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Development of Novel Hydrogen-Bond Donor Catalysts

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Tsubasa Inokuma

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2. Thiourea-Catalyzed Asymmetric Michael Addition of Activated Methylene Compounds to α, β-Unsaturated Imides: Dual Activation of Imide by Intra- and Intermolecular Hydrogen Bonding Tsubasa Inokuma, Yasutaka Hoashi, Yoshiji Takemoto *J. Am. Chem. Soc.* **2006**, *128*, 9413.

3. Asymmetric Synthesis of 4-Substituted 2,6-Dioxopiperidine-3-carbonitrile by Using Thiourea-Catalyzed Asymmetric Michael Addition Tsubasa Inokuma, Yu-ki Nagamoto, Shota Sakamoto, Hideto Miyabe, Kiyosei Takasu, Yoshiji Takemoto *Heterocycles* **2009**, *79*, 573.

4. Hydroxyl Group-Directed Organocatalytic Asymmetric Michael Addition of α, β-Unsaturated Ketones with Alkenylboronic Acids Tsubasa Inokuma, Kiyosei Takasu, Toshiyuki Sakaeda, Yoshiji Takemoto *Org. Lett.* **2009**, *11*, 2425.

5. Synthesis of Optically Active *N*-Aryl Amino Acid Derivatives through the Asymmetric Petasis Reaction Catalyzed by Novel Hydroxy-thiourea Tsubasa Inokuma, Yusuke Suzuki, Toshiyuki Sakaeda, Yoshiji Takemoto *Chem. Asian. J.* **2011**, 2902.

Supervisor's Foreword

In April 2004, Dr. Tsubasa Inokuma joined my group at Kyoto University as an undergraduate student. After his graduation from Kyoto University, he entered the Graduate School of Pharmaceutical Sciences of Kyoto University and started his doctoral study with me in the same laboratory. In November 2011, he obtained his Ph.D. degree from Kyoto University.

Dr. Inokuma's research theme is the development of novel asymmetric catalysts, especially the organocatalysts. Catalytic asymmetric synthesis is one of the major research topics in organic chemistry, and the development of organocatalysts has attracted much attention within the past decade. In terms of practicality, because these catalysts lack harmful metals they are considered to be environmentally benign and friendly to humans. In addition, from the point of view of fundamental chemistry, the behaviors of the catalytic activity of organocatalysts are intriguing. Several types of organocatalysis such as enamine catalysis (proline, secondary amines), phase transfer catalysis (quaternary ammonium salt), and strong Brønsted acid catalysis (phosphoric acids) are widely studied, and Dr. Inokuma is interested in hydrogen bond (HB) donor catalysis. HB is one of the most ubiquitous interactions in the natural world, and enzymes utilize this interaction for furnishing the high levels of chemo- and regioselectivities in a living system. If this system could be applied in vitro, a highly efficient chemical transformation would be expected. Dr. Inokuma's aim was to develop novel and effective HB donor catalysts based on the previously accepted bifunctional thiourea catalyst bearing a tertiary amino group as a basic function.

First, he developed two novel types of HB donors, quinazolines, and benzothiadiazines. These achievements are published in the *Journal of American Chemical Society* and *Chemistry—A European Journal.* In addition, he also developed two novel types of thiourea catalysts bearing additional functions other than the tertiary amino group for developing the novel reactions which had never been achieved before. By using these catalysts, he developed two novel asymmetric

reactions. These findings are published as communications in *Organic Letters* and *Chemistry—An Asian Journal,* respectively. All of these documents were prepared by himself, and he is the first author of each publication. All of his work will contribute to the further development of the chemistry of asymmetric organocatalysis.

Kyoto, Japan, March 4, 2012

Prof. Yoshiji Takemoto
Graduate School of Pharmaceutical Sciences
Kyoto University

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I am also grateful to all colleagues in the Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Kyoto University: Dr. Tomotaka Okino, Dr. Kazumasa Yoshida, Dr. Yusuke Kobayashi, Dr. Xuenong Xu, Dr. Shingo Obika, Mr. Ryuta Asada, Mr. Yasutaka Hoashi, Dr. Jianwu Xie, Dr. Naoya Shindo, Mr. Takaya Yabuta, Ms. Sayo Tsuchida, Mr. Akira Toyoda,

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Lastly, I would especially like to thank my mother, Tomiko Inokuma, for her constant source of emotional, moral, and financial support throughout my life. I am also grateful to my grandmother, Shizue, and my sister, Mai, for their constant encouragement all my life.

Contents

Abbreviations

Å	Ångström
Ac	Acetyl
ACE	Angiotensin converting enzyme
Ar	Aryl
ATR	Attenuated total reflectance
B3LYP	Becke three-parameter lee-yang-parr
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1′-Binaphthyl-2,2′-diol
Bn	Benzyl
Boc	*tert*-Butoxy carbonyl
BOX	2,2-Bis(4-phenyl-2-oxazolin-2-yl)propane
BTMA·ICl_2	Benzyltrimethylammonium dichloroiodate
Bu	Butyl
Cy	Cyclohexyl
d	Days
DBFOX	4,6-Dibenzofurandiyl-2,2′-bis(4-phenyloxazoline)
DIAD	Diisopropylazodicarboxylate
DMAP	Dimetylaminopyridine
DMSO	Dimethyl sulfoxide
DMTMM	4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
EI	Electron ionization
Et	Ethyl
FAB	Fast atom bombardment
Gly	Glycine
h	Hour(s)
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
iPr	Isopropyl
IR	Infrared
LRMS	Low resolution mass spectrometry

Me	Methyl
mp	Melting point
NHC	*N*-heterocyclic carbine
NMDA	*N*-methyl-(*D*)-aspartate
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
Ns	Nitrobenzenesulfonyl
Ph	Phenyl
PKC	Protein kinase C
PMP	*para* methoxyphenyl
rt	Room temperature
TBA	Tetrabutylammonium
TBS	*tert*-butyldimethylsilyl
THF	Tetrahydrofurane
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Tetramethylsilane
UV	Ultraviolet
VAPOL	2,2′-diphenyl-4-biphenanthrol

Chapter 1
Introduction

Abstract The recent developments of the organocatalytic asymmetric reactions are summarized in this chapter. Among them, the hydrogen bond (HB) donor catalysts such as thiourea catalysts are well known as effective organocatalyst motif. My research group has developed the thiourea catalyst bearing a tertiary amino group. In the concept of this catalyst, the thiourea moiety and the tertiary amino group act as a Brønsted acid and a Brønsted base, respectively. These motifs activate both the electrophiles and the nucleophiles, respectively, resulting in a considerable acceleration of the reaction rate. So far, a number of other groups including our own have reported a variety of asymmetric reactions by using this concept. Recently, based on this concept, various bifunctional organocatalysts having other HB donor moieties than thiourea or possessing different functional groups than basic amino group have been developed.

1.1 Introduction

Catalytic asymmetric synthesis is one of the fundamental subjects in organic chemistry and makes a major contribution to the development of pharmaceutical sciences [1–4]. Within this field, organocatalysis has shown remarkable development since the report of the proline-catalyzed asymmetric aldol reaction by Barbas and List in 2000 (Scheme 1.1) [5]. Due to the ease of handling of the reaction, low toxicity to humans and the environment, and economic efficiency, organocatalysis can be regarded as one of the most promising processes for practical synthesis (Fig. 1.1) [6–22].

Organic chemists have discovered that synthetic molecules, possessing distinct hydrogen bond (HB) donor motifs associated with complementary functional and/or structural frameworks can be used to catalyze an array of carbon–carbon and carbon-heteroatom bond-forming reactions with high enantioselectivity and

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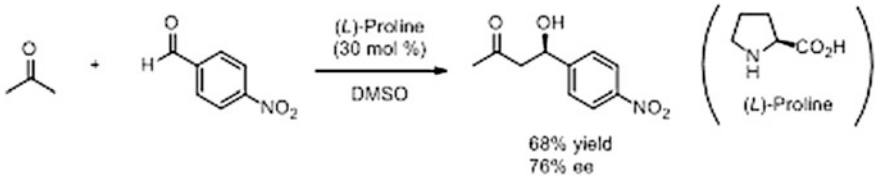


Scheme 1.1 Asymmetric aldol reaction catalyzed by (*L*)-proline

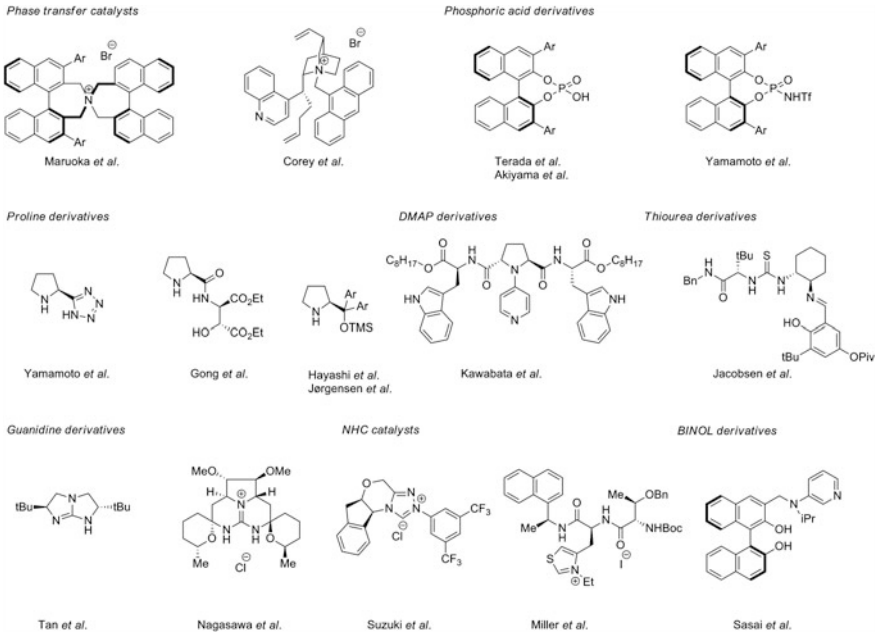
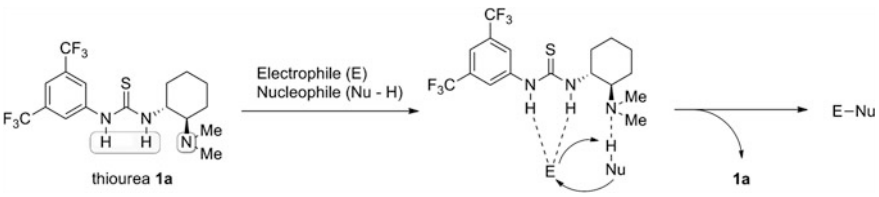


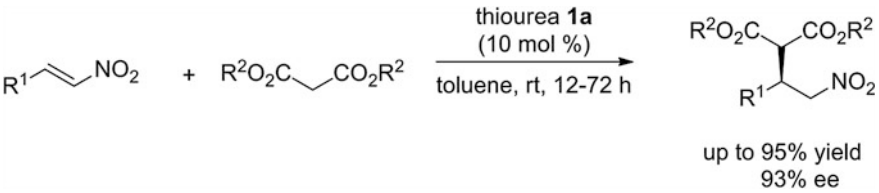
Fig. 1.1 Representative asymmetric organocatalysts

broad substrate scope [23–26]. In 2003, our group reported thiourea **1a** as a bifunctional HB donor catalyst (Scheme 1.2) [27].

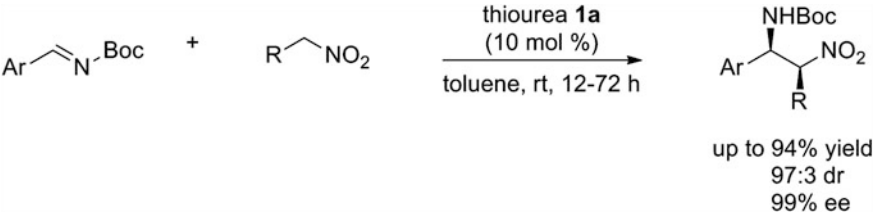
This catalyst contains a thiourea moiety and a tertiary amino group in its structure. The thiourea moiety and the tertiary amino group act as a Brønsted acid



Scheme 1.2 The structure of bifunctional thiourea **1a** and its concept for bifunctional organocatalysis



Scheme 1.3 Asymmetric Michael reaction of nitroolefins and malonates catalyzed by **1a**



Scheme 1.4 Asymmetric aza-Henry reaction of *N*-Boc imines and nitroalkanes catalyzed by **1a**

and a Brønsted base, respectively. These motifs activate both the electrophiles and the nucleophiles, respectively, resulting in a considerable acceleration of the reaction rate. So far, we have reported a variety of asymmetric reactions by using this concept (Schemes 1.3 and 1.4) [27–32].

HB is defined as the attractive interaction of a hydrogen atom with an electronegative atom. In these reactions, the HB donor moiety should coordinate with the Lewis basic sites of the substrates to stabilize the transition states of the reactions. The degree of the electronegativity of the nitrogen atoms of the HB donor moiety, which should be influenced by the acidities of these HB donor protons, would affect the degree of the stabilization. In addition, the positions of the HB donor protons should also be an important factor. Therefore, the abilities of HB donors would vary according to these two parameters. Recently, several groups reported novel HB donor scaffolds other than the thiourea motif (Fig. 1.2). Ellman reported the sulfinyl urea **2**, which possessed an electron-withdrawing sulfinyl group adjacent to the urea moiety for increasing the acidity of the HB donor [33]. In the structure of Rawal's catalyst **3** bearing the squaramide moiety [34], the nitrogen atoms are connected by a two-carbon link, and therefore the distance between the two HB donor protons is longer than in the previous thiourea catalysts, and this long distance affects the structure of the HB complex of the electrophiles and HB donor. Nájera and Park reported the benzimidazole-type catalysts **4a**, **b**, in which one of the two HB donor protons was installed in the cyclic structure [35, 36].

An amine moiety is used as an additional functional group of **1a**, and therefore the nucleophiles which can be used in these reactions are limited to highly acidic compounds such as 1, 3-dicarbonyl compounds or nitroalkanes. Therefore, it is

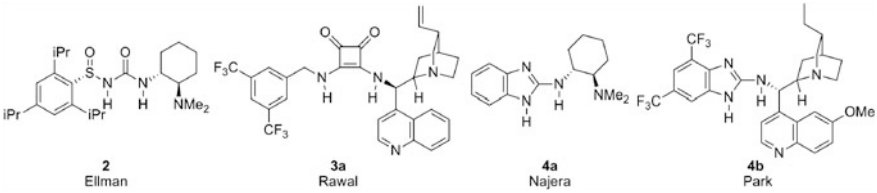
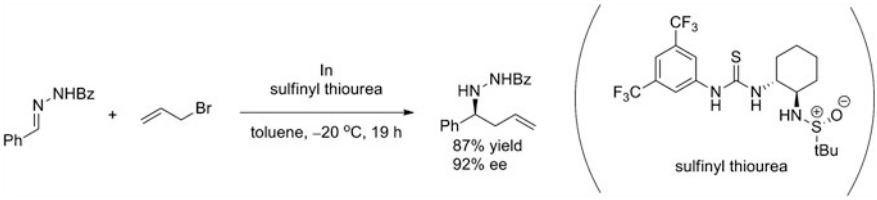
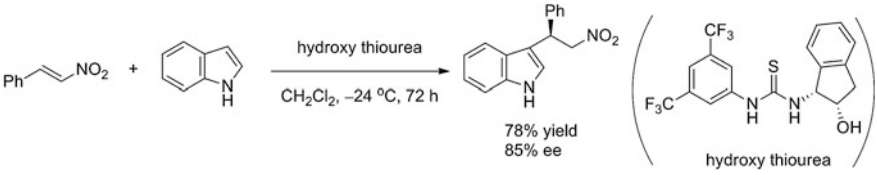


Fig. 1.2 Examples of the HB donor structures



Scheme 1.5 Asymmetric allylation of benzoyl hydrazone catalyzed by the sulfinyl thiourea



Scheme 1.6 Asymmetric Friedel-Crafts reaction of Indole and nitroolefin catalyzed by the hydroxy thiourea

desirable to expand the scope of the nucleophiles in order to improve the efficacy of organocatalysis. On the other hand, several thiourea catalysts bearing additional functionalities other than a basic amino group have been reported. Jacobsen reported sulfinyl thiourea, which catalyzed the 1, 2-addition of benzoyl hydrazone and allylindium species (Scheme 1.5) [37].

Ricci reported the asymmetric Friedel-Crafts reaction of indoles and nitroolefins catalyzed by thiourea derived from (*cis*)-1-amino-2-indanol (Scheme 1.6) [38].

In this thesis, I examine the development of novel HB donor organocatalysts from the standpoint of two methods to increase the utility of the organocatalysts.

In Chap. 2, I describe the development of two novel HB donor motifs and the evaluation of the HB donor activities of these catalysts by using spectroscopic analysis and several asymmetric reactions.

In Chap. 3, for expanding the scopes of the reaction modes, I describe two novel hydroxy thioureas instead of the aminothiourea. Using these catalysts, I developed asymmetric 1, 4- and 1, 2-additions of vinyl boronates to γ-hydroxy enones and imines.

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Chapter 2
Development of HB Donor Catalysts

Abstract Two novel hydrogen bond (HB) donor catalysts were designed and developed. By bridging the HB moiety and aryl group with an electron-withdrawing group such as, ketone or sulfone, the acidities of the N–H protons can be tuned by changing the electronic nature of the electron-withdrawing groups involved. In addition, it is anticipated that the removal of the highly nucleophilic sulfur atom in thiourea would prevent the side reactions that are sometimes problematic in thiourea-catalyzed reactions. The extents of the ability of HB donation of two novel quinazoline and benzothiadiazine-derived catalysts, prepared by using the above approach, were systematically evaluated by analytical methods. It was found that the order of HB donor ability was quinazoline < thiourea < benzothiadiazine. These catalysts were subsequently examined in two asymmetric transformations, namely Michael reactions of α,β-unsaturated imides and hydrazination reactions of 1,3-dicarbonyl compounds. The former worked best with the use of thiourea catalysts whereas the latter gave best results with quinazoline-derived catalysts, which exhibit less HB donor activity than thiourea counterparts. These results show that the strongest HB donors are not necessarily the most active or most suitable catalysts for asymmetric reactions.

2.1 Development and Properties of Novel HB Donor Catalysts

2.1.1 Introduction and Background

Non-metallic organocatalytic asymmetric reactions are powerful and environmentally friendly strategies for the synthesis of highly valuable chiral building blocks [1–17]. HB-donor catalysts are now considered to be important compounds in organocatalysis [18–22]. Among them, thioureas have been recognized as some

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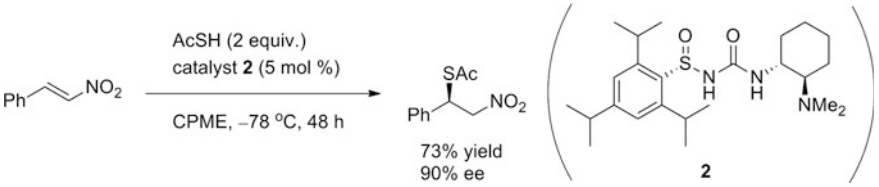
of the most advantageous HB-donating structures due to the suitable positioning of the two N–H protons [23–28]. Since our initial design of bifunctional thiourea catalyst (**1a**) [29–34], my colleagues and I, along with other groups, have used this catalyst in various types of asymmetric reactions [35, 36]. As described in the Preface, several new classes of HB-donor catalysts have recently been developed [37–41]. Ellman demonstrated that sulfonylurea derivative **2**, which has more acidic protons than previously used ureas, efficiently promoted the asymmetric Michael addition of thio acid to nitroolefins (Scheme 2.1) [37].

Rawal reported a different type of HB-donor catalyst **3** bearing a squaramide moiety. The distance of the two HB donor protons was calculated to be 2.72 Å, which is longer than that of thiourea **1a** (2.13 Å). These catalysts were successfully applied to the enantioselective Michael addition of 1,3-diketones to nitroolefins (Scheme 2.2) [38].

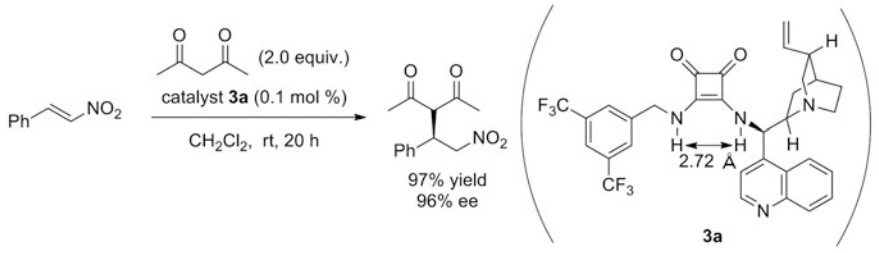
At the same time as my above mentioned studies, Nájera reported the benzimidazole **4a**-catalyzed enantioselective Michael addition of dialkylmalonates and nitroolefins (Scheme 2.3) [39, 40]. The distance between the two acidic protons of **4a** was revealed by crystallographic analysis to be 2.41 Å, which was intermediary between the distances for the two acidic protons of **1a** and **3a**.

Park's group independently developed benzimidazole catalyst **4b**, which bears electron-withdrawing groups at the benzimidazole ring connected to the NH donor moiety to enhance the reaction rate (Scheme 2.4) [41].

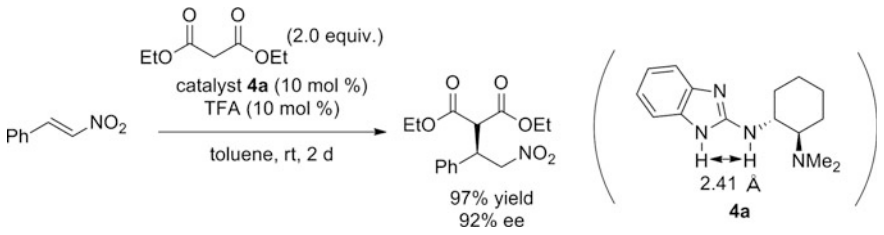
To further develop more efficient double HB-donor catalysts, I designed several novel types of bifunctional catalysts (Fig. 2.1).



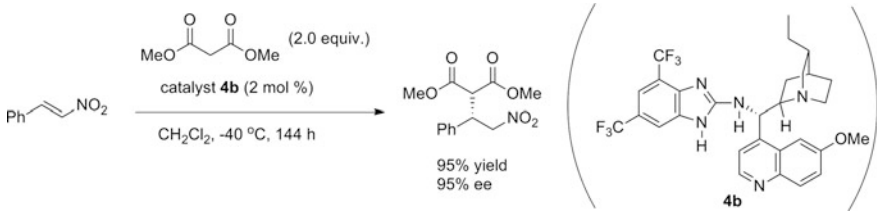
Scheme 2.1 Sulfinylurea-catalyzed asymmetric Michael addition



Scheme 2.2 Squaramide catalyzed asymmetric Michael addition



Scheme 2.3 Benzimidazole catalyzed asymmetric Michael addition



Scheme 2.4 Benzimidazole catalyzed asymmetric Michael addition

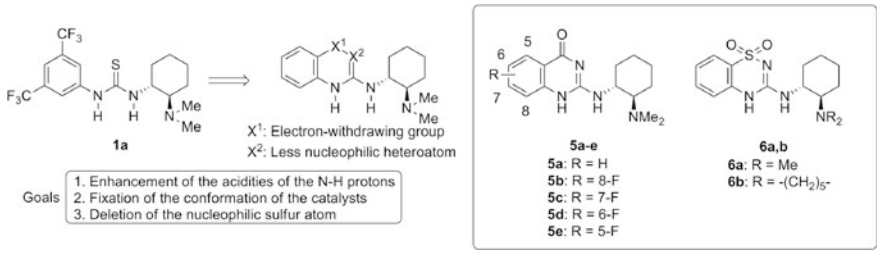


Fig. 2.1 Concept of the novel scaffolds of the HB-donors

When the HB moiety and aryl group of the original aminothiourea **1a** are bridged with an electron-withdrawing group such as carbonyl or sulfone, the acidities of the N–H protons can be tuned by the electronic nature of these electron-withdrawing groups. In addition, I anticipated that removal of the highly nucleophilic sulfur atom in thiourea **1a** would prevent the side reactions that are sometimes problematic in thiourea-catalyzed reactions [34].

This section describes the preparation of novel HB donor catalysts **5** and **6** and their evaluation by analytical methods.

2.1.2 Results and Discussion

To obtain insights into the conformations of these HB donors, a computational analysis was first performed (Fig. 2.2). When the ground state of quinazoline **5a** in gas phase was calculated at the B3LYP/6-31G(d) level of density functional theory (DFT) [42–44], the two N–H bonds aligned *syn* to each other and the difference of the energy between the *syn* form and *anti* form was 3.03 kcal/mol. A similar trend was observed in thiourea **1a**. The benzothiadiazine **6a** also showed a similar alignment. The dihedral angles of N–C–N in **5a**, **6a** and **1a** were 114°, 114° and 113°, respectively. From this analysis, both quinazolines and benzothiadiazines are expected to form HB in a manner similar to thiourea. However, the distance between the HB donor protons of quinazoline **5a** is 2.31 Å, which is longer than the distance between the donor protons in thiourea **1a**. The distance of two protons of benzothiadiazine **6a** was in middle of those in quinazoline **5a** and thiourea **1a**. In addition, the benzene ring in thiourea **1a** was twisted from the surface of the thiourea moiety due to the steric hinderance of bulky sulfur atom, while **5a** and **6a** adapted the planar form due to the fixation of the benzene rings and the HB donor moieties. I conjectured that these differences influenced the catalytic activities of these HB donors.

I then prepared the quinazoline catalysts **5a–e** from commercially available anthranilic acids **7a–e** (Scheme 2.5).

