphenyl
TPP	Triphenylphosphine

List of Publications

1. Chen, G. -Y.**;** Zhong, F.; Lu, Y. “Asymmetric Allylic Alkylation of Isatin-Derived Morita-Baylis-Hillman Carbonates with Nitroalkanes", *Org. Lett.* **2012**, *14,* **DOI:** 10.1021/ol301962e.

2. Chen, G. -Y.**;** Zhong, F.; Lu, Y. “Highly Enantioselective and Regioselective Substitution of Morita-Baylis-Hillman Carbonates with Nitroalkanes", *Org. Lett.* **2011**, *13*, 6070.

3. Zhong, F.**;** Chen, G. -Y.; Lu, Y. "Asymmetric Construction of Functionalized Bicylic Imides via [3+2] Annulation of MBH carbonates Catalyzed by Dipeptide-Based Phosphines", *Org. Lett.* **2012**, *14*, 3764.

4. Zhong, F.**;** Chen, G. -Y.; Lu, Y. " Enatioselective Morita-Baylis-Hillman Reaction of Isatins with Acrylates: Facile Creation of 3-Hydroxy-2-oxinoles", *Org. Lett.* **2011**, *13*, 82.

5. Zhong, F.; Luo, J.; Chen, G. -Y.; Dou, X.; Lu, Y. "Highly Enantioselective Regiodivergent Allylic Alkylations of MBH Carbonates with Phthalides" *J. Am. Chem Soc.* **2012**, *134*, 10222.

Chapter 1 Introduction

1.1 Asymmetric Organocatalysis

1.1.1 The Significance of Chiral Molecules

Chirality, also called handedness which means an object is not superimposable to its mirror image, widely exists in nature. Molecular chirality refers to chiral molecules, which are important in synthetic chemistry. Enantiomers are a pair of mirror image molecules that are non-superimposable. At the molecular level, nature builds our world with only one enantiomer such as amino acid, sugar, nucleic acid and it is the basic way that we obtain chiral molecules. A pair of enantiomers shares identical chemical and physical properties under the conditions of non-chiral environment. Two enantiomers cannot be separated with normal separation method. When the two enantiomers exist the same quantity, they are called racemate. Two enantiomers only exhibit different properties in chiral environments e.g. human body. For example, D-aspargine has a sweet taste, whereas natural L-aspargine is bitter. The importance of selectively obtaining one enantiomer may be well elaborated by thalidomide tragedy which occurred in Europe during the 1950s. Racemic thalidomide was a powerful sedative and anti-nausea drug which was typically used to cure morning sickness. Unfortunately, it was found that the drug caused birth defects. Further studied showed that only (S)-enantiomer was highly effective teratogen, while (R)-enantiomer was effective in curing morning sickness without teratogen (**Figure 1.1**).[1] It is important to prepare molecules in an enantiomerically pure form, especially in the pharmaceutical industry. The significance of chirality in drugs design and development has been well recognized and applied. In 1992, guidelines and policies concerning the development

of chiral compounds were issued by the Food and Drug Administration in the United States.[2] Absolute stereochemistry for compounds with chiral centers was required in drug development process.

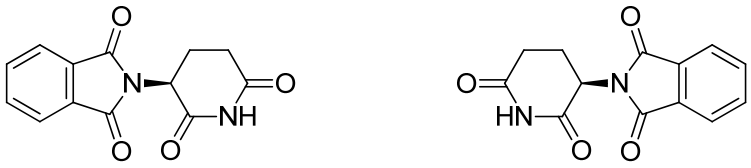


Figure 1.1 Enantiomers of thalidomide

1.1.2 Asymmetric Catalysis

There are several methods to obtain a chiral molecule. The most important and effective approach is asymmetric catalysis which utilizes a catalytic amount of chiral molecules or complexes to generate stoichiometric chiral products. Asymmetric catalysis can be classified as enzyme catalysis, transition metal based catalysis and organocatalysis.[3] Enzymes are Nature's catalysts and can catalyze numerous biotransformations. Although excellent enantioselectivities are often attainable, enzymatic reactions are subjected to the availability of enzymes. The narrow scope of reactions and limitations of specific stereoisomers are also drawbacks of enzymatic catalysis. In addition, the reaction models of enzyme catalyzed transformation are often less reliable and predictable.[4]

As a complementary method, metal-based catalysis has been widely used in organic synthesis in the past few decades. In 2001, the Nobel Prize was awarded to Sharpless, Noyori and Knowles for their contributions to the asymmetric catalysis mediated by metal complexes. The mechanistic insight of certain well-established catalytic systems has been well investigated.[5] Metal catalyzed asymmetric reactions usually rely on the design of chiral ligands, which affect the stereoselectivity of the

reaction. Despite the fact that metal catalysis is the most advanced and useful method in asymmetric synthesis, approaches involving metals do suffer some key disadvantages, such as high cost and toxicity of the metals, sensitivity to air and moisture.

In the past decade, organocatalysis has emerged as an important method in synthetic chemistry, complementing enzyme and metal catalysis. Organocatalysis employs small organic molecules to function as a catalyst in organic reaction. Organocatalysts are often inexpensive, readily available, non-toxic, stable in air and moisture, and easily manipulated. Organocatalytic method holds great potential for industrial application due to absence of toxic metal.[6] Although reactions catalyzed by small organic molecules was first reported at the beginning of last century,[7] this field has been overlooked for a long time. From 1968 to 1997, only a few papers reported the asymmetric reaction using organic molecular as catalyst. The Hajos-Parrish-Eder-Sauer-Wiechert reaction is one of the most important reports during that period, which is an intramolecular aldol reaction catalyzed by proline.[8] However, it was viewed as a unique chemical transformation and the general reaction mode was not recognized. In the late 1990s, several research groups did excellent work on asymmetric reaction catalyzed by small organic molecules.[9] However, the concept of "organocatalysis" was established until 2000. Two publications appeared almost simultaneously in the literature, making the rebirth of modern organocatalysis; List, Barbas and Lerner disclosed enamine catalysis with proline as a catalyst,[10] and MacMillan and co-workers described their first example on iminium catalysis.[11] Between 1998 and 2008, at least 1,500 manuscripts describing the use of organocatalysts in more than 130 discrete reaction types were published.[12] Organocatalysis has become a hot research field, and has drawn attention from

numerous scientists, and some well-known and versatile organocatalysts are illustrated in Figure 1.2

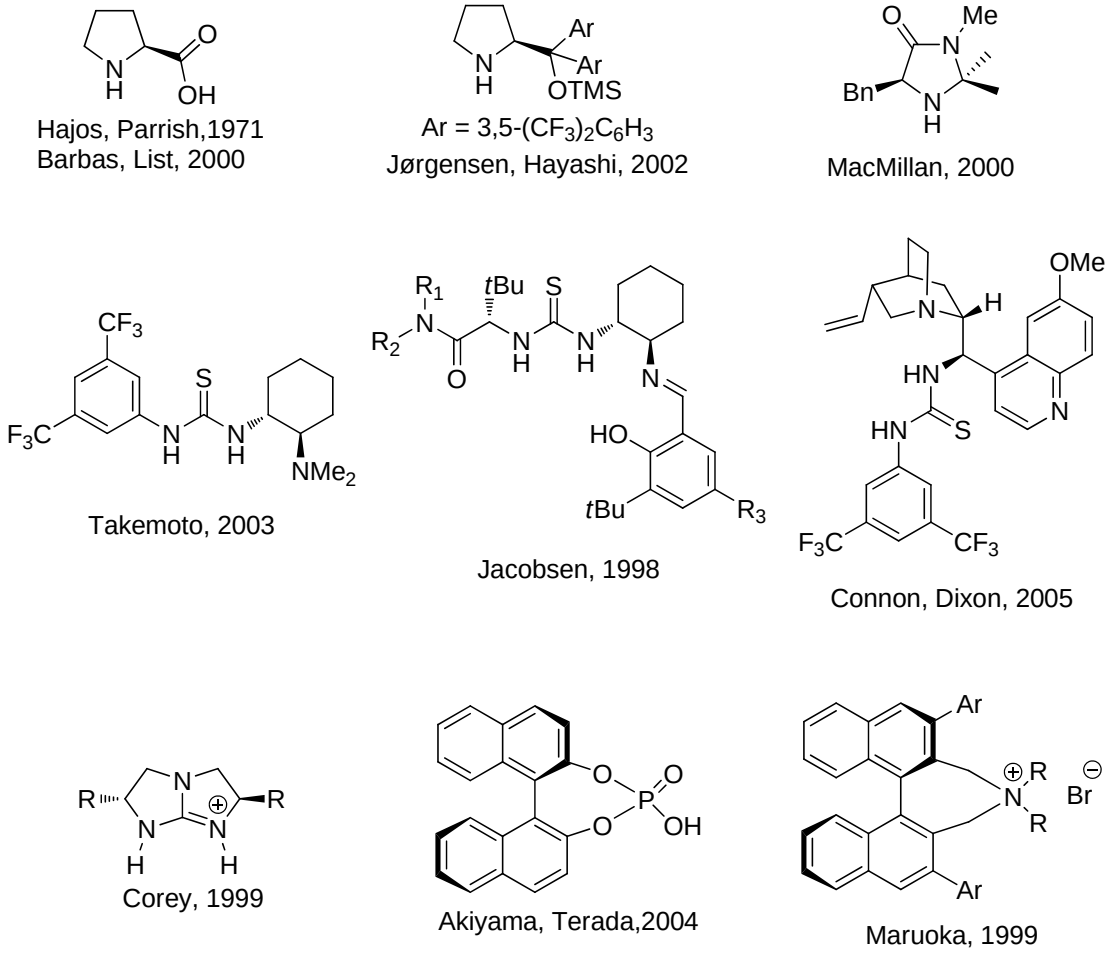


Figure 1.2 Typical and effective chiral organocatalysts

1.1.3 The Activation Modes of Asymmetric Organocatalysis

A generic reaction mode provides a reactive species that can participate in many different reactions, which benefits the design of new reactions and leads to the development of versatile catalysts for a wide range of reactions. According to the bonding interactions between catalyst and substrate, organocatalysis can be classified as covalent bond catalysis and non-covalent bond catalysis.[6] For the covalent bond catalysis, the catalytic process might involve covalent bond formation between catalyst and substrate, which include enamine catalysis, iminium catalysis, SOMO

catalysis and some nucleophilic catalysis such as carbene, DMAP and phosphine.[13]. For example, the enamine catalysis involves a covalent bond formation between the catalyst and the substrate to generate an active species. In the non-covalent bond catalysis, the weak interactions such as hydrogen-bonds and counter ion pair often play an important role in the organic reaction.[14] Both reactivity and selectivity of the reaction could be influenced by these weak interactions. A few common activation modes in Organocatalysis are shown in **Figure 1.3**.

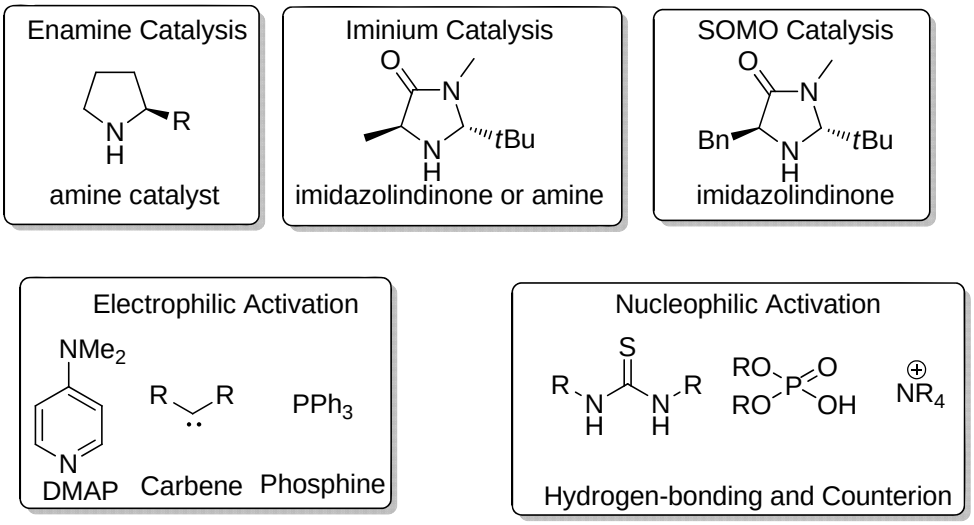


Figure 1.3 Generic activation modes for organocatalysis

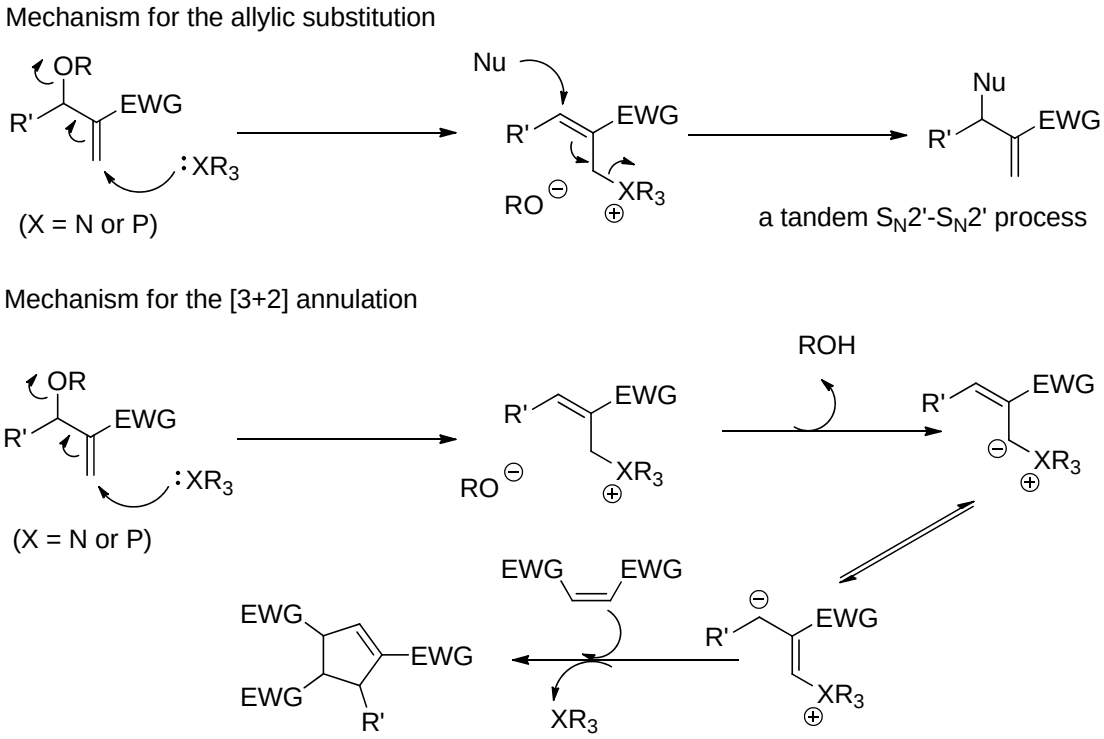
1.2 Organocatalytic Asymmetric Reactions of MBH Adducts

The Morita-Baylis-Hillman (MBH) carbonates are well studied in asymmetric synthesis because they are easily activated by nucleophilic catalysts such as triphenylphosphine, DABCO.

The origin of Morita–Baylis–Hillman (MBH) reaction can date back to 1968.[15] The MBH reaction is an atom-economic carbon-carbon bond forming reaction between the α-position of the activated alkenes (alkynes) and carbon electrophiles under a catalytic system, providing diverse classes of densely functionalized

molecules, which are generally referred to as the MBH adducts. Due to the high functionality in the molecules, the MBH adducts have been widely used in many types of organic transformations.[16] Early work in this field mainly focused on the transformations using stoichiometric reagents or non-chiral version reactions. Among MBH adducts, MBH acetates and carbonates have received much attention for their good reactivity. Recently organocatalytic asymmetric reactions of MBH acetates and carbonates have been well explored because of the development of asymmetric organocatalysis. The MBH adducts could be activated by a nucleophilic catalyst such as a tertiary amine or a phosphine, and function as an electrophile in the reaction.

The general reaction mechanism[17] of allylic substitution reaction of MBH adduct is commonly accepted as a tandem S_N2'-S_N2' process. The nucleophilic catalyst first attacks the MBH adduct in a S_N2' manner, with the concurrent departure of OR group. A second S_N2' reaction would occur to afford the allylic substitution product and regenerate catalyst when nucleophile is added. In the presence of an extra base or the *in situ* generated base OR, when an electron withdrawing alkene is added, it would deprotonate the allylic proton of the intermediate to generate the [3+2] annulation product (**Scheme 1.1**).



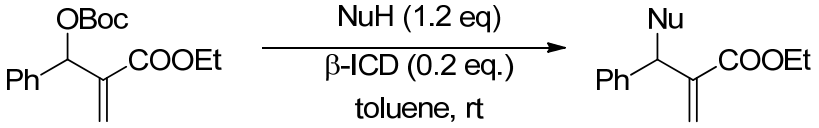
Scheme 1.1 Typical reaction mechanism of two types of reactions of MBH adducts

1.2.1 Organocatalytic Asymmetric Substitution Reactions of MBH Adducts

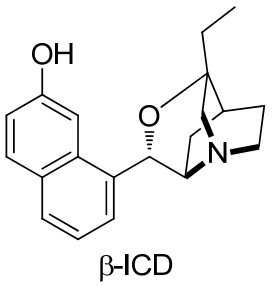
The organocatalystic asymmetric allylic substitution reaction has emerged as a powerful method in organic synthesis.[18] Different types of nucleophiles have been examined for metal catalyzed asymmetric allylic substitution reactions, and the substrates often have a leaving group at the allylic position or an *in-situ* generated a leaving group at the allylic position. The Morita–Baylis–Hillman (MBH) acetates and carbonates contain a good leaving group at the allylic position and can be applied in the allylic substitution reaction. Trost and co-workers have successfully used MBH acetate in the palladium-catalyzed asymmetric allylic substitution reactions.[19]

For the development of organocatalytic asymmetric allylic substitution via a S_N2'-S_N2' process, it is crucial to carefully select the catalyst and the leaving group.

The nucleophilicity of catalyst should be stronger than the nucleophile in the first step, but cannot be stronger than the nucleophile in the second step. In 2004, Lu and co-workers reported the asymmetric allylic substitution reaction of MBH carbonate catalyzed by cinchona alkaloids and their derivatives. A pronucleophile was used to avoid the competition between two nucleophiles. The *tert*-butyl carbonyloxy group which was chosen as a leaving group can produce a *tert*-butoxide ion for the *in situ* deprotonation of the nucleophiles. The different nucleophiles were examined in their study. Although the enantioselectivity was not ideal and the small amount of tri-substituted alkene which was formed, the MBH carbonates have drawn much attention in the tertiary amine-catalyzed asymmetric allylic substitution reaction after this pioneer work (**Scheme 1.2**).[20]



NuH	yield (%)	ee (%)
TsNH2	84	66
Phthalimide	96	68
Phenol	85	61
Dimethyl malonate	90	51

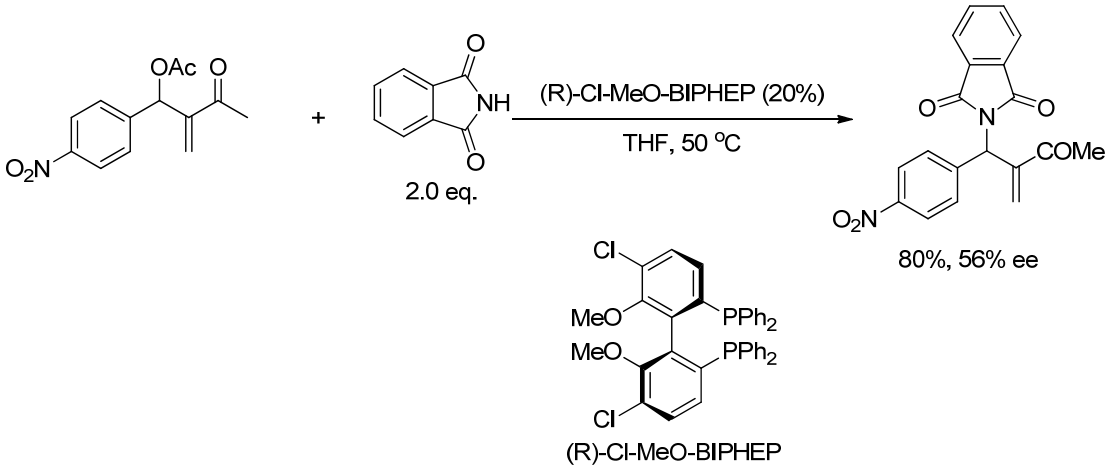


β-ICD

Scheme 1.2 Asymmetric allylic amination reaction of MBH carbonates catalyzed by β-isocupreidine

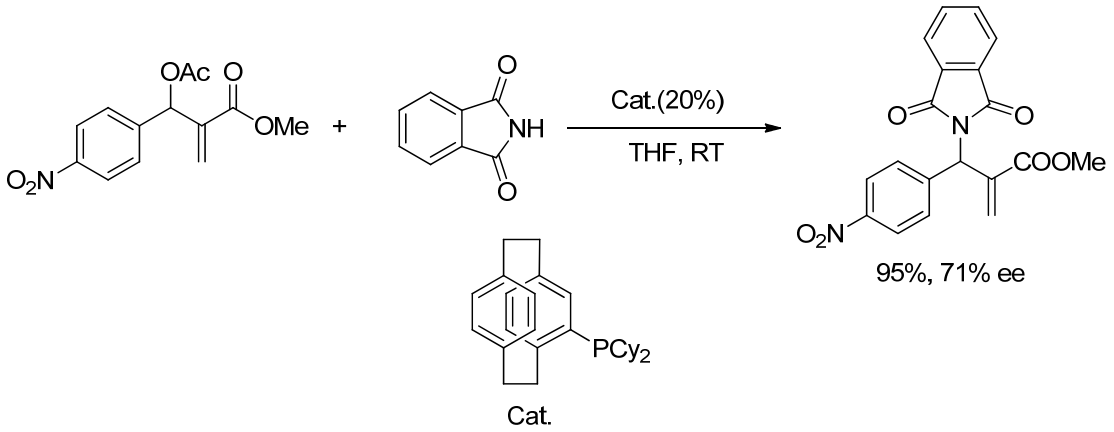
In the same year, the phosphine catalyzed allylic substitution reaction of MBH acetate has been reported by Krische and co-workers.[21] The non-chiral version reaction of MBH acetates with phthalimide was explored under the catalysis of tertiary phosphine with good regioselectivities and yields. A tandem S_N2'-S_N2' mechanism was proposed and supported by the deuterium labeling study. Furthermore, the proposed mechanism involved the destruction and subsequent reconstruction of a

chiral center, suggesting the possibility of realizing a chiral phosphine-catalyzed asymmetric substitution reaction of MBH acetates. Indeed, one asymmetric example catalyzed by chiral phosphine was given in the same study. To the best of our knowledge, this example represented the first example of phosphine catalyzed asymmetric allylic substitution reaction of MBH adduct (**Scheme 1.3**).



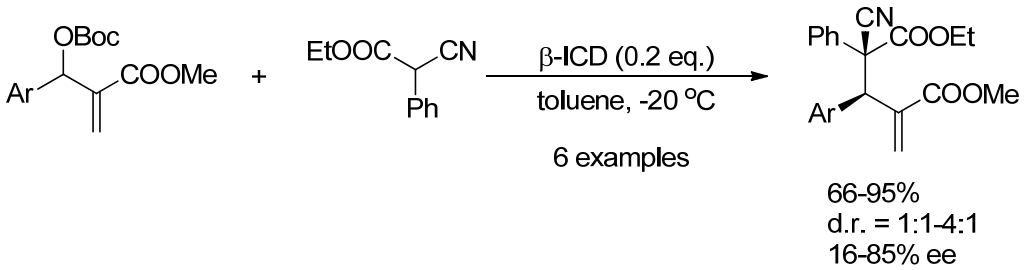
Scheme 1.3 Asymmetric allylic amination reaction of MBH acetates catalyzed by chiral phosphine

In 2007, Hou and co-workers also reported asymmetric allylic amination reaction of MBH acetate catalyzed by planar chiral monophosphine.[22] The planar chiral [2,2] paracyclophane monophosphine was synthesized and applied in the asymmetric allylic substitution reaction of MBH adducts. The allylic amination reaction of MBH acetates with phthalimide gave the products in good yield and up to 71% ee (**Scheme 1.4**). Other types of nucleophile were also tested under the optimized condition. The yield was low using 4-methylbenzenesulfonamide and *para*-methoxylphenol. The asymmetric allylic alkylation reaction using 2-trimethylsilyloxyl furan only provided the product with 36% ee under the same catalytic system. The mono activation of catalyst may lead to the low enantioselectivity. These initial screening results inspired chemists to develop more efficient catalytic system.



Scheme 1.4 Asymmetric allylic amination reaction of MBH acetates catalyzed by chiral planar phosphine catalyst

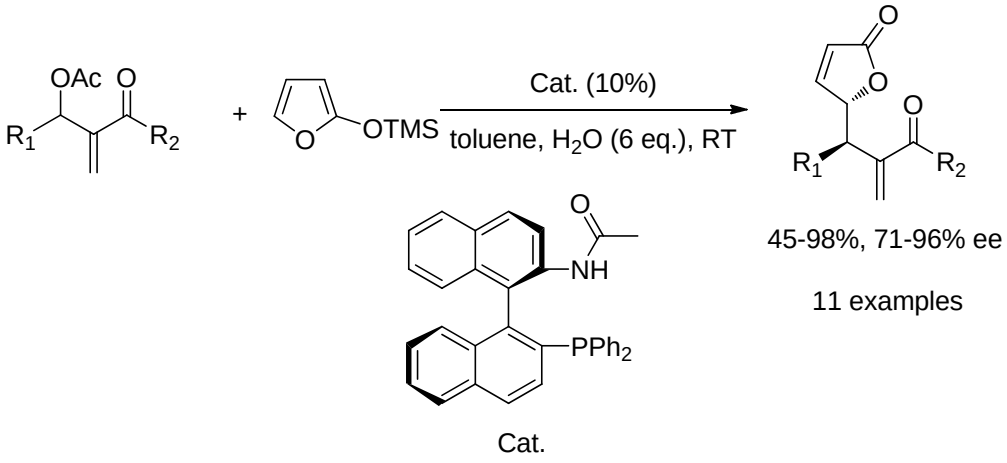
In the same year, Hiemstra's group developed a new asymmetric allylic addition reaction of ethyl α,α-cyanophenylacetate to MBH carbonates catalyzed by cinchona alkaloid derived tertiary amine catalyst. [23] The reaction gave products with adjacent quaternary and tertiary sterecenters. The asymmetric allylic alkylation reaction was catalyzed by β-isocupreidine with up to 4:1 distereoselectivity, but the enantioselectivity was only moderate to good (**Scheme 1.5**). The substrate scope was quite narrow, and the MBH carbonate with electron-withdrawing group gave poor enantioselectivity.



Scheme 1.5 Asymmetric allylic alkylation reaction of MBH carbonates with cyanoesters

The highly enantioselective allylic alkylation reaction of MBH acetates with 2-trimethylsilyloxyl furan was reported by Shi and co-workers in 2008.[24] This is the

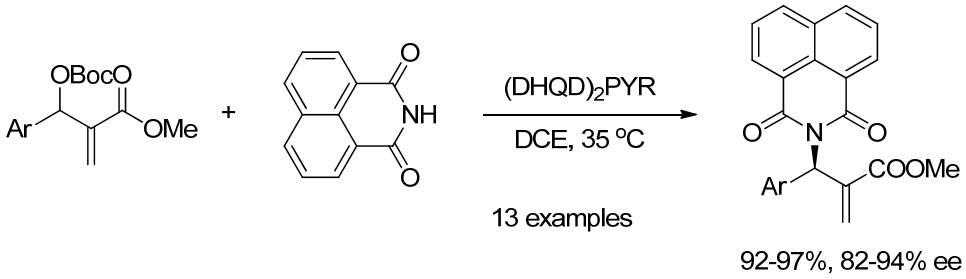
first successful example of phosphine-catalyzed asymmetric allylic alkylation reaction of MBH adducts. The phosphine-amide catalysts were designed and applied in the asymmetric allylic alkylation reaction of MBH adducts. The MBH acetates derived from methyl vinyl ketone were used in the reaction and the allylic alkylation products were obtained with high diastereoselectivity and enantioselectivity (**Scheme 1.6**). The reaction was found to be useful for the production of γ-butenolides scaffolds which widely exist in natural product and pharmaceutical compounds.[25] A mechanism was proposed to explain the good reacitivity and selectivity. The catalyst contains a phosphine which serves to activate electriphiles and an amide bond which functions as a hydrogen bond donor. The hydrogen bonding between catalyst and MBH acetate played a key role in the enantioselectivity. The addition of water will increase the enantioselectivity dramatically without impairing the reactivity. The water may assist the Grob-type fragmentation through hydrogen bonding and the formation of a pentacoordinated silicon intermediate.[26]



Scheme 1.6 Asymmetric allylic alkylation reaction of MBH acetates catalyzed by chiral phosphine catalyst

Besides phosphine catalysts, tertiary amine catalysts derived from cinchona alkaloid have been well applied in the asymmetric allylic substitution reaction

(**Figure 1.4**). Chen and co-workers have made key contributions to this field. In 2009, they reported the allylic aminantion reaction of MBH carbonates with 1,8-naphthalimide catalyzed by cinchona alkaloid derived tertiary amine catalysts.[27] After careful screening of the catalysts, $(DHQD)_2PYR$ was found to be the best catalyst. Under the optimized conditions, a wide range of substrates could be used and good yield and satisfactory enantioselectivity were attainable (**Scheme 1.7**).



Scheme 1.7 Asymmetric allylic amination reaction of MBH carbonates with 1,8-naphthalimide

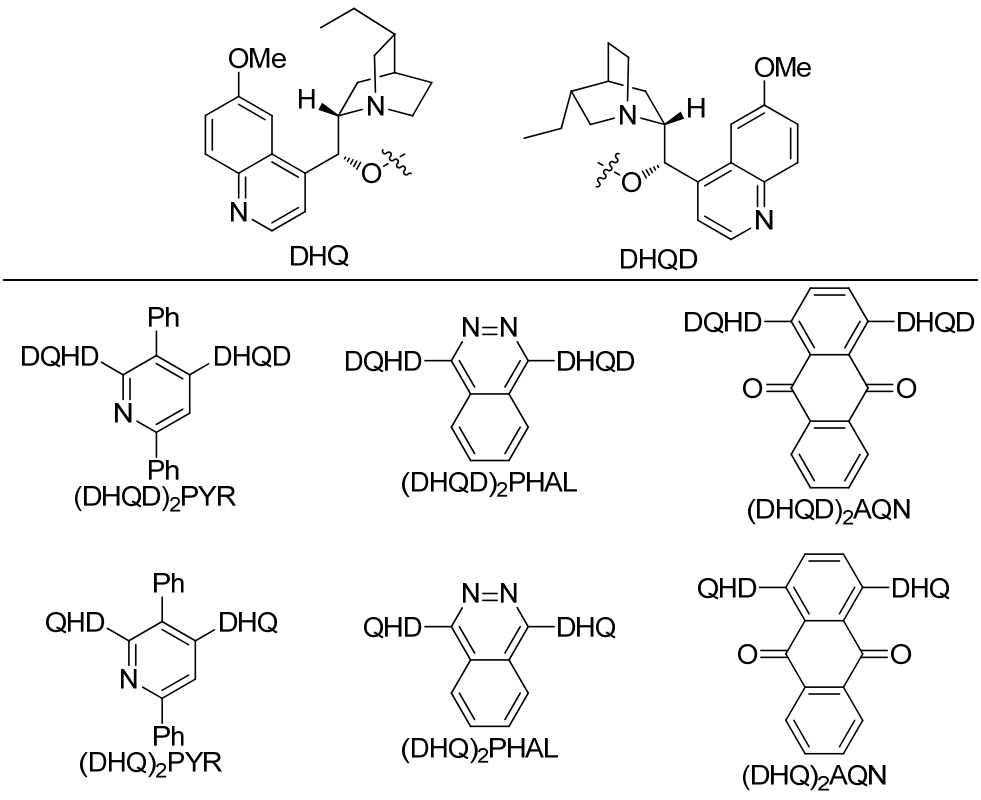
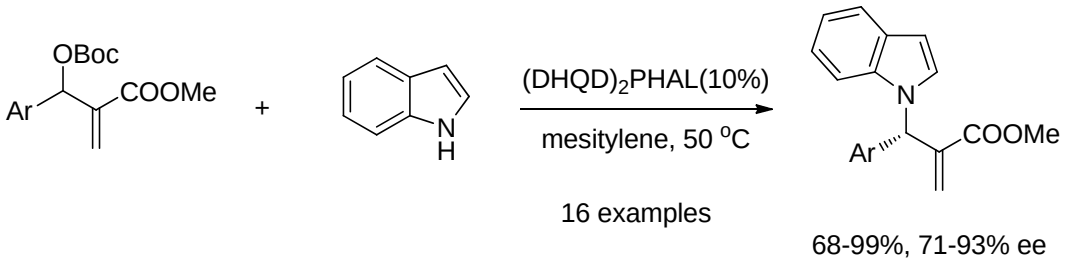


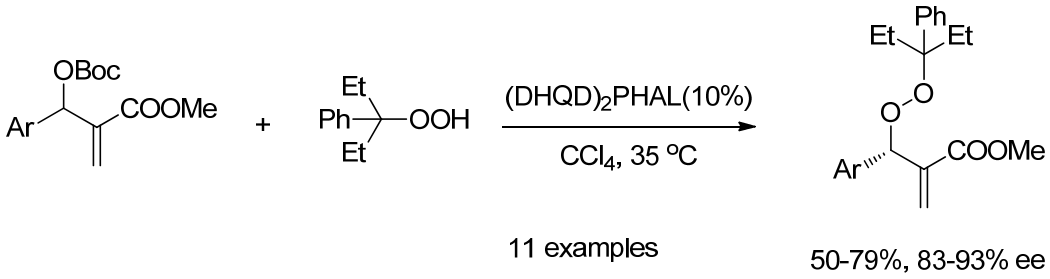
Figure 1.4 Tertiary amine catalyst derived from cinchona alkaloid

Further work on MBH carbonate was reported by Chen and co-workers. The different nucleophile was utilized in the asymmetric allylic substitution reaction of MBH carbonates. Indole motif exists widely in natural products. In contrast to the nucleophilic alkylation reaction at the C3 position of indole, the N-alkylation reactions of indole are very limited.[28] Chen et al. developed chemoselective asymmetric N-allyic alkylation of indole with MBH carbonates in 2009.[29] The NH group of indole was expected be depotonated by *tert*-butyloxide which was generated *in-situ* from MBH carbonates. The N-allylic alkylation products were formed with excellent regioselectivities and enantioselectivities in the presence of $(DHQD)_2PHAL$ at 50 ℃(**Scheme 1.8**).



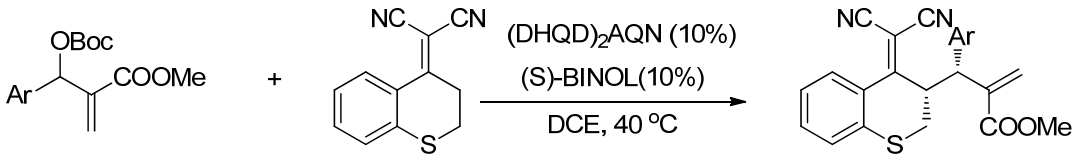
Scheme 1.8 Asymmetric N-allylic alkylation of indole with MBH carbonates

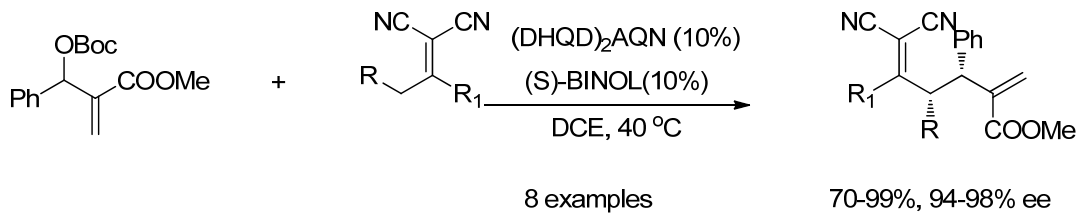
The carbon-oxygen bond formation of asymmetric allylic substitution reaction was first studied by Chen and co-workers.[30] A specific peroxyl acid was used as nucleophile in the allylic substitution reaction of MBH adducts (**Scheme 1.9**). It was found that the best reaction condition is to employ $(DHQD)_2PHAL$ in CCl_4. The reaction products could be easily transformed to MBH products under reductive conditions, providing an alternative method of asymmetric MBH reaction.