8a was synthesized in three steps from the corresponding anthranilic acids **7a–e** according to the literature [45]. Next, the condensation of **8a** and (*R*,*R*)-1,2-diaminocyclohexane [46] in isoamyl alcohol at an elevated temperature gave the

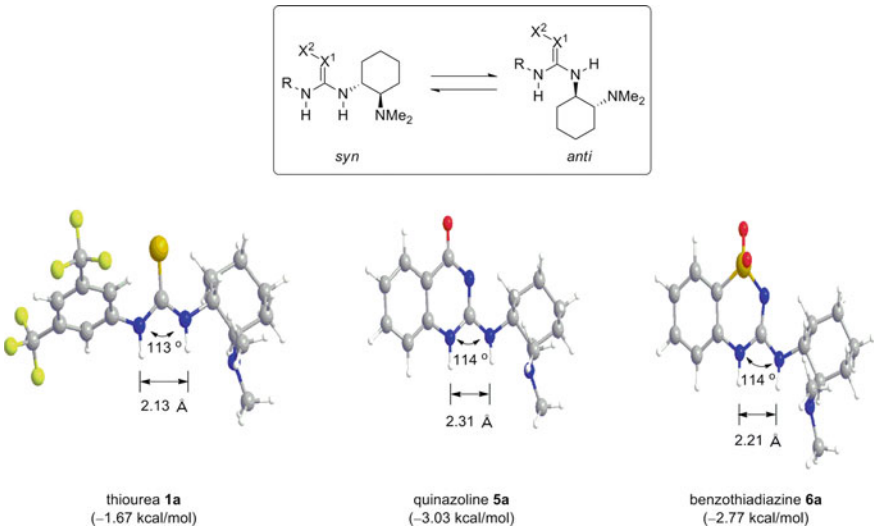
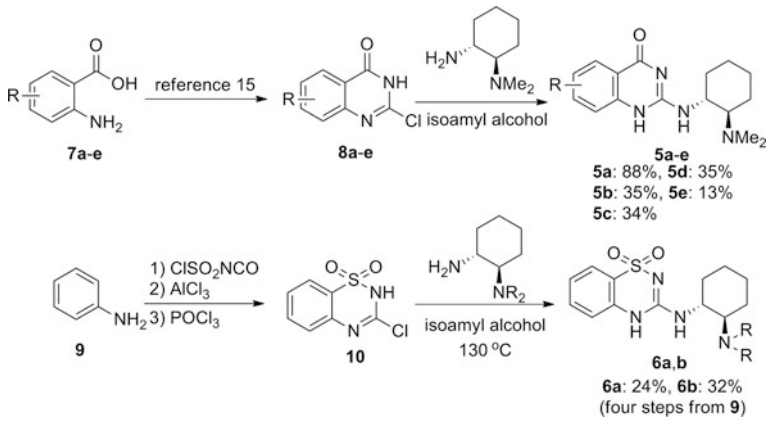


Fig. 2.2 Computational analysis of the ground state of HB donors (the values of the relative energies of the *syn* forms against the *anti* forms are shown in parenthesis)



Scheme 2.5 Synthesis of the novel HB-donor catalysts 5 and 6

desired 2-aminoquinazolin-4-(1*H*)-one-type catalyst **5a** in 88 % yield. Catalysts **5b–e** were synthesized from the corresponding benzoic acids **7b–e** by the same method. For the synthesis of benzothiadiazine-1,1-dioxide-type catalyst **6a**, aniline **9** was converted to **10** in three steps. The desired product **6a** was obtained by the coupling of chloride **10** with (*R*,*R*)-1,2-diaminocyclohexane in 24 % overall yield from **9**. Benzothiadiazine catalyst **6b** was also synthesized in a similar manner.

In an effort to further confirm the structures of the HB donors, single crystals of benzothiadiazine-1,1-dioxide-type catalyst **6b** were obtained and subjected to X-ray crystallography (Fig. 2.3).

As in **1a** [30], the two N–H protons of **6b** are positioned *syn* relative to each other. The distances between these protons and the dihedral angle of N–C–N are 2.27 Å and 117°, respectively (Fig. 2.3), which are almost the same as those in **1a** (2.10 Å and 114°, respectively). However, unlike in **1a**, the aromatic ring and HB-donor moieties of **6b** are coplanar, which suggests that the resonance effect of catalyst **6b** should be stronger than that of **1a**. The result of the crystallography

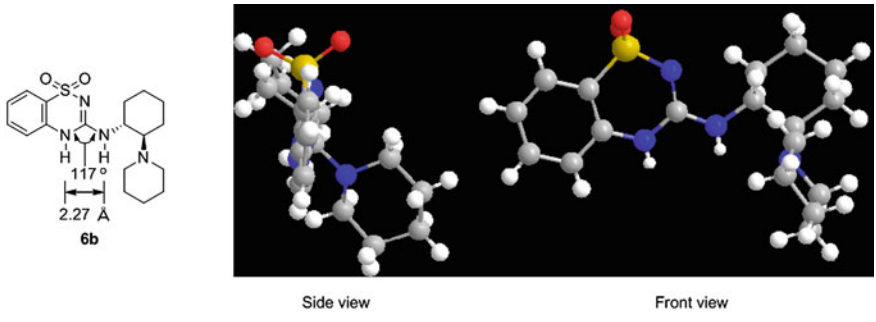
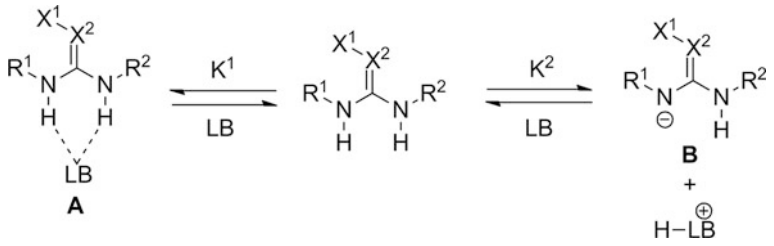


Fig. 2.3 X-ray crystallography of **6b**

also suggests that these new HB-donor catalysts **6** should show catalytic activities like thiourea **1a** in asymmetric reactions.

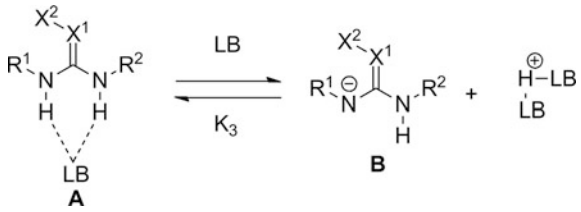
Next, I estimated the activities of the HB formation of these novel HB donor motifs. First the estimation was performed by measuring the p*K*a values of the HB donor protons of each catalyst according to the literature [47, 48]. However, the variabilities of the data were too large to evaluate them properly. However, it was anticipated that if these catalysts were mixed with Lewis bases, they would form the hydrogen-bonded complex **A**. In addition, if the Lewis base is strongly basic, one of the protons should migrate to the Lewis base to form the anion species **B** (Scheme 2.6). In the cases at the border line between these two phenomena, excess Lewis base should react to form the dimer of the Lewis base and deprotonate the catalyst to form **B** (Scheme 2.7) [49, 50]. It can be considered that the equilibrium constants of these processes represent the degree of stabilization of the complex, which in turn should reflect the HB-donating abilities of the HB donors.

Spectrophotometric analyses were conducted to identify the HB-donating abilities of catalysts **1a**, **5a** and **6a** with the Lewis bases [49–55]. When tetrabutylammonium acetate was titrated to a DMSO solution of **6a**, several new absorbances were observed in the UV spectrum and isosbestic points were not observed (Fig. 2.4). I attempted to estimate the binding constant of **6a** and ammonium anion, but this tendency did not fit well to the equation of a one-step binding model. This implied that after forming the complex **A**, the acetate anion interacted with **A** to form species such as the anion **B** due to the strong Lewis basicity of the acetate anion. Therefore, in order to estimate the binding constant properly, I decided to utilize less Lewis basic compounds. When



Scheme 2.6 Association models of the HB-donors and Lewis bases

Scheme 2.7 Association models of the HB-donors and Lewis bases



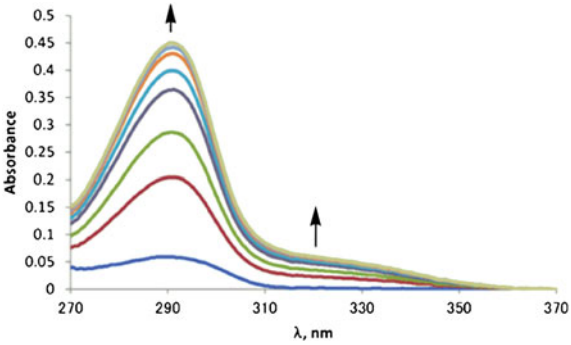


Fig. 2.4 Spectrophotometric titration of **6a** with tetrabutylammonium acetate in DMSO. *Arrows* show the changes of intensity at increasing TBAOAc concentrations

tetrabutylammonium chloride (TBAC) was added to a CH_3CN solution of **6a**, the UV spectrum of **6a** gradually developed as more TBAC was added, and the maximum wavelength shifted to red (Fig. 2.5). No further change was observed when an excess amount of TBAC was added and no signal development at other areas was detected over the course of the titration. In addition, two isosbestic points were observed (283 and 267 nm). These results suggest that **6a** forms only an **A**-type complex with TBAC and the additional reaction to form the anion complex **B** does not occur under these conditions. The values of the absorbance at 250 nm in the course of titration are shown in Fig. 2.6. This tendency well fitted the equation of the one-step binding model. By using Eq. (2.1), where $\Delta\varepsilon$ is the difference in molar absorptivity between free **6a** and complexed **6a** [56], I estimated that the association constant $K_1^{\mathbf{6a}}$ between free **6a** and the complex of **6a** with TBAC was 1.9×10^3 (± 44).

$$\mathrm{Abs} = \mathrm{Abs}_0 + 0.5\Delta\varepsilon[[\mathrm{RH}]_\mathrm{T} + [\mathrm{Cl}^-]_\mathrm{T} + 1/K_1 - (([\mathrm{RH}]_\mathrm{T} + [\mathrm{Cl}^-]_\mathrm{T} + 1/K_1)^2 - 4[\mathrm{RH}]_\mathrm{T}[\mathrm{Cl}^-]_\mathrm{T})^{0.5}] \quad (2.1)$$

The association constants $K_1^{\mathbf{1a}}$ and $K_1^{\mathbf{5a}}$ were calculated in the same manner as above (Figs. 2.7, 2.8, 2.9, and 2.10). Both thiourea **1a** and quinazoline **5a** showed results similar to benzothiadiazine, and the association constants $K_1^{\mathbf{1a}}$ and $K_1^{\mathbf{5a}}$ were estimated to be 1.2×10^3 (± 37) and 4.9×10^2 (± 18), respectively. The Van der Waals radius of the chlorine atom was 1.75 Å. I speculate that **5a** forms the HB complex with chloride anion less effectively than the other catalysts due to the relatively long distance of two acidic protons. In addition, **6a** would possess more acidic protons relative to **1a** due to the strong electron-withdrawing sulfonyl group and thus **6a** would enhance the tendency to form the HB complex.

In summary, novel HB donors **5** and **6** in which the HB moieties are locked in a cyclic structure were prepared. The relative abilities of these HB-donors to associate with Lewis bases were remarkably different and followed the order **6a** > **1a** > **5a**.

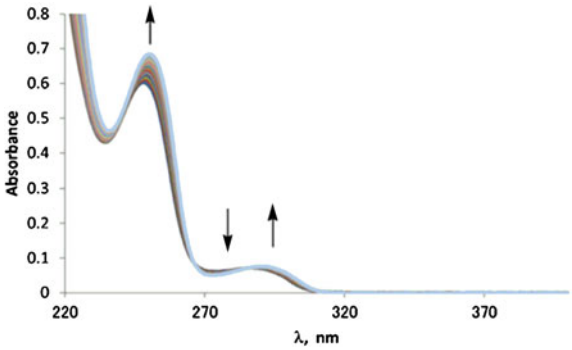


Fig. 2.5 Spectrophotometric titration of **6a** with TBAC in CH_3CN. *Arrows* show the changes of intensity at increasing TBAC concentrations

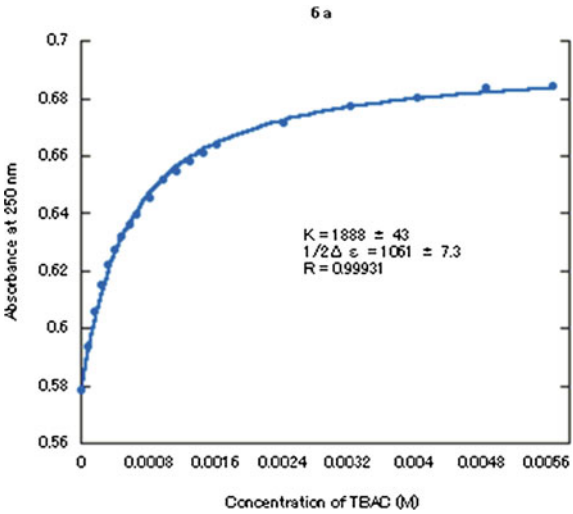


Fig. 2.6 The values of the absorbance at 250 nm in the course of the titration

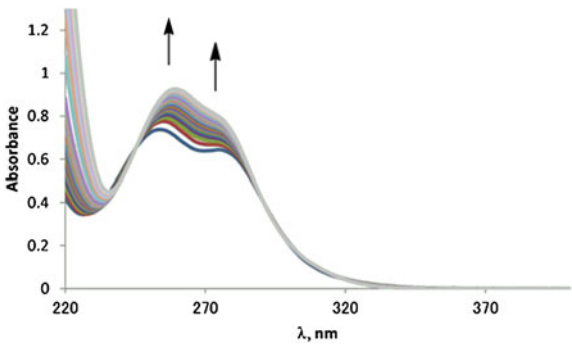


Fig. 2.7 Spectrophotometric titration of **1a** with TBAC in CH_3CN. *Arrows* show the changes of intensity at increasing TBAC concentrations

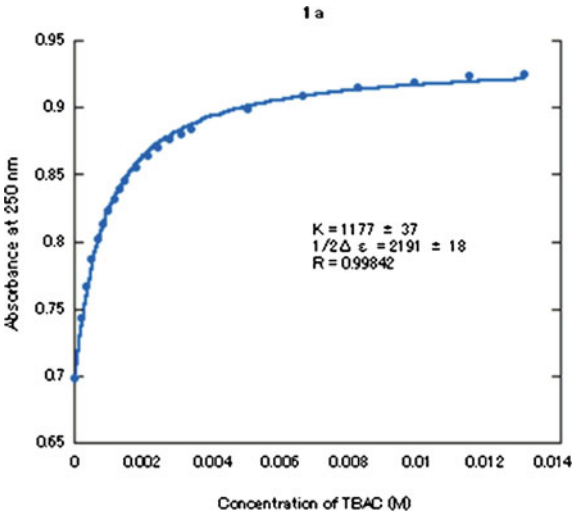


Fig. 2.8 The values of the absorbance at 260 nm in the course of the titration

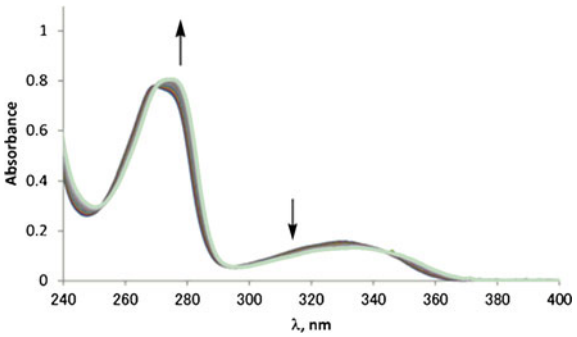


Fig. 2.9 Spectrophotometric titration of **5a** with TBAC in CH_3CN. *Arrows* show the changes of intensity at increasing TBAC concentrations

2.1.3 Experimental Section

2.1.3.1 General

All non-aqueous reactions were carried out under a positive atmosphere of argon in dried glassware unless otherwise noted. Solvents were dried and distilled according to standard protocols. Materials were obtained from commercial suppliers and used without further purification except when otherwise noted. All melting points were determined on YANAGIMOTO micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 or 400 MHz, and at 125 or 100 MHz, respectively; Tetramethylsilane (TMS) was used as an internal standard. IR spectra were recorded on a JASCO FT/IR-4100 Fourier-transform infrared spectrometer. Low and High resolution mass spectra were obtained by EI or FAB method. Optical rotations were recorded on a JASCO

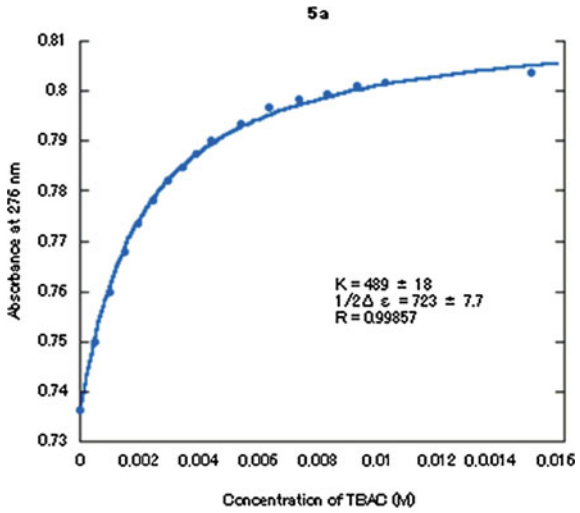


Fig. 2.10 The values of the absorbance at 260 nm in the course of the titration

P-2200 polarimeter with a path length of 1 cm; concentrations are quoted in grams per 100 mL. $[\alpha]_D$ values are measured in 10^{-1} deg cm^2 g^{-1}. Enantiomeric excess was determined by high performance liquid chromatography (HPLC) analysis.

2.1.3.2 Typical Procedure for the Synthesis of the Catalyst 11

8a–**e** were prepared according to the literature procedure [45].

To a mixture of *N*,*N*-dimethylcyclohexanediamine (282 mg, 1.98 mmol) [46] and triethylamine (0.3 mL, 2.14 mmol) in isoamylalcohol (4.0 mL) was added **8a** (393 mg, 2.18 mmol) and stirred at 130 °C for 13 h. Then, the reaction mixture was extracted with $CHCl_3$ three times. The extract was dried over K_2CO_3 and purified by silica gel column chromatography. (EtOAc/MeOH/Et_3N = 97/0/3 to 80/15/5) to afford quinazoline **5a** (537 mg, 88 %).

2-{(1*R*, 2*R*)-2-(Dimethylamino)cyclohexyl}aminoquinazolin-4(1*H*)-one (**5a**): Yellow amorphous; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (dd, $J_1 = 7.9$ Hz, $J_2 = 1.4$ Hz, 1H), 7.52 (ddd, $J_1 = J_2 = 7.9$ Hz, $J_3 = 1.4$ Hz, 1H), 7.22 (d, $J = 7.9$ Hz, 1H), 7.12 (dd, $J_1 = J_2 = 7.9$ Hz, 1H), 3.69–3.57 (m, 1H), 2.52 (ddd, $J_1 = J_2 = 10.3$ Hz, $J_3 = 2.9$ Hz, 1H), 2.45–2.32 (m, 1H), 2.36 (s, 6H), 1.96–1.87 (m, 1H), 1.87–1.69 (m, 2H), 1.52–1.16 (m, 4H); ^{13}C NMR ($(CD_3)_2CO$, 126 MHz) δ 165.5, 153.3, 150.7, 134.6, 127.1, 124.1, 122.5, 118.7, 67.5, 53.0, 40.4, 33.7, 25.8, 25.4, 22.7; IR (KBr) ν 3254, 1679, 1606 cm^{-1}; LRMS (FAB^+) 287 ($M + H^+$, 100); HRMS (FAB^+) Calcd. for $C_{16}H_{23}N_4O$: 287.1872, Found: 287.1881; $[\alpha]_D^{25} = -30$ (c 0.93, $CHCl_3$).

2-[{(1*R*, 2*R*)-2-(dimethylamino)cyclohexyl}amino]-8-fluoroquinazolin-4(1*H*)-one (**5b**): Yellow amorphous; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, $J = 7.9$ Hz, 1H), 7.32–7.20 (m, 1H), 7.04 (ddd, $J_1 = J_2 = 7.9$ Hz, $J_3 = 4.6$ Hz, 1H), 6.56 (brs, 1H), 3.66–3.50 (m, 1H), 2.65–2.50 (m, 1H), 2.44 (s, 6H), 2.01–1.89 (m, 2H), 1.89–1.71

(m, 1H), 1.55–1.14 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.3, 154.2, 154.1 (d, J = 197 Hz), 138.2, 122.2 (d, J = 2.9 Hz), 120.9 (d, J = 5.7 Hz), 120.0 (d, J = 1.9 Hz), 118.5 (d, J = 15.3 Hz), 67.6, 53.0, 40.2, 32.8, 24.62, 24.59, 22.8; IR (KBr) ν 3258, 3033, 2931, 2865, 2781, 1682, 1611, 1553, 1502, 1437, 1380, 1335, 1271, 1246 cm^{-1}; LRMS (FAB$^+$) 305 (M + H$^+$, 100); HRMS (FAB$^+$) Calcd. for $C_{16}H_{21}FN_4O$: 305.1778, Found: 305.1766; $[\alpha]_D^{25} = -11.3$ (c 0.95, $CHCl_3$).

2-[{(1*R*, 2*R*)-2-(dimethylamino)cyclohexyl}amino]-7-fluoroquinazolin-4(1*H*)-one (**5c**): Yellow amorphous; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (dd, J_1 = 8.5 Hz, J_2 = 6.5 Hz, 1H), 6.92 (dd, J_1 = 10.4 Hz, J_2 = 2.3 Hz, 1H), 6.85 (ddd, $J_1 = J_2 =$ 8.5 Hz, J_3 = 2.3 Hz, 1H), 3.51–3.40 (m, 1H), 2.42–2.31 (m, 1H), 2.38 (s, 6H), 1.99–1.89 (m, 1H), 1.89–1.81 (m, 1H), 1.81–1.70 (m, 2H), 1.40–1.16 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7 (d, J = 247 Hz), 165.3, 153.5, 151.7, 129.2 (d, J = 11.9 Hz), 114.4, 110.6 (d. J = 22.7 Hz), 108.2 (d, J = 21.5 Hz), 67.4, 53.1, 40.1, 32.9, 24.8, 24.6, 22.4; IR (KBr) ν 3254, 3028, 2934, 2859, 2787, 1680, 1608, 1509, 1459, 1340, 1298, 1273, 1211 cm^{-1}; LRMS (FAB$^+$) 305 (M + H$^+$, 100); HRMS (FAB$^+$) Calcd. for $C_{16}H_{21}FN_4O$: 305.1778, Found: 305.1789; $[\alpha]_D^{25} = -36.3$ (c 0.95, $CHCl_3$).

2-[{(1*R*, 2*R*)-2-(dimethylamino)cyclohexyl}amino]-6-fluoroquinazolin-4(1*H*)-one (**5d**): Yellow amorphous; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (dd, J_1 = 8.8 Hz, J_2 = 2.9 Hz, 1H), 7.34–7.23 (m, 2H), 6.14 (brs, 1H), 3.56–3.40 (m, 1H), 2.58–2.46 (m, 1H), 2.46–2.27 (m, 1H), 2.42 (s, 6H), 2.00–1.89 (m, 1H), 1.89–1.82 (m, 1H), 1.82–1.69 (m, 1H), 1.45–1.15 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 158.1 (d, J = 240 Hz), 152.9, 145.3, 124.1, 122.1 (d, J = 23.9 Hz), 118.3, 111.3 (d, J = 18.2 Hz), 67.4, 53.0, 40.2, 32.9, 24.8, 24.6, 22.6; IR (KBr) ν 3246, 3066, 2935, 2860, 2820, 2783, 1681, 1620, 1560, 1487, 1401, 1377, 1341, 1242 cm^{-1}; LRMS (FAB$^+$) 305 (M + H$^+$, 100); HRMS (FAB$^+$) Calcd. for $C_{16}H_{21}FN_4O$: 305.1778, Found: 305.1792; $[\alpha]_D^{25} = -26.9$ (c 0.95, $CHCl_3$).

2-[{(1*R*, 2*R*)-2-(dimethylamino)cyclohexyl}amino]-5-fluoroquinazolin-4(1*H*)-one (**5e**): Yellow amorphous; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (dd, $J_1 = J_2 =$ 8.0 Hz, J_3 = 5.5 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.73 (dd, J_1 = 10.5 Hz, J_2 = 8.0 Hz, 1H), 6.23 (brs, 1H), 3.60–3.51 (m, 1H), 2.51 (ddd, $J_1 = J_2$ = 10.5 Hz, J_3 = 3.3 Hz, 1H), 2.41–2.30 (m, 1H), 2.38 (s, 6H), 1.97–1.89 (m, 1H), 1.88–1.80 (m, 1H), 1.80–1.72 (m, 1H), 1.42–1.18 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.5, 161.9 (d, J = 207 Hz), 153.0, 152.3, 134.0 (d, J = 7.6 Hz), 119.0 (d, J = 2.9 Hz), 108.4 (d, J = 15.3 Hz), 107.3 (d, J = 5.7 Hz), 67.2, 52.9, 39.3, 32.9, 24.8, 24.6, 22.4; IR (KBr) ν 3290, 3066, 2933, 2859, 2773, 1682, 1614, 1580, 1486, 1416, 1341, 1271, 1233 cm^{-1}; LRMS (FAB$^+$) 305 (M + H$^+$, 100); HRMS (FAB$^+$) Calcd. for $C_{16}H_{21}FN_4O$: 305.1778, Found: 305.1779; $[\alpha]_D^{25} = -35.4$ (c 0.88, $CHCl_3$).

2.1.3.3 Typical Procedure for the Synthesis of the Catalyst 6

To a solution of **9** (1.04 g, 11.2 mmol) in $EtNO_2$ (20 mL) was added $ClSO_2NCO$ (1.17 mL, 13.4 mmol) at −40 °C and stirred at room temperature. After 30 min,

$AlCl_3$ (2.00 g, 15.0 mmol) was added and stirred at 110 °C for 30 min. Then the reaction mixture was poured into ice water and the resulting brown precipitate was washed with water. This crude product was used without further purifications.

To a mixture of the crude solids and $POCl_3$ (5.10 mL, 54.4 mmol) was added 2,6-lutidine (0.507 mL, 4.35 mmol) at room temperature and stirred at 110 °C for 12 h. Then the reaction mixture was cooled to 0 °C, quenched with water and the resulting brown precipitate was washed with water. This crude product was used without further purifications.

To a solution of the crude solids in isoamylalcohol (15 mL) was added N^1, N^1-dimethylcyclohexanediamine (498 mg, 3.50 mmol) and triethylamine (0.488 mL, 3.50 mmol) and stirred at 130 °C for 24 h. Then the reaction mixture was evaporated *in vacuo*, extracted with $CHCl_3$ three times, dried over Na_2SO_4 and evaporated *in vacuo*. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH/30 %NH_3aq = 85/15/1) to afford benzothiadiazine **6a** (866 mg, 24 % from **9**).

3-{(1*R*, 2*R*)-2-(Dimethylamino)cyclohexyl}amino-4*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide (**6a**): White solids; mp 222–223 °C (hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, J = 7.8 Hz, 1H), 7.42 (dd, $J_1 = J_2$ = 7.8 Hz, 1H), 7.22 (dd, $J_1 = J_2$ = 7.8 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 6.19–4.96 (br, 1H), 3.60–3.40 (m, 1H), 2.48–2.19 (m, 1H), 2.34 (s, 6H), 1.96–1.85 (m, 1H), 1.85–1.77 (m, 1H), 1.77–1.64 (m, 1H), 1.33–1.06 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 151.8, 136.1, 132.5, 124.0, 123.6, 122.1, 116.7, 67.0, 52.5, 40.2, 32.9, 24.6, 24.4, 22.1; IR (ATR) ν 3292, 1626, 1583, 1500, 1257, 1153 cm^{-1}; LRMS (FAB$^+$) 323 (M + H$^+$, 100); HRMS (FAB$^+$) Calcd. for $C_{15}H_{23}N_4O_2S$: 323.1536, Found: 323.1544; $[\alpha]_D^{25}$ = 32.6 (c = 0.97, $CHCl_3$).

3-[{(1*R*, 2*R*)-2-(piperidin-1-yl)cyclohexyl}amino]-4*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide (**6b**): White amorphous solids; ^{1}H NMR (DMSO-d_6, 500 MHz, 100 °C) δ 7.65 (d, J = 8.00 Hz, 1H), 7.51 (dd, $J_1 = J_2$ = 8.00 Hz, 1H), 7.22 (dd, $J_1 = J_2$ = 8.00 Hz, 1H), 7.10 (d, J = 8.00 Hz, 1H), 3.66-3.54 (m, 1H), 3.15–2.82 (m, 1H), 2.69–2.56 (m, 1H), 2.42–2.21 (m, 2H), 1.92–1.81 (m, 2H), 1.81–1.71 (m, 2H), 1.71–1.60 (m, 1H), 1.57–1.10 (m, 11H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 152.7, 137.4, 133.5, 125.0, 124.8, 124.7, 117.5, 69.0, 53.2, 50.5, 34.0, 31.1, 30.8, 27.8, 26.7, 26.0, 25.8, 24.5; IR (ATR) ν 1504, 1221, 1154 cm^{-1}; LRMS (FAB$^+$) 363 (M + H$^+$); HRMS (FAB$^+$) Calcd. for $C_{18}H_{27}N_4O_2S$: 363.1854, Found: 363.1857; $[\alpha]_D^{25}$ = +11 (c 0.32, $CHCl_3$).

2.1.3.4 Experimental Procedure for the Determination of the Association Constants of the HB Donors

The absorbances in the UV range were monitored by Shimadzu UV-2550 UV-Vis spectrophotometer during the titration of TBAC to each HB donor.

Titration of TBAC to **6a**

To 2000 μL of a solution of **6a** (5.40×10^{-5} M in CH_3CN) was added a solution of TBAC (16.2 mM in CH_3CN) gradually. The UV absorbance (400–200 nM) was monitored and for each addition. From the plot of the concentration of TBAC in the sample solution against the value of the absorbance at 250 nm, fitting to the following equation by Kaleida Graph ver 4.1 was performed and the association constant $K^{\mathbf{6a}}$ was determined to be 1888 (±43).

$$\mathrm{Abs} = 0.57873 + 1/2\Delta\varepsilon[0.0000540 + m_0 + 1/K^{\mathbf{6a}} - \{(0.0000540 + m_0 + 1/K^{\mathbf{6a}})^2 - 0.000210 \times m_0\}^{0.5}] \tag{2.2}$$

where m_0 is the concentration of TBAC in the sample solution and $\Delta\varepsilon$ is the difference in molar absorptivities between free **6a** and complexed **6a**.

Titration of TBAC to **1a**

To 2000 μL of a solution of **1a** (5.40×10^{-5} M in CH_3CN) was added a solution of TBAC (32.4 mM in CH_3CN) gradually. The UV absorbance (400–200 nM) was monitored and for each addition. From the plot of the concentration of TBAC in the sample solution against the value of the absorbance at 260 nm, fitting to the following equation by Kaleida Graph ver 4.1 was performed and the association constant $K^{\mathbf{1a}}$ was determined to be 1177 (±37).

$$\mathrm{Abs} = 0.69892 + 1/2\Delta\varepsilon[0.0000540 + m_0 + 1/K^{\mathbf{1a}} - \{(0.0000540 + m_0 + 1/K^{\mathbf{1a}})^2 - 0.000210 \times m_0\}^{0.5}] \tag{2.3}$$

where m_0 is the concentration of TBAC in the sample solution and $\Delta\varepsilon$ is the difference in molar absorptivities between free **1a** and complexed **1a**.

Titration of TBAC to 5**a**

To 2000 μL of a solution of **5a** (5.40×10^{-5} M in CH_3CN) was added a solution of TBAC (97.2 mM in CH_3CN) gradually. The UV absorbance (400–200 nM) was monitored and for each addition. From the plot of the concentration of TBAC in the sample solution against the value of the absorbance at 276 nm, fitting to the following equation by Kaleida Graph ver 4.1 was performed and the association constant $K^{\mathbf{5a}}$ was determined to be 489.0 (±18).

$$\mathrm{Abs} = 0.73629 + 1/2\Delta\varepsilon[0.0000540 + m_0 + 1/K^{\mathbf{5a}} - \{(0.0000540 + m_0 + 1/K^{\mathbf{5a}})^2 - 0.000210 \times m_0\}^{0.5}] \tag{2.4}$$

where m_0 is the concentration of TBAC in the sample solution and $\Delta\varepsilon$ is the difference in molar absorptivities between free **5a** and complexed **5a**.

2.2 Asymmetric Michael Addition to α,β-Unsaturated Imides Catalyzed by HB Donors

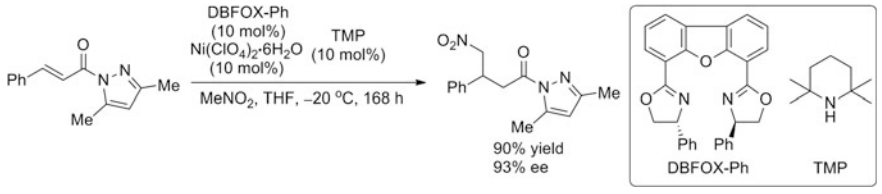
2.2.1 Introduction and Background

The asymmetric Michael addition of carbon nucleophiles to α,β-unsaturated carbonyl compounds is a powerful method for constructing carbon–carbon bonds stereoselectively and for accessing pharmaceutically important compounds [57–64]. Highly reactive nucleophiles such as silyl enol ethers or lithium enolates are widely used for this purpose [65–68]. On the other hand, since Shibasaki's group reported direct catalytic asymmetric Michael addition, several groups have reported such reactions that used carbon nucleophiles such as ketones, aldehydes and 1,3-dicarbonyl compounds [69–83]. Although these reactions are attractive due to the easy handling of the nucleophiles and the high atom-economy relative to organometallic nucleophiles, in almost cases, enones or nitroolefins were used as Michael acceptors, and there have been few reports of direct asymmetric Michael addition to α,β-unsaturated carboxylic acid derivatives, which would provide access to biologically important chiral carboxylic acid derivatives. Kanemasa et al. reported the asymmetric Michael addition of nitromethane to α,β-unsaturated pyrroles with the use of a Ni catalyst and the chiral DBFOX ligand, which they developed independently, in the presence of TMP as an external base (Scheme 2.8) [84–87]. This was the first report of a direct catalytic asymmetric Michael addition to α,β-unsaturated carboxylic acid derivatives and it is considered that the complex of Ni–DBFOX and TMP should act synergistically as a Lewis acid and a Brønsted base, respectively.

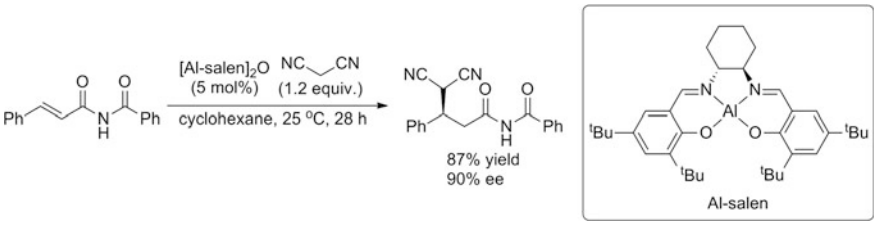
Jacobsen et al. reported the Al–salen-catalyzed Michael reaction of α,β-unsaturated imides and malononitrile or methylcyanomalonate (Scheme 2.9) [88, 89]. They also achieved the construction of a chiral piperidine structure by using the Michael adducts they obtained.

In addition, Evans et al. also reported a similar type of reaction in the presence of a chiral Lewis acid catalyst (Scheme 2.10) [90].

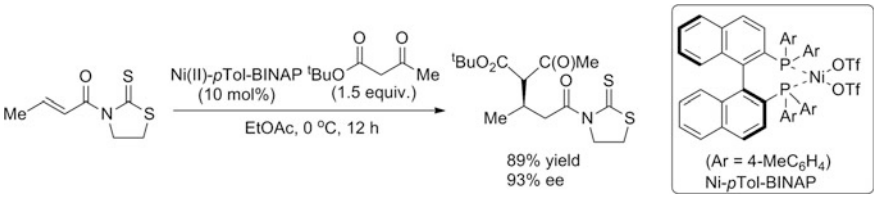
However, there has been only one report of this type of reaction with asymmetric organocatalysts. My colleagues reported the asymmetric Michael addition of α,β-unsaturated imides with malononitrile catalyzed by aminothiourea **1a** (Scheme 2.11) [91].



Scheme 2.8 DBFOX–Ni and TMP catalyzed asymmetric Michael reaction



Scheme 2.9 Al–salen catalyzed asymmetric Michael reaction



Scheme 2.10 Ni-*p*Tol-BINAP catalyzed asymmetric Michael reaction

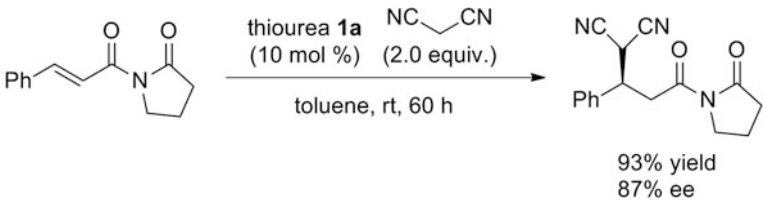
However, the reaction suffered from low reactivities, and more reactive reaction systems are needed. I expected that different HB donors would possess the different reactivities in this asymmetric reaction due to their different HB-donating abilities. In addition, the imides derived from benzamides are more promising substrates because the chemical properties of these substrates can be readily tuned by changing the substituents on the aromatic rings.

In this section, the more effective asymmetric Michael reaction of α,β-unsaturated imides and several activated methylene compounds catalyzed by HB donor catalysts is explored.

2.2.2 Results and Discussion

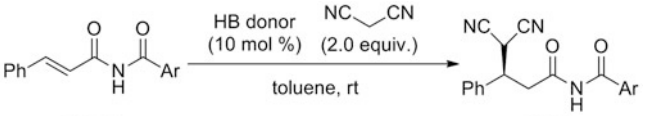
In an initial study to achieve the asymmetric Michael reaction of α,β-unsaturated imides, the substituents on the aromatic ring of the substrates and HB donor catalysts was screened (Table 2.1).

First, I examined non-substituted benzimide derivative **11a**, which are considered to be potential Michael acceptors for Lewis acid-catalyzed Michael reactions [92–95], as a substrate and thiourea **1a** as a catalyst (entry 1). As a result, the reaction proceeded highly enantioselectively and the reactivity was superior to that in the previous work, but it was still insufficient. To increase the electrophilicity of the substrates, electron-withdrawing substituents were introduced into the phenyl ring of the benzimide. Unfortunately, the reaction did not proceed well due to the low solubility of the substrate **11b** (entry 2). Surprisingly, 2-

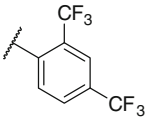
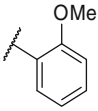
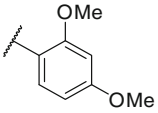
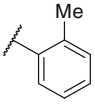
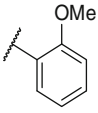
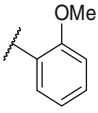


Scheme 2.11 Asymmetric Michael reaction of α,β-unsaturated imides and malononitrile-catalyzed by amino thiourea **1a**

Table 2.1 Screening of the substrates and catalysts[a]



11a-e **12a-e**

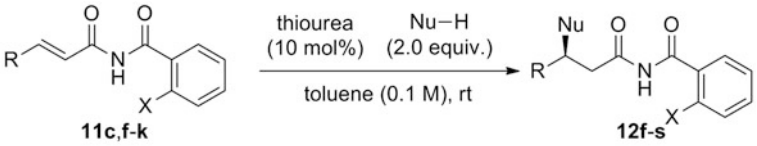
Entry	Ar	11	Catalyst	12	Time (h)	Yield (%)[b]	ee (%)[c]
1		**11a**	**1a**	**12a**	26	84	88
2		**11b**	**1a**	**12b**	94	28	89
3		**11c**	**1a**	**12c**	14	95	91
4		**11d**	**1a**	**12d**	75	90	62
5		**11e**	**1a**	**12e**	24	93	89
6		**11c**	**5a**	**12c**	48	57	72
7		**11c**	**6a**	**12c**	48	81	82

[a] The reactions were conducted with **11** (1.0 equiv.), HB donor (10 mol %), and malononitrile (2.0 equiv.) in toluene at room temperature
[b] Yield of isolated product
[c] Determined by HPLC analysis

methoxybenzimide **11c** reacted smoothly to produce the desired Michael adduct **12c** in high ee and with an acceptable reaction rate (entry 3). However, an additional methoxy group caused diminished reaction rate and enantioselectivity (entry 4). Based on the results with 2-methylbenzimide **11e** (entry 5), it was assumed that the 2-methoxy group would perform efficiently in this reaction. The author assumed that the intramolecular hydrogen bond between the imide proton and the oxygen atom of the methoxy group would accelerate the reaction. In next, other HB donors were screened. When quinazoline **5a** was used as a catalyst, the reaction of **11c** proceeded slowly and was not complete within 48 h (entry 6). In the case of the benzothiadiazine catalyst **6a**, the desired product **12c** was also obtained stereoselectively. However, these results were inferior to those with thiourea catalyst **1a** (entry 7). Although both compounds acted as HB donor catalysts, the catalytic activities of these catalysts were not better than the previously developed thiourea catalyst **1a**.

Having established the optimized substrate and catalyst, next the scope of the substrates and nucleophiles was examined (Table 2.2).

Table 2.2 Screening of substrates and nucleophiles[a]



Entry	R	X	**11**	Nu–H	Temp. (°C)	Time (h)	**12**	Yield (%)[b]	ee (%)[c]
1	4-FC_6H_4	OMe	**11f**	$CH_2(CN)_2$	rt	7	**12f**	99	92
2	4-$MeOC_6H_4$	OMe	**11g**	$CH_2(CN)_2$	rt	24	**12g**	92	90
3	3-furyl	OMe	**11h**	$CH_2(CN)_2$	rt	31	**12 h**	91	92
4	3-furyl	F	**11i**	$CH_2(CN)_2$	rt	24	**12i**	88	95
5	Me	OMe	**11j**	$CH_2(CN)_2$	rt	3	**12j**	96	90
6	$TBSO(CH_2)_5$	OMe	**11k**	$CH_2(CN)_2$	rt	5	**12k**	95	93
7	Ph	OMe	**11c**	$CH_2(CN)CO_2Me$	80	52	**12l**[d]	94	82[e]
8	4-FC_6H_4	OMe	**11f**	$CH_2(CN)CO_2Me$	80	48	**12m**[d]	91	85[e]
9	Me	OMe	**11j**	$CH_2(CN)CO_2Me$	rt	87	**12n**[d]	90	92[e]
10	$TBSO(CH_2)_5$	OMe	**11k**	$CH_2(CN)CO_2Me$	rt	137	**12o**[d]	96	92[e]
11	Ph	OMe	**11c**	$MeNO_2$	60	168	**12p**	56	87
12	4-FC_6H_4	OMe	**11f**	$MeNO_2$	60	168	**12q**	60	86
13	Me	OMe	**11j**	$MeNO_2$	rt	135	**12r**	91	83
14	$TBSO(CH_2)_5$	OMe	**11k**	$MeNO_2$	rt	256	**12s**	82	80

[a] The reactions were conducted with **11** (1.0 equiv.), **1a** (10 mol %) and the nucleophiles (2.0–40 equiv.) in toluene
[b] Yield of isolated product
[c] Determined by HPLC analysis
[d] Product was obtained as a mixture of two diastereoisomers
[e] The ee values were estimated from ee of the decarboxylated nitrile

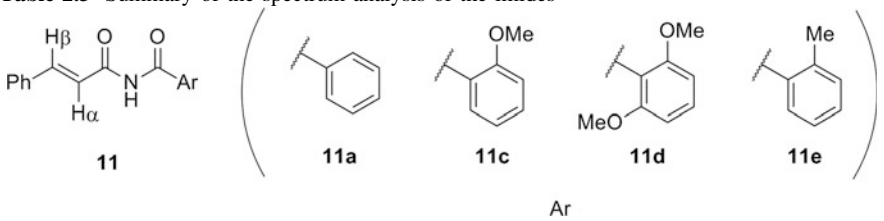
When substrate **11f**, which bears an electron-deficient aromatic ring at the β-position, was used, the reaction proceeded smoothly (entry 1). On the other hand, when other electron-rich substituents such as 4-methoxyphenyl or 3-furyl were introduced at the same position, the reaction rates were decreased (entries 2 and 3). For a substrate that contained a 3-furyl group, the reactivity was improved when the methoxy group was replaced by a fluoro group (entry 4). Substrates with aliphatic groups at the β-position were excellent in terms of reactivity and the enantioselectivities were still high (entries 5 and 6). Although the reactivities of methyl cyanoacetate and nitromethane were low relative to that of malononitrile, the conditions that the author developed could be used with these less-reactive nucleophiles and β-aryl substituted benzimides **11c** and **11f** at elevated temperature (entries 7, 8, 11 and 12). The more reactive substrates **11j** and **11k** reacted with these nucleophiles even at room temperature (entries 9, 10, 13 and 14).

The absolute configurations of the Michael adducts obtained were determined as follows (Scheme 2.12). Treatment of **12f** with MeOH in the presence of a catalytic amount of $Er(OTf)_3$ produced the corresponding methyl ester **13** [88] ($[\alpha]_D^{24} = +17$: *c* 1.2, CH_3CN) in 96 % yield. In the reaction of methyl cyanoacetate, the obtained adduct **12m** was converted into nitrile **14** [88] in two steps according to the reported procedure ($[\alpha]_D^{25} = +7.0$: *c* 1.1, CH_3CN). The same treatment of **12p** gave the corresponding methyl ester **15** [96] ($[\alpha]_D^{29} = -13$: *c* 0.20, $CHCl_3$). Based on a comparison of the specific rotations of **13**, **14** and **15** with the literature, the absolute configurations of **13**, **14** and **15** were determined to be *R*, *S* and *S*, respectively.

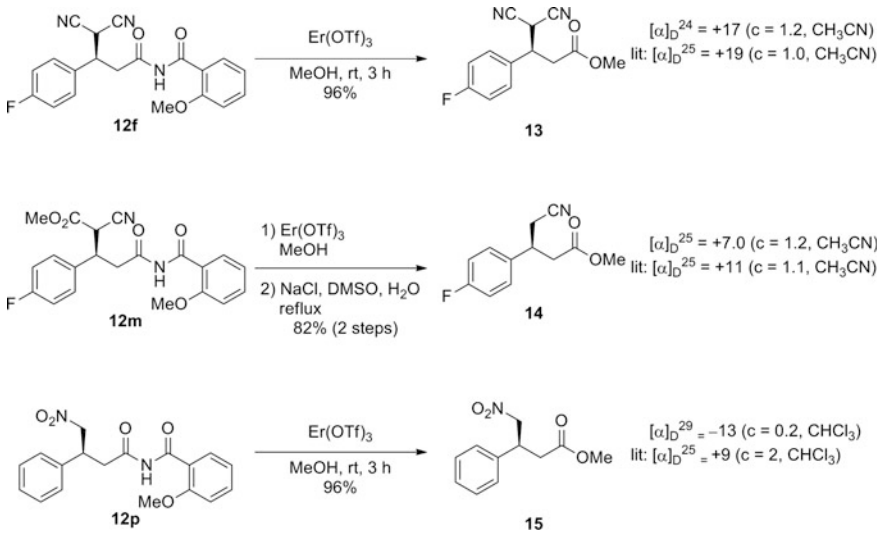
The experiments with IR and ^{1}H NMR spectroscopy were performed to gain insight into the different reactivities of imides **11a**, **c**, **d** and **e** (Table 2.3). Almost all of the ^{1}H NMR signals such as the vinylic protons (Hα and Hβ) of **11a**, **c**, **d** and **e** possessed similar chemical shifts; the signal of the N–H proton of **11c** was observed downfield as compared to those of **11a** and **d**, **e**. On the other hand, IR spectral analysis revealed that the stretching absorption of the N–H bond in the IR spectrum of **11c** (0.01 M, $CHCl_3$) appeared at a slightly lower wavenumber (3330 cm^{-1}) than those of **11a** and **d**, and **e** (3391–3405 cm^{-1}). Based on these findings, an intramolecular hydrogen bond between the imide N–H moiety and the methoxy group was believed to be formed in the case of **11c**. Due to this hydrogen bond, the α,β-unsaturated carbonyl moiety of 2-methoxybenzimide **11c** would be more reactive as a Michael acceptor than the other imides.

Computational studies also suggested an intramolecular HB in **11c** (Fig. 2.11). The directions of the two carbonyl groups in imide moieties were not *syn* to avoid dipolar repulsions in both imides **11c** and **11d**. In **11c**, the surfaces of the imide moiety and the benzene ring were almost parallel. In contrast, the benzene ring of **11d** was distorted from the surface of the imide moiety and the distance between the proton of the imide and the oxygen of the methoxy group was longer than that in **11c**. This can be explained by the dipolar repulsion between the additional methoxy group and the carbonyl group of the imide moiety.

Table 2.3 Summary of the spectrum analysis of the imides



Imide	^{1}H NMR ($CDCl_3$, 0.015 M)	IR ($CHCl_3$, 0.01 M)
11a	8.59 (NH)	3405 (N–H)
	7.86 (Hα)	1680 (C=O)
	7.95 (Hβ)	1619 (C=C)
11c	10.30 (NH)	3330 (N–H)
	7.86 (Hα)	1671 (C=O)
	7.91 (Hβ)	1619 (C=C)
11d	8.19 (NH)	3393 (N–H)
	7.75 (Hα)	1679 (C=O)
	7.89 (Hβ)	1620 (C=C)
11e	8.21 (NH)	3391 (N–H)
	7.76 (Hα)	1680 (C=O)
	7.94 (Hβ)	1618 (C=C)



Scheme 2.12 Determination of the absolute configuration

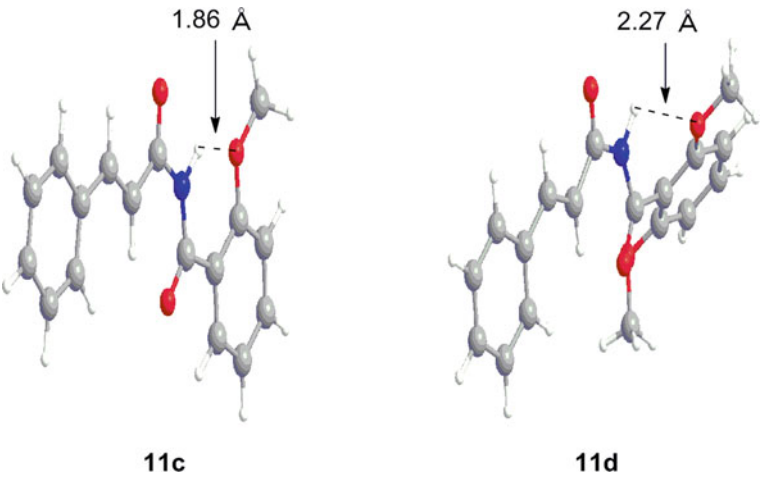


Fig. 2.11 Computational analysis of the ground states of the imides **11c** and **11d**

The kinetic studies were performed to obtain further insight into the reaction mechanism. The amounts of the imide **11c** and the adduct **12c** in the course of the reaction were monitored by ^{1}H NMR analysis in the use of the reaction of **11c**, malononitrile and thiourea **1a** in toluene-d_8. When the reaction was carried out with a large excess of malononitrile, a plot of ln([**11c**]/[**11c**$_0$]) versus time gave a straight line (Fig. 2.12), which indicates that the reaction is first-order with respect to **11c**. A plot of the kinetic rate constant (k_{obs}) against the loading of **1a** showed that the reaction was first-order with respect to **1a** (Fig. 2.13). In addition, Fig. 2.14 shows the relationship (Michaelis–Menten plot) between the substrate concentration [S_0] of **11c** and the reaction rate (VM/min). This result

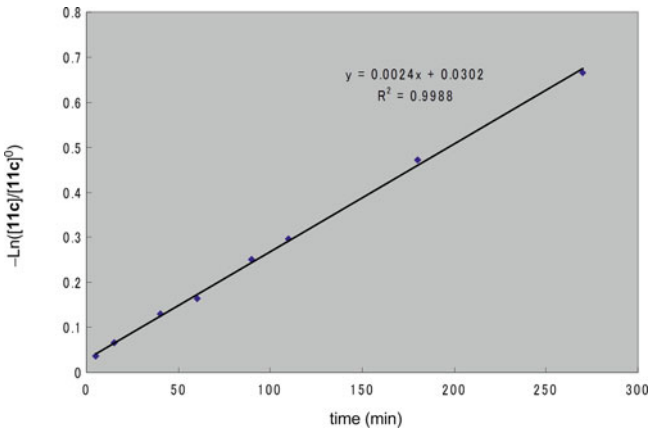


Fig. 2.12 Kinetic studies on the Michael reaction of malononitrile to imide **11c** in the presence of **1a**

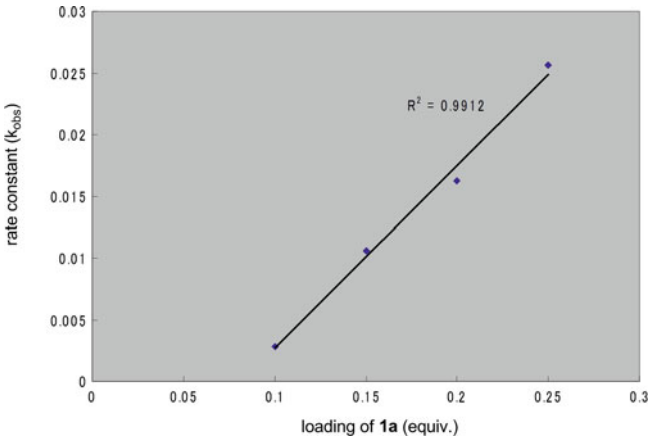


Fig. 2.13 Kinetic studies on the Michael reaction of malononitrile to imide **11c** in the presence of **1a**

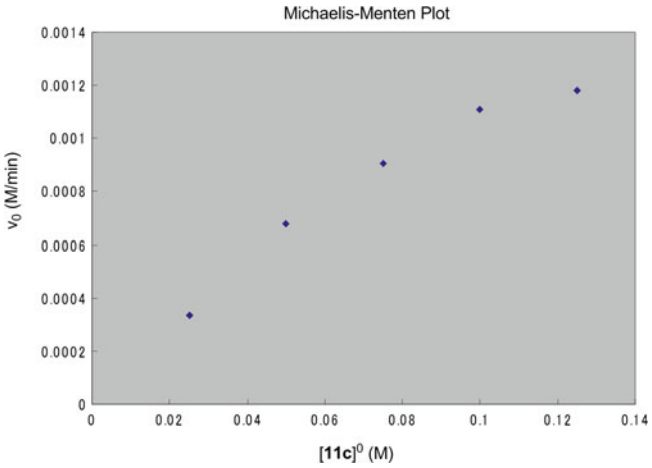


Fig. 2.14 Michaelis–Menten plot of the Michael addition

unambiguously indicates that equilibrium between catalyst **1a** and the binary complex of **1a** and substrate **11c** exists in the **1a**-catalyzed Michael addition. Therefore, the reaction constants K_M, V_{max} and k_{cat} were calculated from the Lineweaver–Burk plot (Fig. 2.15), as follows: $K_M = 0.300$ M, $V_{max} = 4.42 \times 10^{-3}$ M/min, $k_{cat} = 0.442$ min^{-1}, $k_{cat}/K_M = 1.47$ M^{-1} min^{-1}.