Scheme 1.9 Peroxy-asymmetric allylic alkylation reaction catalyzed by $(DHQD)_2PHAL$

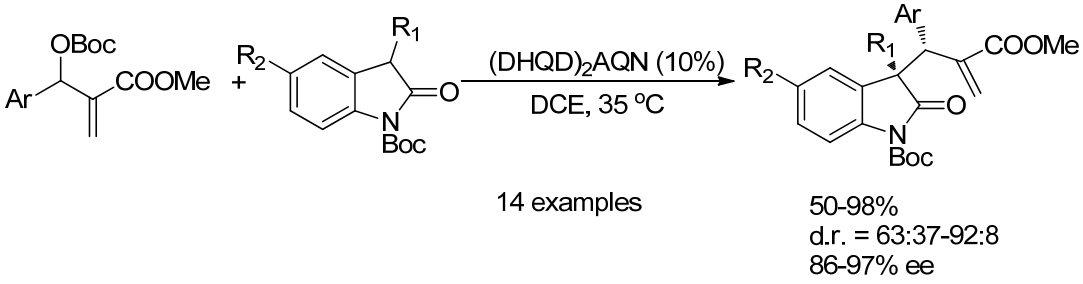
Chen and co-workers also reported the reaction of MBH carbonates with α,α-dicyanoalkene catalyzed by tertiary amine derived from cinchona alkaloid. The α,α-dicyanoalkene as activated ketone has been widely used in the organocatalytic symmetric reaction.[31] If the *tert*-butyloxide ion generated from MBH carbonates deprotonated the α,α-dicyanoalkene, the successive allylic-allylic alkylation would occur. The allylic-allylic alkylation reaction of MBH carbonate and α,α-dicyanoalkene was successfully catalyzed by $(DHQD)_2AQN$ with high enantioselectivity.[32] The addition of catalytic amount of (S)-BINOL can increase the yield dramatically, which indicate that the (S)-BINOL functioned as brønsted acid was a suitable co-catalyst. Different substituted MBH carbonates and several α,α-dicyanoalkene were successfully used in the catalytic system (**Scheme 1.10**).





Scheme 1.10 Asymmetric allylic-allylic alkylation of MBH carbonates

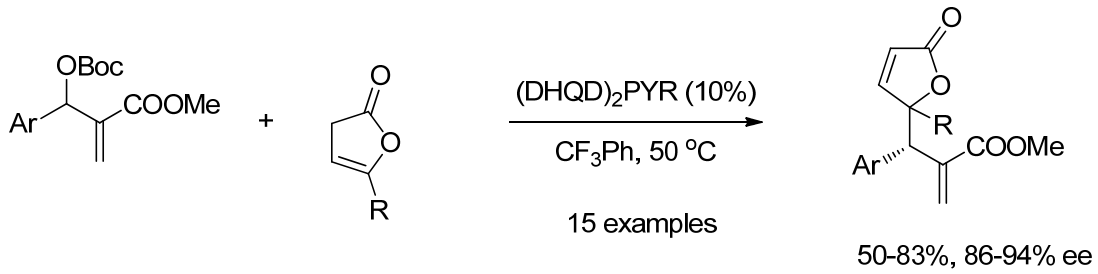
Chen and co-workers later succeeded in utilizing 3-substituted oxindole as potential nucleophiles in the organocatalytic asymmetric allylic substitution reaction of MBH carbonates.[33] Although the good nucleophilicity of 3-substituted oxindole has been widely explored,[34] the asymmetric allylic reaction of oxindole was still limited to metal catalysis. The asymmetric reaction of MBH carbonates with 3-substituted oxindoles proceeded smoothly in the presence of $(DHQD)_2AQN$. The reaction afforded the allylic alkylation products in good yields, moderate diastereoselectivities and excellent enantioselectivities (**Scheme 1.11**). Different substituted oxindoles and MBH carbonates derived from aromatic aldehydes were found to be suitable substrates.



Scheme 1.11 Asymmetric allylic alkylation of MBH carbonates with oxindoles

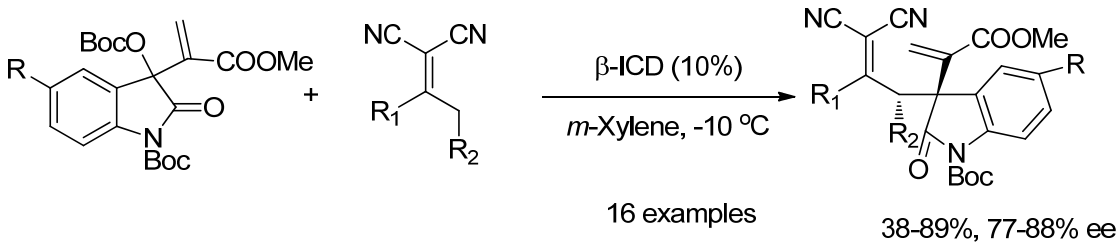
In 2010, the Chen group explored the asymmetric allylic alkylation reaction of MBH carbonate with butenolide catalyzed by cinchona alkaloid derived tertiary amine.[35] The possible difficulty of this reaction would be the steric hindrance which caused by the generation of the product with adjacent quaternary and tertiary stereocenters. After the deprotonation of γ-substituted butenolide by *tert*-butyloxide ion, the subsequent vinylogous addition reaction would occur to give the desired α-addition and γ-addition product. However, the results showed that only γ-selective product was obtained. The yield of the product was moderate to good. The

chemoselectivity, diastereoselectivity and enantioselectivity were excellent (**Scheme 1.12**).



Scheme 1.12 Asymmetric allylic alkylation of MBH carbonates with butenolides

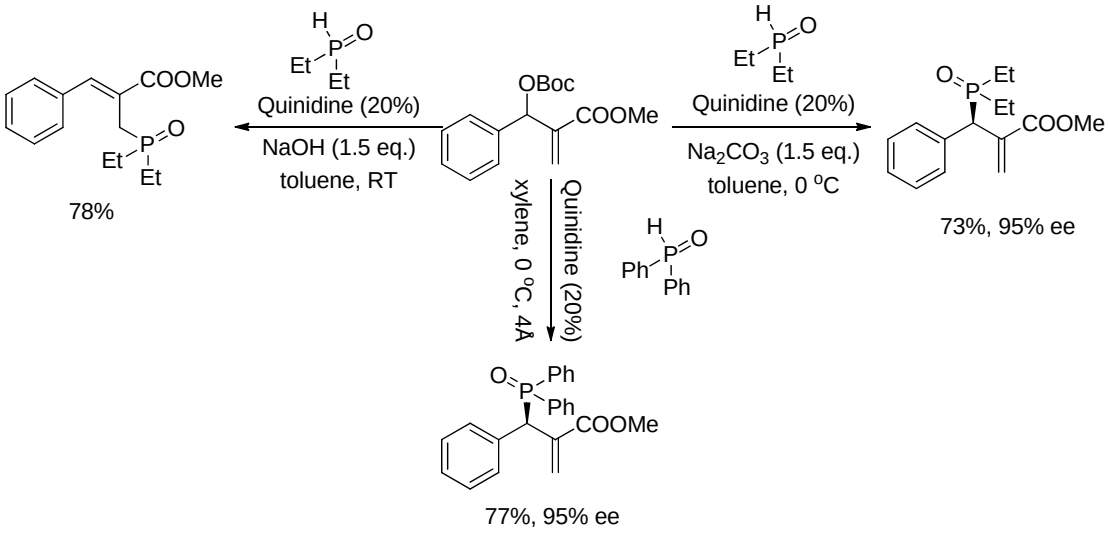
In the same year, the same group applied α,α-dicyanoalkene in the asymmetric allylic substitution reaction of isatin-derived MBH carbonates.[36] A lot of asymmetric reaction of 3-substituted oxindole has been studied.[37] However, few examples used the electrophilic oxindole to construct chiral 3,3'-disubstituted oxindole molecule.[38] The MBH carbonate of isatin can provide an electrophilic approach to achieve chiral 3,3'-disubstituted oxindole. The reaction of MBH carbonate of isatin with α,α-dicyanoalkene proceeded smoothly in the presence of β-isocupreidine and good yields and the enantioselectivities were attainable (**Scheme 1.13**). Different susbstituted MBH carbonates of isatin and α,α-dicyanoalkene were suitable substrates and the product could be transformed to a spirocyclic oxindole.



Scheme 1.13 Asymmetric allylic alkylation of MBH carbonates of isatin

The carbon-phosphorus bond forming reaction of MBH carbonates with phosphine oxide was disclosed by Wang and co-workers in the same year.[39] The nucleophile of phosphorus which was successfully used in asymmetric reaction was

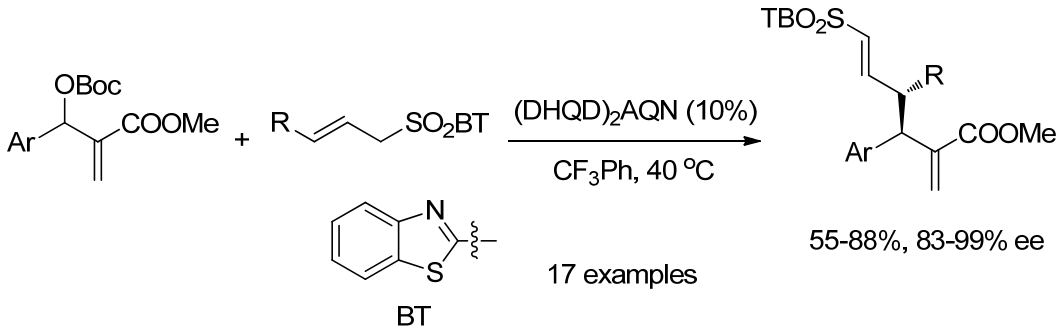
usually phosphite [$(RO)_2P(O)H$]or secondary phosphine (R_2PH).[40] Few examples have been reported using secondary phosphine oxide [$R_2P(O)H$] as nucleophile.[41] The diphenylphosphine oxide was successfully used as nucleophile this study. Quinindine served as the best catalyst, and good yields and good enantioselectivities were obtained (**Scheme 1.14**). The reactivity and enantioselectivity could be improved by the addition of 4Å molecular sieves. The less reactive dialkyl phosphine oxide also could be utilized in the reaction with MBH carbonate in the presence of additional base. These methods described by Wang's group only tolerated the MBH carbonates derived from aromatic aldehydes and provided different valuable allylic phosphine oxides.



Scheme 1.14 Asymmetric allylic substitution reaction of MBH carbonates with phosphine oxides

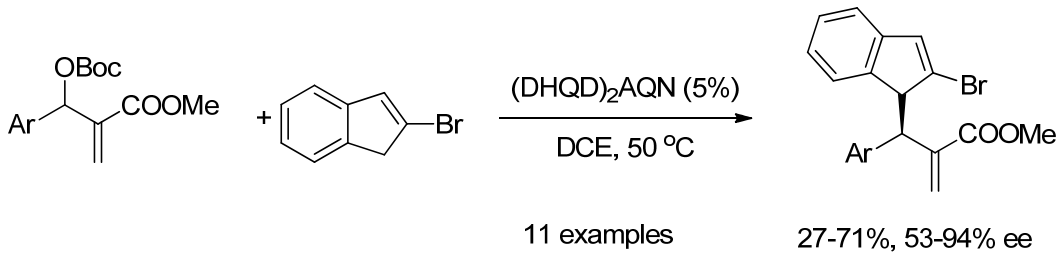
In 2011, more nucleophiles have been utilized in the organocatalytic asymmetric allylic substitution reactions. Chen's group developed a direct regioselective asymmetric vinylogous alkylation of MBH carbonates with allylic sulfones,[42] a class of compounds of great biological importance.[43] The reaction of MBH carbonates and allylic sulfones catalyzed by $(DHQD)_2AQN$ gave highly γ-selective products with

excellent enantioselectivities. When other analogous cinchona alkaloid like $(DHQD)_2PYR$ was used as catalyst, the α-substitution product was observed with moderate yields, diastereoselectivities and enantioselectivities (**Scheme 1.15**). The product could be easily transformed to simple allylic-substituted compounds by removal of the sulfonyl group.



Scheme 1.15 Asymmetric vinylogous alkylation of allylic sulfones with MBH carbonates

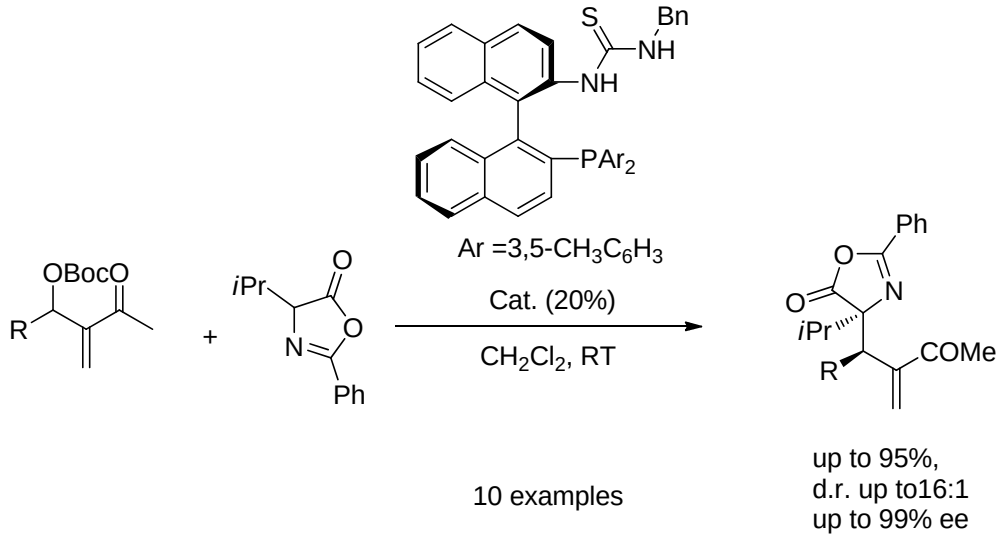
The Chen group also introduced indene as a nucleophile in the asymmetric allylic alkylation of MBH carbonates.[44] Indene motif has been found widely in the biological active compounds.[45] The reaction of indene with MBH carbonate catalyzed by $(DHQD)_2AQN$ was performed in fair to good yields, and moderate to good enantioselectivities (**Scheme 1.16**).



Scheme 1.16 Asymmetric allylic alkylation of MBH carbonates with indene

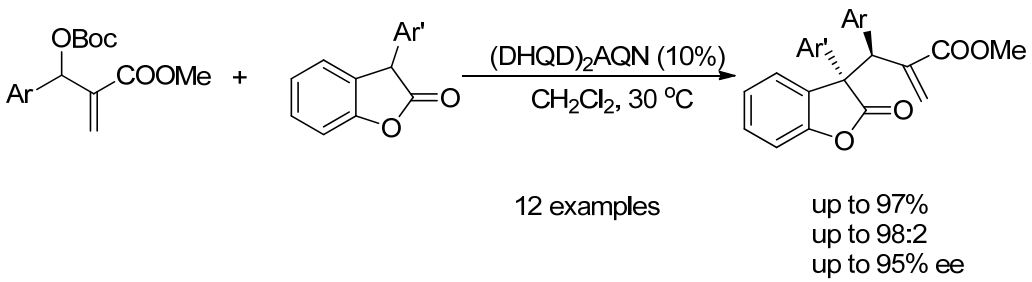
Shi and co-workers developed a phosphine-catalyzed asymmetric allylic substitution reaction of MBH adducts.[46] In their study, the asymmetric allylic

alkylation reaction of MBH carbonates with oxazolones was catalyzed by phosphine-thiourea catalysts. The reaction exhibited good to excellent yields, moderate to good diastereoselectivties and excellent enantioselectivities (**Scheme 1.17**). It was proposed that the thiourea plays a key role for inducing stereoselectivity by forming hydrogen bonding interactions with the substrates. The product could be transformed to allylic substituted quaternary α-amino acid.[47]



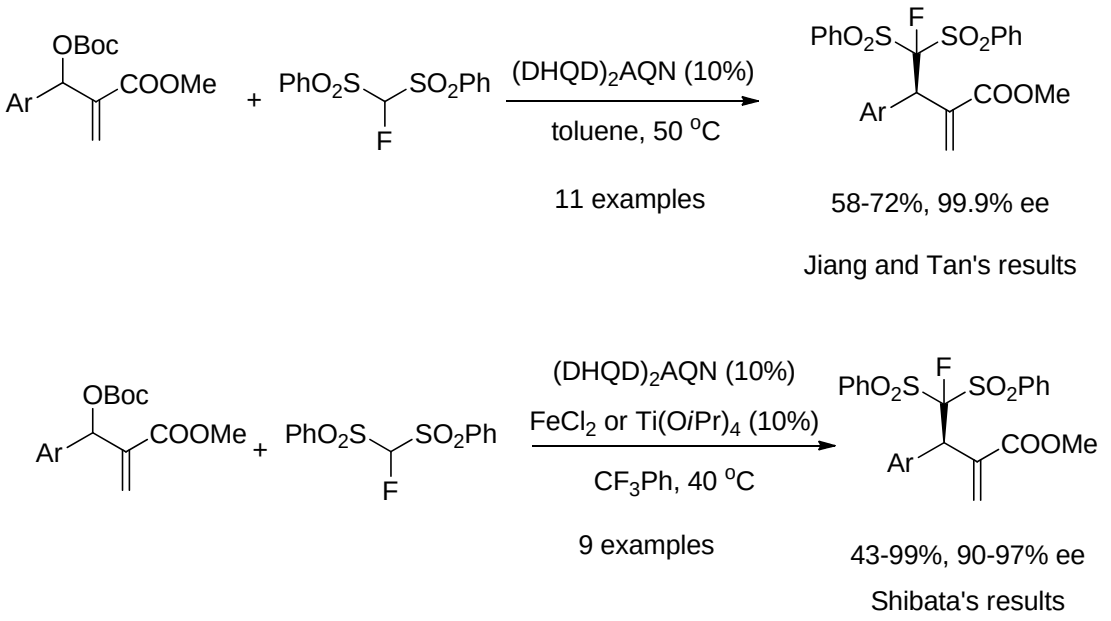
Scheme 1.17 Asymmetric allylic alkylation of MBH carbonates with oxazolone

Cheng and co-workers described the utilization of 3-substituted benzofuranones in the asymmetric allylic alkylation reaction of MBH carbonates.[48] Such reactions are useful since a number of natural products and biologically active compounds contain 3-substituted benzofuranone structural motif.[49] Good yields, good diastereoselectivitiea and excellent enantioselectivities was obtained by using $(DHQD)_2AQN$ as the catalyst (**Scheme 1.18**).



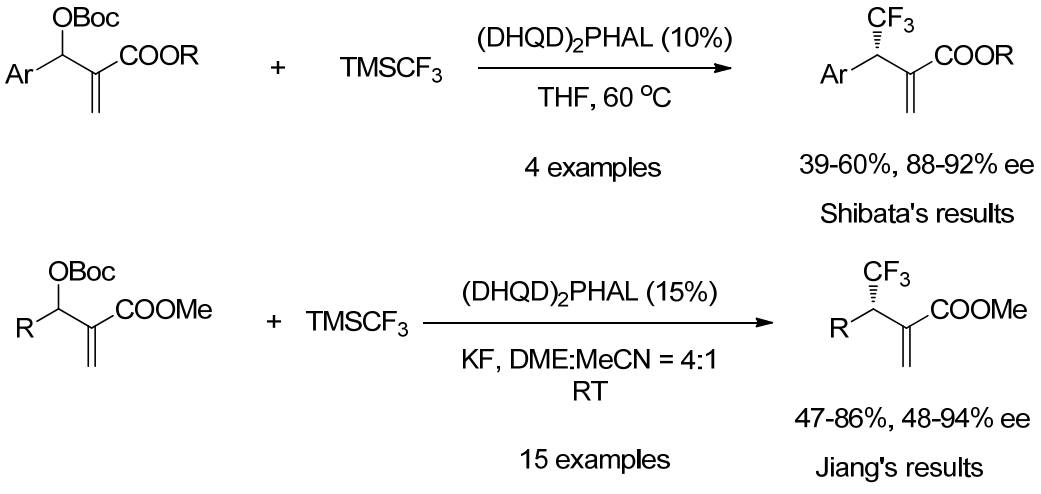
Scheme 1.18 Asymmetric allylic alkylation of MBH carbonates with 3-substituted benzofuran-2(*3H*)-ones

Organoflourine compounds are important in medical chemistry.[50] The fluorine containing nucleophiles have been applied in asymmetric allylic substitution of MBH carbonates. The group of Shibata and Jiang have indenpendently studied the reactions of MBH carbonates with fluorobis(phenylsulfonyl)methane (FBMS).[51] Shibata and co-workers investigated the reaction of the MBH carbonate and FBMS,[52] and $(DHQD)_2AQN$ was found to be the best catalyst. Although the enantioselectivity was excellent using simple organocatalyst, the yield was only moderate to good. Further study showed that a Lewis acid such as ferric chloride or titanium isopropyloxide as a cooperative catalyst could benefit both yield and enantioselectivity (**Scheme 1.19**). The allylic alkylation product could be easily transformed to pure monofluormethylate compounds by removing the sulfonyl group. Jiang et al. independently investigated the reaction of MBH carbonates with FBMS, and $(DHQD)_2AQN$ was the best catalyst. A variety of MBH carbonates derived from aromatic aldehydes were found to be suitable substrates and the synthetic value of the products was also demonstrated.



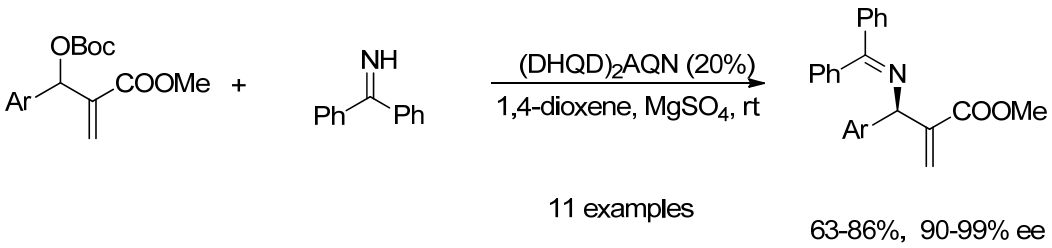
Scheme 1.19 Asymmetric allylic alkylation of MBH carbonates with FBMS

Asymmetric allylic trifluoromethylation of MBH carbonates was developed independently by the Shibata group and the Jiang group.[53] The Ruppert's reagent, (trifluoromethyl)trimethylsilane, is commonly employed for the synthesis of organofluorine compounds.[54] Shibata et al. found that the reaction of MBH acetates with (trifluoromethyl)trimethylsilane in the presence of DABCO yielded fluorine-containing products. The combination of $(DHQD)_2PHAL$ and MBH carbonates led to an asymmetric trifluromethylation (**Scheme 1.20**). Jiang and co-workers also reported the similar finding.



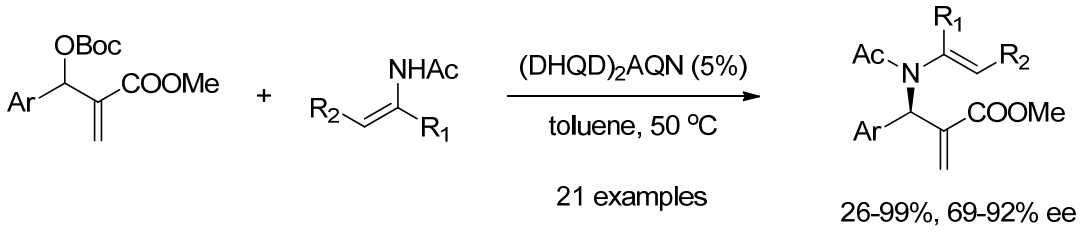
Scheme 1.20 Asymmetric allylic akylation of MBH carbonates with Ruppert's reagent

Cheng and co-workers applied benzophenone imine as masked ammonia in the asymmetric allylic amination reaction of MBH carbonates.[55] The reaction of benzophenone imines with MBH carbonates proceeded smoothly in the presence of $(DHQD)_2AQN$. The amination products were obtained in moderate yields and excellent enantioselectivities (**Scheme 1.21**).



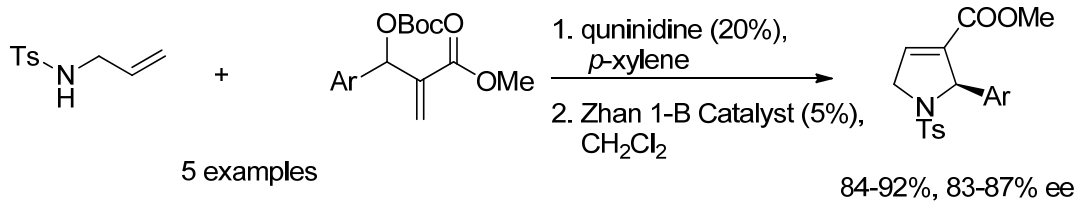
Scheme 1.21 Asymmetric allylic amination of MBH carbonates with masked ammonia

Enamides are interesting sub-structures in a variety of natural products and pharmaceutical molecules,[56] which can function as versatile and stable enamine and the carbon nucleophile.[57] Chen and co-workers discovered a chemoselective N-allylic alkylation of MBH carbonates with enamides.[58] $(DHQD)_2AQN$ catalyzed the reaction of MBH carbonates with enamides effectively, affording the products in good regioselectivities and good enantioselectivities (**Scheme 1.22**). The allylic amination products were converted to dicarbonyl compounds with high selectivity through aza-Cope rearrangement followed by hydrolysis. The α-alkylidene-β-amino carbonyl compounds were also obtained by the treatment of trifluoromethanesulfonic acid without impairing the enantioselectivity.



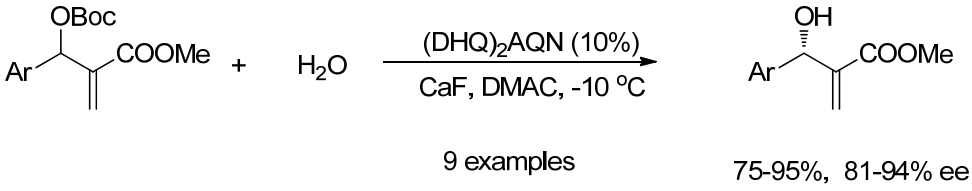
Scheme 1.22 Asymmetric allylic substitution of MBH carbonates with enamides

Wang et al. reported the asymmetric allylic amination reaction of MBH carbonates with an allylamine.[59] The reaction was effectively catalyzed by quinidine and good enantioselectivity was obtained. To explored the utility of the allylic amination products, biologically useful 2,5-dihydropyrroles were synthesized (**Scheme 1.23**).[60]



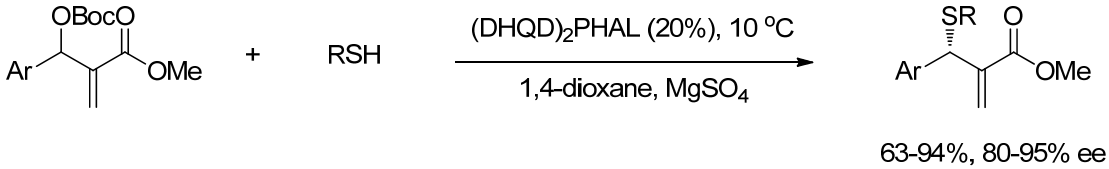
Scheme 1.23 Asymmetric allylic substitution of MBH carbonates with allylamine

Jiang and co-workers explored the asymmetric allylic substitution of MBH carbonates with water,[61] which serves as an alternative of asymmetric MBH reaction. DHQD)$_2$AQN was found to be the best catalyst, and good yields and excellent enantioselectivities were attainable (**Scheme 1.24**). The deuterium labeling experiment supported the mechanism of water as nucleophiles.



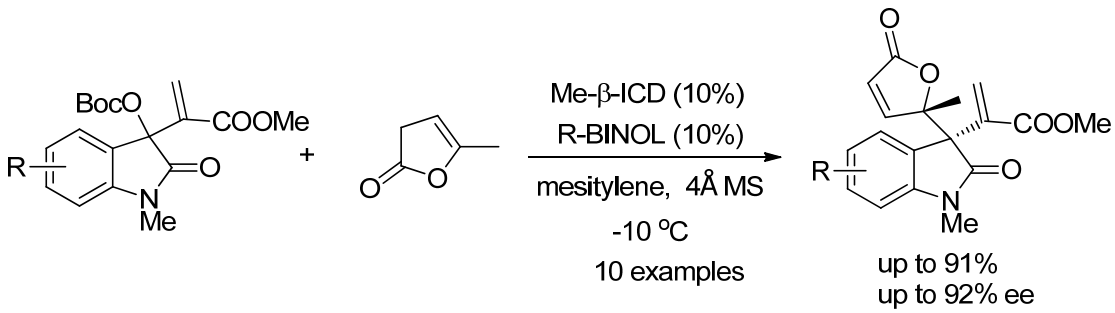
Scheme 1.24 Asymmetric allylic substitution of MBH carbonates with water

The carbon-sulfur bond forming reaction of MBH carbonates has been explored by Cheng and co-workers.[62] Thiols are well-known nucleophile and chiral sulfur-containing compounds are well recognized in organic synthesis.[63] Alkyl thiols were used in the asymmetric allylic substitution reaction of MBH carbonates. $(DHQD)_2PHAL$ turned out to be the most efficient catalyst. The allylic sulphur products were synthesized in good yields and high enantioselectivities (**Scheme 1.25**).



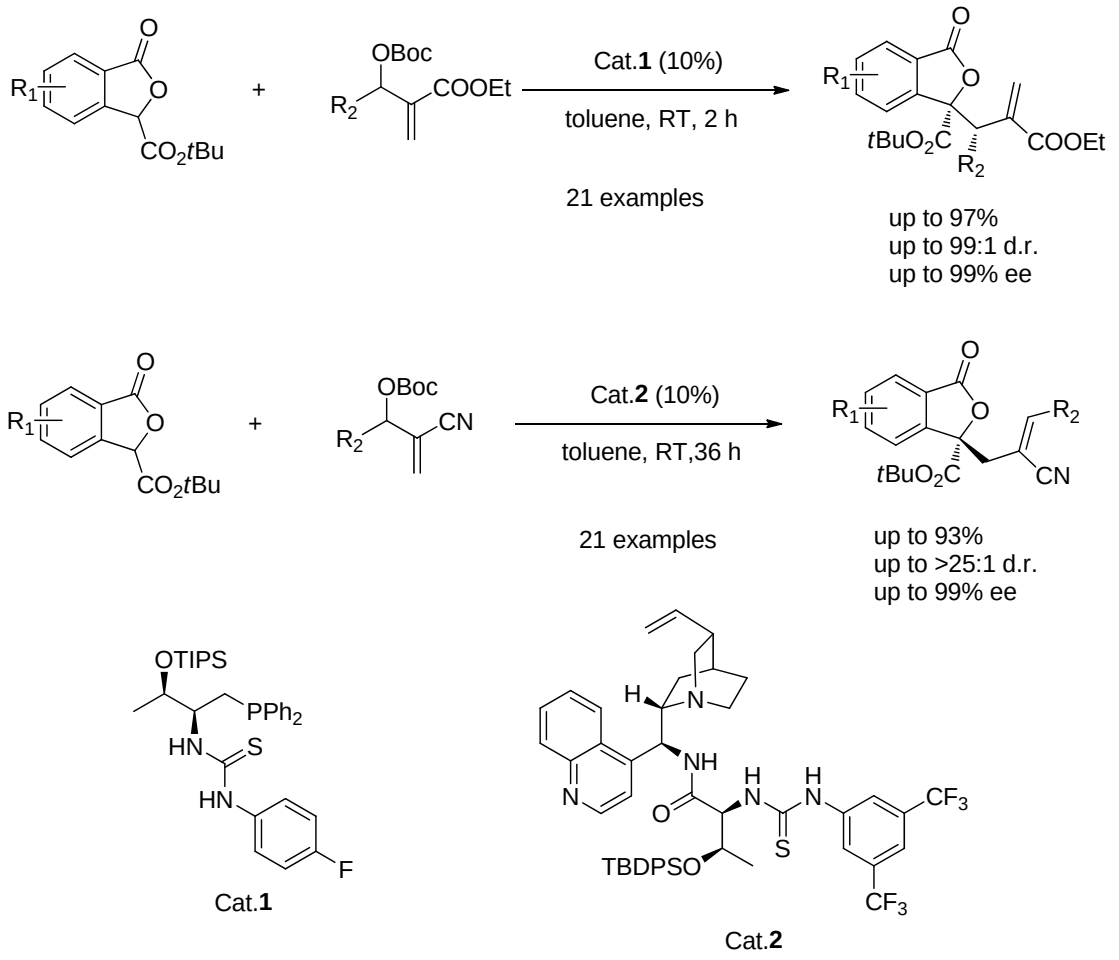
Scheme 1.25 Asymmetric allylic substitution of MBH carbonates with alkyl thiols

In 2012, Chen and co-workers reported the asymmetric allylic alkylation of isatin-derived MBH carbonates with α-Angelica lactone.[64] The readily available O-methylether of β-ICD (Me-β-ICD) was shown to be the best catalyst, and chiral BINOL and 4Å molecular sieves were used as co-catalyst. The products with two quaternary stereocenters were prepared in good yields, excellent diasteroselectivities and excellent enantioselectivities (**Scheme 1.26**). The potential useful spirocyclic structure was synthesized by simple cyclization reaction of the allylic alkylation products.



Scheme 1.26 Asymmetric allylic alkylation of MBH carbonates with α-Angelica lactone

Recently, our group developed the enantioselective regiodivergent allylic alkylations of MBH carbonates with phthalides.[65] Phthalides with electron withdrawing substitutent at 3-position are good nucleophiles which has been proved in several vinylogous reaction.[66] The asymmetric allylic alkylation reaction of MBH carbonates derived from acrylates with 3-carboxylate phthalides in the presence of the phosphine-thiourea catalysderived from amino acid afforded γ-selective products in high yields, high regioselectivities, high diastereoselectivities and enantioselectivities. A wide range of MBH carbonates were suitable in the reaction. The mechanism study indicated that the thiourea functional group plays a key role in both diastereoselectivity and enantioselectivity. Interestingly we found that the solvent could influence the regioselectivity. The β-selective products became major with low enantioselectivity when the reaction performed in strong polar solvent. To develop the diversity of the MBH reaction, we also studied the β-selective product of MBH carbonates with phthalide. The MBH carbonates derived from acrylonitriles afforded the β-selective products in high yields, high Z/E ratios and enantioselectivities in the presence of tertiary amine catalyst (**Scheme 1.27**). The multi-funcational catalyst derived from cinchona alkaloid incorporated with amino acid and thiourea functionality was found to be the best catalyst. Two pathway of the reaction mechanism were proposed for the synthesis of β-selective products. One was the Lewis base initiated addition-elimination sequence which the authors preferred; the other was a tandem S_N2'-S_N2 process. Using MBH acetate as substrate, the yield of β-selective products was decreased without damaging selectivity, which may support the first addition-elimination process.



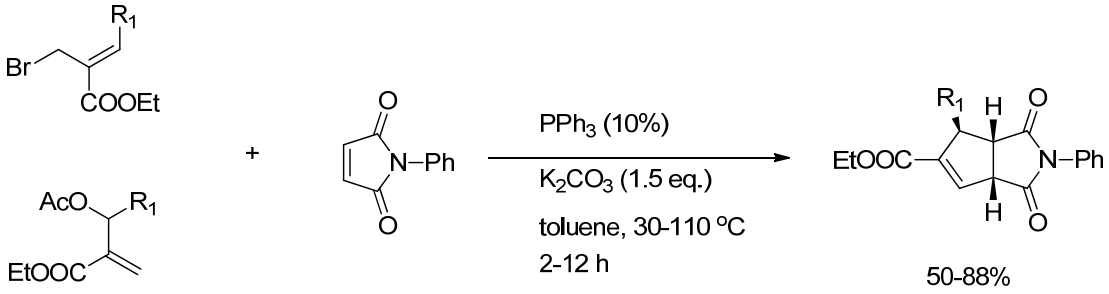
Scheme 1.27 Asymmetric regiodivergent reaction of MBH carbonates and phthalides

1.2.2 Organocatalytic Asymmetric [3+2] Annulation Reactions of MBH Adducts

In addition to their uses in asymmetric allylic substitution reaction, MBH adducts were also examined in the [3+2] annulation reaction. Due to the acidity of the allylic proton of the ammonium or phosphonium intermediate, the MBH carbonate could generate allylic ylides to react with activated alkene to form [3+2] annulation product.[17]

In 2003, the first organocatalytic [3+2] annulation of MBH adducts was reported by Lu and co-workers.[67] The reaction of MBH adducts with electron-deficient alkenes, such as N-phenylmaleimide, was catalyzed by triphenylphosphine in the presence of a

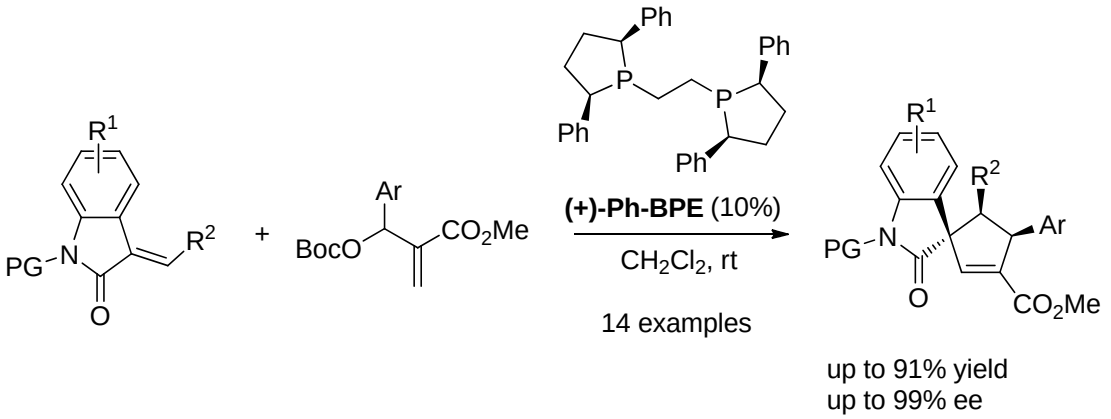
stoichiometric amount of additional base (**Scheme 1.28**). Further study showed that the reaction could also take place without the addition of extra base if MBH carbonates were used. It is reasoned that the *in situ* generated tert-butyloxide anion functions as a suitable base to facilitate the formation of reactive phosphonium ylide.[68]



Scheme 1.28 The first [3+2] annulation reaction of MBH adducts

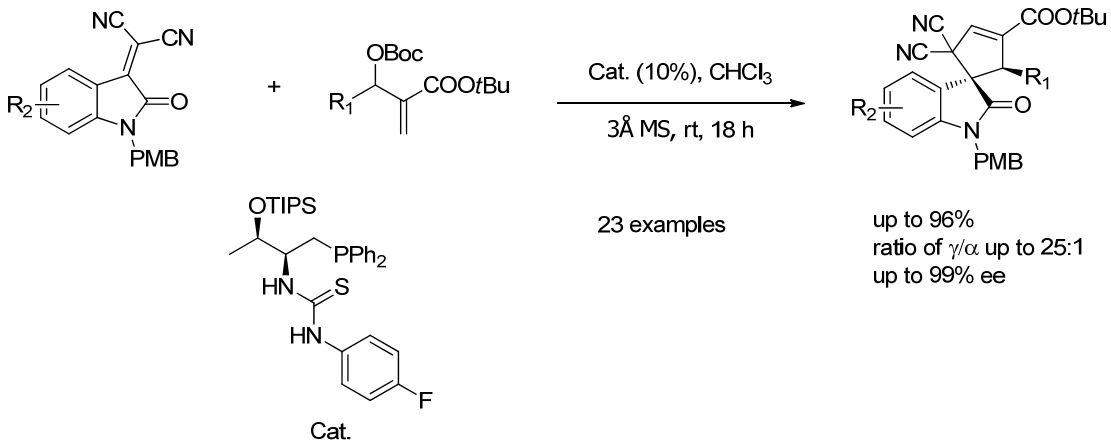
Inspired by the pioneer work, some intramolecular [3+2] annulation reactions were reported. In 2007, Tang and co-workers developed the phosphine-catalyzed intramolecular [3+2] annulation reaction of modified MBH adducts.[69] In 2010, Tang and Zhou described a cooperative catalytic system for the intramolecular [3+2] annulation reaction.[70] The cyclization products were obtained in high yields, high regioselectivities and high enantioselectivities using the catalytic system of chiral phosphine cooperated with Ti(*i*PrO)$_4$. However, the organocatalytic asymmetric [3+2] annulation reaction of MBH carbonates was not reported until 2011. Barbas and co-workers developed a phosphine-catalyzed asymmetric [3+2] annulation reaction of MBH carbonates and methyleneindolinone.[71] Several chiral phosphine ligands were examined and (+)-Ph-BPE containing a trialkylphosphine moiety was found to be the best catalyst. The aromatic π-π stacking interaction between catalyst and substrate might have some influence on the enantioselectivity. Spirocyclopenteneoxindole were obtained in high yields, high regioselectivities, high diastereoselectivities and high

enantioselectivities (**Scheme 1.29**).