I propose complexes **C** (monodentate model) or **D** (bidentate model), which consist of the catalyst **1a** and imide **11c**, as a possible intermediate (Scheme 2.13). The successive interaction of malononitrile with these complexes took place through the deprotonation of malononitrile by the tertiary amine of **1a**, resulting in ternary complexes **E** and **F**, respectively. Consequently, the activated nucleophile

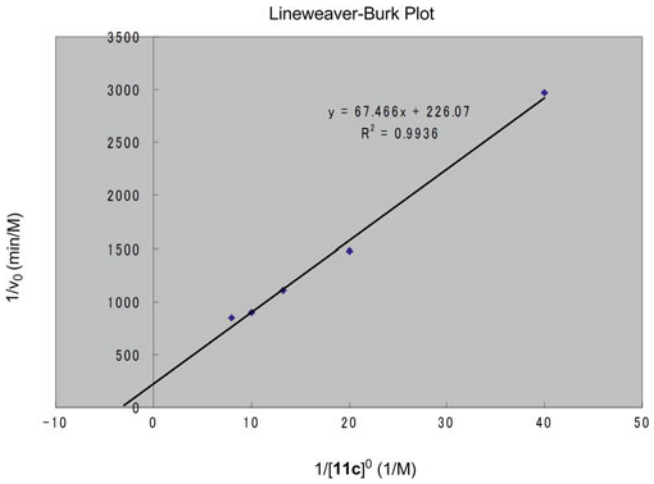
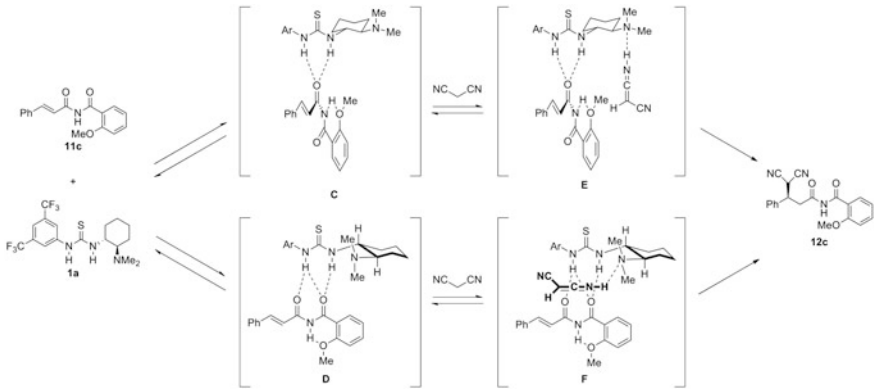


Fig. 2.15 Lineweaver–Burk plot of the Michael reaction



Scheme 2.13 Proposed mechanism of asymmetric Michael addition

attacks the imide **11c** from the front of the ternary complexes to predominately give the (*R*)-adduct **12c**. Intramolecular HB might cause these ternary complexes preferably by fixing the conformation of **11c**. The rate of the reaction under **1a**-catalyzed conditions was faster than those with **5a** or **6a** (Table 2.1, entries 3, 6 and 7). As described in Sect. 2.1, the structure of thiourea **1a** is more flexible than those of **5a** and **6a**. This might affect the coordination mode of HB donors and **11c** to give reaction intermediates with different stabilities than those of **5a** or **6a**.

In conclusion, although among the three HB donors, **5a** and **6a**, which possess rigid structures, were not superior to the previous thiourea catalyst **1a**, I

successfully developed the highly enantioselective organocatalytic Michael addition of several soft nucleophiles with α,β-unsaturated carboxylic acid derivatives with the use of thiourea **1a** and 2-methoxybenzimides **11**, which formed the intramolecular HB.

2.2.3 Experimental Section

2.2.3.1 General

All non-aqueous reactions were carried out under a positive atmosphere of argon in dried glassware unless otherwise noted. Solvents were dried and distilled according to standard protocols. Materials were obtained from commercial suppliers and used without further purification except when otherwise noted. All melting points were determined on YANAGIMOTO micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 or 400 MHz, and at 125 or 100 MHz, respectively; Tetramethylsilane (TMS) was used as an internal standard. IR spectra were recorded on a JASCO FT/IR-4100 Fourier-transform infrared spectrometer. Low and High resolution mass spectra were obtained by EI or FAB method. Optical rotations were recorded on a JASCO P-2200 polarimeter with a path length of 1 cm; concentrations are quoted in grams per 100 mL. $[\alpha]_D$ values are measured in 10^{-1} deg cm^2 g^{-1}. Enantiomeric excess was determined by high performance liquid chromatography (HPLC) analysis. The compound **11a** was prepared according to the literature [88].

2.2.3.2 Typical Procedure for the Synthesis of the α,β-Unsaturated Imides (Method 1)

To a solution of 2-methoxybenzamide (895 mg, 5.92 mmol) in THF (20 mL) was added NaH (658 mg, 16.5 mmol) at 0 °C and stirred for 10 min. Then, cinnamoyl chloride (986 mg, 5.92 mmol) was added at the same temperature and stirred at room temperature for 3 h. After that the reaction was quenched with 1M HClaq, extracted with EtOAc, dried over Na_2SO_4 and evaporated *in vacuo* to afford white solids. This crude product was recrystallized from hexane and EtOAc to afford the desired imide **11c** (942 mg, 56 %).

(*E*)-*N*-3-Phenylacryloyl-3,5-bis-trifluoromethylbenzamide **(11b)**: White solids; mp 234–235 °C (EtOAc); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.53 (s, 1H), 8.56 (s, 2H), 8.41 (s, 1H), 7.77 (d, $J = 15.9$ Hz, 1H), 7.71–7.67 (m, 2H), 7.50–7.45 (m, 3H), 7.30 (d, $J = 15.9$ Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.9, 164.5, 144.0, 136.2, 134.3, 130.2 (q, $J = 36.2$ Hz), 129.3, 128.6 (q, $J = 190$ Hz), 124.1, 122.0, 120.8; IR ($CHCl_3$) δ 3450, 2996, 1662, 1432 cm^{-1}; Anal. Calcd. for $C_{18}H_{11}F_6NO_2$: C, 55.82; H, 2.86; N, 3.62; F, 29.44; Found: C, 55.75; H, 3.02; N, 3.65; F, 29.42.

(*E*)-2-Methoxy-*N*-3-phenylacryloylbenzamide (**11c**): White solid; mp 112–114 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.28 (s, 1H), 8.22 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.8$ Hz, 1H), 7.90 (d, $J = 15.8$ Hz, 1H), 7.86 (d, $J = 15.8$ Hz, 1H), 7.68–7.64 (m, 2H), 7.56 (td, $J_1 = 8.0$ Hz, $J_2 = 1.8$ Hz, 1H), 7.44–7.38 (m, 3H), 7.14 (t, $J = 8.0$ Hz, 1H), 7.04 (d, $J = 8.0$ Hz, 1H), 4.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 164.1, 157.8, 145.8, 134.9, 134.7, 132.9, 130.5, 128.9, 121.8, 120.6, 111.8, 56.2; IR ($CHCl_3$) ν 3230, 3021, 1671, 1619, 1479, 1341 cm^{-1}; Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98; Found: C, 72.58; H, 5.51; N, 4.99.

(*E*)-2,6-Dimethoxy-*N*-3-phenylacryloylbenzamide (**11d**): White solid; mp 159–160 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.87 (d, $J = 15.6$ Hz, 1H), 7.74 (d, $J = 15.6$ Hz, 1H), 7.66–7.61 (m, 2H), 7.43–7.38 (m, 3H), 7.35 (dd, $J_1 = J_2 = 8.5$ Hz, 1H), 6.60 (d, $J = 8.5$ Hz, 2H), 3.85 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 164.9, 157.6, 146.3, 134.7, 132.0, 130.6, 128.9, 128.7, 119.9, 114.3, 104.0, 56.0; IR ($CHCl_3$) ν 3393, 3021, 2942, 2841, 2360, 1717, 1678, 1619, 1597, 1475, 1340, 1257 cm^{-1}; Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50; Found: C, 69.26; H, 5.58; N, 4.50.

(*E*)-2-Methyl-*N*-3-phenylacryloylbenzamide (**11e**): White solids; mp 124–125 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.91 (d, $J = 15.9$ Hz, 1H), 7.74 (d, $J = 15.9$ Hz, 1H), 7.66–7.63 (m, 2H), 7.51 (d, $J = 7.6$ Hz, 1H), 7.44–7.40 (m, 4H), 7.31–7.25 (m, 2H), 2.52 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.3, 167.2, 146.8, 137.5, 134.5, 134.3, 131.7, 131.5, 130.8, 128.9, 128.7, 127.0, 126.1, 119.2, 20.0; IR ($CHCl_3$) ν 3691, 3391, 2398, 1712, 1681, 1619, 1337 cm^{-1}; Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.95; H, 5.70; N, 5.28; Found: C, 77.00; H, 5.77; N, 5.16.

2.2.3.3 Typical Procedure for Enantioselective Michael Addition of Malononitrile to α,β-Unsaturated Imides Catalyzed by Thiourea 1a

A mixture of **11c** (171 mg, 0.61 mmol), malononitrile (80 mg, 1.21 mmol), and thiourea **1a** (25 mg, 0.061 mmol) in toluene (6.1 mL) was stirred at room temperature for 14 h. After concentrated *in vacuo*, the reaction mixture was purified by silica gel column chromatography with hexane/EtOAc (2/1) to afford desired Michael adduct **12c** (201 mg, 95 %).

(3*R*)-*N*-(4,4-Dicyano-3-phenylbutanoyl)benzamide (**12a**): White solids; mp 150–155 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (br s, 1H), 7.82 (d, $J = 7.6$ Hz, 2H), 7.65 (dd, $J_1 = J_2 = 7.6$ Hz, 1H), 7.54 (d, $J = 7.6$ Hz, 2H), 7.48–7.37 (m, 5H), 4.59 (d, $J = 5.5$ Hz, 1H), 3.93–3.86 (m, 1H), 3.79–3.71 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 165.6, 136.1, 133.8, 132.0, 129.3, 129.24, 129.19, 128.1, 127.7, 111.8, 111.5, 41.4, 39.6, 28.9; IR ($CHCl_3$) ν 3396, 3018, 1701 cm^{-1}; MS (EI$^+$) 317 (M^+, 4), 105 (100); HRMS (EI$^+$) Calcd. for $C_{19}H_{15}N_3O_2$: 317.1164, Found: 317.1160; HPLC [Chiralcel AD-H, hexane/2-

propanol = 70/30, 0.5 mL/min, $\lambda = 254$ nm, retention times: (major) 62.8 min, (minor) 33.9 min]; $[\alpha]_D^{26} = -16.5$ (c 1.25, $CHCl_3$, 84 % ee).

(3*R*)-*N*-(4,4-Dicyano-3-phenylbutyryl)-3,5-bis-trifluoromethylbenzamide (**12b**): Colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.29 (s, 2H), 8.14 (s, 1H), 7.46-7.34 (m, 5H), 4.49 (d, $J = 5.8$ Hz, 1H), 3.95–3.87 (m, 1H), 3.76–3.68 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 163.4, 135.8, 134.2, 132.8 (q, $J = 34.2$ Hz), 128.6 (q, $J = 198$ Hz), 128.3, 123.7, 121.5, 111.5, 111.4, 41.3, 39.9, 29.0; IR ($CHCl_3$) ν 3692, 3031, 2360, 1701, 1376, 1280 cm^{-1}; MS (FAB$^+$) 454 (M + H$^+$, 100); HRMS (FAB$^+$) Calcd. for $C_{21}H_{14}F_6N_3O_2$: 454.0990; Found: 454.0991; HPLC [Chiralcel OD-H, hexane/2-propanol = 80/20, 0.3 mL/min, $\lambda = 254$ nm, retention times: (major) 57.7 min, (minor) 52.7 min]; $[\alpha]_D^{21} = 0.00$ (c 2.52, $CHCl_3$, 89 % ee).

(3*R*)-*N*-(4,4-Dicyano-3-phenylbutyryl)-2-methoxybenzamide (**12c**): Colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.14 (dd, $J_1 = 8.0$, $J_2 = 1.5$ Hz, 1H), 7.55 (ddd, $J_1 = J_2 = 8.0$ Hz, $J_3 = 1.5$ Hz, 1H), 7.48–7.35 (m, 5H), 7.11 (dd, $J_1 = J_2 = 7.7$ Hz, 1H), 7.01 (d, $J = 7.7$ Hz, 1H), 4.64 (d, $J = 5.5$ Hz, 1H), 3.99 (s, 3H), 3.93–3.88 (m, 1H), 3.71 (d, $J = 6.4$ Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 164.0, 157.7, 136.3, 135.2, 132.8, 129.2, 129.0, 128.1, 121.8, S7 119.4, 112.0, 111.8, 111.6, 56.2, 41.3, 40.1, 28.7; IR ($CHCl_3$) ν 3314, 2360, 1714, 1683, 1602, 1477 cm^{-1}; MS (FAB$^+$) 348 (M + H$^+$, 42), 135 (100); HRMS (FAB$^+$) Calcd. for $C_{20}H_{18}N_3O_3$: 348.1348, Found: 348.1352; HPLC [Chiralcel OD-H, hexane/2-propanol = 70/30, 0.5 mL/min, $\lambda = 254$ nm, retention times: (major) 86.7 min, (minor) 43.9 min]; $[\alpha]_D^{21} = +9.69$ (c 1.32, $CHCl_3$, 91 % ee).

(3*R*)-*N*-(4,4-Dicyano-3-phenylbutyryl)-2,6-dimethoxybenzamide (**12d**): Colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.47–7.36 (m, 6H), 6.59 (d, $J = 8.5$ Hz, 2H), 4.61 (dd, $J_1 = 4.6$ Hz, $J_2 = 1.2$ Hz, 1H) 3.84 (s, 7H), 3.72–3.68 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 164.4, 157.8, 136.2, 132.7, 129.2, 129.2, 128.2, 111.9, 111.5, 104.3, 104.1, 56.1, 41.5, 39.5, 28.8; IR ($CHCl_3$) ν 3029, 2360, 1699, 1597, 1476, 1259 cm^{-1}; MS (FAB$^+$) 378 (M + H$^+$, 35), 165 (100); HRMS (FAB$^+$) Calcd. for $C_{21}H_{20}N_3O_4$: 378.1454; Found: 378.1449; HPLC [Chiralcel OD-H, hexane/2-propanol = 70/30, 0.5 mL/min, $\lambda = 254$ nm, retention times: (major) 102.7 min, (minor) 60.6 min]; $[\alpha]_D^{21} = +0.39$ (c 1.10, $CHCl_3$, 62 % ee).

(3*R*)-*N*-(4,4-Dicyano-3-phenylbutyryl)-2-methylbenzamide (**12e**): Colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.46-7.39 (m, 7H), 7.32–7.25 (m, 2H), 4.51 (d, $J = 5.2$ Hz, 1H), 3.85–3.80 (m, 1H), 3.71–3.68 (m, 2H), 2.47 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 167.9, 137.9, 136.1, 133.0, 132.1, 131.9, 129.3, 129.2, 128.0, 127.0, 126.1, 111.8, 111.5, 41.4, 39.4, 28.7, 20.0; IR ($CHCl_3$) ν 1729, 1701, 1457, 1386 cm^{-1}; MS (FAB$^+$) 332 (MH$^+$, 46), 119 (100); HRMS (FAB$^+$) Calcd. for $C_{20}H_{18}N_3O_2$: 332.1399, Found: 332.1404; HPLC [Chiralcel OD, hexane/2-propanol = 80/20, 0.5 mL/min, $\lambda = 254$ nm, retention times: (major) 62.5 min, (minor) 54.0 min]; $[\alpha]_D^{25} = +0.35$ (c 1.12, $CHCl_3$, 89 % ee);.

2.2.3.4 Typical Procedure for the Synthesis of the α,β-Unsaturated Imides (Method 2)

The α,β-unsaturated imides **11f–k** were prepared from *o*-methoxy benzamide via three steps.

N-2-Chloroacetyl-2-methoxybenzamide: A mixture of *o*-methoxybenzamide (2.17 g, 14.4 mmol) and chloroacetylchloride (1.93 mL, 24.4 mmol) was stirred at 110 °C for 2 h. After the reaction mixture was evaporated, the obtained residue was purified over silica gel with hexane/EtOAc (3/2) to afford *N*-2-chloroacetyl-2-methoxybenzamide (2.10 g, 64 %). Colorless solid; mp 115–117 °C (hexane/EtOA); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.76 (s, 1H), 8.18 (dd, $J = 7.9$, 1.8 Hz, 1H), 7.58 (ddd, $J_1 = J_2 = 7.9$, 1.8 Hz, 1H), 7.14 (dd, $J_1 = J_2 = 7.9$ Hz, 1H), 7.05 (d, $J = 7.9$ Hz, 1H), 4.67 (s, 2H), 4.05 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 163.7, 157.8, 135.3, 133.1, 121.9, 119.4, 111.8, 56.2, 45.4; IR ($CHCl_3$) ν 3540, 3313, 3026, 2956, 1750, 1726, 1687, 1600, 1479, 1292 cm^{-1}; Anal. Calcd. for $C_{10}H_{10}ClNO_3$: C, 52.76; H, 4.43; N, 6.15; Cl, 15.57; Found: C, 52.56; H, 4.44; N, 6.16; Cl, 15.85.

2-(2-Methoxybenzoylamino)-2-oxoethylphosphonic acid diethyl ester: Triethylphosphite (2.7 mL, 15.7 mmol) was added to *N*-2-Chloroacetyl-2-methoxybenzamide (1.45 g, 6.36 mmol) and the reaction mixture was stirred at 80 °C for 53 h. Purification over silica gel with EtOAc afforded 2-(2-methoxybenzoylamino)-2-oxoethylphosphonicacid diethylester (1.92 g, 91 %). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.53 (s, 1H), 8.17 (dd, $J = 8.0$, 1.9 Hz, 1H), 7.56 (ddd, $J_1 = J_2 = 8.0$, 1.9 Hz, 1H), 7.11 (dd, $J_1 = J_2 = 8.0$ Hz, 1H), 7.04 (d, $J = 8.0$ Hz, 1H), 4.25–4.15 (m, 4H), 4.03 (s, 3H), 3.73 (d, $J = 22.0$ Hz, 2H), 1.33 (t, $J = 7.0$ Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 163.5, 157.6, 134.8, 132.7, 121.5, 119.7, 111.6, 62.4, 62.4, 56.0, 37.5, 36.5, 16.0, 16.0; IR ($CHCl_3$) ν 3320, 3001, 1750, 1710, 1684, 1601, 1479, 1215 cm^{-1}; MS (FAB$^+$) 330 (M + H$^+$, 87), 135 (100); HRMS (FAB$^+$) Calcd. for $C_{14}H_{21}NO_6P$: 330.1106, Found: 330.1103.

(*E*)-*N*-3-(4-Fluorophenyl)acryloyl-2-methoxybenzamide (**11f**): A 1.54 M solution of *n*-buthyl lithium in *n*-hexane (2.0 mL, 3.0 mmol) was added dropwise to a solution of 2-(2-Methoxybenzoylamino)-2-oxoethylphosphonic acid diethyl ester (500 mg, 1.5 mmol) in THF (6.0 L) at –78 °C. The resulting bright yellow solution was stirred at this temperature for 15 min. A solution of *p*-fluorobenzaldehyde (0.16 mL, 1.5 mmol) in THF (0.5 mL) was added and the mixture was stirred at room temperature for 3 h. After the reaction mixture was diluted with H_2O and then acidified by 1 N HCl, the resulting mixture was extracted with $CHCl_3$. The extract was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified over silica gel with hexane/EtOAc (1/1) to afford desired imide **12f** (382 mg, 84 %). White solids; mp 131–132 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.21 (dd, $J_1 = 7.9$ Hz, $J_2 = 1.8$ Hz, 1H), 7.86 (d, $J = 15.8$ Hz, 1H), 7.80 (d, $J = 15.8$ Hz, 1H), 7.67–7.63 (m, 2H), 7.57 (td, $J_1 = 7.9$ Hz, $J_2 = 1.8$ Hz, 1H), 7.15 (dd, $J_1 = J_2 = 7.9$ Hz, 1H), 7.12–7.08 (m, 2H), 7.05 (d, J = 7.9 Hz, 1H), 4.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6,

165.0, 164.1, 163.0, 157.8, 144.5, 133.6 (d, $J = 241$ Hz), 131.1, 130.5, 130.4, 121.7, 120.3, 116.0 (d, $J = 21.7$ Hz), 111.7, 56.2; IR ($CHCl_3$) ν 3329, 3022, 1696, 1670, 1599, 1508, 1480, 1223 cm^{-1}; Anal. Calcd. for $C_{17}H_{14}FNO_3$: C, 68.22; H, 4.71; N, 4.68; F, 6.35; Found: C, 68.22; H, 4.91; N, 4.64; F, 6.34.

(*E*)-2-Methoxy-*N*-3-(4-fluorophenyl)acryloylbenzamide (**11g**): White solids; mp 107–108 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.24 (s, 1H), 8.19 (d, $J = 7.9$ Hz, 1H), 7.85 (d, $J = 15.8$ Hz, 1H), 7.71 (d, $J = 15.8$ Hz, 1H), 7.59 (d, $J = 7.9$ Hz, 2H), 7.53 (dd, $J_1 = J_2 = 7.6$ Hz, 1H), 7.11 (dd, $J_1 = J_2 = 7.6$ Hz, 1H), 7.01 (d, $J = 7.6$ Hz, 1H), 6.91 (d, $J = 7.6$ Hz, 2H), 4.01 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 163.9, 161.5, 157.6, 145.5, 134.5, 132.7, 130.2, 127.5, 121.5, 120.4, 117.9, 114.2, 111.6, 56.1, 55.2; IR ($CHCl_3$) ν 3331, 3009, 2360, 1694, 1668, 1599, 1510, 1479, 1216 cm^{-1}; Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50; Found: C, 69.53; H, 5.64; N, 4.42.

N-(*E*)-(3-(Furan-3-yl)acryloyl)-2-methoxybenzamide (**11h**): White solids, mp 119–120 °C (hexane/EtOAc); ^{1}H NMR δ 10.24 (s, 1H), 8.19 (dd, $J_1 = 7.3$ Hz, $J_2 = 1.8$ Hz, 1H), 7.81 (d, $J = 15.5$ Hz, 1H), 7.71 (s, 1H), 7.58 (d, $J = 15.5$ Hz, 1H), 7.55 (ddd, $J_1 = J_2 = 7.3$, $J_3 = 1.8$ Hz, 1H), 7.45 (s, 1H), 7.13 (dd, $J_1 = J_2 = 7.3$ Hz, 1H), 7.04 (d, $J = 7.3$ Hz, 1H), 6.74 (d, $J = 1.2$ Hz, 1H), 4.04 (s, 3H); ^{13}C NMR δ 167.6, 164.0, 157.8, 145.2, 144.4, 135.9, 134.7, 132.8, 123.3, 121.7, 120.5, 120.2, 111.7, 107.8, 56.2; IR (KBr) ν 3343, 1697 cm^{-1}; MS (FAB^+) 272 ($M + H^+$, 100); Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.13; H, 4.77; N, 5.16.

N-(*E*)-(3-(Furan-3-yl)acryloyl)-2-fluorobenzamide (**12i**): White solids, mp 113–114 °C (hexane/EtOAc); ^{1}H NMR δ 8.89 (d, $J = 13.4$ Hz, 1H), 8.09 (ddd, $J_1 = J_2 = 8.0$ Hz, $J_3 = 1.7$ Hz, 1H), 7.83 (d, $J = 15.4$ Hz, 1H), 7.73 (s, 1H), 7.63-7.56 (m, 1H), 7.46 (d, $J = 15.4$ Hz, 1H), 7.46 (s, 1H), 7.34 (dd, $J_1 = J_2 = 8.0$ Hz, 1H), 7.21 (dd, $J_1 = 12.2$ Hz, $J_2 = 8.9$ Hz, 1H), 6.73 (d, $J = 1.2$ Hz, 1H); ^{13}C NMR δ 166.8, 162.0 (d, $J = 3.8$ Hz), 161.5, 159.5, 144.2 (d, $J = 126$ Hz), 136.8, 135.0 (d, $J = 10.1$ Hz), 132.2, 125.2 (d, $J = 3.6$ Hz), 123.1, 120.4 (d, $J = 11.3$ Hz), 119.3, 116.5, 107.7; IR (KBr) ν 3123, 1678 cm^{-1}; MS (FAB^+) 262 ($M + H^+$, 100); Anal. Calcd. for $C_{14}H_{10}FNO_3$: C, 64.86; H, 3.89; N, 5.40: Found: C, 64.91; H, 3.90; N, 5.35.

(*E*)-*N*-(But-2-enoyl)-2-methoxybenzamide (**11j**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.16 (s, 1H), 8.17 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.8$ Hz, 1H), 7.54 (ddd, $J_1 = J_2 = 8.0$, $J_3 = 1.8$ Hz, 1H), 7.21–7.08 (m, 3H), 7.02 (d, $J = 8.0$ Hz, 1H), 4.02 (s, 3H), 1.98 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 163.9, 157.7, 145.9, 134.6, 132.8, 125.2, 121.6, 120.5, 111.7, 56.1, 18.3; IR ($CHCl_3$) ν 3330, 3017, 1739, 1670, 1479 cm^{-1}; MS (FAB^+) 220 ($M + H^+$, 100); HRMS (FAB^+) Calcd. for $C_{12}H_{14}NO_3$: 220.0974, Found: 290.0967.

(*E*)-*N*-[(*tert*-Buthyldimethylsilanyloxy)-oct-2-enoyl]-2-methoxybenzamide (**11k**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.11 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.6$ Hz, 1H), 7.48 (ddd, $J_1 = J_2 = 7.8$ Hz, $J_3 = 1.6$ Hz, 1H), 7.15–7.01 (m, 3H), 6.97 (d, $J = 7.8$ Hz, 1H), 3.96 (s, 3H), 3.56 (t, $J = 6.4$ Hz, 2H), 2.30–2.20 (m, 2H), 1.53–1.46 (m, 4H), 1.39–1.30 (m, 2H), 0.84 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.3, 163.8, 157.6, 150.6, 134.5, 132.7,

123.7, 121.5, 120.4, 111.6, 62.9, 56.0, 32.5, 32.4, 27.8, 25.8, 25.3, 18.1, –5.5; IR ($CHCl_3$) ν 3331, 2933, 1699, 1673, 1600, 1479, 1347 cm^{-1}; MS (FAB^+) 406 ($M + H^+$, 54), 135 (100); HRMS (FAB^+) Calcd. for $C_{22}H_{36}NO_4Si$: 406.2414, Found: 406.2421.

(3*R*)-*N*-[4,4-Dicyano-3-(4-fluorophenyl)butyryl]-2-methoxybenzamide (**12f**): Colorless amorphous; ^1H NMR (500 MHz, $CDCl_3$) δ 10.42 (s, 1H), 8.15 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.5$ Hz, 1H), 7.58 (ddd, $J_1 = J_2 = 8.0$ Hz, $J_3 = 1.5$ Hz, 1H), 7.48–7.42 (m, 2H), 7.16–7.09 (m, 3H), 7.03 (d, $J = 8.0$ Hz, 1H), 4.63 (d, $J = 5.2$ Hz, 1H), 4.02 (s, 3H), 3.93–3.87 (m, 1H), 3.70 (d, $J = 7.0$ Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 164.1, 162.0, 157.8, 133.6 (d, $J = 311$ Hz), 132.1, 132.1, 130.0, 129.9, 121.9, 119.4, 116.2 (d, $J = 21.8$ Hz), 111.9, 111.8, 111.4, 56.2, 40.7, 40.2, 28.8; IR ($CHCl_3$) ν 3314, 2360, 1710, 1683, 1604, 1514, 1478, 1243 cm^{-1}; MS (FAB^+) 366 ($M + H^+$, 92), 135 (100); HRMS (FAB^+) Calcd. for $C_{20}H_{17}FN_3O_3$: 366.1254, Found: 336.1248; HPLC [Chiralcel OD, hexane/2-propanol = 70/30, 0.5 mL/min, $\lambda = 254$ nm, retention times: (major) 101.6 min, (minor) 44.0 min]; $[\alpha]_D^{28} = +10.2$ (c 1.00, $CHCl_3$, 92 % ee).

(3*R*)-*N*-[4,4-Dicyano-3-(4-methoxyphenyl)butyryl]-2-methoxybenzamide (**12g**): Colorless amorphous; ^1H NMR (500 MHz, $CDCl_3$) δ 10.38 (s, 1H), 8.15 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.8$ Hz, 1H), 7.57 (ddd, $J_1 = J_2 = 8.0$ Hz, $J_3 = 1.8$ Hz, 1H), 7.38 (d, $J = 8.5$ Hz, 2H), 7.13 (dd, $J_1 = J_2 = 8.0$ Hz, 1H), 7.03 (d, $J = 8.0$ Hz, 1H), 6.94 (d, $J = 8.5$ Hz, 2H), 4.59 (d, $J = 5.5$ Hz, 1H), 4.01 (s, 3H), 3.89–3.83 (m, 1H), 3.81 (s, 3H), 3.69 (d, $J = 7.1$ Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 164.0, 160.0, 157.8, 135.3, 132.9, 129.3, 128.2, 121.9, 119.5, 114.5, 112.1, 111.8, 111.7, 56.2, 55.2, 40.8, 40.3, 29.1; IR ($CHCl_3$) ν 3316, 3024, 1709, 1683, 1514, 1479, 1217 cm^{-1}; MS (FAB^+) 378 ($M + H^+$, 87), 135 (100); HRMS (FAB^+) Calcd. for $C_{21}H_{20}N_3O_4$: 378.1454, Found: 378.1447; HPLC [Chiralcel OD-H, hexane/2-propanol = 70/30, 0.5 mL/min, $\lambda = 254$ nm, retention times: (major) 85.4 min, (minor) 48.8 min]; $[\alpha]_D^{24} = +11.0$ (c 1.21, $CHCl_3$, 90 % ee).

(*R*)-*N*-(4,4-Dicyano-3-(furan-3-yl)butanoyl)-2-methoxybenzamide (**12h**): White solids, mp 141–145 °C (hexane/EtOAc); ^1H NMR δ 10.42 (s, 1H), 8.15 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.8$ Hz, 1H), 7.60 (s, 1H), 7.58 (ddd, $J_1 = J_2 = 7.8$ Hz, $J_3 = 1.8$ Hz, 1H), 7.47 (t, $J = 1.5$ Hz, 1H), 7.13 (dd, $J_1 = J_2 = 7.8$ Hz, 1H), 7.04 (d, $J = 7.8$ Hz, 1H), 6.60 (s, 1H), 4.63 (d, $J = 4.9$ Hz, 1H), 4.03 (s, 3H), 3.87 (ddd, $J_1 = 8.5$ Hz, $J_2 = 5.5$ Hz, $J_3 = 4.9$ Hz, 1H), 3.62 (dd, $J_1 = 18.6$ Hz, $J_2 = 5.5$ Hz, 1H), 3.57 (dd, $J_1 = 18.6$ Hz, $J_2 = 8.5$ Hz, 1H); ^{13}C NMR δ 172.9, 164.0, 157.8, 144.0, 140.8, 135.3, 132.9, 121.9, 121.1, 119.4, 112.2, 111.8, 111.6, 109.4, 56.2, 40.1, 33.4, 28.5; IR (KBr) ν 3331, 1748, 1679 cm^{-1}; MS (FAB^+) 338 ($M + H^+$, 97), 135 (100); Anal. Calcd. for $C_{18}H_{15}N_3O_4$: C, 64.09; H, 4.48; N, 12.46; Found: C, 64.10; H, 4.43; N, 12.48; HPLC analysis [Chiralpak AS-H, Hexane/2-propanol = 70:30, 0.5 mL/min, 254 nm retention time: (major) 59.7 min, (minor) 73.9 min]; $[\alpha]_D^{23} = -8.5$ (c 1.2, $CHCl_3$, 92 % ee).

(*R*)-*N*-(4,4-Dicyano-3-(furan-3-yl)butanoyl)-2-fluorobenzamide (**12i**): White solids, mp 105–106 °C (hexane/EtOAc); ^1H NMR δ 9,09 (d, $J = 13.8$ Hz, 1H), 8.06

(dd, $J_1 = J_2 = 7.5$ Hz, 1H), 7.62 (dd, $J_1 = J_2 = 6.9$ Hz, 1H), 7.60 (s, 1H), 7.48 (s, 1H), 7.35 (dd, $J_1 = J_2 = 7.5$ Hz, 1H), 7.21 (dd, $J_1 = 8.6$ Hz, $J_2 = 8.0$ Hz, 1H), 6.58 (s, 1H), 4.58 (d, $J = 5.2$ Hz, 1H), 3.87 (ddd, $J_1 = 8.6$ Hz, $J_2 = J_3 = 5.2$ Hz, 1H), 3.63 (dd, $J_1 = 15.5$ Hz, $J_2 = 5.2$ Hz, 1H), 3.58 (dd, $J_1 = 15.5$ Hz, $J_2 = 8.6$ Hz, 1H); ^{13}C NMR δ 172.3, 162.0 (d, $J = 3.6$ Hz), 160.3 (d, $J = 250$ Hz), 144.1, 140.8, 135.8 (d, $J = 9.6$ Hz), 132.4, 125.5 (d, $J = 2.4$ Hz), 120.9, 119.2 (d, $J = 10.8$ Hz), 116.6 (d, $J = 25.2$ Hz), 112.0, 111.5, 109.3, 40.1, 33.4, 28.6; IR (KBr) ν 2361, 1697 cm^{-1}; MS (FAB$^+$) 326 (M + H$^+$, 100); HRMS (FAB$^+$): Calcd. for $C_{17}H_{13}FN_3O_3$: 326.0941, Found: 326.1003; HPLC [Chiralcel OD-H, hexane:2-propanol = 80/20, 0.5 mL/min, 254 nm, retention times: (major) 71.8 min, (minor): 88.7 min]; $[\alpha]_D^{23} = -7.5$ (c 1.0, $CHCl_3$, 95 % ee).

(3*R*)-*N*-[4,4-Dicyano-3-methylbutyryl]-2-methoxybenzamide (**12j**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.15 (dd, $J_1 = 7.9$, $J_2 = 1.8$ Hz, 1H), 7.58 (ddd, $J_1 = J_2 = 7.9$ Hz, $J_3 = 1.8$ Hz, 1H), 7.14 (dd, $J_1 = J_2 = 7.9$ Hz, 1H), 7.04 (d, $J = 7.9$ Hz, 1H), 4.46 (d, $J = 4.6$ Hz, 1H), 4.04 (s, 3H), 3.28 (dd, $J_1 = 18.7$ Hz, $J_2 = 4.8$ Hz, 1H), 3.20 (dd, $J_1 = 18.7$ Hz, $J_2 = 8.6$ Hz, 1H), 2.84–2.75 (m, 1H), 1.40 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 164.0, 157.8, 135.3, 132.9, 121.9, 119.5, 112.5, 111.8, 111.2, 56.3, 41.1, 31.7, 27.8, 17.0; IR ($CHCl_3$) ν 3316, 3026, 1707, 1685, 1600, 1479, 1383 cm^{-1}; MS (FAB$^+$) 286 (M + H$^+$, 64), 135 (100); HRMS (FAB$^+$) Calcd. for $C_{15}H_{16}N_3O_3$: 286.1192, Found: 286.1187; HPLC [Chiralcel OD-H, hexane/2-propanol = 70/30, 0.5 mL/min, $\lambda = 254$ nm, retention times: (major) 36.1 min, (minor) 27.9 min]; $[\alpha]_D^{20} = -23.3$ (c 1.61, $CHCl_3$, 90 % ee).

(3*R*)-*N*-[(8-*tert*-Buthyldimethylsilanoyloxy)-3, 3-dicyanomethyloctanoyl]-2-methoxybenzamide (**12k**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.14 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.8$ Hz, 1H), 7.57 (ddd, $J_1 = J_2 = 8.0$, $J_3 = 1.8$ Hz, 1H), 7.13 (dd, $J_1 = J_2 = 8.0$ Hz, 1H), 7.03 (d, $J = 8.0$ Hz, 1H), 4.47 (d, $J = 4.5$ Hz, 1H), 4.03 (s, 3H), 3.60 (t, $J = 6.4$ Hz, 2H), 3.39 (dd, $J_1 = 18.8$ Hz, $J_2 = 4.0$ Hz, 1H), 3.11 (dd, $J_1 = 18.8$ Hz, $J_2 = 9.1$ Hz, 1H), 2.65–2.58 (m, 1H), 1.84–1.76 (m, 1H), 1.70–1.62 (m, 1H), 1.58–1.48 (m, 3H), 1.44–1.36 (m, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 164.0, 157.8, 135.3, 133.0, 121.9, 119.6, 112.5, 111.8, 111.7, 62.9, 56.3, 38.7, 36.1, 32.4, 31.2, 26.9, 26.5, 25.9, 25.6, 18.3, –5.4; IR ($CHCl_3$) ν 3316, 3021, 1711, 1477, 1417, 1362, 1221 cm^{-1}; MS (FAB$^+$) 472 (M + H$^+$, 56), 135 (100); HRMS (FAB$^+$) Calcd. for $C_{25}H_{38}N_3O_4Si$: 472.2632, Found: 472.2636; HPLC [Chiralcel OD-H, hexane/2-propanol = 70/30, 0.5 mL/min, $\lambda = 254$ nm, retention times: (major) 21.6 min, (minor) 18.2 min]; $[\alpha]_D^{28} = -25.9$ (c 2.28, $CHCl_3$, 93 % ee).

2.2.3.5 Typical Procedure for Enantioselective Michael Addition of Methyl Cyanoacetate to α,β-Unsaturated Imides Catalyzed by Thiourea

A solution of **11c** (100 mg, 0.36 mmol), methyl cyanoacetate (63 μL, 0.72 mmol) and thiourea 1a (15 mg, 0.036 mmol) in toluene (0.72 mL) was stirred at 80 °C for 52 h. After concentrated *in vacuo*, the reaction mixture was purified by silica gel column chromatography with hexane/EtOAc (3/2) to afford desired Michael adduct **12l** (127 mg, 94 %). To determine the ee value of the Michael adduct, methanolysis and decarboxylation reaction were employed.[5a]

(3*S*)-2-Cyano-5-(2-methoybenzoylamino)-5-oxo-3-phenylpentanoic acid methyl ester (**12l**): Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) (3:2 mixture of diastreomers, with signals corresponding to the major indicated by) δ 10.33 (s, 1H), 8.16 (ddd, $J_1 = J_2 = 7.3$ Hz, $J_3 = 1.8$ Hz, 1H), 7.59–7.52 (m, 1H), 7.42–7.28 (m, 5H), 7.12 (dd, $J_1 = J_2 = 7.3$ Hz, 1H), 7.01 (dd, $J_1 = J_2 = 8.5$ Hz, 1H), 4.37 (d, $J = 5.8$ Hz, 1H), 4.12–4.04 (m, 1H), 4.01 (s, 3H), 3.65 (s, 3H), 3.78–3.58 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 173.0, 165.6, 163.9, 157.7, 139.0, 138.1, 135.0, 135.0, 132.9, 128.9, 128.8, 128.2, 128.1, 127.8, 121.8, 121.7, 119.8, 119.8, 115.5, 115.3, 111.7, 56.2, 56.1, 53.3, 53.2, 43.7, 43.3, 41.3, 41.0, 40.6, 40.4; IR ($CHCl_3$) ν 3316, 2360, 1753, 1710, 1680, 1476 cm^{-1}; MS (FAB$^+$) 381 (M + H$^+$, 50), 135 (100); HRMS (FAB$^+$) Calcd. for $C_{21}H_{21}N_2O_5$: 381.1450, Found: 381.1448; $[\alpha]_D^{22} = -3.18$ (c 1.99, $CHCl_3$).

(3*S*)-2-Cyano-3-phenylpentanedioic acid dimethyl ester : To a stirred solution of **12l** (27 mg, 0.071 mmol) in MeOH (0.30 mL) was added $Er(OTf)_3$ (2.2 mg, 0.0036 mmol) at 0 °C. After 4 h, the reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (hexane/EtOAc = 2/1) to afford desired methylester (17 mg, 92 %). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) (3:2 mixture of diastereomers, with signals corresponding to the major indicated by) δ 7.37–7.26 (m, 5H), 4.24 (d, $J = 5.5$ Hz, 1H), 3.94–3.90 (m, 1H), 3.66 (s, 3H), 3.63 (s, 3H), 3.06–2.85 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 171.0, 165.3, 165.2, 138.2, 137.3, 128.9, 128.8, 128.3, 128.2, 127.7, 127.3, 115.1, 114.9, 53.4, 53.1, 51.9, 51.8, 43.6, 43.1, 41.4, 40.9, 36.9, 36.3; IR ($CHCl_3$) ν 3028, 2956, 2252, 1747, 1454, 1439, 1266 cm^{-1}; MS (FAB$^+$) 262 (M + H$^+$, 67), 154 (100); HRMS (FAB$^+$) Calcd. for $C_{14}H_{16}NO_4$: 262.1079, Found: 262.1082; $[\alpha]_D^{20} = +7.80$ (c 1.44, $CHCl_3$).

(3*S*)-4-Cyano-3-phenylbutanoic acid methyl ester: A mixture of (3*S*)-2-Cyano-3-phenylpentanedioic acid dimethyl ester (16 mg, 0.061 mmol) and NaCl (3.6 mg, 0.061 mmol) in DMSO/H_2O (0.6 mL/0.1 mL) was stirred at 130 °C. After 24 h, the reaction mixture was purified by column chromatography (hexane/EtOAc = 3/2) to afford desired product (11 mg, 92 %). Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.34 (m, 2H), 7.33–7.24 (m, 3H), 3.66 (s, 3H), 3.52 (q, $J = 6.7$ Hz, 1H), 2.86 (dd, $J_1 = 16.4$, $J_2 = 8.0$ Hz, 1H), 2.79 (dd, $J_1 = 16.4$, $J_2 = 9.8$ Hz, 1H), 2.75 (d, $J = 6.7$ Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 140.4, 129.0, 127.9, 127.0, 117.9, 51.9, 38.7, 37.9, 24.2; IR ($CHCl_3$) ν 3026, 2360, 1733,

1438, 1216 cm^{-1}; MS (FAB^+) 204 ($M + H^+$, 94), 154 (100); HRMS (FAB^+) Calcd. for $C_{12}H_{14}NO_2$: 204.1025, Found: 204.1027; HPLC [Chiralcel OD-H, hexane/2-propanol = 90/10, 0.3 mL/min, $\lambda = 254$ nm, retention times: (major) 63.4 min, (minor) 52.8 min] $[\alpha]_D^{21} = +16.3$ (c 1.00, $CHCl_3$, 82 % ee).

(3*S*)-2-Cyano-3-(4-fluorophenyl)-5-(2-methoybenzoylamino)-5-oxo-pentanoic acid methyl ester (**12m**): Colorless amorphous; ^1H NMR (500 MHz, $CDCl_3$) (3:2 mixture of diastereomers, with signals corresponding to the major indicated by) δ 10.34 (s, 1H), 8.16 (ddd, $J_1 = J_2 = 7.4$, $J_3 = 1.9$ Hz, 1H), 7.52–7.50 (m, 1H), 7.48–7.46 (m, 2H), 7.13 (dd, $J_1 = J_2 = 7.9$ Hz, 1H), 7.01–6.98 (m, 3H), 4.34 (d, $J = 5.5$ Hz, 1H), 4.11–4.05 (m, 1H), 4.02 (s, 3H), 3.68 (s, 3H), 3.72–3.55 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 165.5, 163.9, 157.8, 149.4, 146.1, 135.1, 135.1, 133.8, 132.9, 129.8, 129.6, 129.5, 121.8, 121.8, 119.7, 115.9, 115.8, 115.7, 115.7, 115.4, 115.2, 111.8, 56.2, 56.2, 53.4, 53.3, 43.6, 43.3, 41.4, 40.7, 40.4, 39.6; IR ($CHCl_3$) *v* 3319, 3026, 2252, 1750, 1709, 1684, 1602, 1511, 1479, 1385, 1244, 1228 cm^{-1}; MS (FAB^+) 399 ($M + H^+$, 73), 135 (100); HRMS (FAB^+) Calcd. for $C_{21}H_{20}FN_2O_5$: 399.1356, Found: 399.1358; $[\alpha]_D^{22} = -5.86$ (c 2.97, $CHCl_3$).

(3*S*)-4-Cyano-3-(4-fluorophenyl)butanoic acid methyl ester (**14**) [88]: $[\alpha]_D^{25} = +6.68$ (c 1.12, CH_3CN, 85 % ee); HPLC [Chiralcel OJ-H, hexane/ethanol = 85/15, 0.5 mL/min, $\lambda = 254$ nm, retention times: (major) 89.1 min, (minor) 37.3 min].

(3*S*)-2-Cyano-5-(2-methoybenzoylamino)-3-methyl-5-oxo-pentanoic acid methyl ester (**12n**): Colorless oil; ^1H NMR (500 MHz, $CDCl_3$) (3:2 mixture of diastreomers, with signals corresponding to the major indicated by) δ 10.22 (s, 1H), 8.06 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.5$ Hz, 1H), 7.51–7.44 (m, 1H), 7.06–7.01 (m, 1H), 6.96 (d, $J = 7.8$ Hz, 1H), 4.03 (d, $J = 4.3$ Hz, 1H), 3.95 (s, 3H), 3.76 (s, 3H), 3.07 (d, $J = 6.1$ Hz, 2H), 2.88–2.78 (m, 1H), 1.11 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 173.5, 166.2, 165.9, 163.8, 163.7, 157.7, 135.0, 134.9, 132.8, 121.7, 119.8, 119.8, 115.6, 115.0, 111.7, 56.1, 53.3, 53.2, 42.5, 42.2, 41.5, 30.7, 30.0, 18.0, 16.7; IR ($CHCl_3$) *v* 3323, 3023, 2360, 2252, 1749, 1709, 1684, 1480 cm^{-1}; MS (FAB^+) 319 ($M + H^+$, 100); HRMS (FAB^+) Calcd. for $C_{16}H_{19}N_2O_5$: 319.1294, Found: 319.1295; $[\alpha]_D^{27} = -3.90$ (c 1.11, $CHCl_3$).

(3*S*)-2-Cyano-3-methylpentanedioic acid dimethyl ester: Colorless oil; ^1H NMR (500 MHz, $CDCl_3$) (3:2 mixture of diastereomers, with signals corresponding to the major indicated by) δ 3.93 (d, $J = 6.3$ Hz, 1H), 3.78 (s, 3H), 3.66 (s, 3H), 2.76–2.68 (m, 1H), 2.58–2.34 (m, 2H), 1.07 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 171.6, 165.9, 165.7, 115.2, 114.8, 53.4, 53.4, 51.8, 42.7, 42.5, 38.0, 37.3, 31.3, 30.7, 18.0, 16.6; IR ($CHCl_3$) *v* 3028, 2955, 1747, 1439 cm^{-1}; MS (FAB^+) 200 ($M + H^+$, 12), 154 (100); HRMS (FAB^+) Calcd. for $C_9H_{14}NO_4$: 200.0923, Found: 200.0926; $[\alpha]_D^{23} = -17.0$ (c 1.17, $CHCl_3$).

(3*S*)-4-Cyano-3-methylbutanoic acid methyl ester: Colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 3.70 (s, 3H), 2.49–2.35 (m, 5H), 1.16 (d, $J = 5.8$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 118.2, 51.8, 39.4, 27.4, 23.8, 19.4; IR ($CHCl_3$) *v* 3025, 2251, 1734 cm^{-1}; MS (CI+) 142 ($M + H^+$, 100); HPLC [Chiralcel AS-H, hexane/2-propanol = 90/10, 0.5 mL/min, $\lambda = 210$ nm, retention

times: (major) 27.0 min, (minor) 25.8 min]; $[\alpha]_D^{26} = -20.39$ (c 2.28, $CHCl_3$, 92 % ee).

(3*S*)-8-*tert*-Buthyldimethylsilanoyloxy-2-cyano-3-[2-(2-methoybenzoylamino)-2-oxoethyl] octanoic acid methyl ester (**12o**): Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) (3:2 mixture of diastreomers, with signals corresponding to the major indicated by) δ 10.27 (s, 1H), 8.09 (d, $J = 8.0$ Hz, 1H), 7.52 (dd, $J_1 = J_2 = 8.0$ Hz, 1H), 7.08 (dd, $J_1 = J_2 = 8.0$ Hz, 1H), 6.99 (d, $J = 8.0$ Hz, 1H), 4.12 (d, $J = 3.9$ Hz, 1H), 3.98 (s, 3H), 3.77 (s, 3H), 3.55 (t, $J = 4.8$ Hz, 2H), 3.28–2.98 (m, 2H), 2.78–2.69 (m, 1H), 1.58–1.51 (m, 2H), 1.49–1.42 (m, 2H), 1.37–1.25 (m, 4H), 0.84 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 173.6, 166.3, 166.2, 163.8, 163.6, 163.4, 157.6, 134.9, 134.9, 132.7, 121.6, 119.8, 119.7, 115.4, 115.3, 113.0, 111.7, 111.7, 62.9, 62.8, 56.1, 53.4, 53.2, 41.7, 40.9, 39.7, 39.5, 35.2, 34.5, 32.4, 32.3, 31.2, 26.6, 25.8, 25.5, 25.4, 24.3, 18.1, –5.5; IR ($CHCl_3$) ν 3323, 2933, 1753, 1709, 1684, 1479 cm^{-1}; MS (FAB$^+$) 505 (M + H$^+$, 28); HRMS (FAB$^+$) Calcd. for $C_{26}H_{41}N_2O_6Si$: 505.2734, Found: 505.2748; $[\alpha]_D^{25} = -9.82$ (c 1.67, $CHCl_3$).

(3*S*)-2-Cyano-3-(5-hydroxypentyl)pentanedioic acid dimethyl ester: Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) (3:2 mixture of diastereomers, with signals corresponding to the major indicated by) δ 4.06 (d, $J = 7.0$ Hz, 1H), 3.78 (s, 3H), 3.66 (s, 3H), 3.59–3.54 (m, 2H), 2.64–2.59 (m, 1H), 2.54–2.35 (m, 2H), 1.74 (s, 1H), 1.55–1.46 (m, 4H), 1.40–1.30 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 171.9, 166.1, 115.0, 62.5, 60.3, 53.4, 51.9, 51.8, 41.6, 41.0, 35.8, 35.7, 35.3, 35.3, 32.2, 231.1, 26.4, 26.2, 25.4, 25.3, 20.9, 14.0; IR ($CHCl_3$) ν 3021, 1747, 1711, 1362 cm^{-1}; MS (FAB$^+$) 272 (M + H$^+$, 100); HRMS (FAB$^+$) Calcd. for $C_{13}H_{22}NO_5$: 272.1498, Found: 272.1492; $[\alpha]_D^{22} = -12.40$ (c 1.00, $CHCl_3$).

(3*S*)-3-Cyanomethyl-8-hydroxyoctanoic acid methyl ester: Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.63 (s, 3H), 3.56 (t, $J = 6.4$ Hz, 2H), 2.44 (d, $J = 5.8$ Hz, 2H), 2.40 (dd, $J_1 = 11.3$ Hz, $J_2 = 5.5$ Hz, 1H), 2.33 (dd, $J_1 = 11.3$ Hz, $J_2 = 8.2$ Hz, 1H), 2.19–2.13 (m, 1H), 1.75 (s, 1H), 1.55–1.48 (m, 2H), 1.44–1.38 (m, 2H), 1.35–1.27 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 118.1, 62.5, 51.7, 37.4, 33.2, 32.3, 31.8, 26.2, 25.4, 21.5; IR ($CHCl_3$) ν 3021, 2360, 1732, 1439 cm^{-1}; MS (FAB$^+$) 214 (M + H$^+$, 98), 154 (100); HRMS (FAB$^+$) Calcd. for $C_{11}H_{20}NO_3$: 214.1443, Found: 214.1442; $[\alpha]_D^{28} = -10.41$ (c 3.00, $CHCl_3$).

(3*S*)-Benzoic acid 7-cyano-6-methoxycarbonylmethylheptylester: To a solution of (3*S*)-3-Cyanomethyl-8-hydroxyoctanoic acid methyl ester (29.5 mg, 0.138 mmol) in CH_2Cl_2 (0.28 mL) at 0 °C were added pyridine (0.017 mL, 0.207 mmol) and BzCl (0.024 mL, 0.207 mmol) and the solution was stirred at room temperature for 4 h. Then the reaction mixture was extracted with $CHCl_3$, dried over $MgSO_4$ and purified by column chromatography (hexane/EtOAc = 4/1) to afford desired product (39.5 mg, 90 %). Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (dd, $J_1 = 7.4$ Hz, $J_2 = 1.2$ Hz, 2H), 7.56 (dd, $J_1 = J_2 = 7.4$ Hz, 1H), 7.45 (dd, $J_1 = J_2 = 7.4$ Hz, 2H), 4.32 (t, $J = 6.7$ Hz, 2H), 3.69 (s, 3H), 2.51 (dd, $J_1 = 5.7$ Hz, $J_2 = 2.1$ Hz, 2H), 2.48 (dd, $J_1 = 16.5$, $J_2 = 5.5$ Hz, 1H), 2.40

(dd, $J_1 = 16.5$ Hz, $J_2 = 7.9$ Hz, 1H), 2.26–2.19 (m, 1H), 1.83–1.75 (m, 2H), 1.55–1.45 (m, 4H), 1.44–1.37 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 166.6, 132.9, 130.3, 129.5, 128.3, 118.0, 64.7, 51.7, 37.4, 33.1, 31.8, 28.4, 26.2, 25.8, 21.6; IR ($CHCl_3$) ν 3021, 1711, 1436, 1419 cm^{-1}; MS (FAB$^+$) 318 (M + H$^+$, 40), 105 (100); HRMS (FAB$^+$) Calcd. for $C_{18}H_{24}NO_4$: 318.1705, Found: 318.1707. HPLC [Chiralcel AS-H, hexane/2-propanol = 80/20, 0.5 mL/min, $\lambda = 254$ nm, retention times: (major) 54.9 min, (minor) 31.0 min]; $[\alpha]_D^{22} = -4.92$ (c 2.21, $CHCl_3$, 92 % ee).