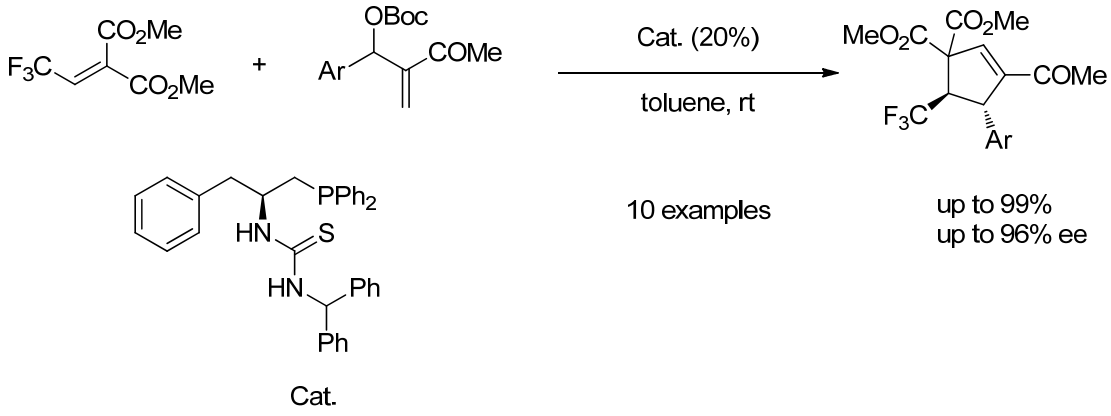
Scheme 1.29 Phosphine-catalyzed asymmetric [3+2] annulation reaction of MBH carbonates with methyleneindolinones

Almost at the same time, our group reported a phosphine-catalyzed asymmetric [3+2] annulation of MBH carbonates with α,α-dicyanokene derived from isatin.[72] We recently developed powerful chiral phosphine catalyst derived from amino acid and applied them in a number of asymmetric reaction.[73] The catalytic effects of various bifunctional phosphines on the annulation reaction of MBH carbonates with α,α-dicyanokene of isatin were examined and phosphine-thiourea catalysts derived from threonine were found to be most efficient. The annulation products could be obtained in good yields, with good regioselectivities and excellent enantioselectivities (**Scheme 1.30**). Interestingly the three component reaction of N-protected isatin, malononitrile and MBH carbonate also worked equally well. The hydrogen bonding interactions between the thiourea group and the substrate were demonstrated to be important for the observed stereoselectivity for the reaction.



Scheme 1.30 Phosphine-catalyzed asymmetric [3+2] annulation reaction of MBH carbonates with α,α-dicyanokenes derived from isatin

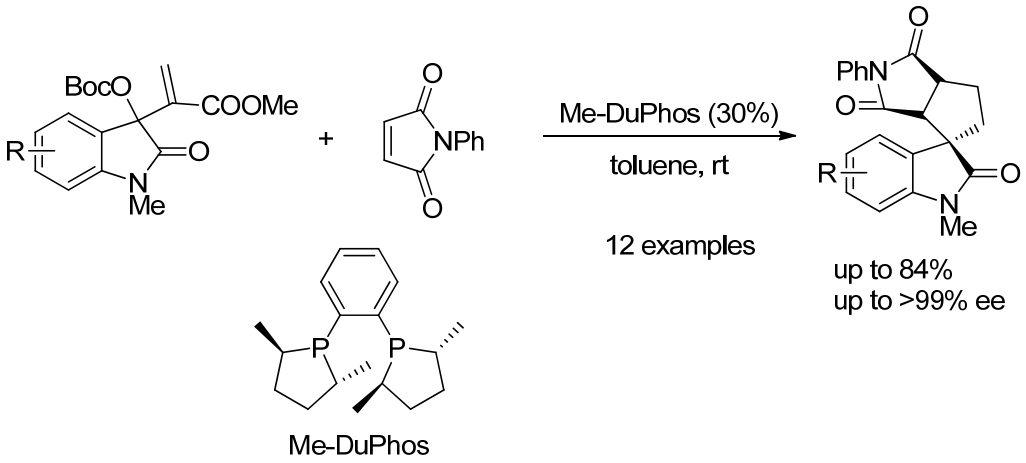
In 2012, Shi and co-workers also developed the asymmetric [3+2] annulation reaction of MBH carbonates catalyzed by amino acid derived chiral phosphines.[74] The electron deficient alkenes containing a trifluoromethyl group was reacted with MBH carbonates to afford the trifluromethyl substituted cyclopentenes. (**Scheme 1.31**).



Scheme 1.31 Asymmetric [3+2] annulation reaction of MBH carbonates with trifluoromethyl substituted alkene

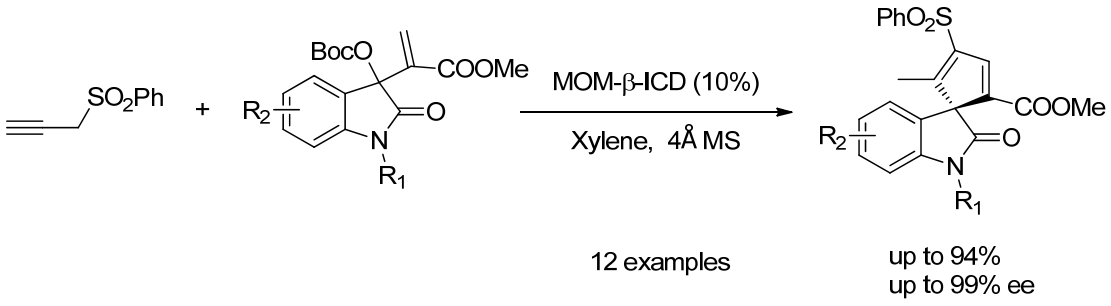
The MBH carbonates derived from ketones was also successfully applied to the [3+2] annulation reaction with electron deficient alkenes. In 2012, Liu and co-workers reported [3+2] annulation reaction of MBH carbonates of isatins and maleimides catalyzed by Me-DuPhos.[75] Spirocyclic oxindoles are wide existence structure in

nature product and pharmaceutical compounds.[76] This method led to the formation of spirocyclopentaneoindole structures with high regioselectivities, good diastereoselectivities and high enantioselectivities (**Scheme 1.32**).



Scheme 1.32 Asymmetric [3+2] annulation reaction of isatin-derived MBH carbonates with N-phenylmaleimide

The asymmetric [3+2] annulation reaction could also be catalyzed by chiral tertiary amine catalyst. In 2011, Chen and co-workers reported the only example of tertiary amine catalyzed [3+2] annulation reaction of MBH carbonates.[77] The *O*-MOM β-ICD was found to be the best catalyst, and a variety of MBH carbonates were showm to be suitable substrates for this [3+2] reaction. The spirocyclopentaneoxindole products were prepared in moderate to good yields, high regioselectivities and enantioselectivities (**Scheme 1.33**).



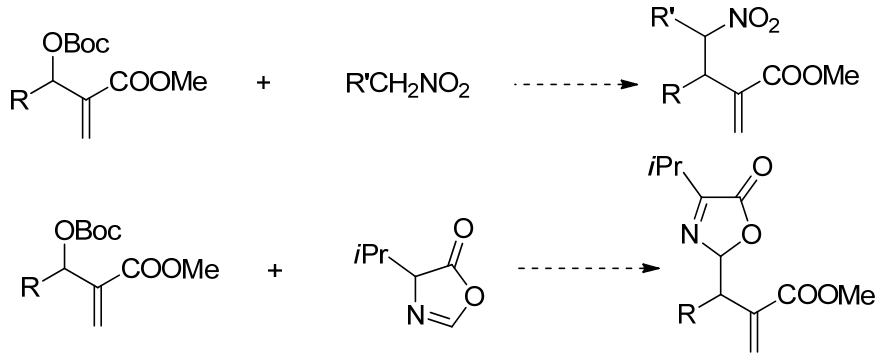
Scheme 1.33 Tertiary amine-catalyzed asymmetric [3+2] annulation reaction of

isatin-derived MBH carbonates with propargyl sulfone

1.3 Project objectives

The organocatalytic asymmetric reactions of MBH adducts have been widely studied since the MBH adducts are readily available and possess intrinsic good reactivity. The main aim of this study is to develop novel organocatalytic asymmetric substitution reactions employing MBH carbonates. We intend to use MBH carbonates in the organocatalytic asymmetric substitution reactions because upon the reaction with suitable nucleophilic catalysts, the *in situ* generated *tert*-butoxide ion may function as a Brønsted base to activate nucleophile. This is the so-called Lewis base assisted Brøsted base catalysis. As discussed above, a wide range of nucleophiles such as cyanoester, buenolide, indole, oxindole and phosphine oxide have been used in nucleophilic allylic substitution reaction of MBH carbonates in the presence of the tertiary amine catalysts. The mechanism of these reactions are believed to be a tandem S_{N2}'- S_{N2}'process (**Scheme 1.1**). Very few examples have been reported on the other regioisomers which may undergo a simple S_{N2}' or S_{N2}'-S_{N2} mechanism.[78] It was our goal to utilize novel nucleophiles in the asymmetric allylic alkylation reactions of MBH carbonates in a regioselective manner.

Two types of nucleophiles designed for the above purpose are shown in **Scheme 1.34**.



Scheme 1.34 Research plan on novel asymmetric allylic substation reactions

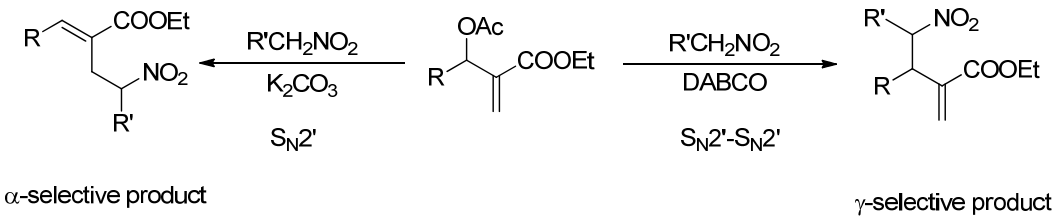
Nitroalkanes are versatile nucleophiles in organic synthesis and extensively explored in asymmetric nucleophilic addition reactions. However, the asymmetric allylic substitution reaction of MBH carbonates with nitroalkanes remained to be unexplored.[80] In this thesis, nitroalkanes will first be examined as nucleophiles for their reaction with simple MBH carbonates and isatin-derived MBH carbonates.

To obtain chiral γ-butyrolactones, the umpolung formyl aldehydes are needed in the reaction with MBH carbonates. 4-Isopropyl-2-oxazolin-5-one has been recognized as masked umpolung synthon for formyl anion.[81] The asymmetric reaction of MBH carbonates and oxazolinones will be explored in this thesis.

Chapter 2 Enantioselective Substitution Reaction of Morita–Baylis–Hillman Carbonates with Nitroalkanes

2.1 Introduction

Nitroakanes are valuable nucleophiles which have been utilized in many organic transformations.[82] The allylic alkylation of MBH adducts and nitroalkanes promoted by simple base has been reported by the groups of Kim and Batra.[83] Different regioselectivity could be achieved by using different bases stoichiometrically.[84, 83b] DABCO could promote the allylic substitution reaction, which are supposed to be a tandem S_N2'-S_N2' process, while the simple S_N2' product could be obtained using other bases (**Scheme 2.1)**. When MBH adducts are employed in the reaction, DABCO functions as a nucleophilic catalyst to activate MBH adducts, while other bases such as K_2CO_3 or NaOH, activate nitroalkane and the nucleophilic nitroalkanes attack the MBH adducts to form α-selective products.



Scheme 2.1 Different regioselectivity of the reaction of MBH adducts with nitroalkanes

The catalytic asymmetric version of the reaction of MBH carbonates and nitroakanes has not been reported. Both the α-selective and γ-selective products are attractive molecules. From the proposed mechanism, the γ-selective product may be obtained by employing a tertiary amine catalyst or tertiary phosphine catalyst. However, the regioselectivity, diastereoselectivity and enantioselectivity of the

reaction would depend on the proper selection of the catalytic systems. The α-selective products and γ-selective products are valuable synthetic intermediates.

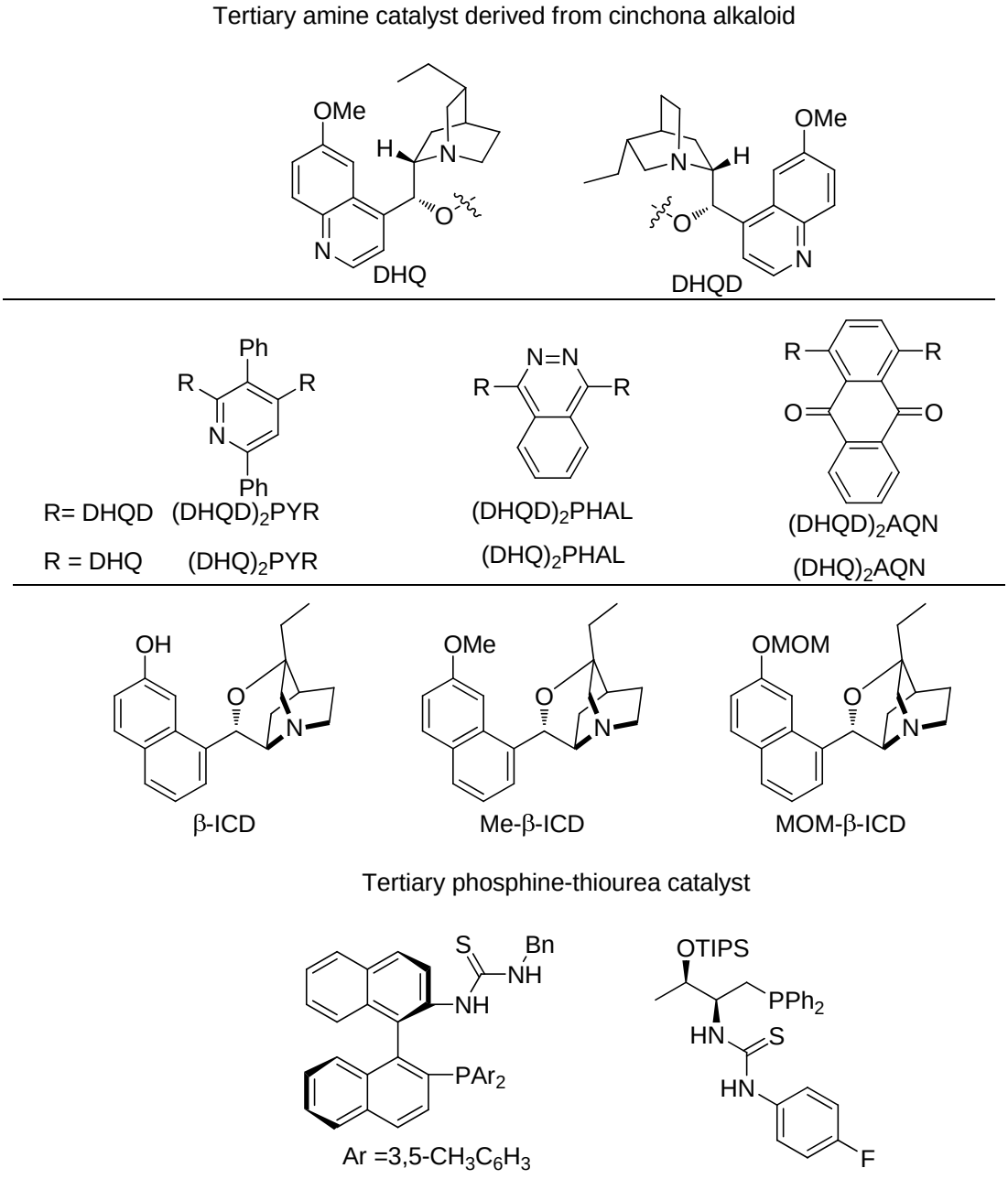
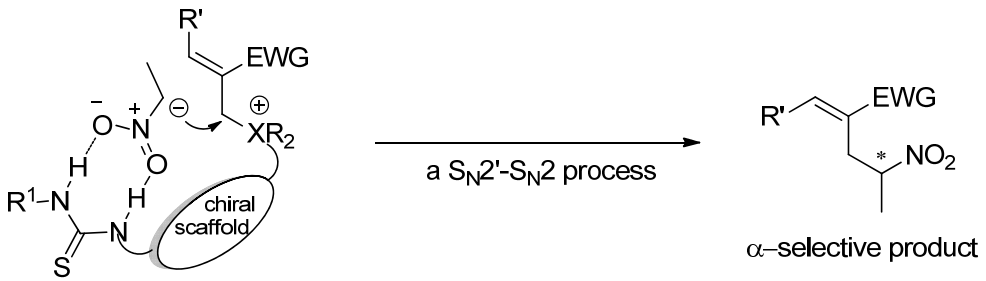


Figure 2.1 Typical catalysts in the reaction of MBH carbonates

Common nucleophilic catalysts used in the reaction of MBH carbonates are Lewis bases, such as tertiary amine catalysts or phosphine catalysts, some organic catalysts of this nature are illustrated in **Figure 2.1**. The mechanism of the asymmetric allylic alkylation reaction was generally accepted as a tandem S_N2'-S_N2'

process. The nucleophilic catalyst (a tertiary amine or phosphine) first adds to the MBH adduct in an S_N2' fashion, with the concurrent departure of the *tert*-butoxide group, which could be utilized to activate the nucleophile. A second S_N2' reaction then affords the γ-selective product, regenerating the catalyst at the same time. In the contrast, there was no examples of catalytic asymmetric reaction of MBH adduct to form the α-selective product. Based on the stoichiometric base promoted reaction, the Lewis base catalyst should activate nitroalkane in the presence of MBH adduct, which seems difficult in screening organocatayst with suitable reactivity. Or a dual catalyst which could activate both substrates may catalyze the reaction of MBH carbonate and nitroalkane. Hydrogen bonding between thiourea functionality and nitro group has been well recognized in organocatalytic reaction.[14a] Tertiaryl amine-thiourea catalyst was successfully used in many transformations of compounds containing nitro group. The substitution reaction of MBH carbonate and nitroalkane would proceed under the tertiary amine catalyst derived from cinchona alkaloid. The novel S_N2'-S_N2 mechanism was proposed to afford α-selective product in the reaction of MBH carbonate and nitroalkane under tertiary amine-thiourea catalyst (**Scheme 2.2**).



Scheme 2.2 A S_N2'-S_N2 reaction to obtain α-selective product

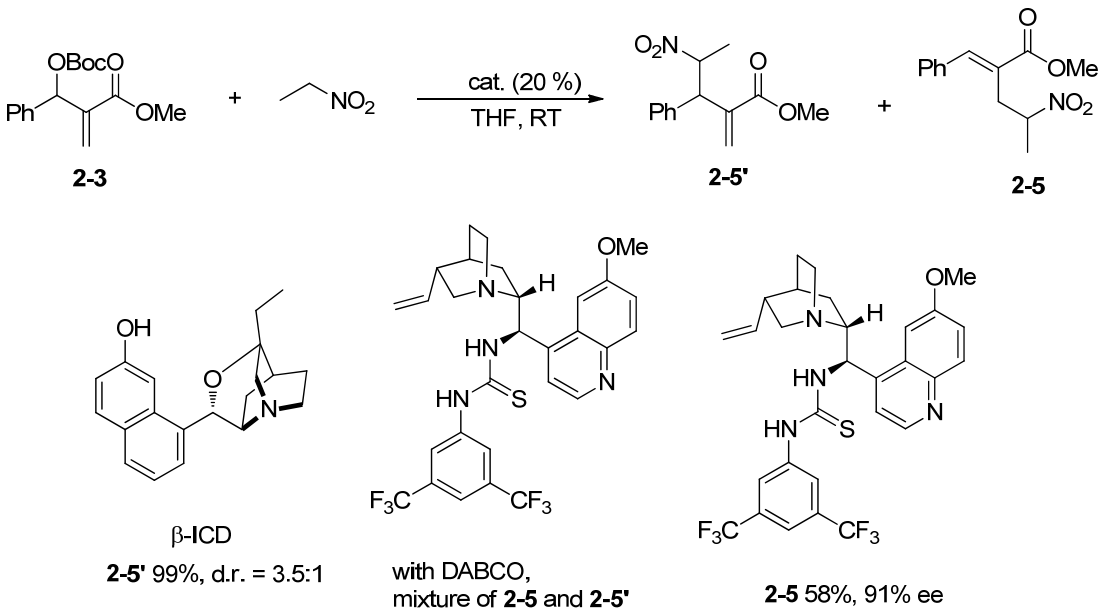
Herein, we describe a new type of substitution reaction of MBH carbonates with nitroalkanes using tertiary amine-thiourea catalyst. The α-selective product could be

achieved with high enantioselectivity. A S_N2'-S_N2 mechanism was proposed in the asymmetric regioselective reaction.

2.2 Results and Discussion

2.2.1 Preliminary Screening

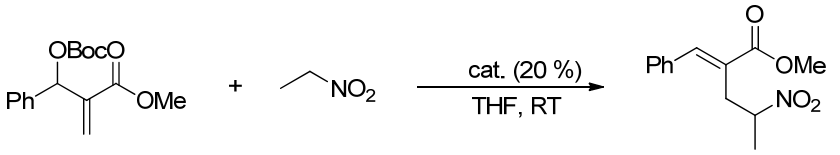
We firstly examined the reaction of MBH carbonate **2-3** with nitromethane. Tertiary amine catalyst derived from cinchona alkaloid was firstly tested. The γ-selective product **2-5'** was obtained with good selectivity using β-ICD as catalyst. The yield and regioselectivity was good, but the diastereoselectivity was only 3.5:1 and the ee of the major isomer was 23%. Other cooperative catalytic systems were also tested in the reaction. DABCO was the effective catalyst in the substitution reaction of MBH adduct to give α-selective product. Tertiary amine-thiourea catalyst derived from cinchona alkaloid was effective in many reaction of nitro compound. The DABCO and thiourea catalyst derived from quinidine was used in the reaction of MBH carbonate and nitroalkane to activate both substrates with good selectivity. However, the mixture of compounds **2-5** and **2-5'** was often observed. The two catalyst seems not working cooperatively. This results may also indicate that the tertiary amine-thiourea catalyst could provide α-selective product **2-5** with high regioselectivity and enantioselectivity (**Scheme 2.3**). The MBH acetate was applied under the same catalytic system and the conversion of the reaction was low. It shows that the strong Brøsted basicity of *tert*-butoxide ion plays a key role in this transformation.

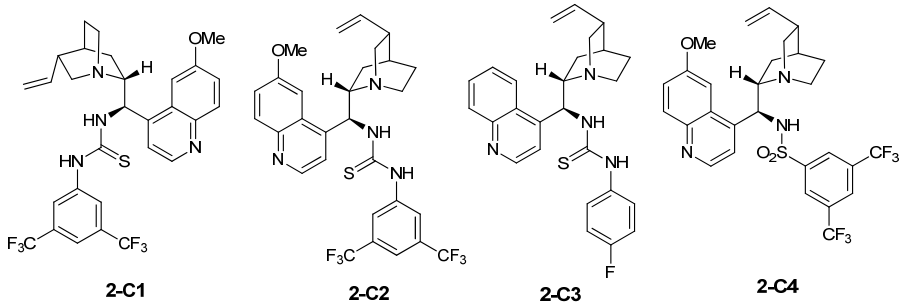


Scheme 2.3 Preliminary results of the reaction of MBH carbonate with nitroalkane

Based on the good regioselectivity and enantioselectivity, the bifunctional catalyst with tertiary amine and hydrogen bonding donor moiety may be effective to achieve the α-selective product in the reaction of MBH carbonate and nitroalkane. A series of bifunctional catalyst was prepared according to literature procedure. The tertiary-sulfonamide with strong hydrogen bonding catalyst cannot catalyze this reaction. Other bifunctional catalysts with different scaffold were also not effective in this transformation. Only tertiary amine-thiourea catalyst can promote this reaction with good regioselectivity and enantioselectivty. The catalyst **2-C1** dervided from quinidine provided the α-selective product with moderate yield, good regioselectivity and enantioselectivity (**Table 2.1**).

Table 2.1 Preliminary screening of bifunctional catalyst in the reaction of MBH carbonate with nitroethane [a]

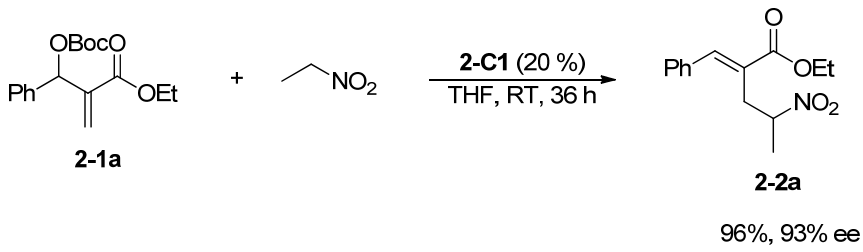




Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	**2-C1**	58	91
2	**2-C2**	71	79
3	**2-C3**	75	82
4	**2-C4**	-	-

[a] The reaction was performed with **2-3** (0.025 mmol), nitroethane (0.25 mmol) and the catalyst (0.005 mmol) in anhydrous THF (0.2 mL) at room temperature for 24 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase.

The different substituent of ester in the MBH carbonates would infulence the enantioselectivity. The readily availabe MBH carbonate was synthesized using different acrylate ester and examined in the reaction of MBH carbonate and nitroethane. The reaction of MBH carbonate with *tert*-butyl ester and nitroethane could not proceed under the best catalyst after two days. The best results were obtained using MBH carbonate **2-1a** with ethyl ester (**Scheme 2.4**).

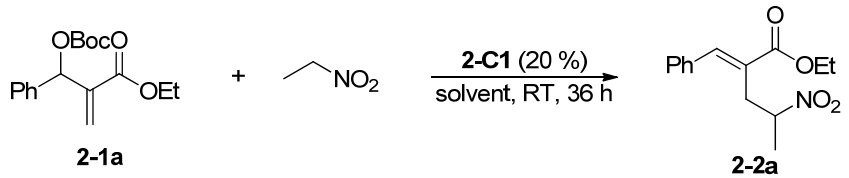


Scheme 2.4 Asymmetric reaction of MBH carbonate **2-1a** with nitroethane

2.2.2 Reaction Optimization

The reaction of MBH carbonate **2-1a** and nitroethane was chose to be the model reaction. The solvents were screening under the best catalyst **2-C1** at roomtemperature. THF was proved to be the best solvent. Other ether type of solvent ether could provide the same level of enantioselectivity with slightly lower yield. Dichloromethane and trichloromethane could afford the product with slightly lower enantioselectivity compared with THF as solvent. Small polar solvent, such as hexane, toluene, could provide moderate yield and good enantioselectivity. The moderate yield and low enantioselectivity was achieved using polar protic solvent MeOH. When polar solvent DMF was used, both yield and enantioselectivity were decrease (Table 2.2).

Table 2.2 Solvent screening for the reaction of MBH carbonate with nitroethane [a]



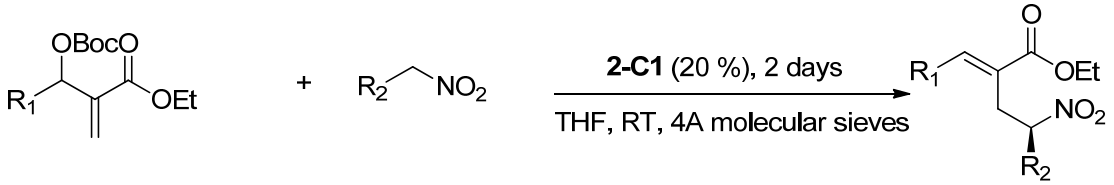
Entry	Solvent	Yield (%)[b]	ee (%)[c]
1	THF	96	93
2	Et_2O	84	90
3	CH_2Cl_2	87	90
4	$CHCl_3$	96	90
5	toluene	95	91
6	hexane	60	92
7	MeOH	76	36
8	DMF	24	8

[a] The reaction was performed with **2-1a** (0.025 mmol), nitroethane (0.25 mmol) and **2-9a** (0.005 mmol) in solvent (0.1 mL) at room temperature for 48 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase.

2.2.3 Substrate Scope

Under the optimized condition, substrate scope was examined (Table 2.3). The MBH carbonate derived from aromatic aldehyde was suitable substrate for this reaction. Other MBH carbonate was utilized in the reaction with nitroethane under the catalyst **2-C1** in THF at room temperature. When the MBH carbonate derived from 4-chlorobenzaldehyde was used, the α-selective product **2-2c** was achieve with good yield and poor enantioselectivity (50% ee). Further study showed that the addition of 4 Å molecular sieves could increase the enantioselectivity dramatically, which could reach to 92% ee (Table 2.3, entry 3 and 4). The reason of the additive effect should be that the trace amount of water will influence the formation of the hydrogen bonding between substrate **2-4** and the bifuncational catalyst.

Table 2.3 Substrate scope of the reaction of MBH carbonates with nitroalkanes[a]



2-1 **2-4** **2-2**

Entry	R_1	R_2	Yield (%)[b]	ee (%)[c]
1	Ph	Me	95	92
2	4-F-Ph	Me	84	95
3	4-Cl-Ph	Me	90	92
4[d]	4-Cl-Ph	Me	89	50
5	4-Br-Ph	Me	97	90
6	3-Br-Ph	Me	94	92
7	2-Br-Ph	Me	84	66
8	4-CF_3-Ph	Me	89	92
9	3-CF_3-Ph	Me	89	92
10	2-CF_3-Ph	Me	89	62
11	4-CH_3-Ph	Me	85	88

12	3-CH_3-Ph	Me	85	92
13	2-CH_3-Ph	Me	84	79
14	4-CH_3O-Ph	Me	87	92
15	2-Naphthyl	Me	76	89
16	1-Naphthyl	Me	43	72
17	2-furyl	Me	84	84
18 [e]	*i*-butyl	Me	<30	-
19[f]	Ph	n-Pr	95	94
20[f]	Ph	n-Bu	90	92
21[f]	Ph	n-Pentyl	87	93
22[g]	Ph	n-Pentyl	93	85

[a] The reaction was performed with **2-1** (0.025 mmol), **2-4** (0.25 mmol), 4 Å molecular sieves (10 mg) and **2-C1** (0.005 mmol) in solvent (0.1 mL) at room temperature for 48 h. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction proceeded without the addition of 4 Å molecular sieves. [e] Reactions were proceed for 5 days. [f] Reactions were performed under neat condition with 50 equivalent nitroalkane without the addition of 4 Å molecular sieves. [g] Reaction was performed at 50 ^oC.

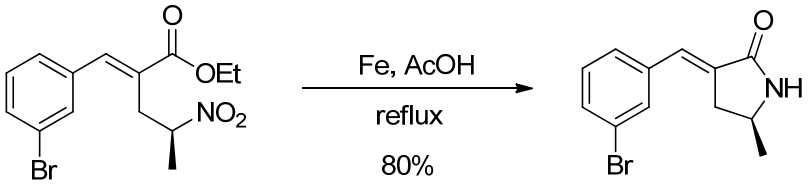
Further study on substrate scope chose the condition of catalyst **2-C1**, and the addition of 4 Å molecular sieves at room temperature. The α-selective asymmetric reaction of MBH carbonates and nitroalkanes was investigated under the best condition. The MBH carbonates derived from aromatic aldehyde possessed good reactivity under the catalytic system. The electron property on the phenyl ring seems not affecting the selectivity. Both the MBH carbonates with electron donating and electron withdrawing group on the phenyl ring could afford the α-selective with high regioselectivity and enantioselectivity (Table 2.3, entry 8, 9, 11, 12and 14). The MBH carbonates with halogen substituted on the phenyl ring had good reactivity and selectivity (Table 2.3, entry 2, 3, 5 and 6) except the *ortho*-substituted substrate (Table 2.3, entry 7). The MBH carbonate with *ortho*-substituent on the phenyl ring

could provide the product with poor enantioselectivity. The enantioselectivity was decreased with the increase of the steric hindrance of the *ortho*-substituent (Table 2.3, entry 7, 10, 13). The MBH carbonates derived from naphthyl aldehyde could provide the desired α-selective product under the best condition. Although the good regioselectivity could be obtained, the reactivity decreased apparently (Table 2.3, entry 15 and 16). The MBH carbonate containing 1-naphthyl substituent could afford the product with lower eanantioselectivity due to the steric hindrance (Table 2.3, entry 16). The MBH carbonate with hetero-aromatic substituent could give the product with good yield but slightly lower enantioselectivity (Table 2.3, entry 17). The MBH carbonate derived from aliphatic aldehyde was also tested under the optimized condition. However, the reactivity was too low (Table 2.3, entry 18). The α-selective product from MBH carbonate with aromatic substituent was a conjugative system, which may benefit the product formation dynamically.

To further explore the substrate scope, other nitroalkane was used in the reaction. Under the optimized condition, the reaction of MBH carbonate **2-1a** and nitropropane was slow. The reactivity of nitroalkanes was dropped with the extension of alkyl chain. To achieve the desire α-selective product, using nitroalkane with longer alkyl chain as substrate, the neat condition or harsh condition was need. Nitrohexane was used in the α-selective substitution reaction of MBH carbonate under the optimized condition at 50 ^{o}C. Good reactivity, regioselectivity and enantioselectivity were observed with desire product (Table 2.3, entry 22). Under the neat condition, the products were achieved with high yield, regioselectivity and enantioselectivity using nitropropane, nitrobutane, and nitrohexane (Table 2.3, entry 19, 20 and 21).

2.2.4 Synthetic Utility

To explore the utility of this regioselective asymmetric reaction, α-methylene- γ-butyrolactams were synthesized by simple reduction. α-Methylene-γ-butyrolactams have been recieved much attetion because these compounds possess biological activity and are useful in medecinal chemistry.[85]



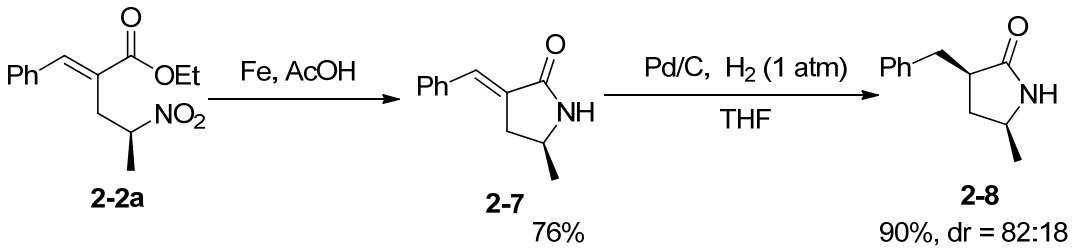
2-2e **2-6**

Scheme 2.5 Synthesis of α-alkylidene- γ-butyrolactam

The α-selective product **2-2e** could transform to α-alkylidene- γ-butyrolactam **2-6** in the presence of iron and acetic acid under the condition of reflux (**Scheme 2.5**). Furthermore, the X-ray structure of the single crystal of **2-6** was obtained. This may induce that the absolute configuration of **2-2e** was S configuraion. The absolute configuration of other compounds **2-2** were asigned by anology of **2-2e**.