2.2.3.6 Typical Procedure for Enantioselective Michael Addition of Nitromethane to α,β-Unsaturated Imides Catalyzed by Thiourea 1a

A solution of **11c** (120 mg, 0.43 mmol), nitromethane (1.00 mL, 17.2 mmol) and thiourea **1a** (18 mg, 0.043 mmol) in toluene (0.86 mL) was stirred at 60 °C for 168 h. After concentrated *in vacuo*, the reaction mixture was purified by silica gel column chromatography with hexane/EtOAc (3/1) to afford desired Michael adduct **12p** (102 mg, 56 %).

(3*S*)-2-Methoxy-*N*-(4-nitro-3-phenylbutyryl)benzamide (**12p**): White solids; mp 115–117 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.15 (dd, $J_1 = 7.9$ Hz, $J_2 = 1.8$ Hz, 1H), 7.56 (ddd, $J_1 = J_2 = 7.9$ Hz, $J_3 = 1.8$ Hz, 1H), 7.37–7.31 (m, 4H), 7.29–7.24 (m, 1H), 7.13 (dd, $J_1 = J_2 = 7.9$ Hz, 1H), 7.02 (d, $J = 7.9$ Hz, 1H), 4.81 (dd, $J_1 = 12.5$ Hz, $J_2 = 6.4$ Hz, 1H), 4.69 (dd, $J_1 = 12.5$ Hz, $J_2 = 8.5$ Hz, 1H), 4.23–4.15 (m, 1H), 4.00 (s, 3H), 3.56 (dd, $J_1 = 17.6$ Hz, $J_2 = 6.8$ Hz, 1H), 3.43 (dd, $J_1 = 17.6$ Hz, $J_2 = 7.4$ Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 164.0, 157.8, 139.1, 135.1, 132.9, 129.0, 127.8, 127.6, 121.8, 119.8, 111.8, 79.6, 56.2, 41.5, 39.4; IR ($CHCl_3$) ν 3320, 3024, 1710, 1684, 1555, 1479, 1379 cm^{-1}; Anal. Calcd. for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18; Found: C, 63.34; H, 5.37; N, 8.13; HPLC [Chiralcel OD-H, hexane/2-propanol = 80/20, 0.5 mL/min, $\lambda = 254$ nm, retention times: (major) 92.4 min, (minor) 63.4 min]; $[\alpha]_D^{29} = -46.0$ (c 1.14, $CHCl_3$, 87 % ee).

(3*S*)-2-Methoxy-*N*-[3-(4-fluorophenyl)-4-nitrobutyryl]benzamide (**12q**): White solids; mp 132–134 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.14 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.9$ Hz, 1H), 7.56 (ddd, $J_1 = J_2 = 7.8$ Hz, $J_3 = 1.9$ Hz, 1H), 7.35–7.26 (m, 2H), 7.13 (dd, $J_1 = J_2 = 7.8$ Hz, 1H), 7.05–6.98 (m, 3H), 4.80 (dd, $J_1 = 12.5$ Hz, $J_2 = 6.1$ Hz, 1H), 4.65 (dd, $J_1 = 12.5$ Hz, $J_2 = 8.5$ Hz, 1H), 4.23–4.15 (m, 1H), 4.00 (s, 3H), 3.52 (dd, $J_1 = 17.7$ Hz, $J_2 = 7.0$ Hz, 1H), 3.40 (dd, $J_1 = 17.7$ Hz, $J_2 = 7.3$ Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 164.1, 157.8, 134.7, 134.0 (d, $J = 287$ Hz), 129.3, 121.8, 119.6, 115.9 (d, $J = 21.8$ Hz) 111.8, 79.6, 56.2, 41.5, 38.7; IR ($CHCl_3$) ν 3319, 3026, 1710, 1684, 1555, 1511, 1479, 1290 cm^{-1}; Anal. Calcd. for $C_{18}H_{17}FN_2O_3$: C, 60.00; H, 4.76; N, 7.77; F, 5.27; Found: C, 59.87; H, 4.69; N, 7.77; F, 5.25; HPLC [Chiralcel OD-H, hexane/2-propanol = 80/20, 0.5 mL/min,

$\lambda = 254$ nm, retention times: (major) 72.4 min, (minor) 84.7 min]; $[\alpha]_D^{23} = -30.2$ (c 1.03, $CHCl_3$, 86 % ee).

(3*S*)-2-Methoxy-*N*-(3-methyl-4-nitro-butyryl)benzamide (**12r**): White solids; mp 82–83 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.16 (d, $J = 8.0$ Hz, 1H), 7.57 (dd, $J_1 = J_2 = 8.0$ Hz, 1H), 7.13 (dd, $J_1 = J_2 = 8.0$ Hz, 1H), 7.04 (d, $J = 8.0$ Hz, 1H), 4.57 (dd, $J_1 = 15.3$ Hz, $J_2 = 5.5$ Hz, 1H), 4.39 (dd, $J_1 = 15.3$ Hz, $J_2 = 7.6$ Hz, 1H), 4.04 (s, 3H), 3.17–3.09 (m, 2H), 3.01–2.94 (m, 1H), 1.17 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 163.9, 157.7, 135.0, 132.9, 121.8, 119.9, 111.7, 80.4, 56.2, 41.7, 28.7, 17.5; IR ($CHCl_3$) ν 3324, 3025, 1709, 1685, 1552, 1480 cm^{-1}; MS (FAB$^+$) 281 (M + H$^+$, 71), 135 (100); HRMS (FAB$^+$) Calcd. for $C_{13}H_{17}N_2O_5$: 281.1137, Found: 281.1135. HPLC [Chiralcel AS-H, hexane/2-propanol = 50/50, 1.0 mL/min, $\lambda = 254$ nm, retention times: (major) 19.9 min, (minor) 13.4 min]; $[\alpha]_D^{26} = +2.88$ (c 1.09, $CHCl_3$, 83 % ee).

(3*S*)-*N*-[8-(*tert*-Buthyldimethylsilanoyloxy]-3-nitromethyloctanoyl]-2-methoxybenzamide (**12s**): Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.26 (s, 1H), 8.12 (dd, $J_1 = 7.9$ Hz, $J_2 = 1.8$ Hz, 1H), 7.52 (ddd, $J_1 = J_2 = 7.9$ Hz, $J_3 = 1.8$ Hz, 1H), 7.09 (dd, $J_1 = J_2 = 7.9$ Hz, 1H), 6.99 (d, $J = 7.9$ Hz, 1H), 4.52 (dd, $J_1 = 12.1$ Hz, $J_2 = 6.1$ Hz, 1H), 4.46 (dd, $J_1 = 12.1$ Hz, $J_2 = 6.1$ Hz, 1H), 3.99 (s, 3H), 3.55 (t, $J = 6.4$ Hz, 2H), 3.14–3.02 (m, 2H), 2.80–2.73 (m, 1H), 1.52–1.43 (m, 4H), 1.40–1.29 (m, 4H), 0.84 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 163.9, 157.8, 135.0, 132.9, 121.8, 120.0, 111.7, 78.6, 65.8, 63.0, 56.2, 39.7, 33.4, 32.5, 31.6, 25.9, 18.3, 15.2, −5.4; IR ($CHCl_3$) ν 3324, 2933, 1709, 1684, 1600, 1551, 1479 cm^{-1}; MS (FAB$^+$) 467 (M + H$^+$, 10), 135 (100); HRMS (FAB$^+$) Calcd. for $C_{23}H_{39}N_2O_6Si$: 467.2577; Found: 467.2575. HPLC [Chiralcel AD-H, hexane/ethanol = 95/5, 0.5 mL/min, $\lambda = 254$ nm, retention times: (major) 25.7 min, (minor) 27.8 min]; $[\alpha]_D^{22} = -6.89$ (c 3.90, $CHCl_3$, 80 % ee).

(3*S*)-4,4-Dicyano-3-(4-fluorophenyl)butanoic acid methyl ester (**13**) [88]: To a stirred solution of **12f** (35 mg, 0.096 mmol) in MeOH (0.35 mL) was added $Er(OTf)_3$ (6.0 mg, 0.0096 mmol) at room temperature. After 3 h, the reaction mixture was concentrated *in vacuo*, and the residue was purified by column chromatography (hexane/EtOAc = 2/1) to afford desired product **13** (23 mg, 96 %). Colorless oil; $[\alpha]_D^{24} = +17.3$ (c 1.24, $CHCl_3$).

(3*S*)-4-Nitro-3-phenylbutanoic acid methyl ester (**15**) [96]: To a stirred solution of **12p** (5.0 mg, 0.015 mmol) in MeOH (0.10 mL) was added $Er(OTf)_3$ (1.0 mg, 0.0015 mmol) at room temperature. After 90 min, the reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (Hexane/AcOEt = 3/2) to afford desired product **15** (2.1 mg, 64 %). Colorless oil; $[\alpha]_D^{29} = -13.3$ (c 0.21, $CHCl_3$).

2.3 Asymmetric Hydrazination of Activated Methylene Compounds Catalyzed by HB Donors

2.3.1 Introduction and Background

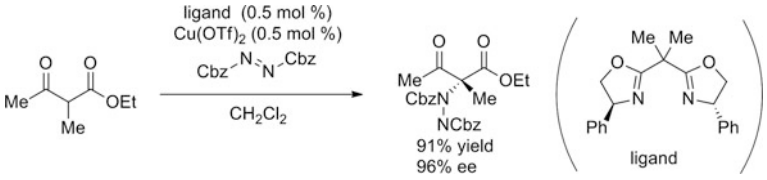
The hydrazination of 1,3-dicarbonyl compounds with azodicarboxylates is a valuable method for installing an amino group. When 2-monosubstituted 1,3-dicarbonyl compounds are used as nucleophiles, the resulting products possess α-amino acid moieties bearing quaternary stereogenic centers. These derivatives are of special interest for the synthesis of biologically important peptides [97, 98] and as building blocks for potential therapeutic agents such as metabotropic glutamate receptor ligands [99], which increases the utility of this reaction [100–102].

There are several examples of the catalytic enantioselective α-hydrazination of 1,3-dicarbonyl compounds using Lewis acids [103–109]. Jørgensen reported the highly enantioselective hydrazination of *β*-ketoesters in the presence of a chiral Lewis acid catalyst (Scheme 2.14) [103].

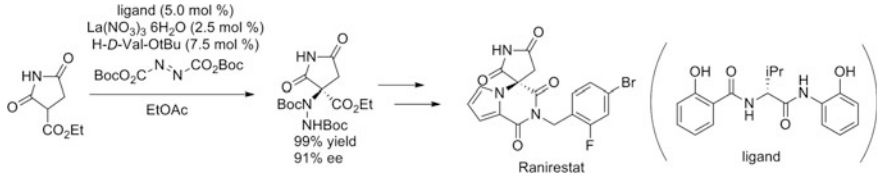
Shibasaki succeeded in developing a lanthanum-catalyzed variation of this reaction that was used in the synthesis of Ranirestat [104], which is a highly potent aldose reductase inhibitor (Scheme 2.15) [110–116].

Organocatalysts can also be used in this type of reaction. [117–127] Pihko used cinchonine as an asymmetric catalyst for the hydrazination of 1,3-dicarbonyl compounds (Scheme 2.16) [117–127].

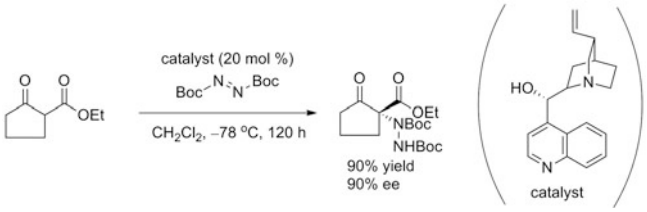
Recently, Rawal's group reported that squaramide **3b** is an effective catalyst for this reaction in terms of the substrate scope and stereoselectivity (Scheme 2.17) [118].



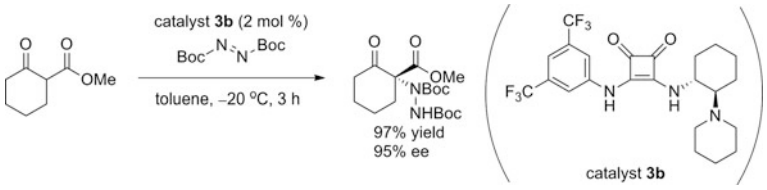
Scheme 2.14 (S)-Ph-BOX-Cu(OTf)$_2$-catalyzed hydrazination of 1,3-dicarbonyl compound



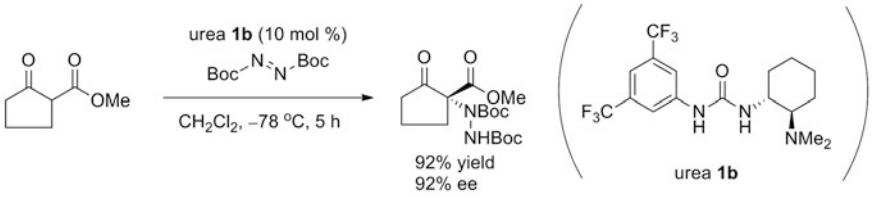
Scheme 2.15 La/Amide-catalyzed hydrazination of 1,3-dicarbonyl compound



Scheme 2.16 Cinchonine-catalyzed hydrazination of 1,3-dicarbonyl compounds



Scheme 2.17 Squaramide-catalyzed hydrazination of 1,3-dicarbonyl compounds

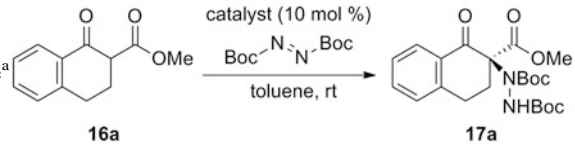


Scheme 2.18 Urea-catalyzed hydrazination of 1,3-dicarbonyl compound

My colleagues also investigated this reaction and found that urea **1b** could be used as a catalyst (Scheme 2.18) [34]. Unfortunately, the corresponding thiourea **1a**, which should be more reactive than **1b**, did not work well due to the strong nucleophilicity of the sulfur atom relative to the oxygen atom. I speculated that the sulfur atom reacted with *N*,*N*-di-*tert*-butylazodicarboxylate, resulting in a loss of catalytic activity.

The HB donors **5** and **6** described in this chapter are predicted to act as bifunctional catalysts similar to urea or thiourea catalysts **1** described earlier in this thesis. In addition, these catalysts do not possess nucleophilic atoms like thiourea catalyst **1a**, and therefore **5** and **6** are expected to avoid this loss of catalytic activity. In this section, novel HB donors **5** and **6** are evaluated in the enantioselective α-hydrazination of 1,3-dicarbonyl compounds compared with existing HB donors.

Table 2.4 Hydrazination of **16a** and *tert*-butyl azodicarboxylate[a]



16a **17a**

Entry	Catalyst	Time (h)	Yield (%)[b]	ee (%)[c]
1	**1a**	20	22	83
2[d]	**1b**	5	99	87
3	**5a**	3	93	96
4	**6a**	3	82	84
5	**5b**	5	Quant	96
6	**5c**	3	98	95
7	**5d**	5	99	95
8	**5e**	3	93	92

[a] Unless otherwise noted, the reactions were conducted with **16a** (1.1 equiv.), di-*tert*-butyl diazodicarboxylate (1.0 equiv.) and the catalysts (10 mol %) in toluene at room temperature
[b] Yield of isolated product
[c] Determined by chiral HPLC analysis
[d] The reaction was performed at −40 °C

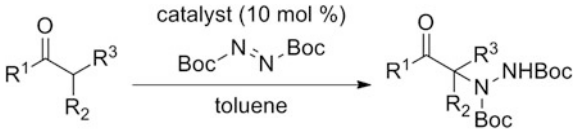
2.3.2 Results and Discussion

Initially, the reaction of **16a** with *N*,*N*-di-*tert*-butylazodicarboxylate in the presence of HB-donor catalysts was examined (Table 2.4).

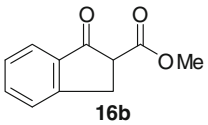
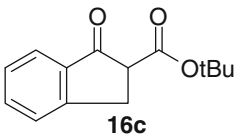
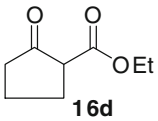
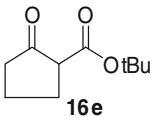
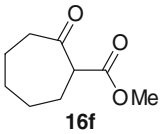
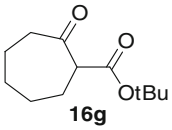
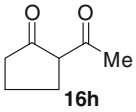
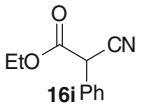
As described in the Introduction and Background, use of thiourea **1a** gave product **17a** in poor yield due to decomposition of the catalyst in the course of the reaction (entry 1). The corresponding urea catalyst **1b** gave full conversion, but the enantioselectivity was only 87 % ee even at a low temperature (entry 2). Rawal's squaramide **3b** could also be used in this reaction, and it has been reported that this catalyst gives the corresponding adduct in 90 % ee at −20 °C [118]. In contrast, the reaction proceeded smoothly in the presence of the new quinazoline catalyst **5a** to give the product in high yield and excellent enantioselectivity even at room temperature (entry 3), which is a major advantage over the cryogenic conditions required for catalyst **1b**. In contrast, while **6a** exhibited a similar reactivity, product **17a** was obtained with somewhat lower enantioselectivity (entry 4). Next, I screened the substituents of the quinazoline catalysts and found that 8-fluoro-substituted quinazoline **5b** was the best catalyst in terms of catalytic activity and enantioselectivity (entries 5–8). The absolute configuration of product **17a** was determined to be (*S*) by comparison in retention time of the chiral HPLC analysis with that in the literature [118].

Thus I identified catalyst for α-hydrazination that is superior to the conventional urea and thiourea catalysts **1a** and **1b**. Next, the scope of the 1,3-dicarbonyl compounds was screened and compared to that of urea catalyst **1a** (Table 2.5).

Table 2.5 Hydrazination of **16** and *tert*-butyl azodicarbozylate by using **5b** or **1b**[a]



16b-i **17b-i**

Entry	**16**	Catalyst	Temp.	Time (h)	**17**	Yield (%)[b]	ee (%)[c]
1	 **16b**	**5b**	−78 °C	5	**17b**	94	91
2	 **16c**	**1b**	−78 °C	4	**17c**	93	90
3	 **16d**	**5b**	−40 °C	8	**17d**	99	92
4	 **16e**	**1b**	−78 °C	15	**17e**	96	91
5	 **16f**	**5b**	rt	78	**17f**	86	81
6	 **16g**	**1b**	−40 °C	48	**17g**	90	90
7	 **16h**	**5b**	−78 °C	16	**17h**	87	94
8	**16h**	**1b**	−78 °C	3	**17h**	97	80
9	 **16i**	**5b**	−78 °C	3	**17i**	Quant	88
10	**16i**	**1b**	−78 °C	10 min	**17i**	93	73

[a] The reactions were conducted with **16** (1.1 equiv.) di-*tert*-butyl diazodicarboxylate (1.0 equiv.) and the catalysts (10 mol %) in toluene

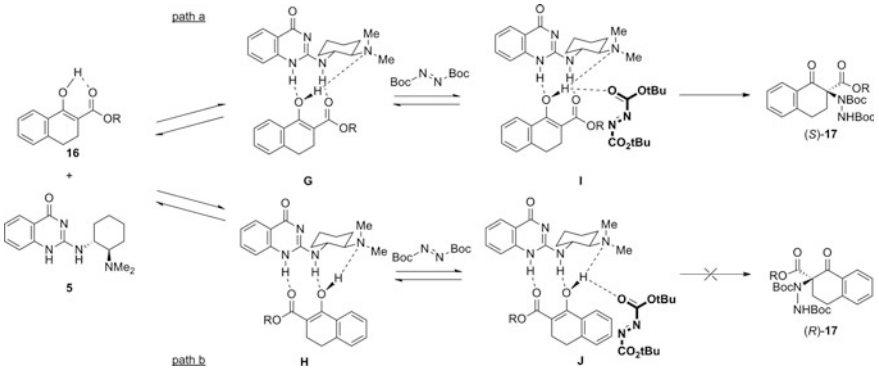
[b] Isolated yield

[c] Determined by chiral HPLC analysis

I first examined five-membered cycles fused with a benzene ring as nucleophiles. With quinazoline catalyst **5b**, even sterically less-hindered methyl ester **16b** could be used and the desired aminated compound **17b** was produced in 94 % yield and 91 % ee (entry 1). In the reaction catalyzed by urea catalyst **1b**, a bulky *tert*-butyl ester was required as a substrate to achieve high enantioselectivity (entry 2). Less-bulky monocyclic ester **16d**, which is so reactive that the reaction should be performed at –78 °C to maintain high stereoselectivity in **1b**-catalyzed amination, gave the adduct **17d** in higher ee even at elevated temperature in the presence of **5b** (entries 3 and 4). Although the seven-membered substrate **16f** was less reactive, a prolonged reaction time led to a good chemical yield with a reasonable ee value (entry 5). In **1b**-catalyzed reactions, reactive substrates such as 1,3-diketone **16h** and α-cyanoester **16i** led to only moderate stereoselectivities (entries 8 and 10) [34]. However, both **16h** and **16i** reacted smoothly in the presence of **5b** to give **17h** and **17i** in good enantioselectivities, which were significantly better than the results with urea catalyst **1b** (entries 7 and 9).

Since catalysts **5b** and **1b** provided the same enantiomers [34], this reaction was assumed to proceed in a manner similar to that with previously reported HB donor catalysts (Scheme 2.19) [128].

When 1,3-dicarbonyl compound **16** is combined with the catalyst **5**, binary complex **G** or **H** should form. Both complexes can react with *N*,*N*-di-*tert*-butylazodicarboxylate to produce reaction products with different absolute configurations via complexes **I** (path a) and **J** (path b), respectively. Based on a computational analysis, complex **G** was 3.42 kcal/mol more stable than the complex **H**. This difference can be explained by the less movement of the enol proton from the ground state of the substrate. There is another possibility that an ion pair complex of **16** and **5** is formed, however the energy of the ion pair was calculated to be 5.81 kcal/mol less stable than that of **G**. In path a, the enol proton can form a hydrogen bond in almost the same configuration as that of the substrate. In contrast, in path b, the enol proton must be aligned with the opposite side of the ester group during the formation of binary complex **H**. Therefore, path a would be



Scheme 2.19 Proposed mechanism of the asymmetric α-hydrazination catalyzed by quinazoline **5**

more favorable than path b and the products with an (*S*)-configuration would be produced selectively. The HB-donating abilities of urea **1b** and benzothiadiazine **6a** should be greater than that of **5,** and strong HB donation might enhance the stability of the complexes even in path b, which would lead to the undesired enantiomer.

In conclusion, the highly enantioselective α-hydrazination of 1,3-dicarbonyl compounds with the use of novel quinazoline catalysts **6b** was demonstrated. Although quinazoline catalysts have weaker HB-donating ability than other catalysts such as urea **1** or benzothiadiazine **5**, the reaction catalyzed by this catalyst gave the best results among these HB donors. The results showed that the strongest HB donors are not always the best catalysts for asymmetric reactions.

2.3.3 Experimental Section

2.3.3.1 General

All non-aqueous reactions were carried out under a positive atmosphere of argon in dried glassware unless otherwise noted. Solvents were dried and distilled according to standard protocols. Materials were obtained from commercial suppliers and used without further purification except when otherwise noted. All melting points were determined on YANAGIMOTO micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 or 400 MHz, and at 125 or 100 MHz, respectively; Tetramethylsilane (TMS) was used as an internal standard. IR spectra were recorded on a JASCO FT/IR-4100 Fourier-transform infrared spectrometer. Low and High resolution mass spectra were obtained by EI or FAB method. Optical rotations were recorded on a JASCO P-2200 polarimeter with a path length of 1 cm; concentrations are quoted in grams per 100 mL. $[\alpha]_D$ values are measured in 10^{-1} deg cm^2 g^{-1}. Enantiomeric excess was determined by high performance liquid chromatography (HPLC) analysis.

2.3.3.2 Typical Procedure for Enantioselective Hydrazination

To a stirred solution of di-*tert*-butylazodicarboxylate (47.8 mg, 0.21 mmol) in toluene (2.0 mL) at room temperature were added **16a** (46.7 mg, 0.23 mmol) and quinazoline-4 on catalyst **5b** (6.2 mg, 0.021 mmol). After 5 h, the reaction mixture was purified by silica gel column chromatography with hexane/EtOAc (9/1 → 1/1) to afford desired **17a** (83.5 mg, 97 %) as white solids.

(S)-di-tert-butyl 1-(2-(methoxycarbonyl)-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)hydrazine-1,2-dicarboxylate (**17a**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.89–7.70 (br, 1H), 7.49–7.29 (br, 1H), 7.25–7.01 (br, 2H), 6.31 (bs, 1H), 3.72 (s, 3H), 3.50–3.08 (br, 1H), 3.08–2.75 (br, 1H), 2.74–2.43 (br, 1H), 1.38–0.79 (m, 18H); HPLC [Chiralcel OD-H, hexane/2-propanol = 95/5, 0.5 mL/min, $\lambda = 254$ nm, retention times: (major) 15.5 min, (minor) 18.2 min].

The adducts **17a–i** are literature known compounds and the ^{1}H NMR spectrum of these compounds were identical to those of the reported data [118].

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Chapter 3
Development of Hydroxy Thiourea Catalysts

Abstract Two novel bifunctional thioureas bearing hydroxy groups were developed. Initially, asymmetric Michael reactions of γ-hydroxyenones and organoboronic acids were examined using these catalysts. These reactions gave low yields due to the competitive, undesired oxy-Michael reaction when thiourea catalysts bearing a basic amino group were employed. In contrast, with the use of newly designed iminophenol-type catalysts, desired asymmetric Michael reactions proceed smoothly and provide vinyl addition products in high yields and ee's. It was found that both the hydroxy groups in the substrates and the catalyst were necessary for effective catalysis in these reactions. Subsequently, the first highly catalytic, enantioselective Petasis-type reaction of *N*-aryl-α-iminoamides was developed using novel hydroxyether-type thioureas as catalysts. This reaction provides rapid access to unnatural vinyl glycine derivatives in high optical purity.

3.1 Asymmetric Michael Addition of γ-Hydroxyenones and Alkenylboronic Acids

3.1.1 Introduction and Background

The amino thiourea catalysts previously developed by my colleagues and I are recognized as being among the privileged structures in the field of asymmetric organocatalysis [1–6]. A large number of reactions catalyzed by such amino thioureas have been reported since 2003 [7, 8]. However, these reactions are limited to reactive nucleophiles which bear highly acidic protons such as malonates, malononitrile, 1,3-dicarbonyl compounds, or thio acids. This limitation could be attributed to the fact that these catalysts utilize basic amine moieties as activators of the nucleophiles. Therefore, to expand the scope of the nucleophiles

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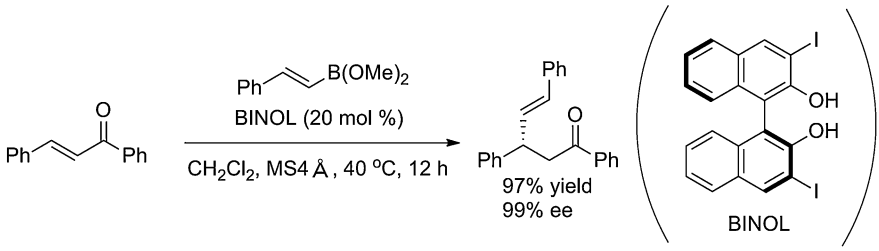
DOI: 10.1007/978-4-431-54231-5_3,



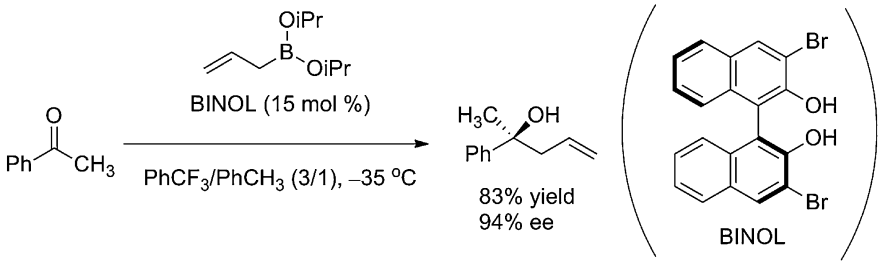
Scheme 3.1 Asymmetric Michael reaction of enones and boronates catalyzed by a BINOL derivative

in the thiourea-catalyzed reactions, I planned to install different functional groups instead of the amino group into bifunctional thioureas.

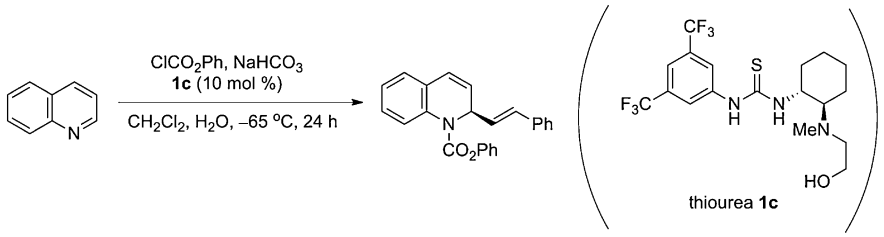
Among the carbon nucleophiles available, organoboronic acids are utilized as one of the most useful carbon nucleophiles in organic reactions due to their stability in air and moisture relative to other typical organometallic reagents such as Grignard reagents [9–11] and organolithium compounds. [12, 13] Therefore, the asymmetric catalytic addition of organoboronic acids to various electrophiles is a powerful tool for the construction of carbon–carbon bonds [14–19]. In addition, alkenyl, alkynyl or aryl boronic acids are readily available, and therefore these nucleophiles are useful for installing sp or sp^2 carbon species directly into the electrophilic molecules. Most of the reported asymmetric catalytic additions with organoboronic acids are performed in the presence of metallic catalysts such as rhodium and chiral phosphine ligands [14–19]. There have been only a few reports on the organocatalyzed asymmetric additions of these species [20–24]. Chong et al. reported the Michael addition of alkenyl boronates to α,β-unsaturated ketones with an electron-deficient BINOL catalyst (Scheme 3.1) [20].

Schaus independently reported the asymmetric 1,2-addition of organoboronic acids by using a BINOL catalyst similar to Chong's catalyst (Scheme 3.2) [24].

In these reactions, the organoboronates should react with the catalyst to form a chiral catalyst-boronate complex, and these species would react with the electrophiles stereo selectively under control of the steric hinderance of the catalysts.



Scheme 3.2 Asymmetric 1,2-addition of allylboronate to ketones catalyzed by a BINOL derivative



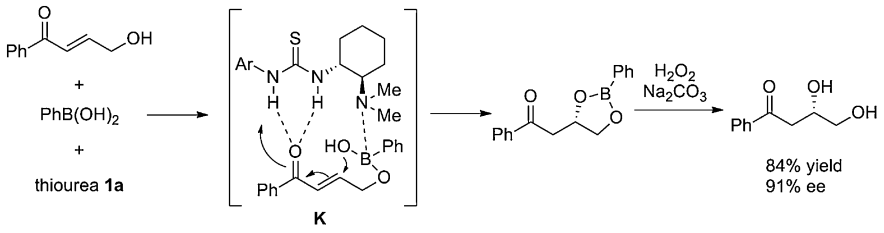
Scheme 3.3 Asymmetric Petasis reaction catalyzed by amino alcohol type thiourea **1c**

At the same time, my colleagues reported that bifunctional amino alcohol thiourea **1c** could be used for the 1,2-addition of organoboronic acids to acylquinolium species (Scheme 3.3) [25]. Although the mechanism of this reaction is not clear, the key factor is speculated to be the formation of the mixed boronates which arise from the catalyst and the organoboronic acids.

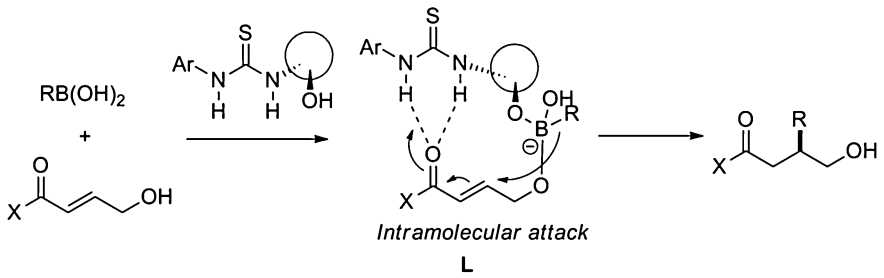
According to these reports, organocatalysts which bear hydroxy groups would be promising as activators of organoboronic acids due to the reversible formation of chiral mixed boronates of the organoboronic acids and the hydroxy catalysts. Therefore, I considered that the development of bifunctional thioureas bearing a hydroxy group would be a valuable research topic for the development of the field of organocatalysis.

In 1993, Petasis reported a Mannich reaction in which organoboronic acids were used as nucleophiles, and found that a three-component reaction of secondary amine, formaldehyde and vinylboronic acids efficiently proceeded even in the absence of catalysts [26]. After this report, many groups, including that of Petasis, addressed this type of reaction [27–30]. For efficient reaction, substrates should have a hydroxy group in their structures. This is because once the organoboronic acids are connected to the substrates covalently, the following nucleophilic attack of the substituents from the boron atom should occur in an intramolecular fashion, which makes the reaction preferable in terms of entropy.

Based on these results, I chose γ-hydroxyenones as promising substrates. At the same time as my research was being conducted, Falck et al. reported a related reaction, which utilized an amino thiourea for the asymmetric oxy-Michael reaction of γ-hydroxyenones (Scheme 3.4) [31].



Scheme 3.4 Asymmetric Oxy-Michael addition



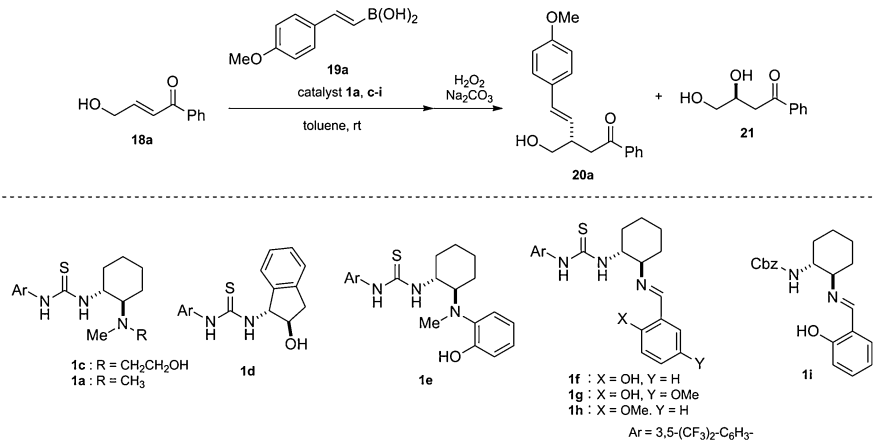
Scheme 3.5 Concept of this work

In this case, they assumed that the substrates should be combined with the organoboronic acids to form the ternary complex **K**. In this complex, the thiourea moiety should form hydrogen bonds with the carbonyl group to enhance the electrophilicity of the Michael acceptor and the amino group should coordinate with the boron atom to increase the nucleophilicity of the oxygen atom. I considered that if the hydroxy thiourea was used as a catalyst, both hydroxy groups of the organoboronic acids should form mixed boronates, but now with substrate and catalyst, leading to complex **L** (Scheme 3.5). The migration of the carbon substituents from the boron atom should occur smoothly to give the desired Michael adducts. In this section, I studied the asymmetric Michael reaction of organoboronic acids by double activation using two covalent bonds [32].

3.1.2 Results and Discussion

Based on the above-described hypothesis, Michael addition of γ-hydroxyphenylketone **18a** and *p*-methoxyphenylvinyl boronic acid **19a** was investigated (Table 3.1). In the presence of amino alcohol-type thiourea **1c**, which had been developed previously, [25] the desired Michael adduct **20a** was indeed obtained in moderate yield, although the enantiomeric excess of **20a** was low (36 % ee). As described in the Introduction and Background section of this section, the oxy-Michael addition of arylboronic acids to **18a** catalyzed by the amino thiourea was reported by Falck et al. [31]. In their reaction, the obtained Michael adduct was converted to diol **21** under an oxidative workup with H_2O_2 and Na_2CO_3. When the reaction mixture was treated with these reagents, diol **21** was isolated in 22 % yield with 64 % ee along with 52 % of the desired product **20a** (entry 1). The same reaction with **1a** [33–37] gave the diol **21** exclusively in high yield with 88 % ee (entry 2). These results suggest that the basic amine might promote the formation of the diol, while the alcohol moiety promotes the production of vinyl adduct **20a**. Therefore, several thioureas which bear a hydroxy group and no basic amino group were examined. Alcoholic thiourea **1d** showed poor reactivity for the Michael addition of the vinylboronic acid, but the production of **21** was completely suppressed (entry 3). The use of thiourea **1e**, which has a more acidic phenolic

Table 3.1 Screening of the catalysts[a]



Entry	Catalyst	Time (h)	**20a**		**21**	
			Yield (%)[b]	ee (%)[c]	Yield (%)[b]	ee (%)[c]
1	**1c**	36	52	36	22	64
2	**1a**	24	<1	–	88	88
3[d]	**1d**	72	20	8	0	–
4	**1e**	72	38	47	0	–
5	**1f**	36	91	95	0	–
6	**1g**	24	92	97	0	–
7	**1h**	72	36	26	16	33
8	**1i**	72	16	14	0	–

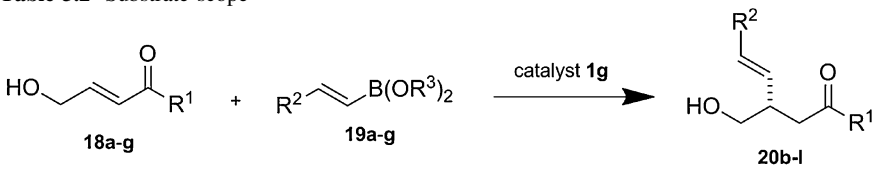
[a] Unless otherwise noted, the reactions were conducted with **18a** (1.0 equiv), **19a** (2.0 equiv) and catalyst **1a**,**c**-**i** (10 mol%) in toluene at room temperature
[b] Yield of isolated product
[c] Determined by chiral HPLC analysis
[d] The catalyst loading was 20 mol%

hydroxy group, resulted in an increase in the chemical yield of **20a** with no production of diol **21** (entry 4). Based on these results, I next screened phenol thiourea catalysts. As a result, it was found that imino thiourea **1f** provided the desired vinyl adduct **20a** in good yield and high ee (entry 5). Thiourea **1g**, which is derived from 2-hydroxy-5-methoxy benzaldehyde, showed increased reactivity in this reaction (entry 6). To investigate the role of the hydroxy group and thiourea moiety of the catalyst, catalysts **1h** and **1i** were synthesized. However, these catalysts gave diminished yield and ee and it was proven that both moieties are essential (entries 7 and 8).

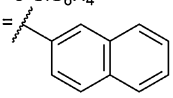
Having established that catalyst **1g** is optimal for this Michael addition, I next screened several γ-hydroxyenones **18b–g** and organoboronic acids **19a–g** (Table 3.2).

First, the four substrates **18b–e** with different substituents at the *para* position of the phenyl group were treated with *p*-methoxyphenylvinylboronic acid **19a** in

Table 3.2 Substrate scope[a]



18a : R^1 = Ph
18b : R^1 = 4-FC_6H_4
18c : R^1 = 4-BrC_6H_4
18d : R^1 = 4-MeC_6H_4
18e : R^1 = 4-ClC_6H_4
18f : R^1 = 3-ClC_6H_4
18g : R^1 =



19a : R^2 = 4-$MeOC_6H_4$, R^3 = H
19b : R^2 = 4-$MeOC_6H_4$, R^3 = Et
19c : R^2 = Ph, R^3 = Et
19d : R^2 = 3,4-di$MeOC_6H_3$, R^3 = H
19e : R^2 = 4-MeC_6H_4, R^3 = H
19f : R^2 = 4-ClC_6H_4, R^3 = Et
19g : R^2 =

R^3 = H

Entry	18	19	Time (h)	Product	Yield (%)[b]	ee (%)[c]
1	**18b**	**19a**	24	**20b**	81	97
2	**18c**	**19a**	24	**20c**	84	94
3	**18d**	**19a**	24	**20d**	86	95
4	**18e**	**19a**	24	**20e**	95	94
5	**18f**	**19a**	24	**20f**	94	77
6	**18f**	**19b**	24	**20f**	82	97
7	**18g**	**19a**	36	**20g**	91	92
8[d]	**18a**	**19c**	72	**20h**	79	92
9	**18a**	**19d**	24	**20i**	99	98
10	**18a**	**19e**	36	**20j**	87	92
11[d]	**18a**	**19f**	72	**20k**	64	93
12	**18a**	**19 g**	24	**20l**	84	91

[a] Unless otherwise noted, the reactions were conducted with **18** (1.0 equiv), **19** (2.0 equiv) and catalyst **1g** (10 mol%) in toluene at room temperature
[b] Yield of isolated product
[c] Determined by chiral HPLC analysis
[d] Catalyst loading was 20 mol%

the presence of imino thiourea **1g** to give the desired products **20b–e** in good yield and ee's (entries 1-4). In the case of *meta*-substituted substrate **18f**, the reaction with **19a** and **1g** gave slightly diminished enantioselectivity (entry 5). It was found that less reactive ethylboronate **19b** improved the stereoselectivity considerably (entry 6). Substrate **18g** with a bulky naphthyl group also gave a good result (entry 7). With regard to the boronic acids, the electrodensity of the reagents significantly affected the yield. When relatively electron-deficient nucleophiles **19c** and **19f** were used in this reaction, 20 mol% of catalyst **1g** and a prolonged reaction time were necessary to achieve a good yield (entries 8 and 11) [38]. In contrast, the electron-rich nucleophiles **19d** and **19e** gave good results under the same reaction

conditions as with **19a** (entries 9,10). In addition, the heteroaromatic vinylboronic acid **19g** could be used for this transformation (entry 12).

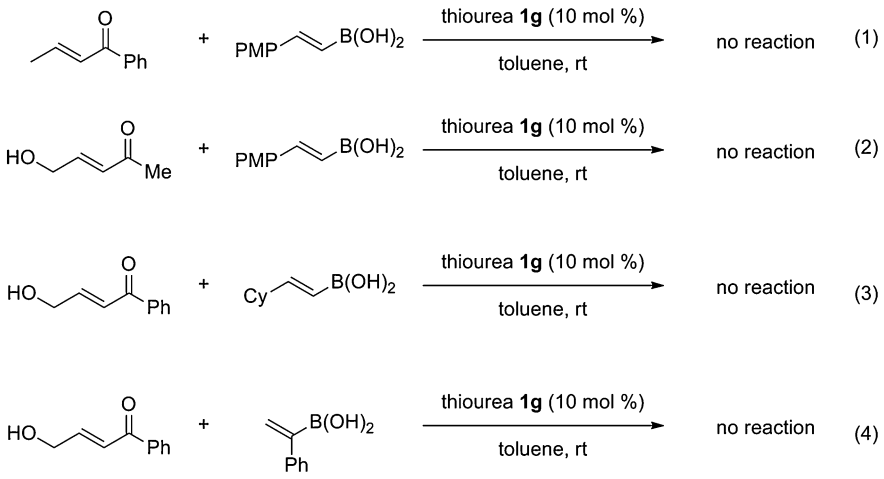
Having established the scope of the reaction, I conducted a mechanistic investigation. From the result shown in Table 3.1, entry 7, it was concluded that the formation of boronates between the organoboronic acids and the hydroxy thiourea is necessary in this reaction. At the same time, the hydroxy groups of the substrates are also necessary (Scheme 3.6, Eq. 1.). It was also found that the use of a methyl ketone moiety in place of phenyl ketone is not tolerated in the reaction (Scheme 3.6, Eq. 2). In addition, 2-cyclohexylvinyl boronic acid and 1-phenyl vinylboronic acid could not be used for this reaction (Scheme 3.6, Eqs. 3 and 4). These results imply that both the phenyl group of the substrates and the β-position of the vinyl boronic acids are important in the reaction.

Based on these results, a plausible reaction mechanism was derived (Scheme 3.7).

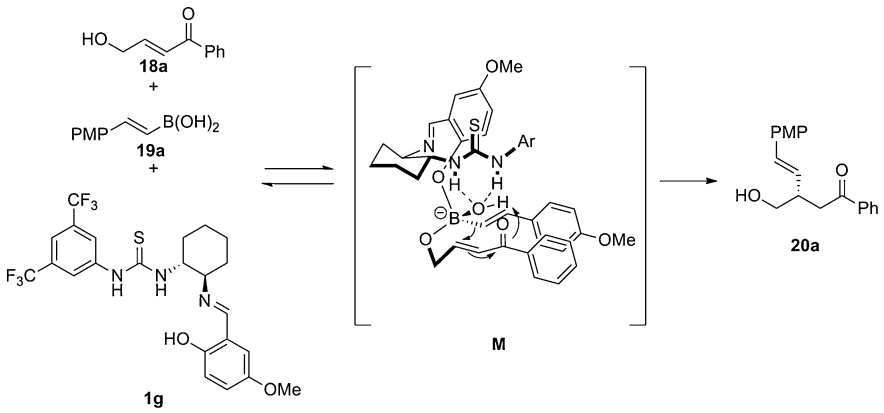
Substrates **18a**, organoboronic acid **19a** and hydroxy thiourea **1g** would form the ternary complex **M** with two covalent bonds. After the Michael addition, the hydroxy group on the boron atom should act as a protonating reagent. Here, I assume that the oxygen atom of the hydroxy group would also interact with the thiourea moiety to stabilize the ternary complex **M**.

Next, the absolute configuration of the Michael adducts was determined (Scheme 3.8). The absolute configuration and the specific rotation of **22** is literature known [39], therefore I tried to convert **20h** to **22** (Scheme 3.8, Eq. 1).

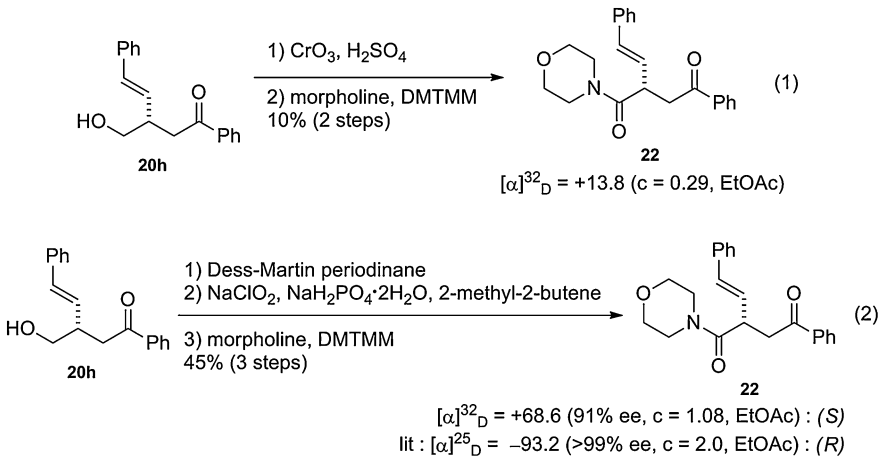
Jones oxidation [40] and condensation with morpholine in the presence of DMTMM [41] gave the desired product **22**. The chemical yield of these reactions was poor and the specific rotation of **22** which was prepared in this way was considerably lower than that reported in the literature. It was suspected that significant racemization would occur under the Jones reaction conditions. Therefore,



Scheme 3.6 Mechanistic studies

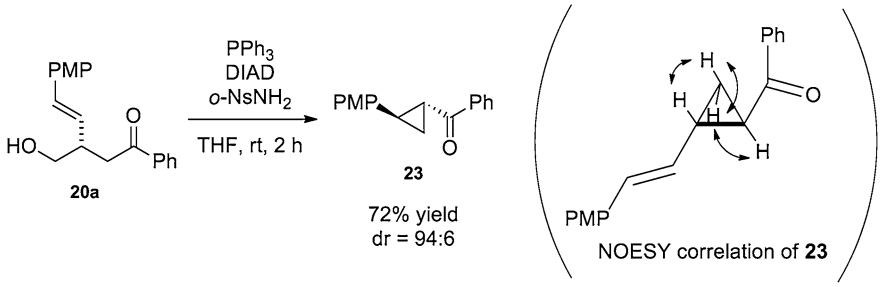


Scheme 3.7 Plausible reaction mechanism



Scheme 3.8 Determination of the absolute configuration

to avoid racemization under harsh conditions, the oxidation was conducted under milder conditions (Scheme 3.8, Eq. 2). When **20h** was treated with Dess-Martin periodinane [42], the corresponding aldehyde was obtained without significant decomposition of the substrate. This aldehyde could be oxidized under Pinnick oxidation conditions [43] to afford the carboxylic acid. Finally, this carboxylic acid was condensed with morpholine under the same conditions as before to obtain the desired morpholine amide **22**. In these sequential reactions, the chemical yield was 45 % overall, which was notably better than that of the Jones oxidation-condensation route. From chiral HPLC analysis, the enantiomeric excess of the obtained compound was 91 %, and thus it was concluded that significant loss of the enantiopurity was avoided. The comparison of the specific rotation of **22** with



Scheme 3.9 Cyclopropanation of Michael adduct **20a**

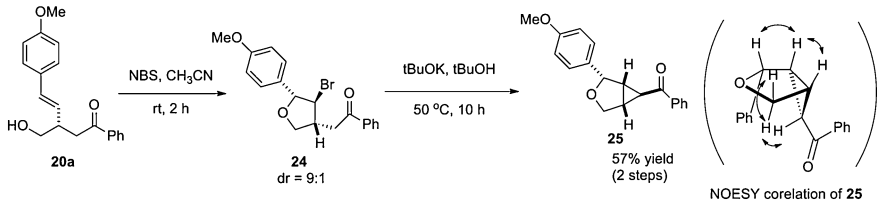
that reported in the literature showed that the Michael adduct **20h** has an *S*-configuration.

Next the transformation of the Michael adduct **20a** into unique cyclic compounds was explored. Unexpectedly, the reaction of Michael adduct **20a** with *o*-nitrobenzenesulfonamide under Mitsunobu conditions [44] produced the cyclopropyl ketone **23** in 72 % yield with high diastereoselectivity (Scheme 3.9). From the NOESY spectrum analysis, the major diastereoisomer was found to have the *anti* relative configuration.

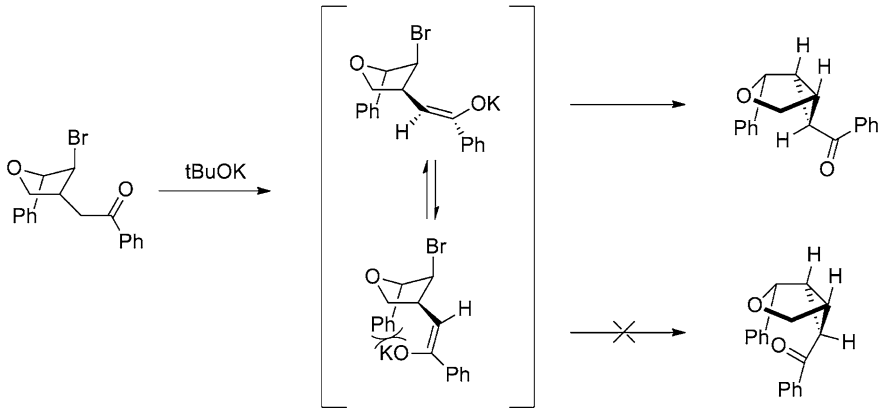
In addition, bromination of the olefin moiety of **20a** with *N*-bromosuccinimide followed by intramolecular etherification provided the bromotetrahydrofurane **24** as a 9:1 diastereomixture. Without purification, this compound was treated with *t*-BuOK to provide the bicyclic [3.1.0] compound **25** in 57 % yield over two steps from **20a** (Scheme 3.10). The relative stereochemistry of **25** was determined by NOESY analysis.

The cyclopropanation from **24** into **25** occured under rate transition state control to give the depicted compound **25**. The formation of the other cyclopropane product was inhibited by steric repulsion (Scheme 3.11). Therefore only one of the possible diastereomers was observed.

In summary, thiourea catalyst **1g** bearing a hydroxy group was developed. By using this catalyst and the activation methodology involving two covalent bonds, the scope of the thiourea-catalyzed asymmetric reactions was successfully expanded into the field of organoboron reagents. The Michael adducts obtained were successfully transformed into cyclopropyl and bicyclic compounds.



Scheme 3.10 Haloetherification-cyclopropanation of Michael adduct **20a**



Scheme 3.11 Rationalization of the stereoselectivity in the intramolecular S_N2 reaction

3.1.3 Experimental Section

3.1.3.1 General

All non-aqueous reactions were carried out under a positive atmosphere of argon in dried glassware unless otherwise noted. Solvents were dried and distilled according to standard protocols. Materials were obtained from commercial suppliers and used without further purification except when otherwise noted. All melting points were determined on YANAGIMOTO micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 or 400 MHz, and at 125 or 100 MHz, respectively; Tetramethylsilane (TMS) was used as an internal standard. IR spectra were recorded on a JASCO FT/IR-4100 Fourier-transform infrared spectrometer. Low and High resolution mass spectra were obtained by EI or FAB method. Optical rotations were recorded on a JASCO P-2200 polarimeter with a path length of 1 cm; concentrations are quoted in grams per 100 mL. $[\alpha]_D$ values are measured in 10^{-1} deg cm^2g^{-1}. Enantiomeric excess was determined by high performance liquid chromatography (HPLC) analysis.

The organoboronates **19b**,**c** and **f** were prepared according to the literature procedure [20, 22].

3.1.3.2 Experimental Procedure for the Synthesis of the Catalyst 1e

The catalyst **1e** was prepared from (1*R*,6*S*)-7-{(*R*)-1-phenylethyl}-7-azabicyclo [4.1.0]heptane via four steps.