Pyrrolidinones are biologically important compounds and useful building block in organic synthesis. Many natural product and biological active compounds possess the motif of pyrrolindiones.[84] Our α-selective product of MBH carbonate and nitroalkane could transform to chiral pyrrolidinone compounds. The Fe/HOAc was used to reduce nitro group of compound **2-2a** to form α-alkylidene- γ-butyrolactam **2-7** (**Scheme 2.6**). Then the hydrogenation was used to form the chiral pyrrolidinone compound **2-8** with moderate but acceptable diastereoselectivity. Several metal catalysts such as $Pd(OH)_2$, Raney-Ni, Pd/AlO(OH), have been examined in this hydrogenation reaction. The palladium carbon provided the best diastereoselectivity. After screening the solvents, the best diastereoselectivity was achieved only 82:18

using the condition of 20 mol% palladium carbon, THF as solvent and hydrogen balloon.



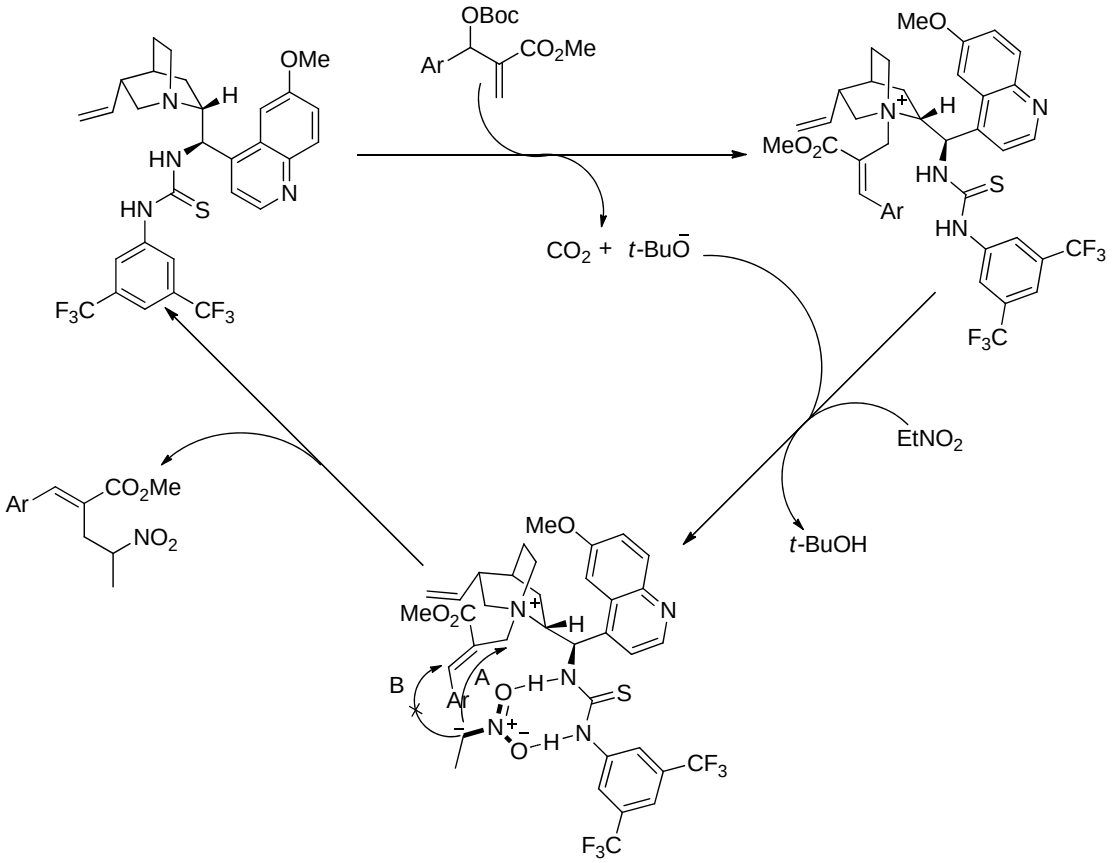
Scheme 2.6 Synthesis of chiral pyrrolidinone compound

2.2.5 Plausible Reaction Mechanism

The organocatalytic asymmetric allylic alkylation reaction of MBH adduct was well explored to achieve γ-selective product. The mechanism was well accepted as a S_N2'-S_N2' process. In the contrast, there was less report on the enantioselective substitution reaction of MBH carbonates with high α-selectivity. The mechanism of α-selective reaction of MBH carbonate was also less studied. This may also result in the less explored reaction of α-selective reaction of MBH carbonate. Only one example has been reported to achieve the α-selective chiral product using organocatalyst.[78] The reaction of MBH acetate and benzophenone imine of glycine ester has been reported under phase transfer catalyst derived from cinchona alkaloid. A tandem addition-elimination was occurred under the base condition. The ion change of phase transfer catalyst and additional base would occur and the nucleophile would generate after deprotonation by base. The nucleophile would add to the MBH acetate in a S_N2' fashion so the OAc group would eliminate to be neutralized by the base in the reaction. The thiourea catalyst derived from quinidine could only activate nitroalkane which has been reported in Henry reaction and aza-Henry reaction.[86] In our catalytic system, the simple S_N2' could happen if the catalyst only activates

nitroalkane. The addition of carbon-carbon double bond of activated nitroalkane would cause the elimination of the leaving group. To test this assumed addition-elimination mechanism, MBH adduct with other leaving group could also give the α-selective product. We used the MBH acetate as substrate in the reaction with nitroethane under the optimized condition. But the reaction cannot proceed. That indicate the reaction may not undergo in a simple S_N2' process or the addition-elimination process.

Herein, we proposed that the reaction mechanism was in a S_N2'-S_N2 process (**Scheme 2.7**). The tertiary amine of the bifunctional catalyst severs as a nucleophile which could attack the carbon-carbon double bond of MBH carbonate and the leaving group Boc would *in situ* generate a *tert* butyl oxide ion and carbon dixoide. The *tert*-butyl oxide ion would function as a base to deprotonate α-proton of nitroethane, which plays a key role in this asymmetric reaction. After the S_N2' reaction, a tandem S_N2 process would happen with the facilitation of the hydrogen bonding between the catalyst and nitroethane. The activated nitroethane would selectively attack the MBH carbonate from the front side through path A and regenerate the catalyst. The product indicates that a S_N2'- S_N2 reaction occurs rather than S_N2'-S_N2' reaction. The good regioselectivity could generate because the reaction would go through path A rather than path B due to the steric hindrance. The thiourea functional also plays a key role in the reaction providing good reactivity, regioselectivity and enantioselectivity.



Scheme 2.7 Proposed mechanism for the α-selective reaction of MBH carbonates with nitroalkanes

Preliminary study on the proposed mechanism has been done. Other tertiary amine catalyst such as quinidine, O-protected quinidine was used, and the reaction of nitroethane and MBH carbonate **2-1a** gave the mixture of α-selective product **2-2a** and γ-selective product **2-2a'**. When the catalyst containing the thiourea group at the 6' position of β-ICD was used, the reaction of MBH carbonate **2-1a** and nitroethane afforded the regioselective product **2-2a'**. The specific thiourea functionality of catalyst **2-C1** plays an important role in the regioselectivity of the reaction. Deng and co-workers has also revealed that the spatial relationship between hydrogen bonding donor and acceptor could alter the orientation of two substrates which would influence the enantioselectivity.[87] Other nucleophile without nitro group could not

provide α-selective product with high regioselectivity. Howerver, nucleophiles such as ethyl 2-nitroacetate could afford the α-selective product with high regioselectivity. This may indicate that the specific interaction of hydrogen bonding between thiourea and nitro group is very important. The *ortho* substituted MBH carbonate only gave the desired product with moderate enantioselectivity. This may be due to the steric hindrance interference on the hydrogen bond formation between nitroethane and catalyst. The existence of water also could decrease the enantioselectivity of the reaction. The reason is that the hydrogen bonding formation may be destroyed in the presence of water.

2.3 Conclusions

In conclusion, we have developed the method that an asymmetric substitution reaction of nitroalkane with MBH carbonates catalyzed by cinchona derived bifunctional catalyst. A novel regioselective reaction of MBH adduct was investigated. A range of α-selective products **2-2** was achieved in the reaction of MBH carbonates **2-1**and nitroalkanes **2-4** under the catalyst of **2-C1**. The α-selective products **2-2** were obtained with high regioselectivity, good to excellent yield and moderate to excellent enantioselectivity. The utility of this method was examined by synthesizing useful compounds. Pyrrolidinones **2-8** and α-alkylidene- γ-butyrolactam **2-6** was prepared by simple transformation of the α-selective products **2-2**. The absolute configuration was assigned by analysis of X-ray determination of compound **2-6** and analogy. The mechanism was proposed as a tandem S_N2'- S_N2 rather than S_N2'- S_N2'. The preliminary results of the mechanism study were also discussed. Although no enough evidence could support the proposed mechanism, the results could be well explained by the proposed mechanism. The hydrogen bonding between thiourea and nitro group

plays an important role in the highly regioselective and enantioselective transformation.

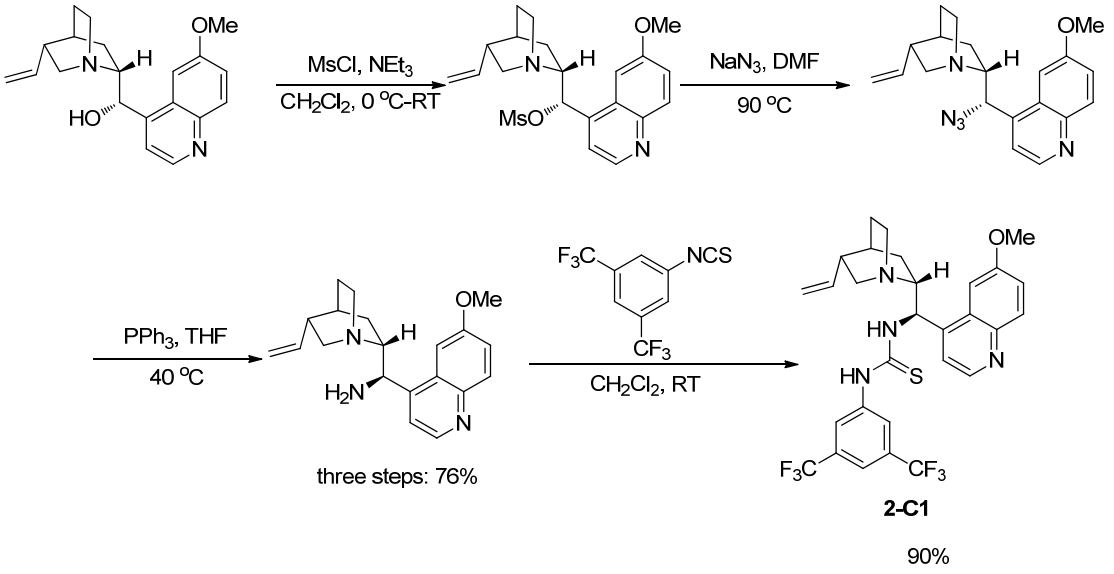
2.4 Experimental section

2.4.1 Material and General Methods

All the starting materials were obtained from commercial sources and used without further purification unless otherwise stated. Toluene, THF and diethyl ether were dried and distilled from sodium benzophenone ketyl prior to use. $CHCl_3$ and CH_2Cl_2 were distilled from CaH_2 prior to use. ^1H and ^{13}C NMR spectra were recorded on a Bruker ACF300 or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in EI mode, and all high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with $KMnO_4$, iodine, or ceric ammonium molybdate followed by heating on a hot plate. Flash chromatographic separationswere performed on Merck 60 (0.040–0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by HPLC analysis on a chiral stationary phase.

The MBH carbonates **2-1** were prepared according literature procedure.[88] The catalysts **2-C** were prepared according literature procedure with small modification.[89]

2.4.2 Catalyst Preparation



Scheme 2.8 Typical procedure for synthesis of tertiary amine-thiourea catalysts derived from cinchona alkaloid

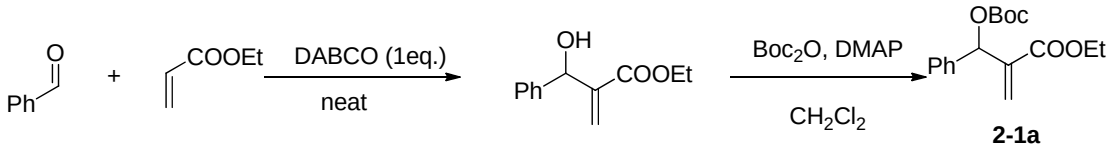
The synthesis of catalyst **2-C1** was taken as an example. Other catalysts were prepared by the same procedure from other cinchona alkaloid (**Scheme 2.8**).

To the solution of quinidine (3.24 g, 10 mmol) in CH_2Cl_2 (50 mL) was added NEt_3 (2.7 mL, 20 mmol) in a 250 mL round bottom flask. At 0 ^oC, methanesulfonyl chloride (0.93 mL, 12 mmol) was slowly added by dropwise to the solution of quinidine. The reaction mixture was allowed to room temperature after the addition of MsCl. The reaction was followed by TLC monitor and quenched with water after the quinidine was consumed completely. The aqueous layer was extracted with dichloromethane for three times. The combined organic layer was washed with brine and dried with anhydrous Na_2SO_4. The crude product was obtained after removing the solvent. Without further purification, the crude product was directly used for the next step. In a 100 mL RBF, to the solution of mesilate protected quinidine in 30 mL DMF was added sodium azide (1.95 g, 30 mmol). The reaction mixture was heated to 90 ^oC

for 24 h. The reaction was cooled to room temperature when the reaction was complete. Water was added and the reaction mixture was extracted with dichloromethane for three times. The combined organic layer was washed with water several times to remove DMF. After removing the solvent, the crude product of azide was obtained and directly used in the next step. To the solution of azide compound in dry THF was added triphenylphosphine (2.62 g, 10 mmol). The reaction mixture was then heated to 40 ^{o}C. The reaction was stopped when there was no gas released from the reaction. The solvent was removed to achieve the crude product. The desired compound (2.46g, 7.6 mmol) of amine derived from qunindine was obtained after purification by column chromatography on silica gel.

To the solution of amine derived from quinidine (232 mg, 1.0 mmol) in 10 mL CH_2Cl_2 was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.2 mL, 1.0 mmol) by dropwise. After the completion of addition, the reaction was followed by TLC analysis. When the amine was consumed completely, the solvent was removed. The crude product was purified by column chromatography on silica gel to afford the desired product **2-C1** (540 mg, 90%).

2.4.3 Representative Procedure for Synthesis of MBH Carbonates

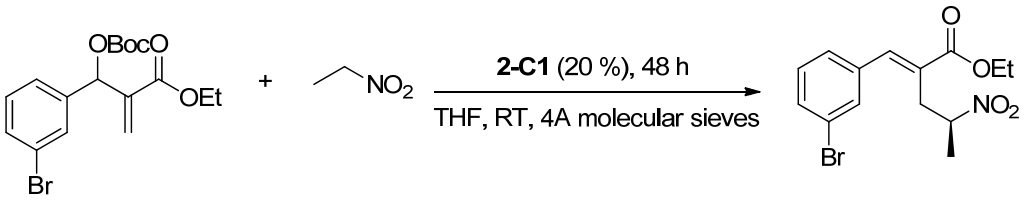


Scheme 2.9 Typical procedure for synthesis of MBH carbonates

The representative procedure of synthesis of MBH carbonates was described as the synthesis of substrate **2-1a** (**Scheme 2.9**). To the mixture of benzaldehyde (0.10 mL, 1.0 mmol) and ethyl acrylate (0.11 mL, 1.0 mmol) was added DABCO (112 mg,

1.0 mmol). The reaction mixture was stirred at room temperature for one day. The mixture was directly purified by column chromatography on silica gel to afford the MBH product (189 mg, 92%). To the MBH product in 5 mL dry CH_2Cl_2 was added the solution of Boc_2O (0.21 mL, 0.92 mmol) and DMAP (5.6 mg, 0.046 mmol) in 2 mL dry CH_2Cl_2 at 0 ^oC by dropwise. The reaction mixture was stirred at room temperature for one day. When the MBH product was consumed completely, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford the MBH carbonate **2-1a** (260 mg, 92%).

2.4.4 Representative Procedure for the Reaction of MBH Carbonates and Nitroalkanes



2-1e **2-2e**
94%, 92% ee

Scheme 2.10 Typical procedure for the reaction of MBH carbonates with nitroalkanes

MBH carbonate **2-1e** (9.6 mg, 0.025 mmol) was mixed with catalyst **2-C1** (3.0 mg, 0.005 mmol) and 4Å molecular sieves (10 mg) in THF (0.1 mL). Nitroethane (18 μL, 0.25mmol) was added to the reaction mixture and the resulting reaction mixture was stirred for 2 days at room temperature. Molecular sieves were filtered off; the filtrate was concentrated under reduced pressure. The residue was directly purified by column chromatography on silica gel to afford the product **2-2e** (8.0 mg, 94 %, 92% ee).

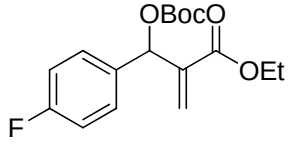
2.4.5 Representative Procedure for Butyrolactams and Pyrrolidinones

To the compound **2-2e** (8.0 mg, 0.023 mmol) in AcOH (1.0 mL) was added Fe (13 mg, 0.23mmol). The reaction mixture was heated to reflux for 2 hours. The reaction mixture was cooled to roomtemperature. The solid was filtered off and wased with dichloromethane 3 mL for 2 times. To the resulting filtrate was added 10 mL water. The aqueous layer was extracted with 10 mL CH_2Cl_2 for 2 times. The combined organic layer was washed with water, brine and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified purified by column chromatography on silica gel to afford the α-alkylidene-γ-butyrolactam **2-6** (4.9 mg, 80 %).

The α-alkylidene-γ-butyrolactam compound **2-7** was obtained using the above method. To the compound **2-7** (50.0 mg, 0.27 mmol) in THF (0.5 mL) was added Pd/C (10.0 mg). The reaction mixture was charged with hydrogen in a balloon and stirred for overnight. The Pd/C was filtered off and the resulting filtrate was concentrated under reduced pressure. The residue was purified purified by column chromatography on silica gel to afford the pyrrolidinone **2-8** (46.0 mg, 90%).

2.4.6 Analytical Data of MBH Carbonates

Ethyl 2-(((*tert*-butoxycarbonyl)oxy)(4-fluorophenyl)methyl)acrylate **2-1b**

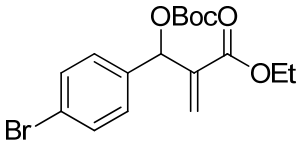


2-1b

A colorless oil, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.18 (t, *J* = 7.1 Hz, 3H), 1.44 (s, 9H), 4.13 (q, *J* = 5.05 Hz, 2H), 5.90 (s, 1H), 6.39 (s, 1H), 6.44 (s, 1H), 6.98-7.01 (m,

2H), 7.35-7.37 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.0, 27.7, 61.0, 75.2, 82.7, 115.3, 115.4, 125.3, 129.6, 129.7, 139.7, 152.3, 164.7; HRMS-EI calcd for $C_{17}H_{21}O_5F_3$ 324.1373, found: 324.1376.

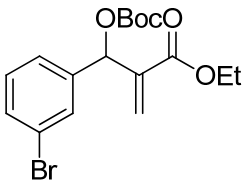
Ethyl 2-((4-bromophenyl)((*tert*-butoxycarbonyl)oxy)methyl)acrylate **2-1d**



2-1d

A colorless oil, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.08 Hz, 3H), 1.48 (s, 9H), 4.15-4.22 (q, *J* = 6.06 Hz, 2 H), 5.94 (s, 1H), 6.43 (s, 1H), 6.45 (s, 1H), 7.31 (d, *J* = 7.44 Hz, 2H), 7.49 (d, *J* = 7.44 Hz, 2H); ^{13}C-NMR(75 MHz, $CDCl_3$) δ 13.9, 27.6, 61.0, 75.1, 82.6, 122.4, 125.6, 129.3, 131.5, 136.8, 139.4, 152.2, 164.6; HRMS-EI calcd for $C_{17}H_{21}O_5{}^{79}Br_1$ and $C_{17}H_{21}O_5{}^{81}Br_1$, 384.0572 and 386.0552, found: 384.0586 and 386.0565.

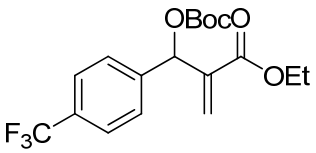
Ethyl 2-((3-bromophenyl)((*tert*-butoxycarbonyl)oxy)methyl)acrylate **2-1e**



2-1e

A colorless oil, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.1 Hz, 3H), 1.46 (s, 9H), 4.11-4.20 (m, 2H), 5.92 (s, 1H), 6.42(s, 2H), 7.20-7.54 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.0, 27.7, 61.1, 75.1, 83.0, 125.4, 126.1, 127.9, 130.7, 139.3, 141.8, 152.2, 164.6; HRMS-EI calcd for $C_{17}H_{21}O_5{}^{79}Br_1$ and $C_{17}H_{21}O_5{}^{81}Br_1$, 384.0572 and 386.0552, found: 384.0586 and 386.0565.

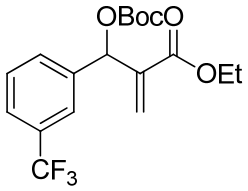
Ethyl 2-(((*tert*-butoxycarbonyl)oxy)(4-(trifluoromethyl)phenyl)methyl)acrylate **2-1g**



2-1g

A colorless oil, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.2 Hz, 3H), 1.45 (s, 9H), 4.12-4.19 (m, 2H), 5.93 (s, 1H), 6.43 (s, 1H), 6.51 (s, 1H), 7.51-7.60 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.9, 27.6, 61.0, 71.5, 82.9, 125.3, 125.4, 126.0, 127.9,139.3, 141.8, 152.2, 164.6; HRMS-EI calcd for $C_{18}H_{21}O_5F_3$ 374.1341, found: 374.1346.

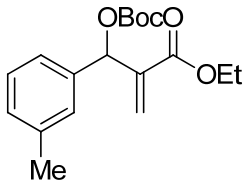
Ethyl 2-(((*tert*-butoxycarbonyl)oxy)(3-(trifluoromethyl)phenyl)methyl)acrylate **2-1h**



2-1h

A colorless oil, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.20 (t, *J* = 7.2 Hz, 3H), 1.44 (s, 9H), 4.10-4.17 (m, 2H), 5.94 (s, 1H), 6.43 (s, 1H), 6.50 (s, 1H), 7.44-7.65 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.8, 27.6, 61.0, 75.1, 82.9,124.3, 124.4, 125.1, 125.2, 125.9, 128.9, 131.0, 138.9, 139.3, 152.1, 164.5; HRMS-EI calcd for $C_{18}H_{21}O_5F_3$ 374.1341, found: 374.1346.

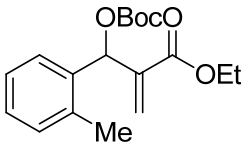
Ethyl 2-(((*tert*-butoxycarbonyl)oxy)(*m*-tolyl)methyl)acrylate **2-1k**



2-1k

A colorless oil, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.2 Hz, 3H), 1.46 (s, 9H), 2.33 (s, 3H), 4.14-4.21 (m, 2H), 5.88 (s, 1H), 6.39 (s, 1H), 6.45 (s, 1H), 7.09-7.26 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.0, 21.3, 27.7, 60.9, 75.9, 82.5, 124.8, 125.4, 128.2, 128.3, 129.1, 137.4, 138.0, 139.9, 152.4, 164.9; HRMS-EI calcd for $C_{18}H_{24}O_5$ 320.1618, found: 320.1611.

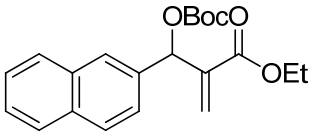
Ethyl 2-(((*tert*-butoxycarbonyl)oxy)(*o*-tolyl)methyl)acrylate **2-1l**



2-1l

A colorless oil, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.1 Hz, 3H), 1.46 (s, 9H), 2.41 (s, 3H), 4.14-4.21 (q, *J* = 7.1 Hz, 2H), 5.70 (s, 1H), 6.42 (s, 1H), 6.73 (s, 1H), 7.17-7.31 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.0, 19.1, 27.7, 60.9, 72.7, 82.4, 126.0, 126.6, 127.0, 128.3, 130.5, 135.6, 136.3, 139.3, 152.5, 165.1; HRMS-EI calcd for $C_{18}H_{24}O_5$ 320.1618, found: 320.1611.

Ethyl 2-(((*tert*-butoxycarbonyl)oxy)(naphthalen-2-yl)methyl)acrylate **2-1n**

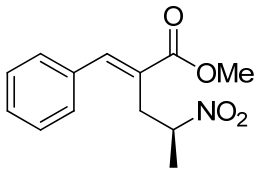


2-1n

A light yellow solid, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.2 Hz, 3H), 1.47 (s, 9H), 4.12-4.19 (q, *J* = 7.2 Hz, 2H), 5.96 (s, 1H), 6.45 (s, 1H), 6.66 (s, 1H), 7.46-7.49 (m, 3H), 7.81-7.88 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.0, 27.8, 61.0, 76.0, 82.7, 125.2, 125.7, 126.2, 126.3, 127.1, 127.6, 128.2, 133.1, 135.0, 139.8, 152.4, 165.0; HRMS-EI calcd for $C_{21}H_{24}O_5$ 356.1624, found: 356.1621.

2.4.7 Analytical Data of Products of MBH carbonates and nitroalkanes

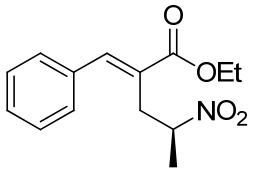
(S,E)-Methyl 2-benzylidene-4-nitropentanoate **2-5**



2-5

A colorless oil, 58% yield; $[\alpha]_c$ = -25.8 (c = 0.48, $CHCl_3$); 91% ee, determined by HPLC analysis [Daicel Chiralpak IB, *n*-hexane/*i*-PrOH = 98/2, 0.5 mL/min, λ = 254 nm, t (major) = 21.41 min, t (minor) = 19.47 min]; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.48 (d, *J* = 5.6 Hz, 3H), 2.95-3.00 (m, 1H), 3.22-3.30 (m, 1H), 3.85 (s, 3H), 4.87-4.92 (m, 1H), 7.28-7.42 (m, 5H), 7.89 (s, 1H).

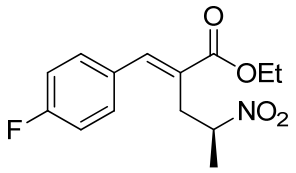
(S,E)-Ethyl 2-benzylidene-4-nitropentanoate **2-2a**



2-2a

A colorless oil, 96% yield; $[\alpha]_c$ = -18.1 (c = 0.42, $CHCl_3$); 92% ee, determined by HPLC analysis [Daicel Chiralcel OJ, *n*-hexane/*i*-PrOH = 98.5/0.5, 0.5 mL/min, λ = 254 nm, t (major) = 49.81min, t (minor) = 44.80 min]; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.38 (t, *J* = 7.6 Hz, 3H), 1.47 (d, *J* = 6.7 Hz, 3H), 2.93-2.99 (m, 1H), 3.22-3.29 (m, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.85-4.94 (m, 1H), 7.28-7.41 (m, 5H), 7.89 (s, 1H).

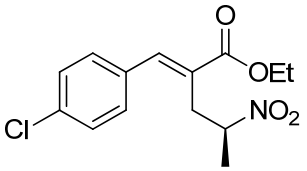
(S,E)-Ethyl 2-(4-fluorobenzylidene)-4-nitropentanoate **2-2b**



2-2b

A colorless oil, 84% yield; $[\alpha]_c$ = -20.9 (c = 0.41, $CHCl_3$); 95% ee, determined by HPLC analysis [Daicel Chiralpak AD, *n*-hexane/*i*-PrOH = 99/1, 0.5mL/min, λ = 254 nm, t (major) = 26.38 min, t (minor) = 30.85 min]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.1 Hz, 3H), 1.48 (d, *J* = 6.7 Hz, 3H), 2.89-2.95 (m, 1H), 3.19-3.26 (m, 1H), 4.26-4.33 (q, *J* = 7.1 Hz, 2H), 4.85-4.94 (m, 1H), 7.07-7.13 (m, 2H), 7.27-7.31 (m, 2H), 7.83 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.2, 18.9, 32.8, 61.4, 81.7, 115.8, 116.0, 127.6, 130.7. 130.8, 142.0, 161.2, 167.0; HRMS-APCI calcd for $C_{14}H_{16}FNO_4$ 280.1001, found: 280.0991.

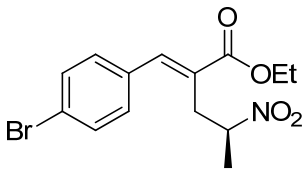
(S,E)-Ethyl 2-(4-chlorobenzylidene)-4-nitropentanoate **2-2c**



2-2c

A colorless oil, 90% yield; $[\alpha]_c$ =+12.0 (c = 0.85, $CHCl_3$); 92% ee, determined by HPLC analysis [Daicel Chiralcel OJ, *n*-hexane/*i*-PrOH = 99/1, 0.5 mL/min, λ = 254 nm, t (major) = 56.71 min, t (minor) = 49.25 min]; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.40 (t, *J* = 7.0 Hz, 3H), 1.51 (d, *J* = 7.0 Hz, 3H), 2.92-2.96 (m, 1H), 3.22-3.27 (m, 1H), 4.32-4.36 (q, *J* = 6.9 Hz, 2H), 4.91-4.98 (m, 1H), 7.28 (d, *J* = 10.1 Hz, 2H), 7.42, (d, 2H), 7.85 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.2, 18.9, 29.7, 61.4, 81.7, 128.2, 129.0, 130.1, 133.1, 134.9, 141.9, 166.9; HRMS-APCI calcd for $C_{14}H_{16}ClNO_4$ 296.0697, found: 296.0695.

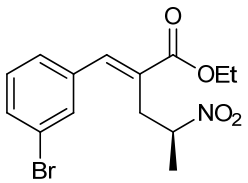
(S,E)-Ethyl 2-(4-bromobenzylidene)-4-nitropentanoate **2-2d**



2-2d

A colorless oil, 97% yield; $[\alpha]_c$ = -23.7 (c = 0.63, $CHCl_3$); 90% ee, determined by HPLC analysis [Daicel Chiralcel OJ, *n*-hexane/*i*-PrOH = 99.5/0.5, 0.5 mL/min, λ = 254 nm, t (major) = 95.91 min, t (minor) = 84.66 min]; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.2 Hz, 3H), 1.47 (d, *J* = 6.7 Hz, 3H), 2.86-2.93 (m, 1H), 3.16-3.24 (m, 1H), 4.26-4.34 (q, *J* = 7.1 Hz), 4.85-4.96 (m, 1H), 7.15-7.18 (d, *J* = 8.6 Hz, 2H), 7.53-7.56 (d, *J* = 8.6 Hz, 2H), 7.79 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.2, 18.9, 29.7, 32.9, 61.5, 81.6, 123.2, 128.3, 130.3, 132.0, 133.6, 141.9, 166.9; HRMS-EI calcd for $C_{14}H_{16}O_4N_1{}^{79}Br_1$ and $C_{14}H_{16}O_4N_1{}^{81}Br_1$ 341.0263 and 343.0242, found: 341.0247 and 343.0228.

(S,E)-Ethyl 2-(3-bromobenzylidene)-4-nitropentanoate **2-2e**

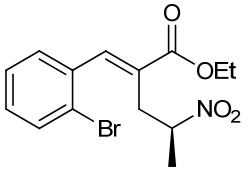


2-2e

A colorless oil, 94% yield; $[\alpha]_c$ = -5.3 (c = 0.60, $CHCl_3$); 92% ee, determined by HPLC analysis [Daicel Chiralcel OJ, *n*-hexane/*i*-PrOH = 99/1, 0.5 mL/min, λ = 254 nm, t (major) = 63.32 min, t (minor) = 56.93 min]; ^{1}H-NMR (300 MHz, $CDCl_3$) 1.31 (t, *J* = 7.1 Hz, 3H), 1.43 (d, *J* = 6.7 Hz, 3H), 2.80-2.87 (m, 1H), 3.11-3.18 (m, 1H), 4.22-4.29 (q, *J* = 7.1 Hz, 2H), 4.82-4.89 (m, 1H), 7.15-7.43 (m, 4H), 7.74 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.2, 18.9, 32.8, 61.5, 81.6, 122.7, 127.1, 129.0, 130.2,

131.5, 131.7, 136.7, 141.4, 166.7; HRMS-EI calcd for $C_{14}H_{16}O_4N_1{}^{79}Br_1$ and $C_{14}H_{16}O_4N_1{}^{81}Br_1$ 341.0263 and 343.0242, found: 341.0247 and 343.0228.

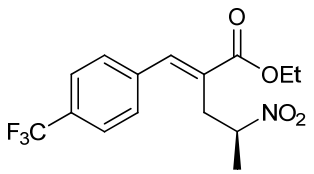
(S,E)-Ethyl 2-(2-bromobenzylidene)-4-nitropentanoate **2-2f**



2-2f

A colorless oil, 84% yield; $[\alpha]_c$ = +11.3 (c = 0.30, $CHCl_3$); 66% ee, determined by HPLC analysis [Daicel Chiralcel OJ, *n*-hexane/*i*-PrOH = 99/1, 0.5 mL/min, λ = 254 nm, t (major) = 33.01 min, t (minor) =45.65 min]; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.35-1.42 (m, 6H), 2.77-2.84 (m, 1H), 3.02-3.09 (m, 1H), 4.28-4.35 (q, *J* = 7.1 Hz, 2H), 4.82-4.93 (m, 1H), 7.15-7.35 (m, 4H), 7.82 (s,1H).^{13}C-NMR (75 MHz, $CDCl_3$) 14.2, 18.7, 32.9, 61.4, 81.5, 123.4, 127.4, 129.1, 129.7, 130.0, 132.8, 135.4, 142.6, 166.5. HRMS-EI calcd for $C_{14}H_{16}O_4N_1Br_1$ 343.0242, found: 343.0228.

(S,E)-Ethyl 4-nitro-2-(4-(trifluoromethyl)benzylidene)pentanoate **2-2g**

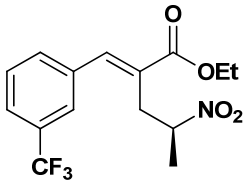


2-2g

A colorless oil, 89% yield; $[\alpha]_c$ = +25.9 (c = 0.54, $CHCl_3$); 92% ee, determined by HPLC analysis [Daicel Chiralcel OJ, *n*-hexane/*i*-PrOH = 99/1, 0.5 mL/min, λ = 254 nm, t (major) = 37.45 min, t (minor) = 33.97 min]; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.38 (t, *J* = 7.2 Hz, 3H), 1.48 (d, *J* = 6.7 Hz, 3H), 2.84-2.91 (m, 1H), 3.13-3.21 (m, 1H), 4.29-4.36 (q, *J* = 7.2 Hz, 2H), 4.87-4.96 (m, 1H), 7.36-7.39 (d, *J* = 7.7 Hz, 2H), 7.66-7.68 (d, *J* = 4.4 Hz, 2H), 7.87 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.2, 19.0,

33.0, 61.6, 81.6, 125.6, 125.7, 128.1, 128.9, 129.6, 141.5, 166.6; HRMS-EI calcd for $C_{15}H_{16}O_4N_1F_3$ 331.1031, found: 331.1028.

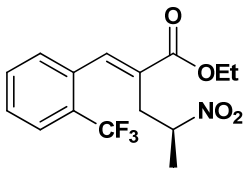
(S,E)-Ethyl 4-nitro-2-(3-(trifluoromethyl)benzylidene)pentanoate **2-2h**



2-2h

A colorless oil, 89% yield; $[\alpha]_c$ = +28.9 (c = 0.45, $CHCl_3$); 92% ee, determined by HPLC analysis [Daicel Chiralcel OB, *n*-hexane/*i*-PrOH = 99.5/0.5, 0.5 mL/min, λ = 254 nm, t (major) = 33.83 min, t (minor) = 44.35 min]; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.37 (t, *J* = 7.1 Hz, 3H), 1.48 (d, *J* = 6.6 Hz, 3H), 2.85-2.91 (m, 1H), 3.14-3.22 (m, 1H), 4.28-4.35 (q, *J* = 7.1 Hz, 2H), 4.89-4.96 (m, 1H), 7.45-7.64 (m, 4H), 7.87 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.2, 19.0, 32.9, 61.6, 81.6, 125.4, 125.5, 129.3, 129.4, 131.8, 135.5, 141.4, 166.6. HRMS-EI calcd for $C_{15}H_{16}O_4N_1F_3$ 331.1031, found: 331.1028.

(S,E)-Ethyl 4-nitro-2-(2-(trifluoromethyl)benzylidene)pentanoate **2-2i**

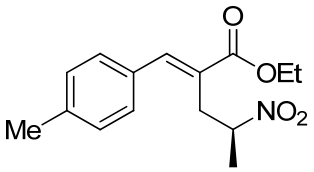


2-2i

A colorless oil, 89% yield; $[\alpha]_c$ = +205.8 (c = 0.31, $CHCl_3$); 62% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 98/2.0, 0.5 mL/min, λ = 254 nm, t (major) = 22.34 min, t (minor) = 25.89 min]; ^{1}H-NMR δ 1.37-1.41 (m, 6H), 2.72-2.78 (m, 1H), 2.91-2.99 (m, 1H), 4.29-4.36 (q, *J* = 7.1 Hz, 2H), 4.77-4.96 (m, 1H), 7.17-7.20 (m, 1H), 7.45-7.73 (m, 3H), 8.01 (s, 1H).^{13}C-NMR (75 MHz, $CDCl_3$)

14.1, 18.8, 33.3, 61.5, 81.4, 126.2, 128.6, 129.8, 130.2, 131.9, 140.1, 166.3. HRMS-EI calcd for $C_{15}H_{16}O_4N_1F_3$ 331.1031, found: 331.1028.

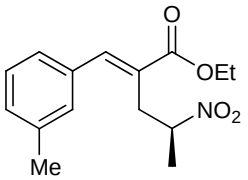
(S,E)-Ethyl 2-(4-methylbenzylidene)-4-nitropentanoate **2-2j**



2-2j

A colorless oil, 85% yield; $[\alpha]_c$ = +21.0 (c = 0.30, $CHCl_3$); 88% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 99/1, 0.5 mL/min, λ = 254 nm, t (major) = 48.48 min, t (minor) = 40.99 min]; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.2 Hz, 3H), 1.47 (d, *J* = 6.6 Hz, 3H), 2.38 (s, 1H), 2.83-3.03 (m, 1H), 3.24-3.32 (m, 1H), 4.26-4.33 (q, *J* = 7.1 Hz, 2H), 4.86-4.93 (m, 1H), 7.22-7.25 (m, 4H), 7.85 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.2, 18.7, 32.8, 61.2, 81.7, 126.6, 128.9, 129.5, 131.8, 139.2, 143.2, 167.3; HRMS-EI calcd for $C_{15}H_{19}O_4N_1$ 277.1314, found: 277.1310.

(S,E)-Ethyl 2-(3-methylbenzylidene)-4-nitropentanoate **2-2k**

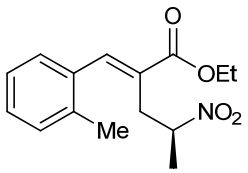


2-2k

A colorless oil, 85% yield; $[\alpha]_c$ = -16.0 (c = 0.37, $CHCl_3$); 92% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 98/2, 0.5 mL/min, λ = 254 nm, t (major) = 27.09 min, t (minor) = 24.65 min]; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.1 Hz, 3H), 1.47 (d, *J* = 1.66 Hz, 3H), 2.38 (s, 3H), 2.93-3.00 (m, 1H), 3.21-3.29 (m, 1H), 4.26-4.33 (q, *J* =7.1 Hz, 2H), 4.86-4.93 (m, 1H), 7.11-7.32 (m,

4H), 7.85 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.4, 18.7, 21.4, 32.8, 61.3, 81.7, 125.8, 127.3, 128.6, 129.5, 129.7, 134.6, 138.4, 143.4, 167.2; HRMS-EI calcd for $C_{15}H_{19}O_4N_1$ 277.1314, found: 277.1310.

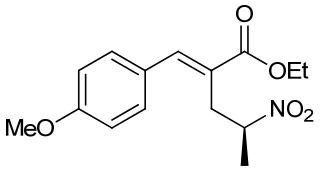
(S,E)-Ethyl 2-(2-methylbenzylidene)-4-nitropentanoate **2-2l**



2-2l

A colorless oil, 84% yield; $[\alpha]_c$ = +21.0 (c = 0.30, $CHCl_3$); 79% ee, determined by HPLC analysis [Daicel Chiralcel OJ, *n*-hexane/*i*-PrOH = 98.5/0.5, 0.5 mL/min, λ = 254 nm, t (major) = 29.39 min, t (minor) = 36.03 min]; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.35-1.41 (m, 6H), 2.75-2.82 (m, 1H), 3.06-3.14 (m, 1H), 4.28-4.35 (q, *J* = 7.1 Hz, 2H), 4.80-4.92 (m, 1H), 7.04-7.25 (m, 4H), 7.91 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.2, 18.8, 19.8, 61.3, 81.8, 125.8, 127.9, 128.2, 128.7, 130.2, 134.1, 136.6, 143.2, 166.9. HRMS-EI calcd for $C_{15}H_{19}O_4N_1$ 277.1314, found: 277.1310.

(S,E)-Ethyl 2-(4-methoxybenzylidene)-4-nitropentanoate **2-2m**

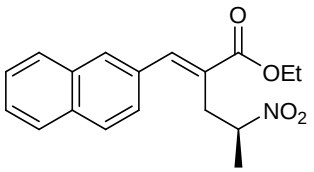


2-2m

A colorless oil, 87% yield; $[\alpha]_c$ = +22.0 (c = 0.30, $CHCl_3$); 92% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 98.5/0.5, 0.5 mL/min, λ = 254 nm, t (major) = 64.93 min, t (minor) = 55.08 min]; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.36 (t, *J* = 7.1 Hz, 3H), 1.49 (d, *J* = 6.5 Hz, 3H), 2.99-3.06 (m, 1H), 3.27-3.34 (m, 1H), 3.85 (s,3H), 4.25-4.32 (q, *J* = 7.1 Hz, 2H), 4.87-4.94 (m, 1H), 6.92-6.95 (d, *J* =

5.9 Hz, 2H), 7.31-7.34 (d, *J* = 8.4 Hz, 2H), 7.82 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.2, 18.7, 32.8, 55.3, 61.2, 114.3, 125.3, 127.0, 130.9, 142.8, 160.3. HRMS-APCI calcd for $C_{15}H_{18}NO_5$ 292.1202, found: 292.1190.

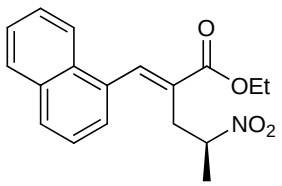
(S,E)-Ethyl 2-(naphthalen-2-ylmethylene)-4-nitropentanoate **2-2n**



2-2n

A colorless oil, 76% yield; $[\alpha]_c$ = -91.9 (c = 0.45, $CHCl_3$); 79% ee, determined by HPLC analysis [Daicel Chiralcel OJ, *n*-hexane/*i*-PrOH = 99/1, 0.5 mL/min, λ = 254 nm, t (major) = 37.84 min, t (minor) = 20.30 min]; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7.1 Hz, 3H), 1.48 (d, *J* = 6.8 Hz, 3H), 3.02-3.09 (m, 1H), 3.32-3.39 (m, 1H), 4.30-4.37 (q, *J* = 7.2 Hz, 2H), 4.93-5.00 (m, 1H), 7.41-7.43 (m, 1H), 7.44-7.54 (m, 2H), 7.80-7.89 (m, 4H), 8.04 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.2, 18.8, 33.0, 61.3, 81.7, 126.0, 126.6, 127.7, 128.4, 128.7, 132.1, 133.1, 143.2, 167.2. HRMS-EI calcd for $C_{18}H_{19}O_4N_1$ 313.1314, found: 313.1310.

(S,E)-Ethyl 2-(naphthalen-1-ylmethylene)-4-nitropentanoate **2-2o**

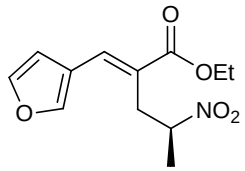


2-2o

A colorless oil, 43% yield; $[\alpha]_c$ = -30.4 (c = 0.30, $CHCl_3$); 72% ee, determined by HPLC analysis [Daicel Chiralcel OJ, *n*-hexane/*i*-PrOH = 99/1, 0.5 mL/min, λ = 254 nm, t (major) = 49.08 min, t (minor) = 54.82 min]; ^{1}H-NMR (300 MHz, $CDCl_3$) δ

1.38-1.43 (m, 6H), 2.63-2.80 (m, 1H), 3.14-3.21 (m, 1H), 4.20-4.23 (m, 1H), 4.30-4.38 (q, *J* = 7.2 Hz, 2H), 7.37-7.56 (m, 6H), 7.69-7.70 (m, 1H), 7.71 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.2, 18.7, 33.4, 61.4, 81.7, 124.5, 125.2, 125.8, 126.4, 126.6, 128.6, 129.1, 142.3, 166.8. HRMS-EI calcd for $C_{18}H_{19}O_4N_1$ 313.1314, found: 313.1310.

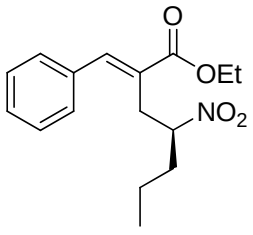
(S,E)-Ethyl 2-(furan-3-ylmethylene)-4-nitropentanoate **2-2p**



2-2p

A colorless oil, 84% yield; $[\alpha]_c$ = +61.8 (c = 0.40, $CHCl_3$); 84% ee, determined by HPLC analysis [Daicel Chiralcel OJ, *n*-hexane/*i*-PrOH = 99/1, 0.5 mL/min, λ = 254 nm, t (major) = 52.01 min, t (minor) = 47.23 min]; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.1 Hz, 3H), 1.55 (d, *J* = 5.3 Hz, 3H), 3.24-3.31 (m, 1H), 3.46-3.53 (m, 1H), 4.23-4.30 (q, *J* = 7.1 Hz, 2H), 4.81-4.90 (m, 1H), 6.51-6.52 (m, 1H), 6.52-6.70 (m, 1H),7.52 (s, 1H), 7.57 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.2, 18.5, 33.1, 61.3, 82.4, 112.3, 117.5, 122.6, 128.1, 145.2, 150.7, 167.4. HRMS-EI calcd for $C_{12}H_{15}O_5N_1$ 253.0950, found: 253.0948.

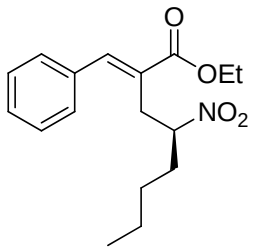
(S,E)-Ethyl 2-benzylidene-4-nitroheptanoate **2-2q**



2-2q

A colorless oil, 95% yield; $[\alpha]_c$ = -12.5 (c =0.73, $CHCl_3$); 94% ee, determined by HPLC analysis [Daicel Chiralcel OJ, *n*-hexane/*i*-PrOH = 99/1, 0.5 mL/min, λ = 254 nm, t (major) = 31.78 min, t (minor) = 27.24 min]; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.0 Hz, 3H), 1.26-1.31 (m, 2H), 1.37 (t, *J* = 7.0 Hz, 3H) 1.60-1.67 (m, 1H), 1.88-1.95 (m, 1H), 2.90-2.96 (m, 1H), 3.20-3.25 (m, 1H), 4.28-4.33 (q, *J* = 7.0 Hz, 2H), 4.80-4.86 (m, 1H), 7.28-7.412 (m, 5H), 7.87 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.3, 14.2, 19.0, 31.7, 35.4, 61.3, 86.8, 127.7, 128.7, 134.8, 143.2, 167.2; HRMS-EI calcd for $C_{16}H_{21}O_4N_1$ 291.1471, found 291.1465.

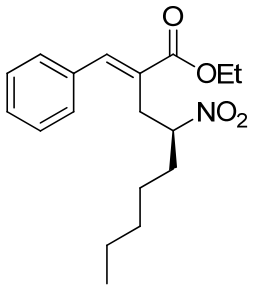
(S,E)-Ethyl 2-benzylidene-4-nitrooctanoate **2-2r**



2-2r

A colorless oil, 90% yield; $[\alpha]_c$ = -153.9 (c = 0.36, $CHCl_3$); 92% ee, determined by HPLC analysis [Daicel Chiralcel OJ, *n*-hexane/*i*-PrOH = 99/1, 0.5 mL/min, λ = 254 nm, t (major) = 23.42 min, t (minor) = 19.59 min]; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7.0 Hz, 3H), 1.20-1.31 (m, 4H), 1.37 (t, *J* = 7.0 Hz, 3H) 1.65-1.70 (m, 1H), 1.87-1.95 (m, 1H), 2.92-2.96 (m, 1H), 3.20-3.24 (m, 1H), 4.28-4.32 (q, *J* = 7.0 Hz, 2H), 4.78-4.83 (m, 1H), 7.28-7.41 (m, 5H), 7.87 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.6, 14.2, 22.0, 27.7, 31.6, 33.1, 61.3, 87.1, 127.6, 128.6, 128.8, 134.7, 143.2, 167.1; HRMS-EI calcd for $C_{17}H_{23}O_4N_1$ 305.1627, found 305.1626.

(S,E)-ethyl 2-benzylidene-4-nitrononanoate **2-2s**

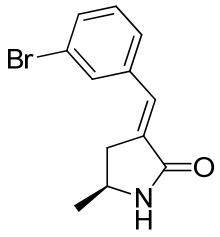


2-2s

A colorless oil; 87% yield; $[\alpha]_c$ = +28.1 (c = 0.26, $CHCl_3$); 93% ee, determined by HPLC analysis [Daicel Chiralcel OJ, *n*-hexane/*i*-PrOH = 99/1, 0.5 mL/min, λ = 254 nm, t (major) = 20.70 min, t (minor) = 18.17 min]; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.24-1.25 (m, 6H), 1.37 (t, *J* = 7.0 Hz, 3H), 1.63-1.67 (m, 1H), 1.87-1.93 (m, 1H), 2.92-2.95 (m, 1H), 3.20-3.24 (m, 1H), 4.28-4.32 (q, *J* = 7.0 Hz, 2H), 4.78-4.83 (m, 1H), 7.28-7.42 (m, 5H), 7.87 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.8, 14.2, 22.2, 25.3, 31.0, 31.6, 33.4, 61.3, 87.1, 127.6, 128.6, 128.7, 128.8, 134.7, 153.6, 167.1; HRMS-EI calcd for $C_{18}H_{25}O_4N_1$ 319.1784, found: 319.1781.

2.4.8 Analytical Data of α-Alkylidene-γ-butyrolactam 2-6 and Pyrrolidine 2-8

(S,E)-3-(3-Bromobenzylidene)-5-methylpyrrolidin-2-one **2-6**

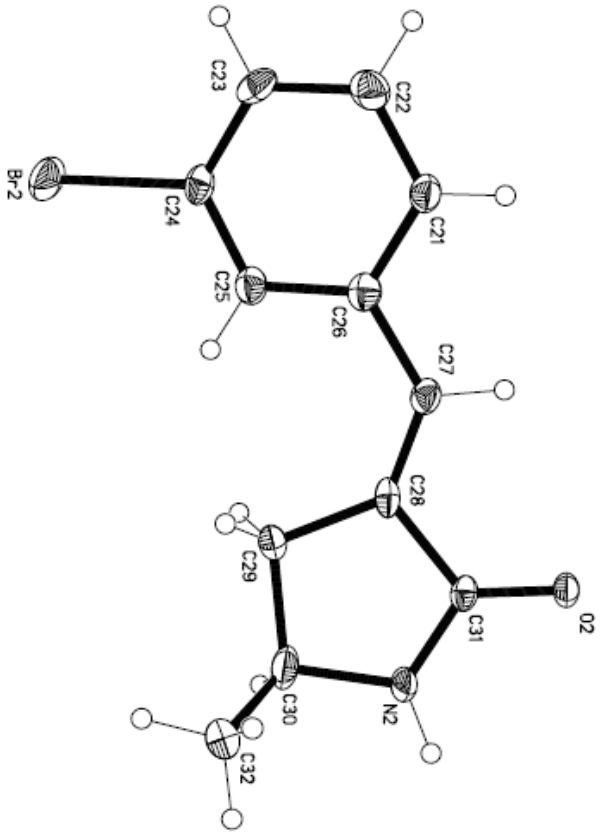


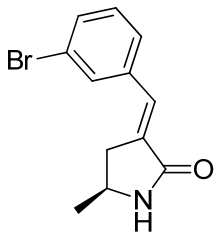
2-6

A white solid; 80% yield; $[\alpha]_c$ = +33.3 (c = 2.9, $CHCl_3$); 92% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 80/20, 1.0 mL/min, λ = 254

nm, t (major) = 19.01 min, t (minor) = 16.78 min]; ^{1}H-NMR (300MHz, $CDCl_3$) δ 1.33 (d, *J* = 6.2 Hz, 3H), 2.61-2.69 (m, 1H), 3.26-3.35 (m, 1H), 3.87-3.97 (m, 1H), 6.79 (s, 1H), 7.24-7.47 (m, 4H), 7.59 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 23.4, 34.9, 47.4, 122.8, 128.3, 129.1, 130.2,131.4, 131.9, 137.8, 171.2; HRMS-EI calcd for $C_{12}H_{12}O_1N_1Br_1$ 267.0082, found: 267.0064.

Data of X-ray diffraction of compound 2-6



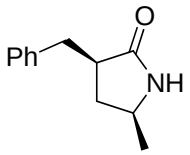


2-6

Identification code	**2-6**
Empirical formula	C_{12} H_{14} Br N O_2
Formula weight	284.15
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic

Space group	P2(1)
Unit cell dimensions	a = 12.722(3) Å = 90°.
	b = 4.8282(11) Å = 96.755(5)°.
	c = 19.810(5) Å = 90°.
Volume	1208.4(5) $Å^3$
Z	4
Density (calculated)	1.562 Mg/m^3
Absorption coefficient	3.387 mm^{-1}
F(000)	576
Crystal size	0.50 x 0.20 x 0.06 mm^3
Theta range for data collection	1.04 to 27.50°.
Index ranges	-15<=h<=16, -6<=k<=6, -24<=l<=25
Reflections collected	8403
Independent reflections	5107 [R(int) = 0.0351]
Completeness to theta = 27.50°	99.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8226 and 0.2822
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5107 / 5 / 309
Goodness-of-fit on F^2	0.993
Final R indices [I>2sigma(I)]	R1 = 0.0443, wR2 = 0.1054
R indices (all data)	R1 = 0.0569, wR2 = 0.1118
Absolute structure parameter	0.021(14)
Largest diff. peak and hole	1.552 and -0.563 $e.Å^{-3}$

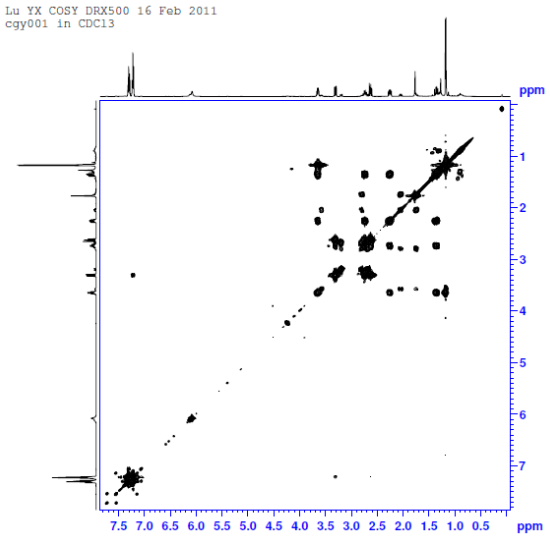
(3R,5S)-3-benzyl-5-methylpyrrolidin-2-one **2-8**

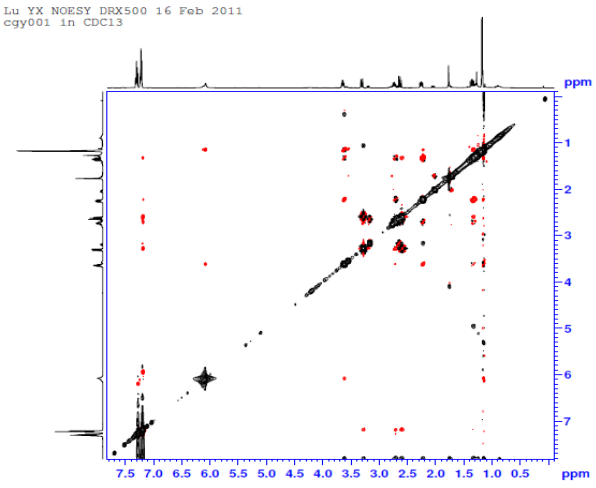


2-8

^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.16 (m, 3H), 1.33-144 (m, 1H), 2.24-2.29 (m, 1H), 2.61-2.75 (m, 2H), 3.30-3.33 (m, 1H), 3.65-3.66 (m, 1H), 6.03 (s, 1H), 7.22-7.31 (m, 5H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 22.0, 36.2, 36.8, 44.2, 48.0, 126.2, 128.4, 128.9, 129.0, 139.7, 178.6; HRMS-ESI calcd for [M + Na] $C_{12}H_{15}NNaO$, 212.1046, found: 212.1040.

The relative configuration was determined by COSY and NOESY spectrum which was shown in the following.




Lu YX NOESY DRX500 16 Feb 2011
cgy001 in CDCl3
ppm
1
2
3
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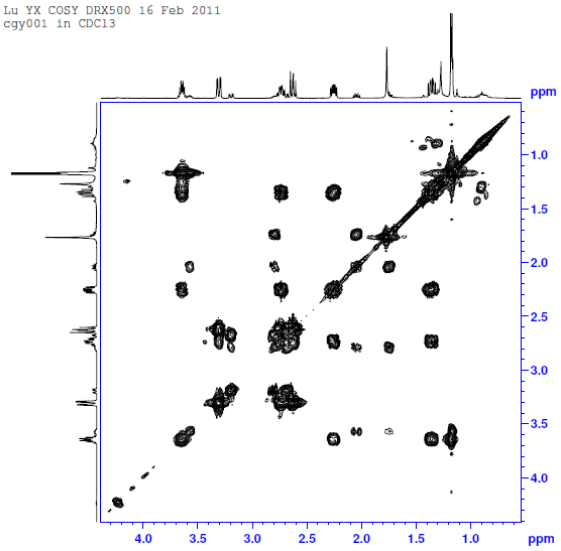
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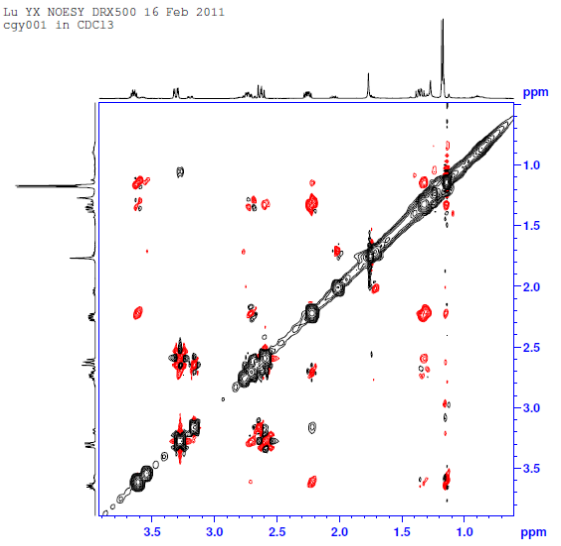
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Chapter 3 Enantioselective Allylic Substitution Reaction of Isatin-Derived Morita–Baylis–Hillman Carbonates with Nitroalkanes

3.1 Introduction

The 3,3'-disubstituted oxindole motifs are widely present in natural products and pharmaceutical compounds.[90] Due to the significance of the oxindole scaffolds, many methods have been developed for the synthesis of chiral 3,3'-disubstituted oxindoles (**Figure 3.1**). Utilization of isatins as a precursor to obtain versatile oxindole compounds has become an important approach for constructing oxindole motifs. The nucleophilicity of 3-substituted oxindole has been well realized and utilized in the organocatalytic asymmetric reactions.[34, 37] Our group reported the asymmetric reaction of 3-substituted oxindole and vinyl sulfones employing multi-funcational catalysts derived from cinchona alkaloids and amino acids.[91] The electrophilic approaches were also explored by several research groups.[38] The MBH carbonates derived from isatins would serve as an ideal reaction partner to access 3,3'-disubstituted oxindoles. The allylic substitution of MBH carbonates of isatins with α,α-dicyanoalkene was reported by Chen and co-workers in 2010.[36] The nucleophilic catalyst β-isocupreidine promoted the reaction well, affording products with up to 88% ee. This method provided the first example of organocatalytic asymmetric allylic substitution reaction using MBH carbonates derived from ketones. It was till 2012 that other nucleophiles were successfully applied in the organocatalytic asymmetric allylic alkylation reaction with MBH carbonates of isatins. Chen and co-workers reported an asymmetric allylic alkylation of MBH carbonates with aliphatic substituted γ-butenolides in the presence of Me-β-isocupreidine and (R)-BINOL.[64]

The reaction could be slightly accelerated by the addition of 4Å molecular sieves and (R)-BINOL.

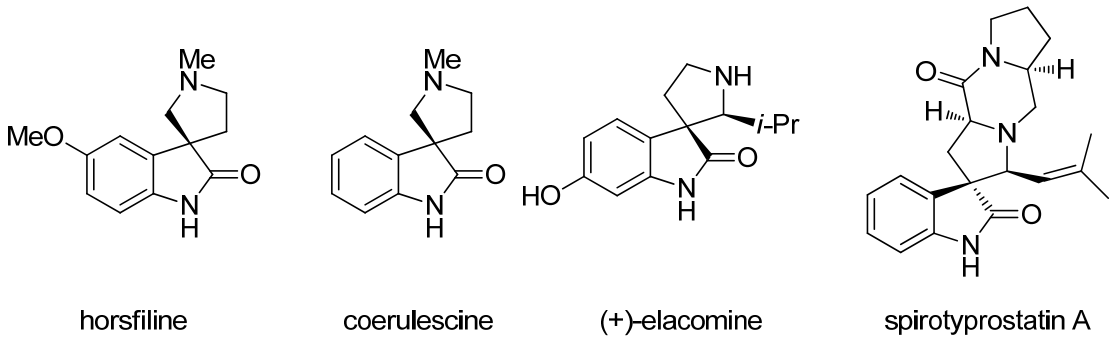
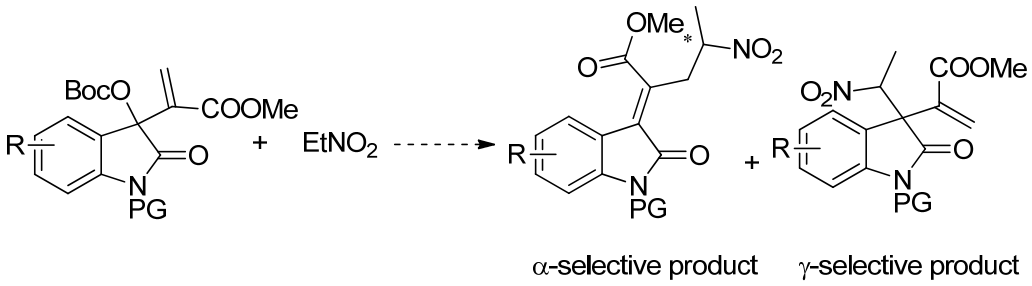


Figure 3.1 Representative natural products and bioactive compounds with the 3,3'-disubstituted oxindole framework

Our group has developed several organocatalytic asymmetric reactions of MBH carbonates.[92] To develop practical synthetic method, we reported the reaction of MBH carbonates and nitroalkanes in a proposed S_N2'-S_N2 mechanism, which has been well elaborated in the Chapter 2. The asymmetric reaction of MBH carbonates of isatins has attracted much attention, although nucleophiles employed in this type of reaction are very limited. There was no report on the application of nitroalkanes in the reaction with MBH carbonates. In this thesis, we investigated asymmetric allylic alkylation of MBH carbonates of isatins and nitroalkanes. The products of MBH carbonates of isatins and nitroalkanes could be derived to interesting structural motifs which may be important in medicinal chemistry or pharmaceutical industry.



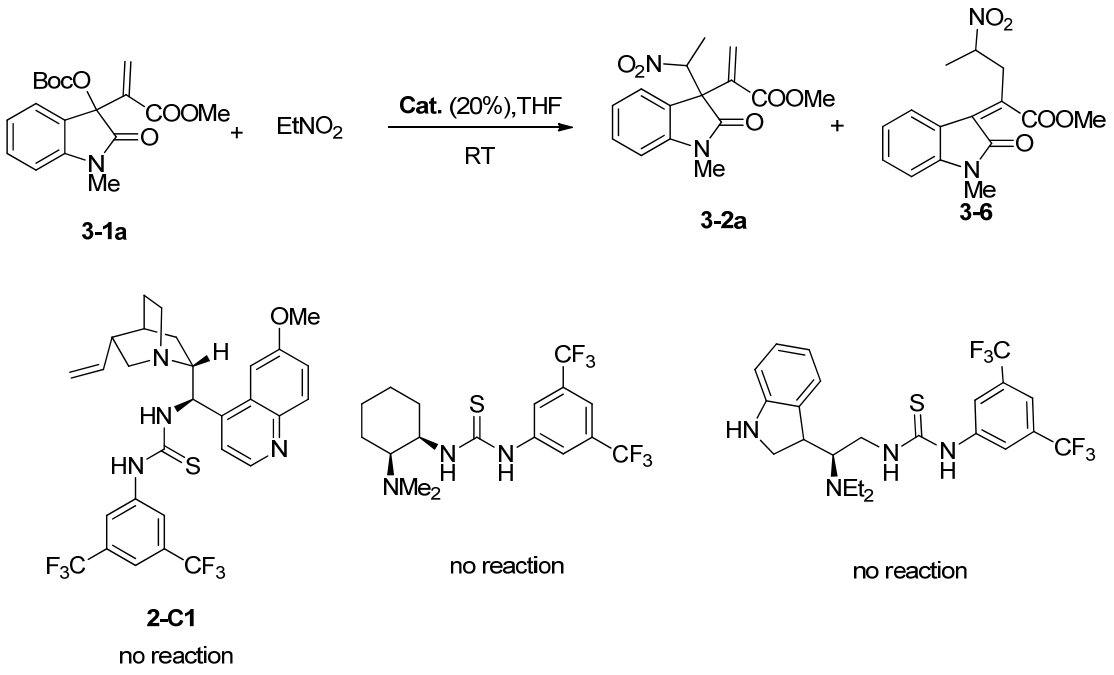
Scheme 3.1 Research plan for the asymmetric reaction of MBH carbonates of isatin

Herein, we will discuss the organocatalytic asymmetric reaction of MBH carbonates of isatins and nitroalkanes. Based on the successful reaction of MBH carbonates and nitroalkanes catalyzed by tertiary amine-thiourea catalyst, both types of products were our target molecules (**Scheme 3.1**).

3.2 Results and Discussion

3.2.1 Preliminary Screening

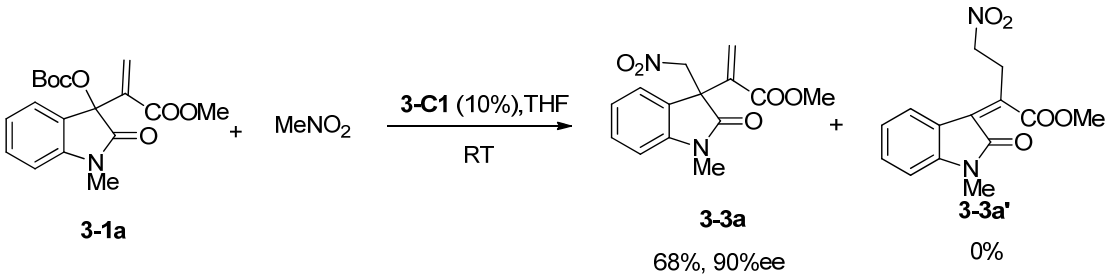
The reaction of MBH carbonates with nitroalkanes was examined in the presence of the tertiary amine-thiourea catalyst derived from quinidine and the α-selective products were obtained in high regioselectivity and enantioselectivity. We first planned to test the reaction of isatin-derived MBH carbonates with nitroalkane using the same catalytic system to afford the α-selective product with oxindole scaffold. The reaction of MBH carbonate **3-1a** derived from N-methylisatin with nitroethane was examined in the presence of tertiay amine-thiourea catalyst **2-C1.** However, only starting material MBH carbonates could be seen from TLC even the reaction mixture was heated to 50 ℃ for two days (**Scheme 3.2**). We reasoned that the big steric hindrance of quinidine scaffold and isatin unit suppress the first step of nucleophilic addition of catalyst **2-C1** to MBH carbonate **3-6**. Then we decided to use other tertiary amine-thiourea catalysts with less rigid scaffold such as Takemoto's catalyst in the asymmetric reaction of MBH carbonate **3-1a** and nitroethane. However, the same result was obtained. This may indicate that the steric hindrance of isatin unit plays a key role in this reaction.



Scheme 3.2 Preliminary screening of asymmetric reaction of isatin-derived MBH carbonate with nitroethane

Other nucleophilic catalysts were also tested in the reaction of MBH carbonates of isatin with nitroalkanes. Nitromethane which is more nucleophilic than nitroethane was chosen in the reaction of MBH carbonate **3-1a** derived from N-methylisatin. When other catalysts such as quinindine, catalyst **2-C2**, were applied in the reaction, the same results were obtained. This also may be caused by the big steric hindrance. The other type of catalyst β-isocupreidine which has been found effective in the asymmetric catalytic MBH reaction of isatin and acrylate with high enantioselectivity could catalyze the asymmetric allylic amination reaction of MBH carbonate to afford γ-selective product. The reaction of compound **3-1a** and nitromethane proceeded smoothly under the condition of β-isocupreidine **3-C1** at room temperature in less than one day. The compound **3-3a** was obtained with high regioselectivity, moderate yield and high enantioselectivity (**Scheme 3.3**). The starting material **3-1a** was consumed completely and other by-products could not be identified. Futhermore,

isatin-derived MBH carbonates with different protecting group were used in this reaction. When MBH carbonates derived N-Boc isatin was used in the asymmetric allylic alkylation reaction with nitromethane, no desired product could be obtained. The MBH carbonates derived from N-Bn isatin was used in the same condition and the allylic substitution product was obtained with fair yield and good enantioselectivity (33%, 86% ee).



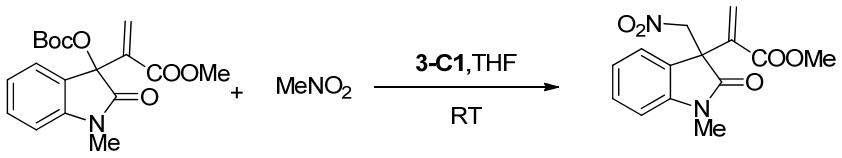
Scheme 3.3 Preliminary screening of asymmetric reaction of isatin-derived MBH carbonate with nitromethane

3.2.2 Reaction Optimization

Further study has been done due to the highly enantioselective allylic substitution of isatin-derived MBH carbonates with nitromethane. To improve the reaction yield, the reaction concentration, catalyst loading and solvent were screened consecutively. Lowering the catalyst loading could decrease the reaction rate and the yield and selectivity of major product **3-3a** dropped (Table 3.1, entry 1, 2 and 3). Decreasing the concentration of the reaction mixture could generate the desired product **3-3a** with the same yield and higher enantioselectivity. Increasing the concentration would decrease both yield and enantioselectivity (Table 3.1, entry 1, 4 and 5). It seems that the yield and enantioselectivity of the compound **3-3a** could not be improved by simple adjustment of concentration and catalyst loading. Then solvents were screen to pursue better reaction condition. The ether type of solvent

diethyl ether could provide the product **3-3a** with the similar yield but lower enantioselectivity (Table 3.1, entry 6). The reaction using dichloromethane or chloroform could afford the product **3-3a** with lower yield and lower enantioselectivity (Table 3.1, entry 7 and 8). Small polar solvent such as toluene also coud not provide the good result (Table 3.1, entry 9). The strong polar solvent DMF and polar protic solvent MeOH could give the compound **3-3a** with both lower yield and lower enantioselectivity (Table 3.1, entry 10 and 11).

Table 3.1 Optimization of asymmetric allylic substitution of MBH carbonate of isatin with nitromethane

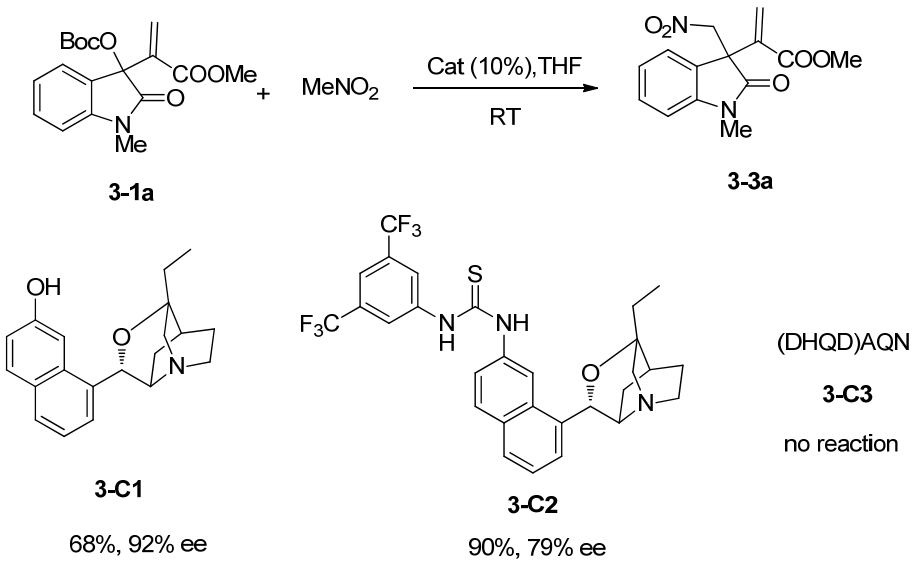


3-1a **3-3a**

Entry	concentration (mol/L)	Catalyst loading (%)	solvent	Yield (%)[c]	ee (%)[d]
1	0.25	10	THF	68	90
2[d]	0.25	5	THF	51	89
3[d]	0.25	1	THF	28	74
4	0.50	10	THF	32	86
5	0.13	10	THF	68	92
6	0.25	10	Et_2O	68	83
7	0.25	10	CH_2Cl_2	55	81
8	0.25	10	CH_3Cl	50	65
9	0.25	10	toluene	68	85
10	0.25	10	DMF	17	<60
11	0.25	10	MeOH	<10	64

[a] Reactions were conducted with **3-1a** (0.025 mmol), nitromethane (0.25 mmol) and the catalyst (x mol%) at room temperature for one day. [b] Isolated yield. [c] The ee value was determined by HPLC analysis on a chiral stationary phase. [d] The reaction proceeded for two days.

It seems that the reaction yield could not be improved under the catalyst **3-C1**. Other nucleophilic catalysts were also tested in the asymmetric allylic substitution reaction (**Scheme 3.4**). $(DHQD)_2AQN$ which was successful in many asymmetric allylic substitution reaction was utilized in the asymmetric reaction of MBH carbonate of isatin **3-1a** and nitromethane. The reaction could not proceed which would be expected as the steric hindrance between catalyst and substrate **3-1a**. The thiourea catalyst **3-C2** derived from **3-C1** could give better yield of the desire product **3-3a** (90, 79% ee). However the enantioselectivity was dropped a lot. For further study, we chose the catalyst 3-C1 as the best catalyst and THF as the best solvent.



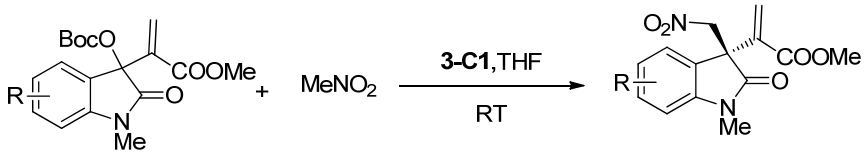
Scheme 3.4 Catalyst screening of asymmetric reaction of MBH carbonate of isatin with nitromethane

3.2.3 Substrate Scope

With the optimized reaction conditions in hand, the substrate scope of MBH carbonate **3-1a** derived from isatin was studied in the reaction with nitromethane (**Table 3.2**). The MBH carbonate **3-1** with different substituent was used in the reaction with nitromethane under the catalyst β-isocupreidine. The MBH catbonate

containing substituent on the oxindole ring at 5-position would be suitable substrate in this asymmetric allylic substitution reaction with nitromethane. The desired product **3-3** could be obtained with reasonable yield and good enantioselectivity (Table 3.2, entry 2, 3, 4 and 5). However, the reaction of MBH carbonate **3-1g** with a 5-nitro substituent and nitromethane could not provide the desired product **3-3g** and the complicated result would be observed (Table 3.2, entry 7). The good electron withdrawing property result in the good reactive of the MBH carbonate **3-1g** which could be too reactive to obtain the desired product. The 7-substituent on the MBH carbonate could also not provide the desired allylic product and messy reaction was observed (Table 3.2, entry 8 and 9). The good reactivity of substrate **3-3h** and **3-3i** caused the complicated reaction of MBH carbonate and nitromethane under the catalyst **3-C1**. Moreover, the MBH carbonate **3-3f** with 5,7-dimethyl substituent could provide the desired product **3-3f** with moderate yield and good enantioselectivity.

Table 3.2 Enantioselective allylic substitution reactions of MBH carbonate **3-1** with nitromethane[a]



3-1 **3-3**

Entry	R	Product	Yield (%)[b]	ee (%)[c]
1	H	**3-3a**	68	92
2[d]	5-F	**3-3b**	81	88
3	5-Cl	**3-3c**	52	95
4	5-Br	**3-3d**	65	92
5	5-MeO	**3-3e**	50	90
6[d]	5,7-Dimethyl	**3-3f**	50	88
7[e]	5-NO_2	**3-3g**	-	-
8[e]	7-F	**3-3h**	-	-

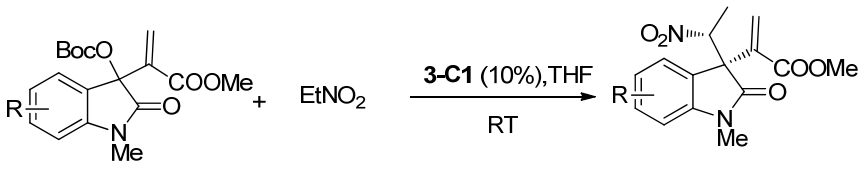
9[e]	7-Cl	**3-3i**	-	-

[a] Unless otherwise specified, reactions were conducted with **3-1** (0.025 mmol), nitromethane (0.25 mmol) and **3-C1** (10 mol%) in THF (0.2 mL) at room temperature. [b] Isolated yield. [c] The ee value was determined by HPLC analysis on a chiral stationary phase. [d] The solvent was used in 0.1 mL. [e]No desired product.

Although the yield of the asymmetric allylic alkylation reaction of MBH carbonate derived from isatin and nitromethane was not satisfying, the enantioselectivity was good. The reason for the low yield may be that the reactivity of nitromethane and MBH carbonate was too good to form byproducts. Less reactive nitroalkane was examined in the allylic substitution reaction of MBH carbonate of isatin. Considering that the increased stereocenter would cause more stereoisomer, we decided to use 2-nitropropane as substrates in the reaction with MBH carbonate **3-1a**. The reaction could not go due to the steric hindrance which would generate in the process of forming the product **3-2a**. The low acidity of α-proton of 2-nitropropane may also suppress the reaction with MBH carbonate **3-1a**. Therefore nitroethane was utilized in the asymmetric allylic substitution reaction of MBH carbonate of isatin. The reaction of MBH carbonate **3-1a** and nitroethane was firstly examined under the catalyst **3-C1**. The reaction could proceed with full conversion (90% conversion from crude ^{1}H-NMR), low diastereoselectivity, high regioselectivity and enantioselectivity. The two diastereomer **3-2a** and **3-2a'** could be separated easily by simple column chromatography. The major isomer **3-2a** was tested with reasonable yield and high enantioselectivity (Table 3.2, entry 1). The minor isomer **3-2a'** was also obtained with 33% yield and 91% ee. Other MBH carbonates of isatin were also useful under this catalytic system. The MBH carbonate of isatin with 5-substituent could provide the desired product with high enantioselectivity except the 5-nitro substituted MBH carbonate **3-1g** (Table 3.2, entry 2, 3, 4, 5 and 7). The MBH carbonate **3-1g** could not

provide desired product. In the reaction of MBH carbonate **3-1g** and nitroethane, the nitro substituent may interact with the catalyst which would result in the messy reaction. Other 5-substituted MBH carbonate of isatin would provide the product with low diastereoselectivity and high enantioselectivity. As expected, 5,7-dimethyl substituted substrate **3-1f** would react with nitroethane to afford the product with excellent conversion, low diastereoselectivity and high enantioselectivity (Table 3.2, entry 6). The 7-substituent of MBH carbonate of isatin was also applicable in the reaction with nitroethane under the catalyst **3-C1**. The desired product could be obtained with excellent conversion, low diastereoselectivity and high enantioselectivity (Table 3.2, entry 8 and 9). In contrast with 5-substituted MBH carbonate, the enantioselectivity was slightly decreased. It should be noted that the diastereoselectivity was the same for all the asymmetric allylic alkylation reaction (d.r. = 2:1). All the diastereomers generated from each reaction could be sepereated easily by column chromatography.

Table 3.3 Enantioselective allylic substitution reaction of MBH carbonates **3-1** with nitroethane[a]



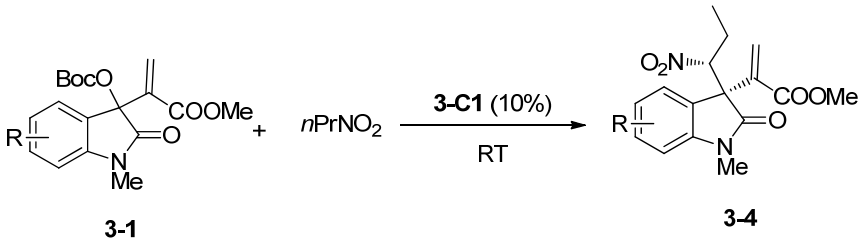
3-1 **3-2**

Entry	R	Yield (%)[b]	d.r.[c]	ee (%)[d]
1	H	66	2:1	90/91
2	5-F	54	2:1	89/89
3	5-Cl	54	2:1	89/87
4	5-Br	55	2:1	89/89
5	5-MeO	57	2:1	90/85
6	5,7-Dimethyl	55	2:1	90/89

7	5-NO_2	-	-	-
8	7-F	50	2:1	87/86
9	7-Cl	62	2:1	84/81

[a] Unless otherwise specified, reactions were conducted with **3-1** (0.025 mmol), nitromethane (0.25 mmol) and **3-C1** (10 mol%) in THF (0.1 mL) at room temperature. [b] Isolated yield of major isomer. [c] The diastereoselectiuvity was determined by crude ^{1}H-NMR. [d] The ee value was determined by HPLC analysis on a chiral stationary phase.

Moreover, we intended to explore the substrate scope with other nitroalkanes. Nitropropane was chose to react with MBH carbonate **3-1a** under the catalyst **3-C1**. The sluggish reaction happened when nitropropane and nitrobutane were used. The neat condition was used in the reaction of MBH carbonate and nitropropane (**Scheme 3.5**). The reaction of MBH carbonate **3-1a** and nitropropane (50 equivalents) could provide the compound **3-4a** with full conversion under neat condition. The product (**3-4a**) could be obtained with high yield, high diastereoselectivity and high enantioselectivity. The MBH carbonate with 5-Methoxyl substituent was used in the reaction with nitropropane to afford the product **3-4e**. The best diastereoselectivity was achieved in this asymmetric allylic alkylation reaction. The compound **3-4e** was obtained with high yield, high diastereoselectivity and high enantioselectivity. In the contrast, 5-bromo substituted MBH carbonate **3-1d** would provide the allylic product with full conversion, low diastereoselectivity and high enantioselectivity. The reaction of MBH carbonate and nitropropane catalyzed by bifuncational catalyst 3-C1 possess good reactivity and good enantioselectivity under the neat condition. The substrate with electron donating substituent on the 5 position could give the product with high diastereoselectivity. The substrate with halogen substituent on the 5 position could give the product with lower diastereoselectivity.

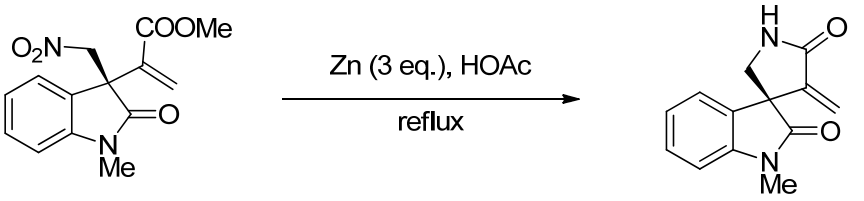


R = H, 90%, d.r. = 10: 1, 88% ee
R = 5-MeO, 92%, d.r. = 13: 1, 89% ee
R = 5-Br, 70%, d.r. = 2.5: 1, 87% ee

Scheme 3.5 Asymmetric allylic substitution reaction of MBH carbonates of isatin with nitropropane

3.2.4 Synthetic Utility

The product of asymmetric allylic alkylation of MBH carbonate and nitroalkane could be transforedm to a spirocyclic oxindole compound, which possesses interesting structure and may be potentially useful in medicinal chemistry. [76, 90] The compound **3-5** could be achieved by simple treatment of asymmetric allylic alkylation product **3-3a** using Zn/HOAc (**Scheme 3.5**).

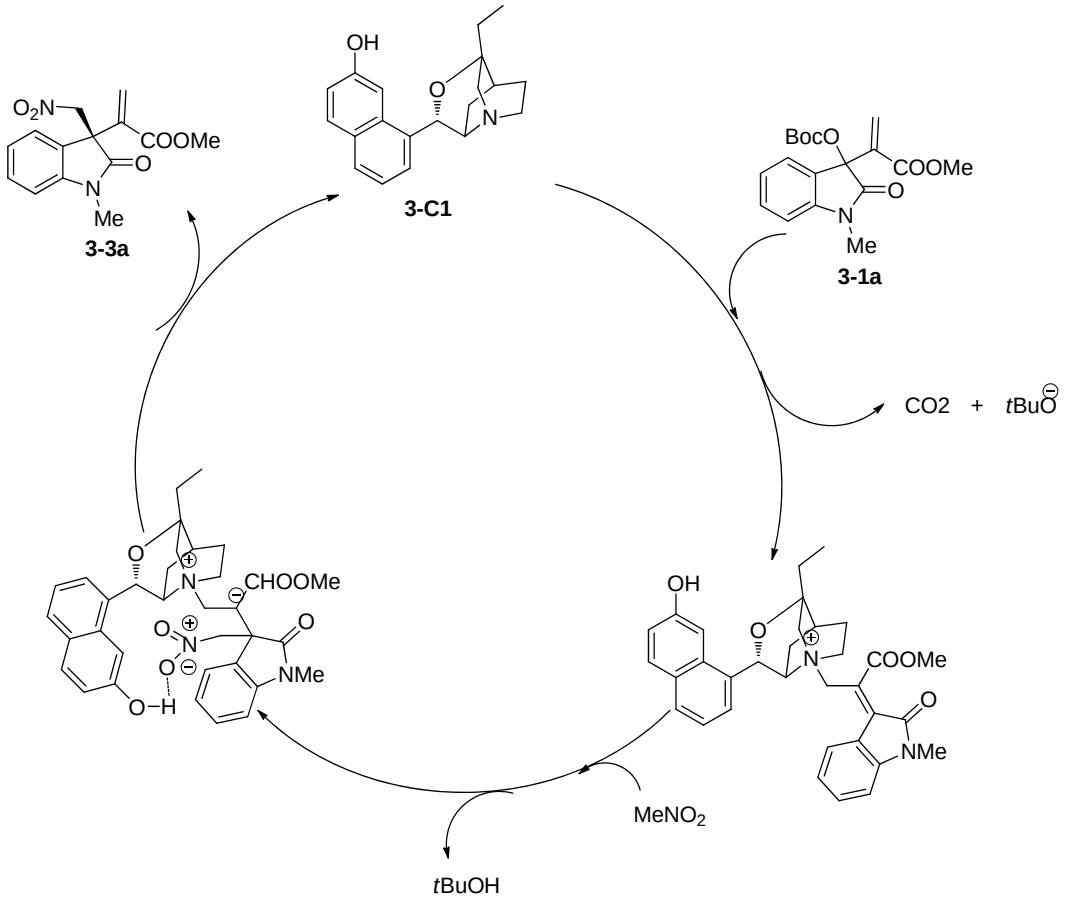


Scheme 3.5 Preparation of a spirocyclic oxindole derivative

The absolute configuration of the chiral allylic product was determined by the analysis of single crystal of compound **3-4d**. The X-ray diffraction experiment showed that the absolute configuration of compound **3-4d** was (R, R). The absolute configuration of other allylic products **3-2**, **3-3**, and **3-4** was determined by the analogy of compound **3-4d**.

3.2.5 Plausible Reaction Mechanism

Since the asymmetric allylic alkylation reaction of MBH carbonate of isatin and nitroalkanes was successfully developed, the reaction mechanism was proposed (**Scheme 3.6**). The asymmetric allylic substitution reaction of MBH carbonate has been well explored under the tertiary amine catalyst derived from cinchona alkaloid and the well accepted mechanism was a S_N2'-S_N2' process. Herein, we also proposed a S_N2'-S_N2' reaction mechanism for this reaction.



Scheme 3.7 Proposed mechanism of asymmetric allylic substitution reaction of isatin-derived MBH carbonates with nitroalkane

The nucleophilic catalyst **3-C1** could attack the carbon-carbon double bond of MBH carbonate **3-1a**. A S_N2' reaction occurred and dicarbon oxide and *tert*-butyl oxide ion were generated *in situ*. When nitromethane was added, it would be

deprotonated by the Brønsted base *tert*-butyl oxide ion. With the assistance of hydrogen bonding between hydroxyl group on catalyst and nitro group, the nucleophilic nitromethane could attack the activated MBH carbonate. The catalyst **3-C1** could be regenerate after a second S_N2' and the product **3-3a** was formed.

The π-π stacking effect could exist between nucleophilic catalyst **3-C1** and MBH carbonate **3-1** which may benefit the good reactivity. The nucleophile nitromethane could attack from the front side of isatin due to the catalyst configuration and hydron bonding which result in the R configuration of the product **3-3a**. For other nucleophiles, the absoluate configuration at 3 position of oxindole was also R configuration. The diastereoselectivity may be mainly influenced by the electron property of MBH carbonate **3-1**. The less stereocontrol of the prochiral center nitroethane may also the reason for low diatereoselectivity.

3.3 Conclusions

In summary, we have developed a new organocatalytic asymmetric allylic alkylation reaction of MBH carbonate derived from isatin. The reaction of MBH carbonate **3-1** and nitroalkane would occur under the bifunctional catalyst **3-C1** derived from cinchona alkaloid. The allylic alkylation product **3-2**, **3-3**, **3-4** could be obtained with moderate to high yield, low to high diastereoselectivity and high enantioselectivity. The allylic product **3-3a** with oxindole scaffold could easily transform to the spiro compound **3-5** under reducing condition without impairing the enantioselectivity. The spiro compounds could be potentially useful in medicinal chemistry because there are wide existence of biologically active molecules with spirooxindole motif in nature and pharmaceutical industry.

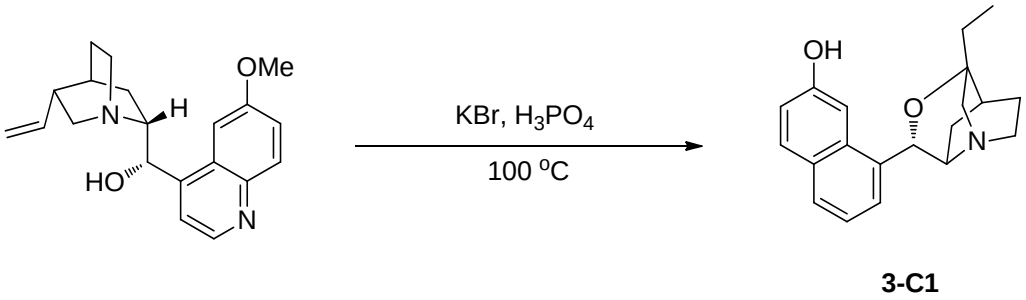
3.4 Experimental Section

3.4.1 General Methods

All the starting materials were obtained from commercial sources and used without further purification unless otherwise stated. Toluene, THF and diethyl ether were dried and distilled from sodium benzophenone ketyl prior to use. $CHCl_3$ and CH_2Cl_2 were distilled from CaH_2 prior to use. ^1H and ^{13}C NMR spectra were recorded on a Bruker ACF300 or AMX500 (500 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Coupling constants were reported in Hertz (Hz). Low resolution mass spectra were obtained on a Finnigan/MAT LCQ spectrometer in EI mode, and all high resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. For thin layer chromatography (TLC), Merck pre-coated TLC plates (Merck 60 F254) were used, and compounds were visualized with a UV light at 254 nm. Further visualization was achieved by staining with $KMnO_4$, iodine, or ceric ammonium molybdate followed by heating on a hot plate. Flash chromatographic separationswere performed on Merck 60 (0.040–0.063 mm) mesh silica gel. The enantiomeric excesses of products were determined by HPLC analysis on a chiral stationary phase.

The MBH carbonates **3-1** were prepared according to the similar procedure of MBH carbonates **2-1**.[93] The catalysts **3-C1** and **3-C2** were prepared according to the literature procedure.[94]

3.4.2 Catalyst Preparation

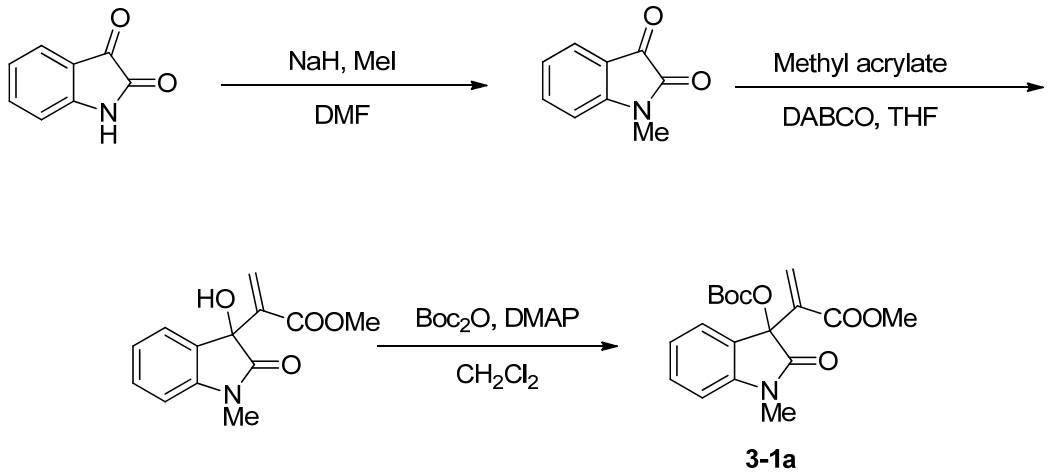


3-C1

Scheme 3.8 Synthesis of catalyst **3-C1**

To the solution of quinidine (1.62 g, 5.0 mmol) in phosphoric acid (25 mL) was added potassium bromide (5.95 g, 5.0 mmol) at room temperature. The reaction mixture was then heated to 100℃ and stirred for 10 days. To the solution was slowly added 25% KOH at 0 ℃. The reaction mixture was acidified to PH = 5 using concentrate HCl, and then neutralized with aqueous ammoniua to PH = 8. The resulting solution was extracted with $CHCl_3$ (100 mL) for three times. The combined organic layer was washed with water, brine and dried with anhydrous Na_2SO_4. After filtration, the organic solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford the white solid as the compound **3-C1** (821 mg, 53%).

3.4.3 Preparation of MBH carbonates of isatin



Scheme 3.9 Preparation of MBH carbonate of isatin

The representative procedure of synthesis of MBH carbonate **3-1a** was described as following (**Scheme 3.8**). Other MBH carbonates **3-1** were prepared in the same method.

To isatin (147 mg, 1.0 mmol) in 5 mL anhydrous DMF was added sodium hydride (60% dispersion in oil, 48 mg, 1.2 mmol) in one portion at 0℃. The reaction mixture was stirred for 5 min. Then iodomethane (0.09 mL, 1.5 mmol) was added to the reaction mixture. After 30 min, the reaction mixture was poured into saturated NH_4Cl and extracted with EtOAc (4 × 10 mL). The combined organic layer was washed with water and brine, and dried with anhydrous Na_2SO_4. The product N-methyl isatin could be obtained with enough purity after removing the solvent under reduced pressure.

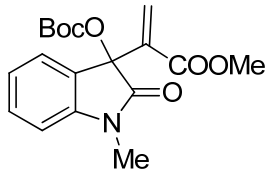
The N-methyl isatin was mixed with methyl acrylate (0.10 mL, 1.0 mmol) and DABCO (112 mg, 0.1 mmol) in 0.2 mL THF. The reaction mixture was stirred at room temperature for 6 days. After removing solvent under reduced pressure, the residue was purified by column chromatography on silica gel to afford the MBH product (240 mg, 97%).

To the MBH product in 10 mL dry CH_2Cl_2 was added the solution of di-*tert*-

butyl dicarbonate (0.28 mL, 1.2 mmol) and DMAP (5.9 mg, 0.049 mmol) in 2 mL dry CH_2Cl_2 by dropwise at 0 ℃. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure. The residue was directly purified by column chromatography on silica gel to afford the product MBH carbonate 3-1a (230 mg, 68%).

3.4.4 Analytical Data of MBH carbonates of isatin

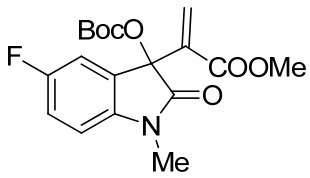
Methyl 2-(3-((*tert*-butoxycarbonyl)oxy)-1-methyl-2-oxoindolin-3-yl) acrylate **3-1a**



3-1a

A white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 9H), 3.29 (s, 3H), 3.57 (s, 3H), 6.53 (s, 1H), 6.56 (s, 1H), 6.85 (m, 1H), 6.98-7.01 (m, 1H), 7.17-7.18 (m, 1H), 7.32-7.35 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.7, 27.5, 52.0, 83.4, 108.2, 122.4, 123,3, 126.5, 128.5, 130.5, 136.5, 145.8, 149.8, 164.0, 172.6; HRMS-ESI calcd for [M+Na] $C_{18}H_{21}NNaO_6$, 370.1261, found: 370.1261.

Methyl 2-(3-((*tert*-butoxycarbonyl)oxy)-5-fluoro-1-methyl-2-oxoindolin-3-yl) acrylate **3-1b**

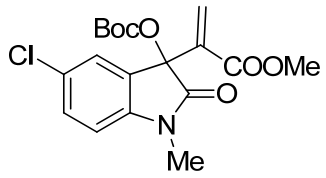


3-1b

A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 9H), 3.28 (s, 3H), 3.59 (s, 3H), 6.53 (s, 1H), 6.58 (s, 1H), 6.76-6.80 (m, 1H), 6.94-7.26 (m, 2H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 26.9, 27.5, 52.1, 83.7, 108.7, 108.8, 111.4, 111.8, 116.4, 116.7, 129.1, 136.0, 141.8, 149.8, 163.8, 172.4; HRMS-ESI calcd for [M+Na] $C_{18}H_{20}FNNaO_6$, 388.1167, found: 388.1182.

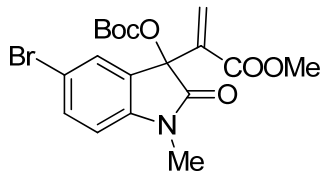
Methyl 2-(3-((*tert*-butoxycarbonyl)oxy)-5-chloro-1-methyl-2-oxoindolin-3-yl) acrylate **3-1c**



3-1c

A white solid; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 9H), 3.28 (s, 3H), 3.59 (s, 3H), 6.55 (s, 1H), 6.59 (s, 1H), 6.78-6.79 (m, 1H), 7.14-7.15 (m, 1H), 7.29-7.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.8, 27.6, 52.1, 79.3, 83.7, 109.2, 123.8, 127.6, 128.1, 129.1, 130.3, 136.0, 144.5, 149.8, 163.8, 172.3; HRMS-ESI calcd for [M+Na] $C_{18}H_{20}ClNNaO_6$, 404.0871, found: 404.0887.

Methyl2-(5-bromo-3-((*tert*-butoxycarbonyl)oxy)-1-methyl-2-oxoindolin-3-yl) acrylate**3-1d**

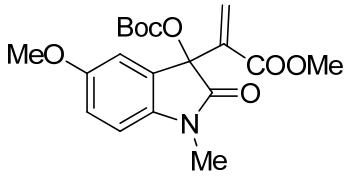


3-1d

A white solid; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 9H), 3.27 (s, 3H), 3.60 (s, 3H), 6.55 (s, 1H), 6.60 (s, 1H), 6.72-6.75 (m, 1H), 7.27-7.28 (m, 1H), 7.44-7.47 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.8, 27.6, 52.1, 83.8, 109.7, 114.8, 126.4, 128.5, 129.1, 133.2, 136.0, 145.0, 149.8, 163.8, 172.2; HRMS-ESI calcd for [M+Na]

$C_{18}H_{20}{}^{79}BrNNaO_6$ and $C_{18}H_{20}{}^{81}BrNNaO_6$, 448.0366 and 450.0370, found: 448.0372 and 450.0352.

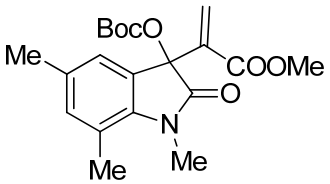
Methyl 2-(3-((*tert*-butoxycarbonyl)oxy)-5-methoxy-1-methyl-2-oxoindolin-3-yl) acrylate **3-1e**



3-1e

A light yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 9H), 3.26 (s, 3H), 3.57 (s, 3H), 3.75 (s, 3H), 6.51 (s, 1H), 6.55 (s, 1H), 6.74-6.76 (m, 1H), 6.80-6.86 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.8, 27.5, 52.0, 55.7, 70.5, 80.0, 83.4, 108.5, 110.8, 114.4, 123.5, 127.6, 128.6, 136.4, 139.2, 149.7, 155.8, 163.9, 172.3; HRMS-ESI calcd for [M+Na] $C_{19}H_{23}NNaO_7$, 400.1367, found: 400.1376.

Methyl 2-(3-((*tert*-butoxycarbonyl)oxy)-1,5,7-trimethyl-2-oxoindolin-3-yl) acrylate **3-1f**

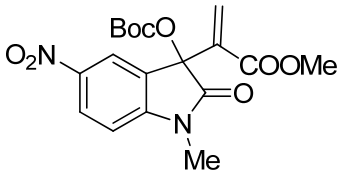


3-1f

A yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 9H), 2.22 (s, 3H), 2.53 (s, 3H), 3.53 (s, 3H), 3.58 (s, 3H), 6.51 (s, 1H), 6.53 (s, 1H), 6.80 (s, 1H), 6.85 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 20.7, 27.6, 30.2, 52.0, 83.1, 119.4, 121.9, 127.1, 128.1, 131.7, 134.7, 137.0, 141.1, 149.7, 164.0, 173.5; HRMS-ESI calcd for [M+Na] $C_{20}H_{25}NNaO_6$, 398.1574, found: 398.1571.

Methyl 2-(3-((*tert*-butoxycarbonyl)oxy)-5-nitro-1-methyl-2-oxoindolin-3-yl) acrylate

3-1g

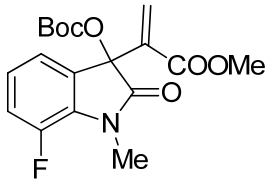


3-1g

A yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 9H), 3.36 (s, 3H), 3.60 (s, 3H), 6.65 (s, 1H), 6.67 (s, 1H), 6.92-6.94 (m, 1H), 8.03-8.04 (m, 1H), 8.31-8.33 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.1, 27.5, 52.2, 78.4, 84.3, 107.8, 119.1, 127.6, 127.7, 129.9, 135.5, 143.2, 149.9, 151.7, 163.8, 172.3; HRMS-ESI calcd for [M+Na] $C_{18}H_{20}N_2NaO_8$, 415.1117, found: 415.1110.

Methyl2-(3-((*tert*-butoxycarbonyl)oxy)-7-fluoro-1-methyl-2-oxoindolin-3-yl) acrylate

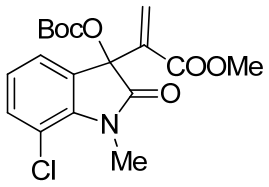
3-1h



3-1h

A light yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 9H), 3.50 (s, 3H), 3.59 (s, 3H), 6.55 (s, 1H), 6.57 (s, 1H), 6.89-7.26 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.5, 29.3, 52.1, 79.4, 83.8, 118.5, 118.8, 119.0, 119.1, 123.0, 128.8, 136.2, 149.2, 149.7, 163.9, 172.4; HRMS-ESI calcd for [M+Na] $C_{18}H_{20}FNNaO_6$, 388.1167, found: 388.1182.

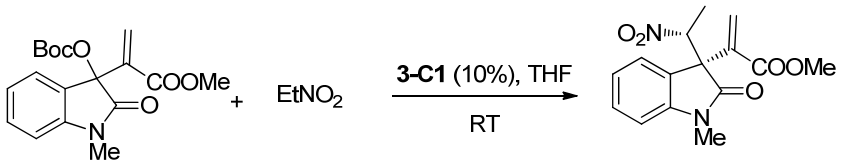
Methyl 2-(3-((*tert*-butoxycarbonyl)oxy)-7-chloro-1-methyl-2-oxoindolin-3-yl) acrylate **3-1i**



3-1i

A white solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 9H), 3.59 (s, 3H), 3.64 (s, 3H), 6.55 (s, 1H), 6.57 (s, 1H), 6.87-6.92 (m, 1H), 7.02-7.05 (m, 1H), 7.23-7.26 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.5, 30.1, 52.1, 79.0, 83.7, 115.6,121.7, 123.1, 128.8, 129.3, 132.8, 136.2, 141.8, 149.6, 163.8, 173.1; HRMS-ESI calcd for [M+Na] $C_{18}H_{20}ClNNaO_6$, 404.0871, found: 404.0887.

3.4.5 Representative Procedure of Reaction of MBH Carbonates of Isatin with Nitroalkanes



3-1a **3-2a**

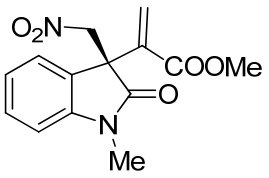
Scheme 3.10 Representative procedure for reaction of MBH carbonates of isatin with nitroethanes

The representative procedure of asymmetric allylic alkylation reaction of MBH carbonate **3-1** and nitroalkanes was described as following (**Scheme 3.8**). To MBH carbonate **3-1a** (8.7 mg, 0.025 mmol) derived from isatin in 0.25 mL dry THF was added catalyst **3-C1** (0.8 mg, 0.0025 mmol) and nitroethane (18 μL, 0.25mmol) at room temperature. After the compound **3-1a** was completely consumed, the reaction was stopped. The solvent was removed under reduced pressure. The diastereoselectivity was determined by ^{1}H-NMR analysis of the residue. Then the

residue was purified by column chromatography on silica gel to afford the desired product 3-2a (5.0 mg, 66%) and 3-2a' (2.5 mg, 33%).

3.4.6 Analytical Data of Products

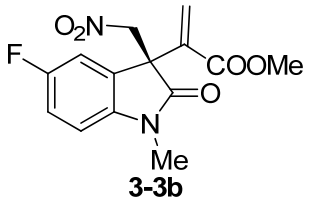
(*R*)-methyl 2-(1-methyl-3-(nitromethyl)-2-oxoindolin-3-yl)acrylate **3-3a**



3-3a

A light yellow solid; 68% yield; $[\alpha]_D^{25}$ = +105 (c = 0.13, $CHCl_3$); 92% ee, determined by HPLC analysis [Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, λ = 254 nm, t (major) = 12.4 min, t (minor) = 16.1 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.30 (s, 3H), 3.71 (s, 3H), 5.11-5.14 (d, *J* = 13.3 Hz, 1H), 5.46-5.49 (d, *J* = 13.3 Hz, 1H), 5.85 (s, 1H), 6.39 (s, 1H), 6.88-6.90 (m, 1H), 7.04-7.06 (m, 1H), 7.32-7.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.9, 52.4, 54.1, 108.9, 123.0, 124.4, 126.5, 128.5, 129.7, 144.3, 165.4, 174.4; HRMS-ESI calcd for [M+Na] $C_{14}H_{14}N_2NaO_5$, 313.0795, found: 313.0795.

(*R*)-Methyl 2-(5-fluoro-1-methyl-3-(nitromethyl)-2-oxoindolin-3-yl) acrylate **3-3b**

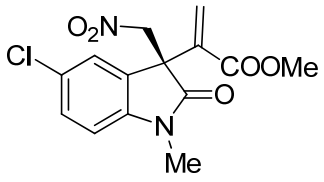


3-3b

A light yellow solid; 42% yield; $[\alpha]_D^{25}$ =+11.7 (c = 0.51, $CHCl_3$); 90% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, λ = 254 nm, t (major) = 28.8 min, t (minor) = 50.8 min]; ^{1}H NMR (500 MHz,

$CDCl_3$) δ 3.30 (s, 3H), 3.75 (s, 3H), 5.07-5.10 (d, *J* = 13.5 Hz, 1H), 5.49-5.52 (d, *J* = 14.3 Hz, 1H), 6.44 (s, 1H), 6.81-6.83 (m, 1H), 7.02-7.06 (m, 1H), 7.22-7.24 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.0, 29.7, 52.5, 54.5, 109.3, 109.4, 112.9, 113.1, 113.3, 115.9, 116.1, 118.8, 129.2, 135.5, 165.3; HRMS-ESI calcd for [M+Na] $C_{14}H_{13}FN_2NaO_5$, 331.0701, found: 331.0708.

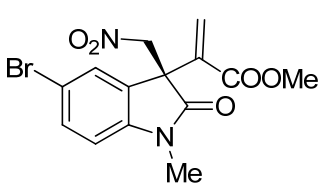
(*R*)-Methyl 2-(5-chloro-1-methyl-3-(nitromethyl)-2-oxoindolin-3-yl) acrylate **3-3c**



3-3c

A light yellow solid; 40% yield; $[\alpha]_D^{25}$ = +53.0 (c = 0.37, $CHCl_3$); 90% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min,, λ = 254 nm, t (major) = 26.6 min, t (minor) = 36.7 min]; ^1H NMR (500 MHz, $CDCl_3$) δ 3.30 (s, 3H), 3.75 (s, 3H), 5.08-5.10 (d, *J* = 13.9 Hz 1H), 5.46-5.49 (d, *J* = 13.9 Hz, 1H), 5.88 (s, 2H), 6.45 (s, 1H), 7.22-7.33 (m, 2H), 7.42 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.0, 29.7, 52.6, 54.2, 109.8, 125.0, 128.4, 129.1, 129.7, 135.5, 143.0, 165.1, 174.1; HRMS-ESI calcd for $C_{14}H_{13}ClN_2NaO_5$ 347.0405, found: 347.0407.

(*R*)-methyl 2-(5-bromo-1-methyl-3-(nitromethyl)-2-oxoindolin-3-yl)acrylate **3-3d**

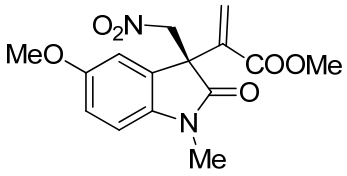


3-3d

A light yellow solid; 43% yield; $[\alpha]_D^{25}$ = +14.2 (c = 0.43, $CHCl_3$); 92% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 90/10, 1.0

mL/min, λ = 254 nm, t (major) = 28.8 min, t (minor) = 50.3 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.29 (s, 3H), 3.74 (s, 3H), 5.06-5.11 (d, *J* = 22.8 Hz, 1H), 5.44-5.49 (d, *J* = 22.8 Hz, 1H), 5.88 (s, 1H), 6.46 (s, 1H), 6.76-6.79 (m, 1H), 7.45-7.48 (m, 1H), 7.54-7.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.8, 27.6, 52.1, 79.3, 83.7, 109.7, 114.8, 126.5, 128.6, 129.0, 133.2, 136.1, 145.0, 149.8, 163.8, 172.2; HRMS-ESI calcd for [M+Na] $C_{14}H_{13}{}^{79}BrN_2NaO_5$ and $C_{14}H_{13}{}^{81}BrN_2NaO_5$, 390.9900 and 392.9880, found: 390.9910 and 392.9881.

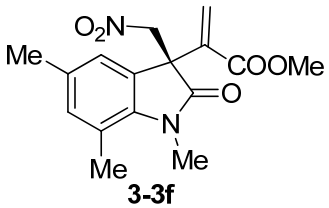
(*R*)-Methyl 2-(5-methoxy-1-methyl-3-(nitromethyl)-2-oxoindolin-3-yl)acrylate **3-3e**



3-3e

A light yellow solid; 50% yield; $[\alpha]_D^{25}$ = +21.2 (c = 0.42, $CHCl_3$); 89% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 80/20, 1.0 mL/min, λ = 254 nm, t (major) = 30.5 min, t (minor) = 53.3 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.28 (s, 3H), 3.73 (s, 3H), 3.77 (s, 3H), 5.09-5.12 (d, *J* = 13.9 Hz, 1H), 5.46-5.49 (d, *J* = 13.25 Hz, 1H), 5.86 (s, 1H), 6.40 (s, 1H), 6.78-6.80 (m, 1H), 6.84-6.86 (m, 1H), 7.04-7.05 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.0, 29.7, 52.4, 54.5, 55.8, 109.2, 112.1, 113.9, 127.9, 128.7, 136.0, 137.7, 156.2, 165.4, 174.1; HRMS-ESI calcd for [M+Na] $C_{15}H_{16}N_2NaO_6$, 343.0901, found: 343.0911.

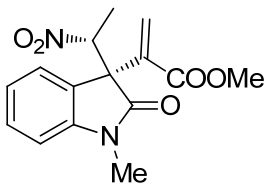
(R)-methyl 2-(1,5,7-trimethyl-3-(nitromethyl)-2-oxoindolin-3-yl)acrylate **3-3f**



3-3f

A light yellow solid; 50% yield; $[\alpha]_D^{25}$ = -279 (c = 0.01, $CHCl_3$); 88% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 80/20, 1.0 mL/min, λ = 254 nm, t (major) = 21.5 min, t (minor) = 26.7 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.53 (s, 3H), 3.54 (s, 3H), 3.71 (s, 3H), 5.12-5.15 (d, *J* = 13.9 Hz, 1H), 5.34-5.37 (d, *J* = 13.9 Hz, 1H), 5.78 (s, 1H), 6.37 (s, 1H), 6.86 (s, 1H), 6.69 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.0, 29.7, 52.4; 54.5, 55.8, 109.2, 112.1, 113.9, 12.9, 12.7, 1360, 17.7, 156.2, 1.4, 174.1; HRMS-ESI calcd for [M+Na] $C_{16}H_{18}N_2NaO_5$, 341.1108, found: 341.1098.

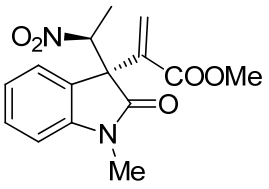
Methyl 2-((*R*)-1-methyl-3-((*R*)-1-nitroethyl)-2-oxoindolin-3-yl)acrylate **3-2a**



3-2a

A light yellow solid; 66% yield; $[\alpha]_D^{25}$ = -72.1 (c = 0.10, $CHCl_3$); 90% ee, determined by HPLC analysis [Daicel Chiralcel OD, *n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, λ = 254 nm, t (minor) = 13.2 min, t (major) = 16.0 min]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (d, *J* = 7.1 Hz, 3H), 3.27 (s, 3H), 3.74 (s, 3H), 5.92 (s, 1H), 6.06-6.13 (q, *J* = 7.1 Hz, 1H), 6.37 (s, 1H), 6.84-6.87 (m, 1H), 7.03-7.08 (m, 1H), 7.29-7.30 (m, 1H), 7.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.1, 26.6, 52.4, 56.9, 85.1, 108.6, 123.0, 125.1, 126.9, 129.0, 129.5, 136.4, 143.9, 166.1, 173.7; HRMS-ESI calcd for [M+Na] $C_{15}H_{16}N_2NaO_5$, 327.0951, found: 327.0939.

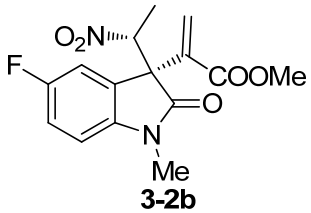
Methyl 2-((*R*)-1-methyl-3-((*S*)-1-nitroethyl)-2-oxoindolin-3-yl)acrylate **3-2a'**



3-2a'

A light yellow solid; 33% yield; $[\alpha]_D^{25}$ = +22.6 (c = 0.23, $CHCl_3$); 91% ee, determined by HPLC analysis [Daicel Chiralcel OD, *n*-hexane/*i*-PrOH = 95/5, 1.0 mL/min, λ = 254 nm, t (minor) = 26.0 min, t (major) = 31.5 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48 (d, *J* = 6.9 Hz, 3H), 3.25 (s, 3H), 3.83(s, 3H), 5.62 (s, 1H), 6.03-6.07 (q, *J* = 6.9 Hz, 1H), 6.22 (s, 1H), 6.88-6.89 (m, 1H), 7.08-7.11 (m, 1H), 7.34-7.35 (m, 1H), 7.37 (m, 1H).

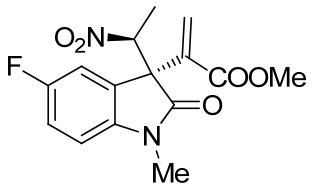
Methyl 2-((*R*)-5-fluoro-1-methyl-3-((*R*)-1-nitroethyl)-2-oxoindolin-3-yl)acrylate **3-2b**



3-2b

A light yellow solid; 89% yield; $[\alpha]_D^{25}$ = +37.1 (c = 0.56, $CHCl_3$); 89% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, λ = 254 nm, t (major) = 12.9 min, t (minor) = 20.7 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.71 (d, *J* = 7.0 Hz, 3H), 3.26 (s, 3H), 3.76 (s, 3H), 5.96 (s, 1H), 6.01-6.05 (q, *J* = 6.9 Hz, 1H), 6.42 (s, 1H), 6.77-6.79(m, 1H), 7.01-7.05 (m, 1H), 7.31-7.33(m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 15.2, 26.8, 52.6, 57.1, 85.1, 109.0, 109.1, 113.5, 113.7, 115.7, 115.9, 129.7, 135.8, 139.9, 165.8, 173.5; HRMS-ESI calcd for [M+Na] $C_{15}H_{15}FN_2NaO_5$, 345.0863, found: 345.0858.

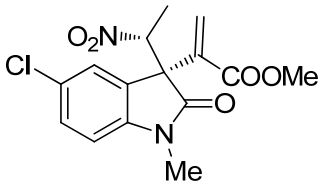
Methyl 2-((*R*)-5-fluoro-1-methyl-3-((*S*)-1-nitroethyl)-2-oxoindolin-3-yl)acrylate **3-2b'**



3-2b'

A light yellow solid; 25% yield; $[\alpha]_D^{25}$ = +11.6 (c = 0.37, $CHCl_3$); 89% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 80/20, 1.0 mL/min, λ = 254 nm, t (major) = 32.7min, t (minor) = 56.3 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (d, *J* = 7.0 Hz, 3H), 3.25 (s, 3H), 3.84 (s, 3H), 5.65 (s, 1H), 5.99-6.03 (q, *J* = 7.0 Hz, 1H), 6.27 (s, 1H), 6.80-6.83 (m, 1H), 7.05-7.09 (m, 1H), 7.37-7.39 (m, 1H).

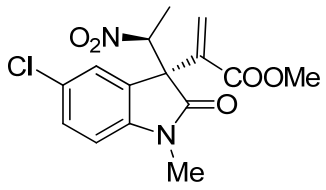
Methyl 2-((*R*)-5-chloro-1-methyl-3-((*R*)-1-nitroethyl)-2-oxoindolin-3-yl)acrylate **3-2c**



3-2c

A light yellow solid; 54% yield; $[\alpha]_D^{25}$ = +24.2 (c = 0.73, $CHCl_3$); 89% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, λ = 254 nm, t (major) = 12.1 min, t (minor) = 20.0 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.72 (d, *J* = 7.0 Hz, 3H), 3.26 (s, 3H), 3.76 (s, 3H), 5.95 (s, 1H), 5.99-6.03 (q, *J* = 6.9 Hz, 1H), 6.43 (s, 1H), 6.78 (m, 1H), 7.29-7.31 (m, 1H), 7.51 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.2, 26.8, 52.6, 56.8, 85.1, 109.5, 125.6, 129.5, 129.7, 135.8, 142.4, 165.7, 173.4; HRMS-ESI calcd for [M+Na] $C_{15}H_{15}ClN_2NaO_5$, 361.0562, found: 361.0557.

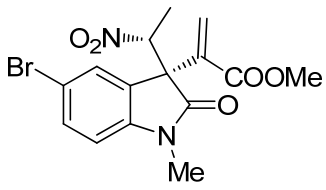
Methyl 2-((*R*)-5-chloro-1-methyl-3-((*S*)-1-nitroethyl)-2-oxoindolin-3-yl)acrylate **3-2c**'



3-2c'

A light yellow solid; 25% yield; $[\alpha]_D^{25}$ = +33.7 (c = 0.46, $CHCl_3$); 87% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 80/20, 1.0 mL/min, λ = 254 nm, t (major) = 30.3 min, t (minor) = 51.2 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (d, *J* = 7.0 Hz, 3H), 3.25 (s, 3H), 3.84 (s, 3 H), 5.64 (s, 1 H), 5.98-6.02 (q, *J* = 7.0 Hz, 1H), 6.27 (s, 1 H), 6.81-6.82 (m, 1 H), 7.33-7.35 (m, 1 H), 7.56-7.57 (m, 1 H).

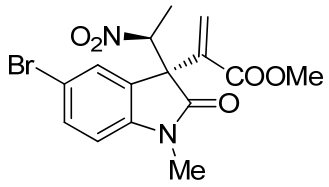
Methyl 2-((*R*)-5-bromo-1-methyl-3-((*R*)-1-nitroethyl)-2-oxoindolin-3-yl)acrylate **3-2d**



3-2d

A light yellow solid; 55% yield; $[\alpha]_D^{25}$ = +24.4 (c = 0.59, $CHCl_3$); 89% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, λ = 254 nm, t (major) = 12.5 min, t (minor) = 20.7 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.72 (d, *J* = 7.0 Hz, 3H), 3.26 (s, 3H), 3.76 (s, 3H), 5.95 (s, 1H), 5.97-6.02 (q, *J* = 7.0 Hz, 1H), 6.42 (s, 1H), 6.72-6.74 (m, 1H), 7.44-7.46 (m, 1H), 7.6-7.65 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.2, 26.8, 52.6, 56.8, 85.1, 110.0, 115.6, 128.3, 129.6, 132.4, 135.9, 143.0, 165.7, 173.4; HRMS-ESI calcd for [M+Na] $C_{15}H_{15}{}^{79}BrN_2NaO_5$ and $C_{15}H_{15}{}^{81}BrN_2NaO_5$, 405.0057 and 407.0036, found: 405.0056 and 407.0040.

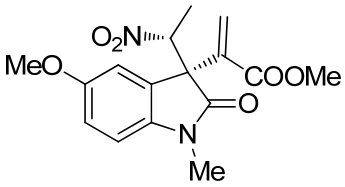
Methyl 2-((*R*)-5-bromo-1-methyl-3-((*S*)-1-nitroethyl)-2-oxoindolin-3-yl)acrylate **3-2d'**



3-2d'

A light yellow solid; 25% yield; $[\alpha]_D^{25}$ = -58.2 (c = 0.44, $CHCl_3$); 89% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 80/20, 1.0 mL/min, λ = 254 nm, t (major) = 31.1 min, t (minor) = 51.7 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (d, *J* = 6.3 Hz, 3H), 3.24 (s, 3H), 3.84 (s, 3H), 5.64 (s, 1H), 5.98-6.02 (q, *J* = 6.3 Hz, 1H), 6.28 (s 1H), 6.76-6.78 (m, 1H), 7.48-7.50 (m, 1H), 7.70 (s, 1H).

Methyl 2-((*R*)-5-methoxy-1-methyl-3-((*R*)-1-nitroethyl)-2-oxoindolin-3-yl)acrylate **3-3e**

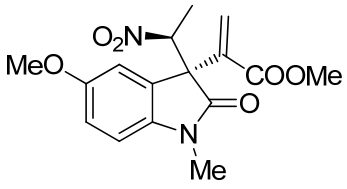


3-3e

A light yellow solid; 57% yield; $[\alpha]_D^{25}$ = +15.0 (c = 0.34, $CHCl_3$); 90% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 80/20, 1.0 mL/min, λ = 254 nm, t (major) = 15.8 min, t (minor) = 24.1 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.68 (d, *J* = 6.9 Hz, 3H), 3.24 (s, 3H), 3.75 (s, 3H), 3.77 (s, 3H), 5.92 (s, 1H), 6.04-6.08 (q, *J* = 6.9 Hz, 1H), 6.37 (s, 1H), 6.75-6.77 (m, 1H), 6.84-6.86 (m, 1H), 7.13 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.4, 21.4, 26.7, 29.7, 52.4, 55.8, 58.9,

90.3, 109.1, 113.3, 113.6, 127.8, 128.2, 137.0,137.3, 166.3, 172.8; HRMS-ESI calcd for [M+H] $C_{16}H_{19}N_2O_6$, 335.1238, found: 335.1241.

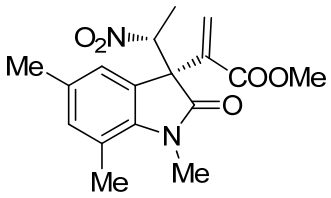
Methyl 2-((*R*)-5-methoxy-1-methyl-3-((*S*)-1-nitroethyl)-2-oxoindolin-3-yl)acrylate **3-3e'**



3-3e'

A light yellow solid; 25% yield; $[\alpha]_D^{25}$ = +11.3 (c = 0.31, $CHCl_3$); 85%, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 70/30, 1.0 mL/min, λ = 254 nm, t (major) = 40.3 min, t (minor) = 73.8 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (d, *J* = 7.0 Hz, 3H), 3.23 (s, 3H), 3.79 (s, 3H), 3.83 (s, 3H), 5.64 (s, 1H), 6.00-6.04 (q, *J* = 7.0 Hz, 1H), 6.24 (s, 1H), 6.78-6.79 (m, 1H), 6.86-6.88 (m, 1H), 7.21 (m, 1H).

Methyl 2-((*R*)-1,5,7-trimethyl-3-((*R*)-1-nitroethyl)-2-oxoindolin-3-yl)acrylate **3-3f**

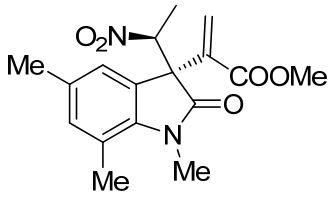


3-3f

A light yellow solid; 55% yield; $[\alpha]_D^{25}$ = +58.5 (c = 0.49, $CHCl_3$); 90% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, λ = 254 nm, t (major) = 21.9 min, t (minor) = 38.8 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.70 (d, *J* = 6.9 Hz, 3H), 2.25 (s, 3H), 2.51 (s, 3H), 3.51 (s, 3H), 3.74 (s, 3H), 5.84 (s, 1H), 6.01-6.06 (q, *J* = 7.0 Hz, 1H), 6.34 (s, 1H), 6.84 (s, 1H), 7.05 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.1, 19.0, 20.9, 30.0, 52.3, 56.3, 85.4, 119.7,

123.1, 128.6, 132.3, 133.8, 166.1, 174.5; HRMS-ESI calcd for [M+Na] $C_{17}H_{20}N_2NaO_5$, 355.1264, found: 355.1268.

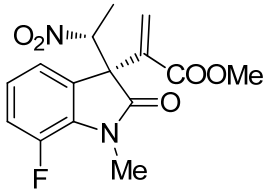
Methyl 2-((*R*)-1,5,7-trimethyl-3-((*R*)-1-nitroethyl)-2-oxoindolin-3-yl)acrylate **3-3f'**



3-3f'

Minor isomer: 25% yield; $[\alpha]_D^{25}$ = +18.6 (c = 0.26, $CHCl_3$); 89% ee, determined by HPLC analysis [Daicel Chiralpak AD, *n*-hexane/*i*-PrOH = 70/30, 1.0 mL/min, λ = 254 nm, t (major) = 9.3 min, t (minor) = 12.9 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (d, *J* = 6.4 Hz, 3H), 2.28 (s, 3H), 2.52 (s, 3H), 3.50 (s, 3H), 3.82 (s, 3H), 5.59 (s, 1H), 5.97-6.01 (q, *J* = 6.4 Hz, 1H), 6.20 (s, 1H), 6.87 (s, 1H), 7.16 (s, 1H).

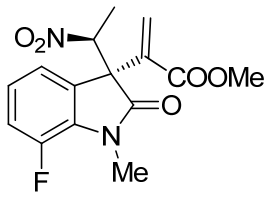
Methyl 2-((*R*)-7-fluoro-1-methyl-3-((*R*)-1-nitroethyl)-2-oxoindolin-3-yl)acrylate **3-3h**



3-3h

A light yellow solid; 50% yield; $[\alpha]_D^{25}$ = +111.7 (c = 0.36, $CHCl_3$); 87% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, λ = 254 nm, t (major) = 9.8 min, t (minor) = 12.3 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.73(d, *J* = 7.0 Hz, 3H), 3.49 (d, *J* = 2.5 Hz, 3H), 3.75 (s, 3H), 5.93 (s, 1H), 6.03-6.07 (q, *J* = 7.0 Hz, 1H), 6.40 (s, 1H), 6.97-7.06 (m, 2H), 7.26 (m, 1H); ^{13}C-NMR (125MHz, $CDCl_3$) δ 15.0, 29.1, 29.2, 29.7, 52.5, 85.2, 117.5, 117.6, 120.7, 123.4, 129.4, 136.1, 146.8, 148.7, 165.8, 173.5; HRMS-ESI calcd for [M+Na] $C_{15}H_{15}FN_2NaO_5$, 345.0863, found: 345.0858.

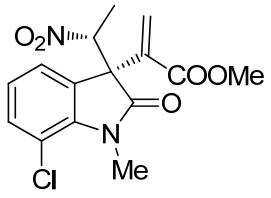
Methyl 2-((*R*)-7-fluoro-1-methyl-3-((*R*)-1-nitroethyl)-2-oxoindolin-3-yl)acrylate **3-3h'**



3-3h'

A light yellow solid; 25% yield; $[\alpha]_D^{25}$ = -129.0 (c = 0.10, $CHCl_3$); 86% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 80/20, 1.0 mL/min, λ = 254 nm, t (major) = 26.8 min, t (minor) = 48.4 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50 (d, *J* = 7.0 Hz, 3H), 3.47 (s, 3H), 3.82 (s, 3H), 5.61 (s, 1H), 6.00-6.04 (q, *J* = 7.0 Hz, 1H), 6.25 (s, 1H), 7.00-7.11 (m, 2H), 7.31-7.32 (m, 1H).

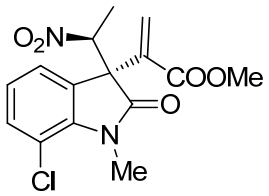
Methyl 2-((*R*)-7-chloro-1-methyl-3-((*R*)-1-nitroethyl)-2-oxoindolin-3-yl)acrylate **3-3i**



3-3i

A light yellow solid; 62% yield; $[\alpha]_D^{25}$ = +36.1 (c = 0.64, $CHCl_3$); 84% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, λ = 254 nm, t (major) = 9.7 min, t (minor) = 11.2 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74 (d, *J* = 6.8 Hz, 3H), 3.65 (s, 3H), 3.74 (s, 3H), 6.02-6.06 (q, *J* = 6.8 Hz, 1H), 6.41 (s, 1H), 6.93-6.97 (m, 1H), 7.23-7.25 (m, 1H), 7.35-7.37 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.1, 30.1, 52.5, 56.3, 85.3, 116.0, 123.2, 123.6, 129.8, 131.9, 136.1, 139.8, 165.8, 174.2; HRMS-ESI calcd for [M+Na] $C_{15}H_{15}ClN_2NaO_5$, 361.0562, found: 361.0557.

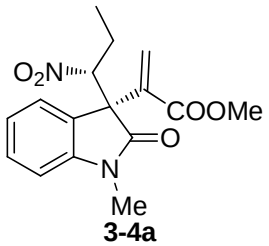
Methyl 2-((*R*)-7-chloro-1-methyl-3-((*R*)-1-nitroethyl)-2-oxoindolin-3-yl)acrylate **3-3i'**



3-3i'

A light yellow solid; 30% yield; $[\alpha]_c$ = -20.8 (c = 0.50, $CHCl_3$); 81% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 80/20, 1.0 mL/min, λ = 254 nm, t (major) = 29.2 min, t (minor) = 59.4 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (d, *J* = 7.0 Hz, 3H), 3.63 (s, 3H), 3.82 (s, 3H), 5.60 (s, 1H), 5.99-6.03 (q, *J* = 7.0 Hz, 1H), 6.26 (s,1H), 6.98-7.00 (m, 1H), 7.26-7.27 (m, 1H), 7.29-7.43 (m, 1H).

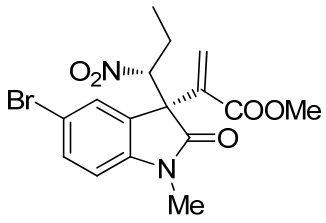
Methyl 2-((*R*)-1-methyl-3-((*R*)-1-nitropropyl)-2-oxoindolin-3-yl)acrylate **3-4a**



3-4a

A light yellow solid; 90% yield; $[\alpha]_D^{25}$ = +13.1 (c = 0.45, $CHCl_3$); 88% ee, determined by HPLC analysis [Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90/10, 1.0 mL/min, λ = 254 nm, t (minor) = 8.6 min, t (major) = 10.5 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.6 Hz, 3H), 3.65 (s, 3H), 3.74 (s, 3H), 6.02-6.06 (q, *J* = 6.8 Hz, 1H), 6.41 (s, 1H), 6.93-6.97 (m, 1H), 7.23-7.25 (m, 1H), 7.35-7.37 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.1, 30.1, 52.5, 56.3, 85.3, 116.0, 123.2, 123.6, 129.8, 131.9, 136.1, 139.8, 165.8, 174.2; HRMS-ESI calcd for [M+Na] $C_{16}H_{18}N_2NaO_5$, 341.1108, found: 341.1114.

Methyl 2-((*R*)-5-bromo-1-methyl-3-((*R*)-1-nitropropyl)-2-oxoindolin-3-yl)acrylate **3-4d**

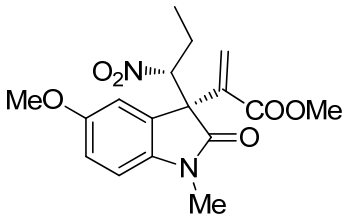


3-4d

A light yellow solid; 70% yield; $[\alpha]_D^{25}$ = -80.0 (c = 0.30, $CHCl_3$); 87% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 80/20, 1.0 mL/min, λ = 254 nm, t (major) = 19.7 min, t (minor) = 27.9 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74 (d, *J* = 6.8 Hz, 3H), 3.65 (s, 3H), 3.74 (s, 3H), 6.02-6.06 (q, *J* = 6.8 Hz, 1H), 6.41 (s, 1H), 6.93-6.97 (m, 1H), 7.23-7.25 (m, 1H), 7.35-7.37 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.1, 30.1, 52.5, 56.3, 85.3, 116.0, 123.2, 123.6, 129.8, 131.9, 136.1, 139.8, 165.8, 174.2; HRMS-ESI calcd for [M+Na] $C_{16}H_{18}N_2NaO_5{}^{79}Br$ and $C_{16}H_{18}N_2NaO_5{}^{80}Br$, 397.0394 and 399.0373, found: 397.0404 and 399.0380.

Methyl 2-((*R*)-5-methoxy-1-methyl-3-((*R*)-1-nitropropyl)-2-oxoindolin-3-yl)acrylate

3-4e

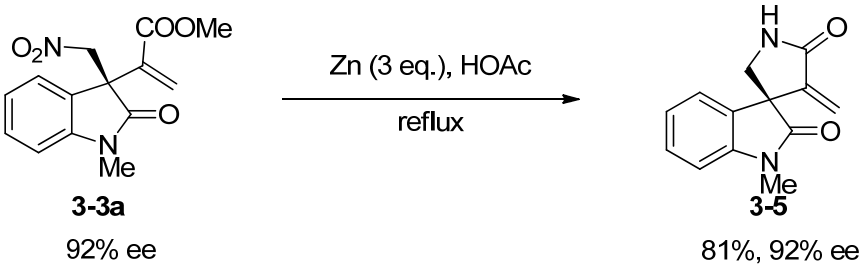


3-4e

A light yellow solid; 92% yield; $[\alpha]_D^{25}$ = -37.7 (c = 0.61, $CHCl_3$); 90% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 70/30, 1.0 mL/min, λ = 254 nm, t (major) = 23.8 min, t (minor) = 39.9 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74 (d, *J* = 6.8 Hz, 3H), 3.65 (s, 3H), 3.74 (s, 3H), 6.02-6.06 (q, *J* = 6.8 Hz, 1H), 6.41 (s, 1H), 6.93-6.97 (m, 1H), 7.23-7.25 (m, 1H), 7.35-7.37 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.1, 30.1, 52.5, 56.3, 85.3, 116.0, 123.2, 123.6, 129.8, 131.9,

136.1, 139.8, 165.8, 174.2; HRMS-ESI calcd for [M+H] $C_{17}H_{21}N_2O_6$, 349.1394, found: 349.1403.

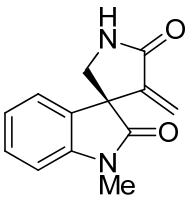
3.4.7 Procedure of Synthesis Derivatives



Scheme 3.11 Synthetic procedure for compound **3-5**

To the chiral allylic alkylation product **3-3a** (7.3 mg, 0.025 mmol) in 1.0 mL HOAc was added Zn (4.8 mg, 0.075 mmol) in one portion at room temperature. Then the reaction mixture was heated to reflux for 2 hours. Then the reaction mixture was cooled to room temperature. The solid was filtered off; the filtrate was added to water. The reaction mixture was extracted with EtOAc and the combined organic layer was washed with water, brine and dried with anhydrous Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford the spiral oxindole compound **3-5** (5.1 mg, 89%).

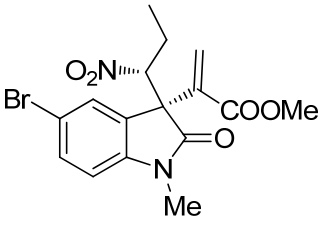
(*R*)-1-methyl-4'-methylenespiro[indoline-3,3'-pyrrolidine]-2,5'-dione **3-5**



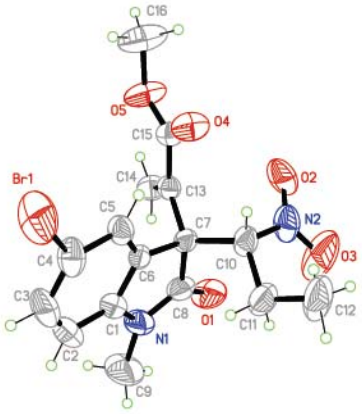
3-5

A light yellow solid; 89% yield; $[\alpha]_D^{25}$ = -8.5 (c = 0.60, $CHCl_3$); 92% ee, determined by HPLC analysis [Daicel Chiralpak IB, *n*-hexane/*i*-PrOH = 80/20, 1.0 mL/min, λ = 254 nm, t (major) = 16.8 min, t (minor) = 21.8 min]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (s, 3H), 3.60 (d, *J* = 9.7 Hz, 1H), 3.87 (d, *J* = 9.7 Hz, 1H), 5.04 (s, 1H), 6.11 (s, 1H), 6.52 (br s, 1H), 6.89-6.92 (m, 1H), 7.08-7.11 (m, 1H), 7.13-7.25 (m, 1H), 7.32-7.37 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.7, 48.9, 53.4, 108.5, 118.3, 123.1, 123.6, 129.1, 132.3, 142.1, 143.5, 168.7, 176.5; HRMS-ESI calcd for [M+Na] $C_{13}H_{12}N_2NaO_2$, 251.0791, found: 251.0797.

3.4.8 X-Ray Crystallographic Analysis of Compounds 3-4d



3-4d



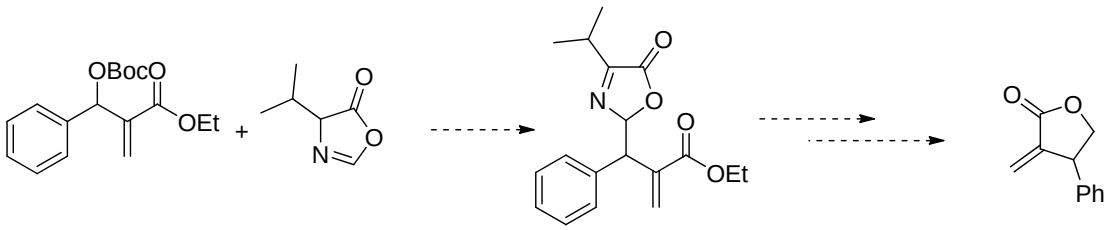
Identification code	**3-4d**	
Empirical formula	C16 H17 Br N2 O5	
Formula weight	397.23	
Temperature	223(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.9316(5) Å	= 90°.
	b = 11.5927(7) Å	= 90°.
	c = 19.0616(12) Å	= 90°.

Volume	1752.69(19) $Å^3$
Z	4
Density (calculated)	1.505 Mg/m^3
Absorption coefficient	2.373 mm^{-1}
F(000)	808
Crystal size	0.60 x 0.50 x 0.20 mm^3
Theta range for data collection	2.06 to 27.47°.
Index ranges	-10<=h<=10, -15<=k<=11, -24<=l<=24
Reflections collected	12370
Independent reflections	4010 [R(int) = 0.0407]
Completeness to theta = 27.47°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.6483 and 0.3302
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4010 / 0 / 220
Goodness-of-fit on F^2	0.977
Final R indices [I>2sigma(I)]	R1 = 0.0403, wR2 = 0.0860
R indices (all data)	R1 = 0.0663, wR2 = 0.0945
Absolute structure parameter	0.018(9)
Largest diff. peak and hole	0.199 and -0.377 $e.Å^{-3}$

Chapter 4 Enantioselective Allylic Substitution Reaction of Morita-Baylis-Hillman Carbonates with an Azlactone

4.1 Introduction

We have developed the asymmetric reactions of MBH carbonates with nitroalkanes, and the products of these reactions could be easily converted to α-methylene-γ-butyrolactams, which are protentially useful molecules in medicinal chemistry. α-Methylene-γ-butyrolactones are also often found in biologically active molecules. We thus intend to develop a practical method using MBH carbonates as substrate to access chiral α-methylene-γ-butyrolactones (**Scheme 4.1**).



Scheme 4.1 Research plan for asymmetric reaction of MBH carbonates with azlactone

In our projected reaction, we required a formyl anion as a potential nucleophile in the allylic substitution reaction. One strategy is to use carbene catalyst to form umpolung synthons, which seemed to be inappropriate because the catalyst may activate either the MBH carbonates or formic aldehyde. 4-Isopropyl-2-oxazolin-5-one was found as a masked umpolung synthon for formyl or hydroxylcarbonyl anions, which has been reported in several reactions.[95] The products of the allylic substitution reaction of MBH carbonates with the masked umpolung formyl anion could be transformed readily to α-methylene-γ-butyrolactones.

Utilization of 4-isopropyl-2-oxazolin-5-one as a nucleophile has been investigated in organocatalytic asymmetric reactions by the Ooi group. In 2009, Ooi

and co-workers developed a Michael reaction of 4-isopropyl-2-oxazolin-5-one with α,β-unsaturated ketone, providing the products with high regioselectivity and enantioselectivity in the presence of the phase transfer catalyst derived from amino acid.[81a] The highly regioselective reaction took place at the 2-position of 4-isopropyl-2-oxazolin-5-one. Two years later, the same group investigated the asymmetric Michael reaction of 4-isopropyl-2-oxazolin-5-one to nitroolefin in the presence of the same catalyst.[81b] In the contrast, employment of 4-isopropyl-2-phenyloxazol-5(4H)-one often led to nucleophilic substitution at the 4-position. In 2011, Shi and coworkers developed an asymmetric reaction of MBH adducts with 4-isopropyl-2-phenyloxazol-5(4H)-one.[46]

The reaction of MBH adducts with 4-isopropyl-2-oxazolin-5-one has not been investigated. We envisioned that a reaction of MBH carbonates with 4-isopropyl-2-oxazolin-5-one may be promoted by nucleophilic catalyst via a S_N2'-S_N2' process. Herein we describe the first asymmetric allylic substitution reaction of MBH carbonates with 4-isopropyl-2-oxazolin-5-one. The allylic substitution products were obtained in high yields, and with good regioselectivity, diastereoselectivity and enantioselectivity.

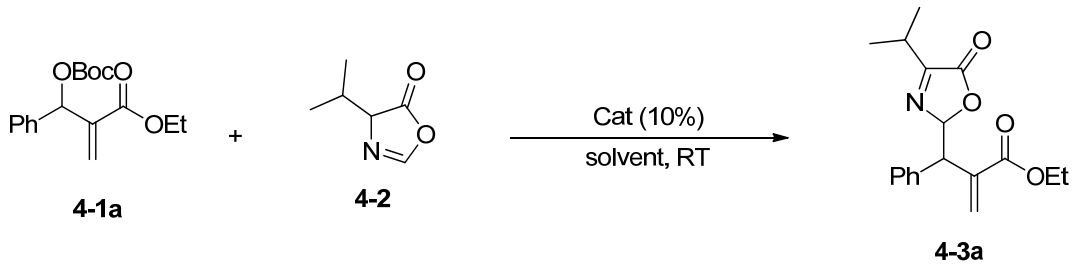
4.2 Results and Discussion

4.2.1 Reaction Optimization

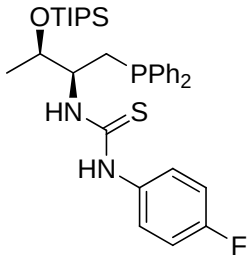
We first took the reaction of MBH carbonate **4-1a** and 4-isopropyl-2-oxazolin-5-one 4-2 as a model reaction. The cinchona alkaloid derived tertiary amine catalyst β-ICD was chosen to catalyze the model reaction. The product **4-3a** could be obtained as the only product in low yield and low enantioselectivity (Table 4.1, entry 6). Since

our group has developed bifunctional phosphine catalysts which have been successfully applied in several reactions as nucleophlic catalysts, we decided to screen some phosphine catalysts. The phosphine-thiourea catalysts were tested in the model reaction. The catalyst **4-C1** derived from threonine could provide the product **4-3a** in good yield, high diastereoselectivity and high enantioselectivity (Table 4.1, entry 1 and 11). The catalyst **4-C2** also gave the product **4-3a** with slightly lower enatioselectivity, which means that the silyl group on the catalysts could slightly influence the enantioselectivity (Table 4.1, entry 2). The phosphine-thiourea catalyst **4-C3** derived from valine could provide the product **4-3a** with moderate enantioselectivity which may indicate the impotence of scaffold of catalysts (Table 4.1, entry 3). Other bifunctional catalysts e.g. **4-C4**, **4-C5** with stronger or weaker hydrogen bonding moiety could give the product **4-3a** with low enantioselectivity (Table 4.1, entry 4 and 5).

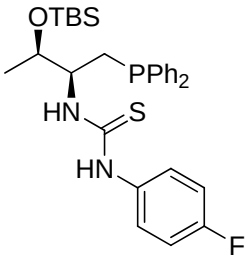
Table 4.1 Optimization of reaction condition of MBH carbonate **4-1a** with azlctone **4-2** [a]



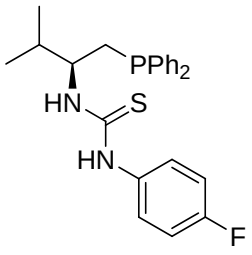
4-1a **4-2** **4-3a**



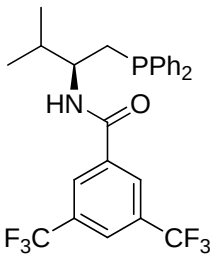
4-C1



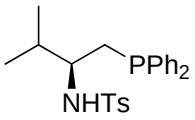
4-C2



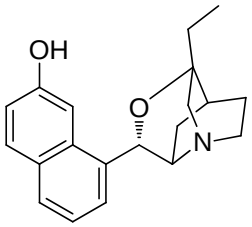
4-C3



4-C4



4-C5



4-C6

Entry	Catalyst	Solvent	Yield (%)[b]	ee (%)[c]
1	**4-C1**	toluene	76	98
2	**4-C2**	toluene	76	94
3	**4-C3**	toluene	51	82
4	**4-C4**	toluene	62	6
5[d]	**4-C5**	toluene	51	31
6	**4-C6**	toluene	-	26
7	**4-C1**	CH_2Cl_2	83	92
8	**4-C1**	Et_2O	58	95
9	**4-C1**	THF	61	92
10[d]	**4-C1**	CH_3CN	-	84
11[e]	**4-C1**	toluene	87	98

[a] The reaction was performed with **4-1a** (0.025 mmol), **4-2** (0.050mmol) and catalyst (10 mol%) in solvent (0.10 mL) at room temperature for 24 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction yield was low and not calculated. [e] The reaction was performed for 48 h.

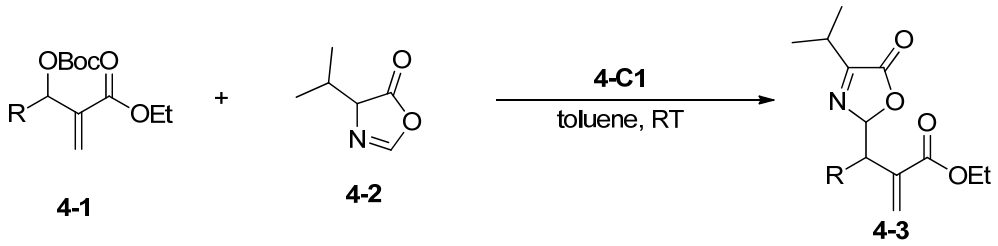
The solvent was also screened in the presence of the best catalyst **4-C1**. The strong polar solvent acetonitrile could provide the product with low yield and moderate enantioselectivity (Table 4.1, entry 10). When other solvents such as CH_2Cl_2, THF, Et_2O were used, the product with good enantioselectivity could be

obtained (Table 4.1, entry 7, 8 and 9). Toluene was found to be the best solvent.

4.2.2 Substrate Scope

The scope of the reaction was next investigated under the best reaction condition (Table 4.2). Different substituted MBH carbonates **4-1** were used in the allylic substitution reaction. All the substrates **4-1** could provide the products **4-3** with excellent diastereoselectivity and good to excellent enantioselectivity. The MBH carbonates with halogen substituent could give the product with moderate to good yield and high enantioselectivity (Table 4.2, entry 2, 3, 4, 5, 6 and 7). Even the disubsituted substrate **4-1g** could afford the product with moderate yield and high enantioselectivity (Table 4.2, entry 7). The MBH carbonates containing electron withdrawing group on the phenyl ring could provide the product with excellent yield and high enantioselectivity (Table 4.2, entry 8, 9 and 10). In the contrast, when the MBH carbonate with electron donating group on the phenyl ring was used, the product was also obtained with high enantioselectivity, but the yield was slightly lower (Table 4.2, entry 11, 12 and 13). The high enantioselectivity could also be obtained using MBH carbonates with naphthyl group or heteroaromtic substituent (Table 4.2, entry 14, 15, 16 and 17). Even the MBH carbonate derived from aliphatic aldehyde **4-1r** could give the product with moderate yield and high enantioselectivity using 20 mol% catalyst loading (Table 4.2, entry 18). The reactivity could decrease using MBH carbonate with steric hindrance (Table 4.2, entry 6, 13 and 14). We reasoned that the first S_N2' reaction may be suppressed by the steric hindrance.

Table 4.2 Asymmetric allylic substitution reaction of MBH carbonates **4-1** and azlactone **4-2**[a]



Entry	R	*d. r.*[b]	Yield (%)[c]	ee (%)[d]
1	Ph	>19:1	87	98
2	4-FPh	>19:1	99	93
3	4-ClPh	>19:1	99	95
4	4-BrPh	>19:1	87	96
5	3-BrPh	>19:1	87	94
6	2-BrPh	>19:1	49	94
7	3,4-Cl-C_6H_3	>19:1	77	93
8	4-CF_3Ph	>19:1	99	96
9	3-CF_3Ph	>19:1	99	90
10	4-NO_2Ph	>19:1	99	90
11	4-MePh	>19:1	87	94
12	3-MePh	>19:1	77	92
13	2-MePh	>19:1	66	94
14	1-naphthyl	>19:1	65	95
15	2-naphthyl	>19:1	98	94
16	3-furyl	>19:1	79	91
17	2-thioyl	>19:1	59	92
18[e]	*i*-Butyl	>19:1	63	89

[a]The reaction was performed with **4-1** (0.025 mmol), **4-2** (0.050 mmol)andcatalyst **4-C1** (10 mol%) in toluene (0.1 mL) at room temperature for 48 h. [b] Diastereoselectivity was determined by ^{1}H NMR. [c] Yield of isolated product. [d] Determined by HPLC analysis on a chiral stationary phase. *e* The catalyst loading was 20 mol%.

4.3 Conclusions

In summary, we have developed the asymmetric allylic substitution reaction of MBH carbonate with an azlactone. A number of MBH carbonates **4-1** could react with

azlactone **4-2** to afford the products **4-3** with high diastereoselectivity and enantioselectivity (49-99%, 89-98% ee). The product **4-3** could transform to α-methylene-γ-butyrolactones because azlactone **4-2** could function as masked formyl anion.

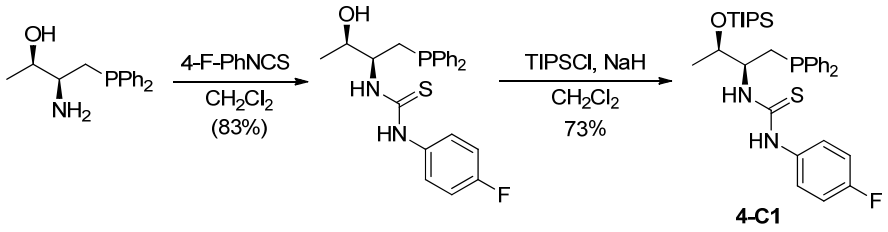
4.4 Experimental Section

4.4.1 General Methods

All starting materials were obtained from commercial sources and were used without further purification unless otherwise stated. Toluene, THF and Et_2O were dried and distilled from sodium and benzophenone prior to use. $CHCl_3$ and CH_2Cl_2 were distilled from CaH_2 prior to use. All solvents used in reactions involving phosphorus-containing compounds were degassed using N_2. Melting points were determined using a Büchi B-540 melting point apparatus. Optical rotations were measured using a Jasco DIP-1000 polarimeter. ^1H and ^{13}C NMR spectra were recorded on a Bruker ACF300 or AMX500 (500 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton ($CHCl_3$, δ 7.26), carbon ($CHCl_3$, δ 77.0). Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet). Coupling constants are reported in hertz (Hz). High-resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. TLC was accomplished using Merck pre-coated TLC plates (Merck 60 F254), and compounds were made visual with UV light at 254 nm. Flash chromatographic separations were performed on Merck 60 (0.040–0.063 mm) mesh silica gel. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase.

4-Isopropyl-2-oxazolin-5-one was prepared according to the literature reported procedure and stored under N_2 at room temperature.[95,]

4.4.2 Representative Procedure for Catalyst synthesis

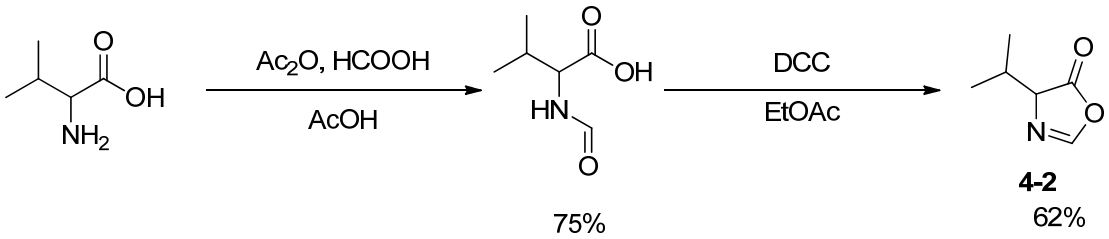


Scheme 4.2 Procedure for the catalyst synthesis

To a solution of (2*R*,3*S*)-3-amino-4-(diphenylphosphino)butan-2-ol (273 mg, 1.0 mmol) in CH_2Cl_2 (6 mL) was added 4-fluorophenyl isothiocyanate (170 mg, 1.1 mmol) under N_2, and the resulting mixture was stirred at room temperature for 2 hrs. Solvent was removed under reduced pressure, and the residue was directly subjected to column chromatographic separation on silica gel using hexane/ethyl acetate (12:1 to 8: 1) as an eluent to afford1-((2S,3R)-1-(diphenylphosphino)-3-hydroxybutan-2-yl)-3-(4-fluorophenyl)thiourea as a white solid (354 mg, 83% yield). To a solution of the above phosphine thiourea catalyst (57.5 mg, 0.14 mmol) in THF (1 mL) at 0 ^oC was added NaH (22.4 mg, 0.60 mmol, 60% (w/w) in mineral oil) and the mixture was stirred at this temperature for 10 min, followed by the addition of *tert*-butyldimethylsilyl chloride (27.1 mg, 0.18 mmol). The reaction mixture was stirred for 2 hours, and then water (2 mL) was added to quench the reaction. The reaction mixture was extracted with EtOAc (3 x 3 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography using hexanes/ethyl acetate (10:1 to 5:1) as an eluent to afford **4-C1** as a white solid (59.5 mg, 73% yield).[72] ^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (br, 21H),

1.01 (d, *J* = 6.2 Hz, 3H), 2.06 (t, *J* = 10.5 Hz, 1H), 2.51-2.58 (m, 1H), 4.34 (d, *J* = 5.7 Hz, 2H), 6.25 (d, *J* = 8.5 Hz, 1H), 6.87-6.90 (m, 2H), 6.92-7.00 (m, 2H), 7.12-7.27 (m, 8H), 7.48-7.53 (m, 2H), 7.83 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.49, 18.06, 18.09, 32.11 (d, *J* = 15.8 Hz), 58.90 (d, *J* = 18.5 Hz), 69.20 (d, *J* = 8.2 Hz), 116.96 (d, *J* = 22.4 Hz), 128.07 (d, *J* = 8.7 Hz), 128.27, 128.37, 128.40, 128.48, 128.74, 131.82, 132.62, 132.87, 132.98, 133.23, 137.34, 137.50, 139.00, 161.48 (d, *J* = 246.6 Hz), 180.48; ^{31}P NMR (121 MHz, $CDCl_3$) δ -23.69; HRMS (ESI) m/z calcd for $C_{39}H_{45}FN_2OPSSi$ $[M+H]^+$ =583.2665, found 583.2746.

4.4.3 Procedure for Synthesis Azlactone 4-2



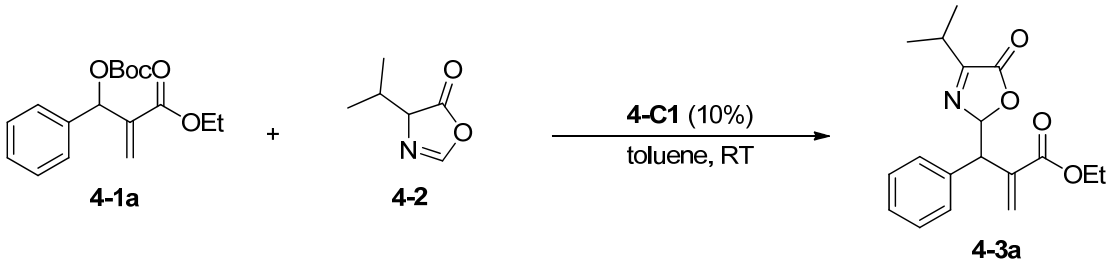
Scheme 4.3 Procedure for the synthesis of azlactone **4-2**

The mixture of valine (4.68 g, 40 mmol), formic acid (7.5 mL, 200 mmol) and acetyl anhydride (15.1 mL, 160 mmol) was dissolved in acetic acid (160 mL) at room temperature. The reaction mixture was stirred for 4 hours. Afterwards, all the volatiles were removed under reduced pressure and the residue was recrystallized from ethyl acetate to afford the white solid as N-formyl-valine (4.35 g, 75%).

To a solution of N-formyl-valine (4.35, 30 mmol) in EtOAc (40 mL) was added dicyclohexylcarbodiimide (6.2 g, 30 mmol) at 0 ℃. The reaction mixture was allowed to room temperature and stirred for 2 hours. The precipitated urea was removed by filtration and the organic solvent was removed under reduced pressure. The crude

residue was purified by distillation (b.p. 60-62 ℃, 3 mm/Hg) to afford the compound **4-2** as colorless oil (2.39 g, 62%).[96]

4.4.4 Representative Procedure

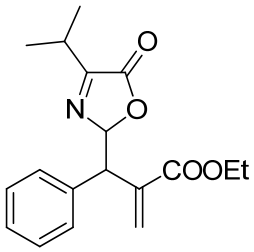


Scheme 4.4 Procedure for asymmetric allylic substitution reaction of MBH carbonates **4-1** with azlactone **4-2**

To the mixture of MBH carbonate **4-1a** (7.7 mg, 0.025 mmol), azlactone **4-2** (6.4 mg, 0.05 mmol), and Catalyst **4-C1** (1.5 mg, 0.0025 mmol) was added toluene (0.1 mL) at room temperature. The reaction mixture was stirred for 48 hours. The resulting solution was directly purified by column chromatography on silica gel to afford the colorless oil (6.5 mg, 82%).

4.4.5 Analytical Data of Product 4-3

Ethyl 2-((4-isopropyl-5-oxo-2,5-dihydrooxazol-2-yl)(phenyl)methyl)acrylate ***4-3a***

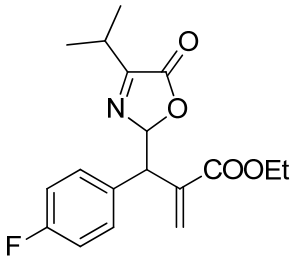


4-3a

A colorless oil; 82%; $[\alpha]^{25}_{D}$ = +47.1(*c* 0.27, $CHCl_3$); 98% ee, determined by HPLC analysis [Daicel Chiralpak IB, *n*-hexane/*i*-PrOH = 99.0 /1.0, 0.5 mL/min, λ =

220 nm, t (major) = 17.2 min, t (minor) = 20.5 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (d, *J* = 6.3 Hz, 3H), 1.13 (d, *J* = 6.9 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H), 2.72-2.77 (m, 1H), 4.08-4.19 (m, 2H), 4.62 (d, *J* = 3.8 Hz, 1H), 6.31-6.32 (m, 1H), 6.37 (s, 1H), 6.61 (s, 1H), 7.15-7.26 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 18.6, 18.7, 27.9, 49.2, 61.2, 99.1, 127.7, 128.1, 129.8, 134.0, 138.0, 164.4, 166.0, 169.0. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{22}NO_4$: 316.1543; found: 316.1548.

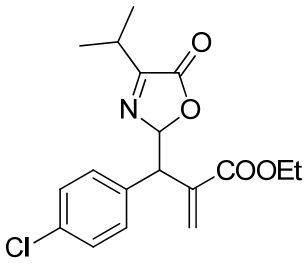
Ethyl 2-((4-fluorophenyl)(4-isopropyl-5-oxo-2,5-dihydrooxazol-2yl)methyl)acrylate ***4-3b***



4-3b

A colorless oil; 99%;$[\alpha]^{25}_D$ = +8.8 (*c* 1.74, $CHCl_3$); 93% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 99.0 /1.0, 0.5 mL/min, λ = 220 nm, t (major) = 10.3 min, t (minor) = 16.5 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (d, *J* = 7.0 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.21 (t, *J* = 6.9 Hz), 2.73-2.79 (m, 1H), 4.10-4.18 (m, 2H), 4.60 (d, *J* = 3.8 Hz, 1H), 6.28-6.29 (m, 1H), 6.41 (s, 1H), 6.61 (s, 1H), 6.91-6.95 (m, 2H), 7.10-7.13 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 18.6, 18.7, 27.9, 48.5, 61.2, 98.8, 114.9, 115.0, 127.9, 131.4, 131.5, 137.9, 163.2, 164.3, 165.9, 169.3. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{21}FNO_4$: 334.1449; found: 334.1447.

Ethyl 2-((4-chlorophenyl)(4-isopropyl-5-oxo-2,5-dihydrooxazol-2yl)methyl)acrylate ***4-3c***

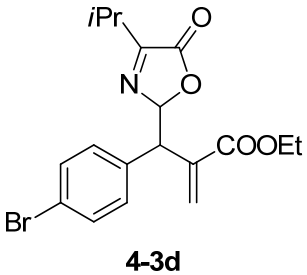


4-3c

A colorless oil; 99%; $[\alpha]^{25}_{D}$ = +9.8 (*c* 2.20, $CHCl_3$); 95% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 99.0 /1.0, 0.5 mL/min, λ = 220 nm, t (major) = 10.2 min, t (minor) = 16.4 min];^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (d, *J* = 7.0 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.21 (t, *J* = 6.9 Hz, 3H), 2.74-2.80 (m, 1H), 4.09-4.19 (m, 2H), 4.58 (d, *J* = 3.8 Hz, 1H), 6.28-6.30 (m, 1H), 6.39 (s, 1H), 6.62 (s, 1H), 7.08-7.10 (m, 2H), 7.21-7.23 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 18.7, 27.9, 48.6, 61.3, 98.7, 128.1, 128.2, 131.1, 132.5, 133.7, 137.7, 164.3, 165.8, 169.3. HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{18}H_{20}ClNNaO_4$: 372.0973; found: 372.0966.

Ethyl 2-((4-bromophenyl)(4-isopropyl-5-oxo-2,5-dihydrooxazol-2yl)methyl)acrylate

4-3d



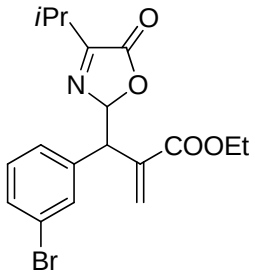
4-3d

A colorless oil; 87%; $[\alpha]^{25}_{D}$ = +48.8 (*c* 0.34, $CHCl_3$); 96% ee, determined by HPLC analysis [Daicel Chiralpak IB, *n*-hexane/*i*-PrOH = 99.0 /1.0, 0.5 mL/min, λ = 220 nm, t (major) = 10.6 min, t (minor) = 16.6 min];^{1}H NMR (500 MHz, $CDCl_3$): δ 0.98 (d, *J* = 6.9 Hz, 3H) 1.14 (d, *J* = 0.69 Hz, 3H), 1.22 (t, *J* = 6.9 Hz, 3H), 2.72-2.82

(m, 1H), 4.10-4.18 (m, 2H), 4.56 (d, *J* = 3.8 Hz, 1H), 6.28-6.30 (m, 1H), 6.38 (s, 1H), 6.62 (s, 1H), 7.01-7.04 (m, 2H), 7.36-7.39 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 18.7, 27.9, 48.7, 61.3, 98.7, 121.9, 128.2, 131.2, 131.5, 133.1, 137.7, 164.3, 165.8, 169.3; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{21}BrNO_4$: 394.0648; found: 394.0658.

Ethyl 2-((3-bromophenyl)(4-isopropyl-5-oxo-2,5-dihydrooxazol-2yl)methyl)acrylate

4-3e

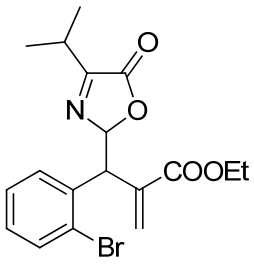


4-3e

A colorless oil; 87%; $[\alpha]^{25}_D$ = +45.8 (*c* 0.44, $CHCl_3$); 94% ee, determined by HPLC analysis [Daicel Chiralpak IB, *n*-hexane/*i*-PrOH = 99.0 /1.0, 0.5 mL/min, λ = 220 nm, t (major) = 20.3 min, t (minor) = 22.8 min]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.98 (d, *J* = 6.9 Hz, 3H) 1.16 (d, *J* = 6.9 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 2.73-2.83 (m, 1H), 4.10-4.21 (m, 2H), 4.59 (d, *J* = 3.3 Hz, 1H), 6.28-6.30 (m, 1H), 6.42 (s, 1H), 6.64 (s, 1H), 7.12-7.14 (m, 2H), 7.24 (m, 1H), 7.33-7.37 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 18.7, 28.0, 48.8, 61.3, 98.6, 122.0, 128.4, 129.0, 129.7, 130.8, 132.5, 136.3, 137.4, 164.2, 165.7, 169.4; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{21}BrNO_4$: 394.0648; found: 394.0658.

Ethyl 2-((2-bromophenyl)(4-isopropyl-5-oxo-2,5-dihydrooxazol-2-yl)methyl)acrylate

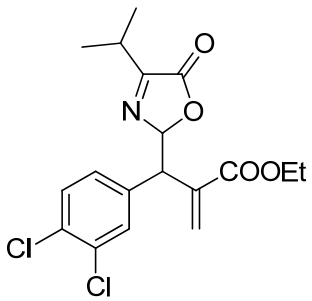
4-3f



4-3f

A colorless oil; 49%; $[\alpha]^{25}_{D}$ = +17.6 (*c* 0.46, $CHCl_3$); 94% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 95.0 /5.0, 0.5 mL/min, λ = 220 nm, t (major) = 14.2 min, t (minor) = 30.0 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (d, *J* = 7.0 Hz), 1.20-1.24 (m, 6H), 2.94-2.90 (m, 1H), 4.10-4.17 (m, 2H), 5.07 (d, *J* = 5.1 Hz, 1H), 6.12 (s, 1H), 6.32-6.33 (m, 1H), 6.59 (s, 1H), 7.08-7.12 (m, 1H), 7.22-7.25 (m, 1H), 7.29-7.31 (m, 1H), 7.57-7.59 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 18.7, 18.8, 28.1, 48.4, 61.2, 99.4, 126.4, 127.0, 128.6, 129.1, 130.2, 133.4, 135.2, 137.5, 164.3, 165.7, 169.1. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{21}BrNO_4$: 394.0648; found: 394.0658.

Ethyl 2-((3,4-dichlorophenyl)(4-isopropyl-5-oxo-2,5-dihydrooxazol-2-yl)methyl)acrylate ***4-3g***

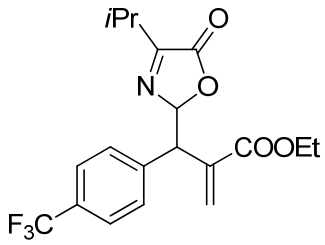


4-3g

A colorless oil; 77%; $[\alpha]^{25}_{D}$ = +25.6 (*c* 0.40, $CHCl_3$); 93% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 95.0 /5.0, 0.5 mL/min, λ = 220 nm, t (major) = 10.2 min, t (minor) = 17.6 min];^{1}H NMR (500 MHz, $CDCl_3$) δ

1.13 (d, *J* = 7.0 Hz, 3H), 1.20-1.23 (m, 6H), 2.85-2.91 (m, 1H), 4.10-4.16 (m, 2H), 5.01 (d, *J* = 6.3 Hz, 1H), 6.14 (s, 1H), 6.30 (m, 1H), 6.59 (s, 1H), 7.17-7.18 (m, 1H), 7.19-7.24 (m, 1H), 7.41 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 18.8, 18.9, 28.1, 45.4, 61.3, 99.0, 126.6, 128.7, 129.8, 130.9, 132.2, 134.1, 136.2, 137.1, 164.2, 165.4, 169.4. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{20}ClNO_4$: 384.0764; found: 384.0762.

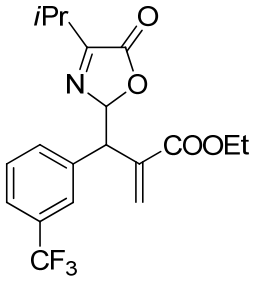
Ethyl 2-((4-isopropyl-5-oxo-2,5-dihydrooxazol-2-yl)(4(trifluoromethyl)phenyl)methyl) acrylate ***4-3h***



4-3h

A colorless oil; 99%; $[\alpha]^{25}_D$ = +33.6 (*c* 0.43, $CHCl_3$); 96% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 99.0 /1.0, 0.5 mL/min, λ = 220 nm, t (major) = 18.4 min, t (minor) = 20.7 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (d, *J* = 6.9 Hz, 3H), 1.12 (d, *J* = 6.9 Hz, 3H), 1.19-1.24 (t, *J* = 7.2 Hz, 3H), 2.71-2.81 (m, 1H), 4.09-4.20 (m, 2H), 4.66 (d, *J* = 3.8 Hz, 1H), 6.31-6.34 (m, 1H), 6.42 (s, 1H), 6.66 (s, 1H), 7.28-7.30 (m, 2H), 7.50-7.53 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 18.6, 27.9, 49.0, 61.4, 98.5, 125.0,128.6, 130.1, 137.4, 164.2, 165.7, 169.4; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{21}F_3NO_4$: 384.141.7; found: 384.1426.

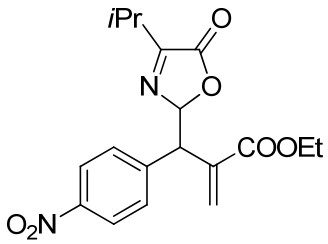
Ethyl2-((4-isopropyl-5-oxo-2,5-dihydrooxazol-2-yl)(3-(trifluoromethyl)-phenyl)-methyl) acrylate ***4-3i***



4-3i

A colorless oil; 99%; $[\alpha]^{25}_{D}$ = +24.8 (*c* 0.73, $CHCl_3$); 90% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 99.0 /1.0, 0.5 mL/min, λ = 220 nm, t (major) = 18.7 min, t (minor) = 20.4 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (d, *J* = 6.9 Hz, 3H), 1.13 (d, *J* = 6.9 Hz, 3H), 1.19-1.23 (t, *J* = 7.1 Hz, 3H), 2.69-2.79 (m, 1H), 4.09-4.20 (m, 2H), 4.68 (d, *J* = 3.8 Hz, 1H), 6.31-6.32 (m, 1H), 6.48 (s, 1H), 6.68 (s, 1H), 7.36-7.38 (m, 1H), 7.39-7.40 (m, 1H), 7.46-7.50 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 18.5, 18.6, 27.9, 48.9, 61.4, 98.5, 124.6, 126.1, 126.2, 128.6, 133.6, 135.1, 137.3, 164.1, 165.7, 169.6; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{21}F_3NO_4$: 384.141.7; found: 384.1426.

Ethyl 2-((4-isopropyl-5-oxo-2,5-dihydrooxazol-2-yl)(4-nitrophenyl)methyl)acrylate 4-3j

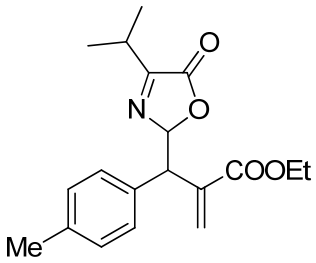


4-3j

A yellow oil; 99%; $[\alpha]^{25}_{D}$ = +18.8 (*c* 0.81, $CHCl_3$); 90% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 95.0 /5.0, 1.0 mL/min, λ = 220 nm, t (major) = 30.7 min, t (minor) = 41.2 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (d, *J* = 7.0 Hz, 3H), 1.14 (d, *J* = 6.3 Hz, 3H), 1.20-1.23 (t, *J* = 6.9 Hz, 3H), 2.75-

2.81 (m, 1H), 4.11-4.17 (m, 2H), 4.68 (d, *J* = 3.8 Hz, 1H), 6.34-6.35 (m, 1H), 6.44 (s, 1H), 6.68 (s, 1H), 7.35-7.37 (m, 2H), 8.11-8.13 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 18.8, 28.0, 49.1, 61.5, 98.3, 123.2, 128.9, 130.7, 137.1, 141.9, 147.4, 164.0, 165.5, 169.7; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{19}N_2O_6$: 359.1249; found: 359.1239.

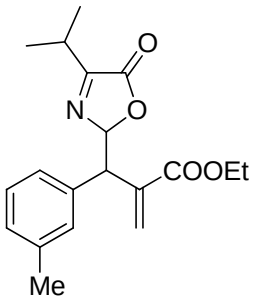
Ethyl 2-((4-isopropyl-5-oxo-2,5-dihydrooxazol-2-yl)(p-tolyl)methyl)acrylate ***4-3k***



4-3k

A colorless oil; 87%; $[\alpha]^{25}_D$ = +68.4 (*c* 0.14, $CHCl_3$); 94% ee, determined by HPLC analysis [Daicel Chiralpak IB, *n*-hexane/*i*-PrOH = 99.0 /1.0, 0.5 mL/min, λ = 220 nm, t (major) = 15.2 min, t (minor) = 17.7 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (d, *J* = 7.0 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.21 (t, *J* = 7.5 Hz, 3H), 2.27 (s, 3H), 2.73-2.79 (m, 1H), 4.10-4.17 (m, 2H), 4.57 (d, *J* = 2.8 Hz, 1H), 6.29-6.30 (m, 1H), 6.33 (s, 1H), 6.56 (s, 1H), 7.04 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 18.6, 18.7, 21.0, 27.9, 48.9, 61.1, 99.2, 127.8, 128.8, 129.7, 130.9, 137.3, 138.1, 164.6, 166.1, 168.9; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{24}NO_4$: 330.1700; found: 330.1713.

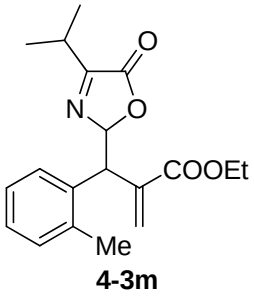
Ethyl 2-((4-isopropyl-5-oxo-2,5-dihydrooxazol-2-yl)(m-tolyl)methyl)acrylate ***4-3l***



4-3l

A colorless oil; 77%; $[\alpha]^{25}_{D}$ = +41.2 (*c* 0.54, $CHCl_3$); 94% ee, determined by HPLC analysis [Daicel Chiralpak IB, *n*-hexane/*i*-PrOH = 99.0 /1.0, 0.5 mL/min, λ = 220 nm, t (major) = 15.2 min, t (minor) = 17.7 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.21 (t, *J* = 7.5 Hz, 3H), 2.28 (s, 3H), 2.73-2.78 (m, 1H), 4.11-4.18 (m, 2H), 4.59 (d, *J* = 3.8 Hz, 1H), 6.30-6.31 (m, 3H), 6.34 (s, 1H), 6.58 (s, 1H), 6.95-6.97 (m, 2H), 7.01-7.02(m, 1H), 7.11-7.14 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 18.6, 18.7, 21.3, 27.9, 49.1, 61.2, 99.1, 126.9, 127.9, 128.4,130.4, 133.9, 137.5, 138.0, 164.5, 166.1, 168.9; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{24}NO_4$: 330.1700; found: 330.1713.

Ethyl 2-((4-isopropyl-5-oxo-2,5-dihydrooxazol-2-yl)(o-tolyl)methyl)acrylate ***4-3m***



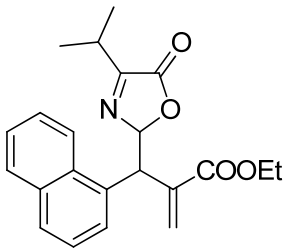
4-3m

A colorless oil; 66%; $[\alpha]^{25}_{D}$ = +15.7 (*c* 0.60, $CHCl_3$); 94% ee, determined by HPLC analysis [Daicel Chiralpak IB, *n*-hexane/*i*-PrOH = 99.0 /1.0, 0.5 mL/min, λ = 220 nm, t (major) = 15.3 min, t (minor) = 17.5 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (d, *J* = 7.0 Hz), 1.17 (m, 1.22), 2.40 (s, 1H), 2.77-2.83 (m, 1H), 4.08-4.16 (m, 2H), 4.88 (d, *J* = 4.5 Hz, 1H), 6.28 (s, 1H), 6.31-6.32 (m, 1H), 6.56 (s, 1H), 7.06-7.14

(m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 18.6, 18.8, 19.8, 28.0, 44.7, 61.1, 99.8, 123.6, 125.2, 127.5, 127.9, 129.0, 130.7, 132.9, 138.0, 138.3, 164.3, 166.1, 168.9. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{24}NO_4$: 330.1700; found: 330.1713.

Ethyl 2-((4-isopropyl-5-oxo-2,5-dihydrooxazol-2-yl)(naphthalen-1-yl)methyl)acrylate

4-3n

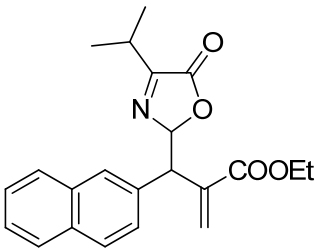


4-3n

A colorless oil; 65%; $[\alpha]^{25}_D$ = +11.0 (*c* 0.64, $CHCl_3$); 95% ee, determined by HPLC analysis [Daicel Chiralpak IB, *n*-hexane/*i*-PrOH = 99.0 /1.0, 0.5 mL/min, λ = 220 nm, t (major) = 23.9 min, t (minor) = 38.6 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.9 Hz, 3H), 1.15-1.21 (m, 6H), 2.83-2.89 (m, 1H), 4.13-4.17 (q, *J* = 7.0 Hz, 2H), 5.60 (d, *J* = 3.8 Hz, 1H), 5.96 (s, 1H), 6.49-6.50 (m, 2H), 7.42-7.53 (m, 3H), 7.62-7.64 (m, 1H), 7.77-7.84 (m, 2H), 8.11-8.13 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 18.8, 18.9, 28.0, 43.9, 61.3, 99.7, 123.7, 124.8, 125.7, 126.4, 126.5, 128.4, 128.8, 129.5, 134.0, 137.4, 164.5, 166.2, 169.0. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{24}NO_4$: 366.1700; found: 366.1698.

Ethyl 2-((4-isopropyl-5-oxo-2,5-dihydrooxazol-2-yl)(naphthalen-2-yl)methyl)acrylate

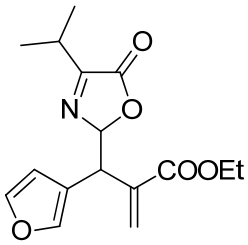
4-3o



4-3o

A colorless oil; 98%; $[\alpha]^{25}_{D}$ = +17.5 (*c* 0.96, $CHCl_3$); 94% ee, determined by HPLC analysis [Daicel Chiralpak IB, *n*-hexane/*i*-PrOH = 99.0 /1.0, 0.5 mL/min, λ = 220 nm, t (major) = 22.3 min, t (minor) = 24.7 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.21 (t, *J* = 7.0 Hz), 2.67-2.73 (m, 1H), 4.09-4.16 (m, 2H), 4.80 (d, *J* = 3.8 Hz, 1H), 6.42 (s, 2H), 6.65 (s, 1H), 7.27-7.29 (m, 1H), 7.44-7.45 (m, 2H), 7.63-7.78 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 18.6, 18.7, 27.8, 49.3, 61.2, 99.2, 126.1, 127.5, 127.7, 127.9, 128.1, 128.8, 131.7, 132.7, 132.9, 138.0, 164.4, 166.0, 169.1. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{24}NO_4$: 366.1700; found: 366.1698.

Ethyl 2-(furan-3-yl(4-isopropyl-5-oxo-2,5-dihydrooxazol-2-yl)methyl)acrylate ***4-3p***

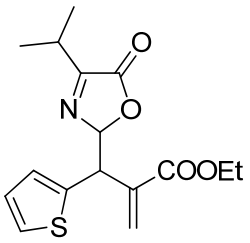


4-3p

A colorless oil; 79%; $[\alpha]^{25}_{D}$ = +37.8 (*c* 0.31, $CHCl_3$); 94% ee, determined by HPLC analysis [Daicel Chiralpak IB, *n*-hexane/*i*-PrOH = 99.0 /1.0, 0.5 mL/min, λ = 220 nm, t (major) = 17.4 min, t (minor) = 19.9 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (d, *J* = 7.0 Hz, 3H), 1.21 (d, *J* = 7.0 Hz, 3H), 1.29 (t, *J* = 7.6 Hz, 3H), 2.85-2.91 (m, 1H), 4.19-4.24 (q, *J* = 7.6 Hz, 2H), 4.59 (d, *J* = 3.8 Hz, 1H), 6.09 (s, 1H), 6.22-

6.24 (m, 2H), 6.50 (s, 1H), 7.32-7.33 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 18.8, 28.1, 40.6, 61.3, 99.0, 111.2, 119.8, 128.9, 137.1, 141.3, 142.9, 164.6, 166.1, 169.4. HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{20}NO_5$: 306.1336; found: 306.1345.

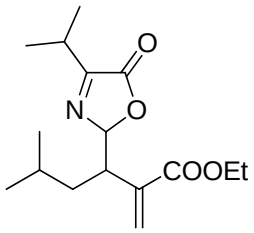
Ethyl 2-((4-isopropyl-5-oxo-2,5-dihydrooxazol-2-yl)(thiophen-2-yl)methyl)acrylate ***4-3q***



4-3q

A yellow oil; 59%; $[\alpha]^{25}_D$ = +21.9 (*c* 0.44, $CHCl_3$); 92% ee, determined by HPLC analysis [Daicel Chiralpak IB, *n*-hexane/*i*-PrOH = 99.0 /1.0, 0.5 mL/min, λ = 220 nm, t (major) = 17.4 min, t (minor) = 19.9 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (d, *J* = 7.0 Hz, 3H), 1.18 (d, *J* = 7.0 Hz), 1.27 (t, *J* = 7.0 Hz), 2.80-2.86 (m, 1H), 4.18-4.23 (m, 2H), 4.96 (d, *J* = 3.8 Hz), 6.27-6.28 (m, 1H), 6.35 (s, 1H), 6.60 (s, 1H),6.88-6.92 (m, 2H), 7.17-7.18 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 18.7, 28.0, 44.2, 61.4, 98.7, 125.4, 126.8, 127.7, 129.1, 137.5, 164.5, 165.8, 169.4; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{20}NO_4S$: 322.1108; found: 322.1094.

Ethyl 3-(4-isopropyl-5-oxo-2,5-dihydrooxazol-2-yl)-5-methyl-2-methylenehexanoate ***4-3r***



4-3r

A colorless oil; 63%; $[\alpha]^{25}_{D}$ = +90.2 (*c* 0.13, $CHCl_3$); 89% ee, determined by HPLC analysis [Daicel Chiralpak IC, *n*-hexane/*i*-PrOH = 95.0 /5.0, 0.5 mL/min, λ = 220 nm, t (major) = 7.2 min, t (minor) = 9.7 min]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89-0.93 (m, 6H), 1.20-1.35 (m, 10H), 2.90-2.94 (m, 1H), 3.47-3.51 (m, 1H), 4.01-4.04 (m, 1H), 4.18-4.23 (m, 1H), 5.62 (s, 1H), 5.96-5.97 (m, 1H), 6.37 (s, 1H),; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 18.9, 19.1, 21.7, 23.3, 25.3, 39.1,41.4, 61.0, 100.6, 123.6, 128.2, 136.9, 165.2, 166.5, 168.8; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{26}NO_4$: 296.1856; found: 296.1850.

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