A mixture of (1*R*,6*S*)-7-{(*R*)-1-phenylethyl}-7-azabicyclo[4.1.0]heptane (4.12 g, 20.5 mmol), oxazolidine (3.04 g, 22.6 mmol) in MeCN (30 mL) was added $LiClO_4$ (2.40 g, 22.6 mmol) at 0 °C. After the reaction mixture was heated

under reflux for 24 h, the reaction mixture was extracted with $CHCl_3$, dried over Na_2SO_4, evaporated in vacuo to give diaminocyclohexane derivative. A solution of this compound in MeOH (100 mL) was added 10 % PdOH/C (2.00 g) at room temperature under H_2 atmosphere. After being stirred at the same temperature for 3 h, the reaction mixture was filtered through Celite, evaporated in vacuo to give debenzylated diaminocyclohexane derivative. A solution of this compound in THF (150 mL) was added $LiAlH_4$ (4.52 g, 119 mmol) at 0°C. After being stirred at room temperature for 24 h, the reaction mixture was filtered through Celite, evaporated in vacuo to give crude reaction product. A solution of this crude product and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (87.0 mL, 0.477 mmol) in THF (4.0 mL) was stirred at room temperature for 24 h. Then the reaction mixture was evaporated in vacuo, the resulting solid was recrystallized from hexane and ethylacetate to give the thiourea **1e** (93.7 mg, 0.191 mmol, 0.93 %).

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((2*R*)-2-((2-hydroxyphenyl)(methyl) amino)cyclohexyl)thiourea (**1e**): White solids; mp 170–171 °C (hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (brs, 1H), 7.77 (s, 2H), 7.67 (s, 1H), 7.08 (d, $J = 7.8$ Hz, 1H), 6.95 (dd, $J_1 = J_2 = 7.8$ Hz, 1H), 6.84 (dd, $J_1 = J_2 = 7.8$ Hz, 1H), 6.74 (d, $J = 7.8$ Hz, 1H), 6.59 (d, $J = 7.1$ Hz, 2H), 4.51-4.43 (m, 1H), 2.85 (ddd, $J_1 = J_2 = 11.7$ Hz, $J_3 = 3.6$ Hz, 1H), 2.73 (s, 3H), 2.55-2.46 (m, 1H), 1.93-1.76 (m, 2H), 1.74-1.61 (m, 2H), 1.46-1.31 (m, 1H), 1.24-1.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 149.7, 139.3, 139.0, 132.6 (q, $J = 34$ Hz), 124.14, 124.11, 123.7 (q, $J = 216$ Hz), 121.4, 119.2, 118.7, 114.9, 65.4, 56.2, 34.2, 32.7, 26.3, 25.0, 24.6; IR (KBr) ν 3277, 2940, 1560 cm^{-1}; MS (FAB$^+$) 492 (M + H$^+$, 100); HRMS (FAB$^+$) Calcd. for $C_{22}H_{24}F_6N_3OS$: 492.1544, Found: 492.1547; $[\alpha]^{27}{}_D$ + 109.9 (c 0.30, $CHCl_3$).

3.1.3.3 General Procedure for the Synthesis of the Catalyst 1f-i

A solution of 1-{(1*R*,2*R*)-2-aminocyclohexyl}-3-{3,5-bis(trifluoromethyl)phenyl} thiourea or benzyl {(1*R*,2*R*)-2-aminocyclohexyl}carbamate (1.87 mmol) [45] and appropriate benzaldehyde (1.87 mmol) in MeOH (5.0 mL) was stirred at room temperature for 24 h. Then the reaction mixture was evaporated in vacuo to give the imino-thiourea **1f–1h** or imino carbamate **1i**.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*R*,2*R*)-2-((*E*)-2-hydroxybenzylideneamino)cyclohexyl)thiourea (**1f**): Yellow amorphous; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.7 (brs, 1H), 8.45 (s, 1H), 7.74 (s, 2H), 7.59 (s, 1H), 7.35 (dd, $J_1 = J_2 = 8.1$ Hz, 1H), 7.30-7.25 (m, 3H), 6.92 (dd, $J_1 = J_2 = 8.1$ Hz, 1H), 6.24 (brs, 1H), 4.13-3.75 (m, 1H), 3.19-3.08 (m, 1H), 2.30-2.21 (m, 1H), 1.98-1.86 (m, 2H), 1.82-1.70 (m, 1H), 1.67-1.54 (m, 2H), 1.50-1.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7, 174.0, 158.4, 152.9, 133.4, 127.0, 125.2, 124.8 (q, $J = 35$ Hz), 115.2 (q, $J = 276$ Hz), 111.0, 110.6, 51.2, 25.9, 24.1, 17.4, 16.7, 11.1; IR (KBr) ν 3270, 2939, 1633, 1536 cm^{-1}; MS (FAB$^+$) 490 (M + H$^+$, 100); HRMS (FAB$^+$) calcd for $C_{22}H_{22}F_6N_3OS$: 490.1388, Found: 490.1389; $[\alpha]^{27}{}_D$ − 118.1 (c 1.03,$CHCl_3$).

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*R*,2*R*)-2-((*E*)-2-hydroxy-5-methoxybenzylideneamino)cyclohexyl)thiourea (**1g**): Yellow amorphous; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.3 (brs, 1H), 8.35 (s, 1H), 7.70 (s, 2H), 7.54 (s, 1H), 6.89 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.2$ Hz, 1H), 6.83 (brs, 1H), 6.77 (d, $J = 8.8$ Hz, 1H), 6.73 (d, $J = 2.2$ Hz, 1H), 3.72 (s, 3H), 3.24-3.07 (m, 1H), 2.24-2.11 (m, 1H), 1.96-1.65 (m, 3H), 1.50-1.19 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 180.6, 165.6, 155.0, 152.3, 139.9, 131.7, 125.3 (q, $J = 25$ Hz), 122.9 (q, $J = 271$ Hz), 120.5, 117.9, 117.8, 115.2, 77.2, 58.6, 55.7, 33.2, 31.4, 24.4, 23.7; IR (KBr) ν 3354, 2939, 1728, 1633, 1535 cm^{-1}; MS (FAB$^+$) 521 (M + H$^+$, 100); HRMS (FAB$^+$) calcd for $C_{23}H_{25}F_6N_3O_2S$: 521.1572, Found: 521.1573; $[\alpha]^{27}{}_D$ − 78.0 (c 1.01, $CHCl_3$).

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*R*,2*R*)-2-((*E*)-2-hydroxy-4-methoxybenzylideneamino)cyclohexyl)thiourea (**1h**): Yellow amorphous; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (brs, 1H), 8.78 (s, 1H), 7.85-7.74 (m, 2H), 7.75 (s, 2H), 7.55 (s, 1H), 7.46 (dd, $J_1 = J_2 = 8.3$ Hz, 1H), 7.04-6.92 (m, 1H), 6.44 (brs, 1H), 3.96-3.81 (m, 1H), 3.87 (s, 3H), 3.29-3.21 (m, 1H), 2.22-2.15 (m, 1H), 1.90-1.73 (m, 2H), 1.70-1.58 (m, 2H), 1.49-1.30 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9, 176.1, 153.1, 152.0, 134.5, 128.9, 126.4, 124.4 (q, $J = 27$ Hz), 121.6, 116.4, 116.1 (q, $J = 248$ Hz), 113.9, 113.6, 111.0, 68.4, 53.5, 48.6, 27.1, 17.7, 16.9; IR (KBr) ν 3241, 2938, 1635, 1543 cm^{-1}; MS (FAB$^+$) 504 (M + H$^+$, 100); HRMS (FAB$^+$) calcd for $C_{23}H_{24}F_6N_3OS$: 504.1544, Found: 504.1548; $[\alpha]^{27}{}_D$ + 74.1 (c 1.01, $CHCl_3$).

Benzyl (1*R*,2*R*)-2-((*E*)-2-hydroxybenzylideneamino)cyclohexylcarbamate (**1i**): Yellow amorphous; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.2 (brs, 1H), 8.29 (s, 1H), 7.40-7.15 (m, 5H), 7.03-6.84 (m, 4H), 4.97 (s, 2H), 4.71 (s, 1H), 3.68-3.60 (m, 1H), 3.21-2.97 (m, 1H), 2.24-2.08 (m, 1H), 1.95-1.61 (m, 4H), 1.48-1.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 161.1, 155.6, 136.5, 132.2, 131.3, 128.4, 128.0, 127.9, 118.7, 118.4, 117.1, 72.2, 66.5, 54.7, 33.4, 31.4, 24.6, 23.9; IR (KBr) ν 2940, 1690, 1637, 1529 cm^{-1}; MS (FAB$^+$) 353 (M + H$^+$, 100); HRMS (FAB$^+$) calcd for $C_{21}H_{25}N_2O_3$: 353.1865, Found: 353.1867; $[\alpha]^{27}{}_D$ − 31.5 (c 1.77, $CHCl_3$).

3.1.3.4 General Procedure for the Synthesis of the Substrates 18

To a solution of appropriate stabilized ylide (7.5 mmol) in THF (20 mL) was added glycolaldehyde dimer (6.0 mmol), and the resulting solution was heated under reflux for 3 h. The solution was cooled and the solvent was evaporated in vacuo. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc = 1/1) to give the γ-hydroxyenone **18**.

(*E*)-4-hydroxy-1-phenylbut-2-en-1-one (**18a**): White solids; mp 74–76 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, $J = 6.9$ Hz, 2H), 7.56 (dd, $J_1 = J_2 = 6.9$ Hz, 1H), 7.46 (dd, $J_1 = J_2 = 6.9$ Hz, 2H), 7.22 (dt, $J_1 = 15.5$ Hz, $J_2 = 2.3$ Hz, 1H), 7.11 (dt, $J_1 = 15.5$ Hz, $J_2 = 3.5$ Hz, 1H), 4.47 (s, 2H), 2.47 (brs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.6, 147.3, 137.6, 132.9, 128.60, 128.57, 123.7, 62.3; IR (KBr) ν 3437, 1659, 1610 cm^{-1}; MS (FAB$^+$) 163

($M + H^+$, 88), 107 (100); Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21; Found: C, 73.94; H, 6.27.

3.1.3.5 Typical Procedure for Asymmetric Michael addition

To a mixture of γ-hydroxyenone **18a** (52.5 mg, 0.324 mmol) in toluene (1.6 mL) were added 4-methoxyphenylvinylboronic acid **19a** (115 mg, 0.648 mmol) and catalyst **1** (0.0324 mmol) at room temperature (Table 3.1). After being stirred at the same temperature for several hours, the reaction mixture was added aqueous hydrogen peroxide (0.1 mL, 30 % in water) and saturated sodium carbonate solution (1 mL). The reaction mixture was stirred at room temperature for 15 min, before quenching with saturated $NaHCO_3$-$Na_2S_2O_3$ solution (5/1, v/v, 5 mL). After stirring for 10 min, the mixture was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc = 4/3 to 1/10) to give **20a** and **21** respectively. The ^{1}H NMR spectrum of **21** was identical to that of the reported data.[44]

(*S*,*E*)-3-(Hydroxymethyl)-5-(4-methoxyphenyl)-1-phenylpent-4-en-1-one (**20a**): White solids; mp 80–82 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, $J = 7.5$ Hz, 2H), 7.57 (dd, $J_1 = J_2 = 7.5$ Hz, 1H), 7.46 (dd, $J_1 = J_2 = 7.5$ Hz, 2H), 7.27 (d, $J = 9.2$ Hz, 2H), 6.83 (d, $J = 9.2$ Hz, 2H), 6.47 (d, $J = 15.5$ Hz, 1H), 6.01 (dd, $J_1 = 15.5$ Hz, $J_2 = 8.0$ Hz, 1H), 3.79 (s, 3H), 3.75-3.68 (m, 2H), 3.24 (dd, $J_1 = 17.8$ Hz, $J_2 = 8.6$ Hz, 1H), 3.15 (dd, $J_1 = 17.8$ Hz, $J_2 = 6.3$ Hz, 1H), 3.19-3.13 (m, 1H), 1.85 (brs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.4, 159.1, 137.1, 133.1, 131.5, 129.7, 128.6, 128.2, 127.4, 127.3, 113.9, 65.7, 55.3, 41.3, 40.6; IR (KBr) ν 3442, 1681, 1605, 1176 cm^{-1}; MS (FAB^+) 297 ($M + H^+$, 25), 105 (100); Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80; Found: C, 76.71; H, 6.77; HPLC [Chiralcel OD-H, hexane/2-propanol = 85/15, 0.5 ml/min, $\lambda = 254$ nm, retention times: (major) 23.9 min (minor) 28.8 min]; $[\alpha]^{24}_D$ + 61.9 (c = 1.05, $CHCl_3$, 95 % ee).

(*E*)-1-(4-Fluorophenyl)-4-hydroxybut-2-en-1-one (**18b**): White solids; mp 52–53 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (dd, $J_1 = 7.5$ Hz, $J_2 = 5.8$ Hz, 2H), 7.27-7.10 (m, 4H), 4.48 (dd, $J_1 = J_2 = 1.2$ Hz, 2H), 2.15 (brs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.8, 165.7 (d, $J = 255$ Hz), 147.3, 133.9, 131.2 (d, $J = 9.6$ Hz), 123.3, 115.7 (d, $J = 21.6$ Hz), 62.3; IR (KBr) ν 3446, 1664, 1616 cm^{-1}. MS (FAB^+) 181 ($M + H^+$, 100); Anal. Calcd. for $C_{10}H_9FO_2$: C, 66.66; H, 5.03; Found: C, 66.48; H, 5.14.

(*E*)-1-(4-Bromophenyl)-4-hydroxybut-2-en-1-one (**18c**): White solids; mp 77–78 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, $J = 8.6$ Hz, 2H), 7.62 (d, $J = 8.6$ Hz, 2H), 7.21-7.12 (m, 2H), 4.49 (dd, $J_1 = 5.2$ Hz, $J_2 = 1.7$ Hz, 2H), 1.74 (dd, $J_1 = J_2 = 5.7$ Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.5, 148.0, 136.2, 131.9, 130.1, 128.2, 123.1, 62.2; IR (KBr) ν 3429, 1665, 1612 cm^{-1}. MS (FAB^+) 241 ($M + H^+$, 100); Anal. Calcd. for $C_{10}H_9BrO_2$: C, 49.82; H, 3.76; Found: C, 49.59; H, 3.65.

(*E*)-4-Hydroxy-1-*p*-tolylbut-2-en-1-one (**18d**): Yellow solids; mp 44–45 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.6 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H), 7.21 (dt, J_1 = 15.5 Hz, J_2 = 1.7 Hz, 1H), 7.11 (dt, J_1 = 15.5 Hz, J_2 = 3.5 Hz, 1H), 4.46 (dd, J_1 = 3.5 Hz, J_2 = 1.7 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.1, 146.7, 143.8, 135.0, 129.3, 128.8, 123.7, 62.3, 21.6; IR (KBr) ν 3425, 1664, 1613 cm^{-1}. MS (FAB$^+$) 177 (M + H$^+$, 100); Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86; Found: C, 74.68; H, 6.77.

(*E*)-1-(4-Chlorophenyl)-4-hydroxybut-2-ene-1-one (**18e**): Yellow solids; mp 35–36 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 7.6 Hz, 2H), 7.43 (d, J = 7.6 Hz, 2H), 7.21-7.09 (m, 2H), 4.47 (d, J = 1.5 Hz, 2H), 2.61 (brs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.3, 140.9, 132.5, 128.9, 123.0, 121.9, 116.2, 55.2; IR (KBr) ν 3442, 1671, 1625 cm^{-1}. MS (FAB$^+$) 139 (M + H$^+$, 100); Anal. Calcd. for $C_{10}H_9ClO_2$: C, 61.08; H, 4.61; Found: C, 61.17; H, 4.61.

(*E*)-1-(3-Chlorophenyl)-4-hydroxybut-2-ene-1-one (**18f**): Yellow solids; mp 57–58 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.83 (d, J = 7.5 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.41 (dd, J_1 = J_2 = 7.5 Hz, 1H), 7.23-7.12 (m, 2H), 4.49 (s, 2H), 2.55 (brs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.2, 148.1, 139.1, 134.9, 132.9, 129.9, 128.6, 126.6, 123.2, 62.2; IR (KBr) ν 3467, 1667, 1626 cm^{-1}. MS (FAB$^+$) 197 (M + H$^+$, 33), 73 (100); HRMS (FAB$^+$) $C_{10}H_{10}ClO_2$: 197.0369, Found: 197.0368.

(*E*)-4-Hydroxy-10-(naphthalene-2-yl)but-2-ene-1-one (**18g**): Yellow solids; mp 74–75 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.05 (d, J = 8.6 Hz, 1H), 7.94 (d, J = 7.5 Hz, 1H), 7.89 (d, J = 8.6 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.59 (dd, J_1 = J_2 = 7.5 Hz, 1H), 7.54 (dd, J_1 = J_2 = 7.5 Hz, 1H), 7.40 (d, J = 15.5 Hz, 1H), 7.21 (dt, J_1 = 15.5 Hz, J_2 = 2.9 Hz, 1H), 4.52 (d, J = 2.9 Hz, 2H), 2.21 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.2, 150.0, 135.5, 134.9, 132.5, 130.3, 129.5, 128.54, 128.46, 127.8, 126.8, 124.3, 123.6, 62.4; IR (KBr) ν 3479, 1666, 1617 cm^{-1}. MS (FAB$^+$) 213 (M + H$^+$, 100); HRMS (FAB$^+$) $C_{14}H_{13}O_2$: 213.0916. Found: 213.0914.

3.1.3.6 Typical Procedure for Asymmetric Michael addition

To a mixture of γ-hydroxyenone **18a** (156 mg, 0.964 mmol) in toluene (5.0 mL) were added phenylvinylboronic acid diethyl ester **19c** (393 mg, 1.93 mmol) and catalyst **1g** (100 mg, 0.193 mmol) at room temperature (Table 3.2). After being stirred at the same temperature for 72 h, the reaction mixture was purified by silica gel column chromatography (hexane/EtOAc = 4/3) to give **20h** (189 mg, 79 %).

(*S*,*E*)-1-(4-Fluorophenyl)-3-(hydroxymethyl)-5-(4-methoxyphenyl)pent-4-en-1-one (**20b**): White solids; mp 89–90 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (dd J_1 = 8.6 Hz, J_2 = 5.8 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H), 7.13 (dd, J_1 = J_2 = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.47 (d, J = 16.0 Hz, 1H), 6.00 (dd, J_1 = 16.0 Hz, J_2 = 6.0 Hz, 1H), 3.80 (s, 3H), 3.75-3.68 (m, 2H), 3.28-3.20 (m, 1H), 3.18-3.09 (m, 2H), 1.79 (dd, J_1 = J_2 = 6.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8, 165.7 (d, J = 256.0 Hz), 159.1, 133.5, 131.5, 130.8 (d,

J = 9.7 Hz), 129.6, 127.3, 127.2, 114.6 (d, J = 21.6 Hz), 113.9, 65.6, 55.2, 41.3, 40.4; IR (KBr) ν 3554, 1680 cm^{-1}; MS (FAB^+) 315 ($M + H^+$, 38), 123 (100); Anal. Calcd. for $C_{19}H_{19}FO_3$: C, 72.60; H, 6.09; Found: C, 72.34; H, 5.91; HPLC [Chiralcel OJ-H, hexane/2-propanol = 80/20, 0.5 ml/min, λ = 254 nm, retention times: (major) 74.9 min (minor) 48.5 min]; $[\alpha]^{26}_D$ + 56.1 (c, 1.23, $CHCl_3$, 93 % ee).

(*S*,*E*)-1-(4-Bromophenyl)-3-(hydroxymethyl)-5-(4-methoxyphenyl)pent-4-en-1-one (**20c**): White solids; mp 90–92 °C (hexane/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 8.6 Hz, 2H), 7.61 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 9.2 Hz, 2H), 6.83 (d, J = 9.2 Hz, 2H), 6.46 (d, J = 16.0 Hz, 1H), 5.99 (dd, J_1 = 16.0 Hz, J_2 = 8.0 Hz, 1H), 3.80 (s, 3H), 3.75-3.68 (m, 2H), 3.22 (dd, J_1 = 14.9 Hz, J_2 = 5.8 Hz, 1H), 3.16-3.08 (m, 2H), 1.74 (dd, $J_1 = J_2$ = 5.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.3, 159.2, 135.8, 131.9, 131.6, 129.7, 129.6, 128.3, 127.3, 127.0, 113.9, 65.6, 55.3, 41.3, 40.4; IR (KBr) ν 3339, 1649 cm^{-1}; MS (FAB^+) 375 ($M + H^+$, 20), 57 (100); Anal. Calcd. for $C_{19}H_{19}BrO_3$: C, 60.81; H, 5.10; Found: C, 60.55; H, 5.20; HPLC [Chiralcel OJ-H, hexane/2-propanol = 90/10, 0.5 ml/min, λ = 254 nm, retention times: (major) 71.0 min (minor) 47.2 min]; $[\alpha]^{26}_D$ + 41.8 (c, 1.02, $CHCl_3$, 92 % ee).

(*S*,*E*)-3-(Hydroxymethyl)-5-(4-methoxyphenyl)-1-p-tolylpent-4-en-1-one (**20d**): White solids; mp 80–81 °C (hexane/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.47 (d, J = 16.0 Hz, 1H), 6.01 (dd, J_1 = 16.0 Hz, J_2 = 7.4 Hz, 1H), 3.79 (s, 3H), 3.75-3.69 (m, 2H), 3.21 (dd, J_1 = 17.8 Hz, J_2 = 8.6 Hz, 1H), 3.17-3.09 (m, 2H), 2.41 (s, 3H), 1.87 (dd, $J_1 = J_2$ = 6.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.0, 159.1, 144.0, 134.5, 131.4, 129.7, 129.3, 128.3, 127.5, 127.3, 113.9, 65.7, 55.2, 41.4, 40.5, 21.6; IR (KBr) ν 3557, 1671 cm^{-1}; MS (FAB^+) 311 ($M + H^+$, 74), 119 (100); Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14; Found: C, 77.14; H, 7.09.; HPLC [Chiralpak AD-H, hexane/ethanol = 70/30, 0.5 ml/min, λ = 254 nm, retention times: (major) 49.4 min (minor) 28.0 min]; $[\alpha]^{27}_D$ + 57.8 (c = 1.89, $CHCl_3$, 93 % ee).

(*S*,*E*)-1-(4-chlorophenyl)-3-(Hydroxymethyl)-5-(4-methoxyphenyl)ent)-4-en-1-one (**20e**): White solids; mp 80–81 °C (hexane/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.6 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 6.45 (d, J = 15.5 Hz, 1H), 5.98 (dd, J_1 = 15.5 Hz, J_2 = 8.0 Hz, 1H), 3.79 (s, 3H), 3.71 (dd, $J_1 = J_2$ = 5.2 Hz, 2H), 3.24 (dd, J_1 = 14.9 Hz, J_2 = 5.8 Hz, 1H), 3.16-3.08 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.6, 159.1, 131.9, 131.7, 130.4, 129.1, 127.4, 127.2, 126.9, 126.7, 113.9, 55.3, 44.9, 41.8; IR (KBr) ν 3355, 1649, 1604 cm^{-1}; MS (FAB^+) 331 ($M + H^+$, 25), 139 (100); HRMS (FAB^+) $C_{19}H_{19}ClO_2$: 314.1068. Found: 314.1069; HPLC [Chiralpak AS-H, hexane/2-propanol = 70/30, 1.0 ml/min, λ = 254 nm, retention times: (major) 24.8 min (minor) 12.1 min (minor)]; $[\alpha]^{28}_D$ + 45.28 (c 1.06, $CHCl_3$, 93 % ee).

(*S*,*E*)-1-(3-chlorophenyl)-3-(Hydroxymethyl)-5-(4-methoxyphenyl)ent)-4-en-1-one (**20f**): Yellow amorphous; ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, $J_1 = J_2$ = 1.7 Hz, 1H), 7.83 (ddd, J_1 = 7.8 Hz, $J_2 = J_3$ = 1.7 Hz, 1H), 7.53

(ddd, $J_1 = 7.8$ Hz, $J_2 = J_3 = 1.7$ Hz, 1H), 7.39 (dd, $J_1 = J_2 = 7.8$ Hz, 1H), 7.26 (d, $J = 7.8$ Hz, 2H), 6.81 (d, $J = 7.8$ Hz, 2H), 6.45 (d, $J = 15.6$ Hz, 1H), 5.99 (dd, $J_1 = 15.6$ Hz, $J_2 = 7.8$ Hz, 1H), 3.78 (s, 3H), 3.76-3.68 (m, 2H), 3.26-3.08 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.0, 152.1, 131.5, 127.9, 126.1, 124.6, 123.0, 122.6, 121.2, 120.3, 120.0, 119.1, 106.9, 58.7, 48.3, 34.4, 33.6; IR (KBr) ν 3458, 1687, 1607 cm^{-1}; MS (FAB$^+$) 313 (M–H_2O, 22), 139 (100); HRMS (FAB$^+$) $C_{19}H_{18}ClO_2$: 313.0990. Found: 313.0989; HPLC [Chiralcel OD-H, hexane/2-propanol = 90/10, 1.0 ml/min, $\lambda = 254$ nm, retention times: (major) 16.1 min (minor) 20.5 min (minor)]; $[\alpha]^{27}_D$ + 40.84 (c 1.26, $CHCl_3$, 97 % ee).

(*S*,*E*)-3-(Hydroxymethyl)-5-(4-methoxyphenyl)-1-(naphthalene-2-yl)pent-4-en-1-one (**20g**): Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.03 (dd, $J_1 = 8.6$ Hz, $J_2 = 2.7$ Hz, 1H), 7.95 (d, $J = 6.9$ Hz, 2H), 7.89 (dd, $J_1 = J_2 = 8.6$ Hz, 2H), 7.60 (dd, $J_1 = J_2 = 6.9$ Hz, 1H), 7.26 (d, $J = 7.5$ Hz, 2H), 6.81 (d, $J = 7.5$ Hz, 2H), 6.50 (d, $J = 15.5$ Hz, 1H), 6.05 (dd, $J_1 = 15.5$ Hz, $J_2 = 8.1$ Hz, 1H), 3.70 (s, 3H), 3.79-3.70 (m, 2H), 3.38 (dd, $J_1 = 15.7$ Hz, $J_2 = 6.9$ Hz, 1H), 3.28 (dd, $J_1 = 15.7$ Hz, $J_2 = 6.9$ Hz, 1H), 3.21 (ddd, $J_1 = 8.1$ Hz, $J_2 = J_3 = 6.9$ Hz, 1H), 1.92 (brs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.4, 159.1, 135.6, 134.3, 132.5, 131.5, 129.9, 129.7, 129.6, 128.53, 128.48, 127.8, 127.4, 127.3, 126.8, 123.9, 65.8, 55.3, 41.5, 40.6; IR (neat) ν 3445, 1679, 1606 cm^{-1}; MS (FAB$^+$) 329 (M–H_2O, 18), 155 (100); HRMS (FAB$^+$) $C_{23}H_{21}O_2$: 329.1536, Found: 329.1538; HPLC [Chiralcel OD-H, hexane/2-propanol = 90/10, 1.0 ml/min, $\lambda = 254$ nm, retention times: (major) 34.5 min (minor) 44.3 min]; $[\alpha]^{27}_D$ + 23.82 (c 0.91, $CHCl_3$, 92 % ee).

(*S*,*E*)-3-(Hydroxymethyl)-1,5-diphenylpent-4-en-1-one (**20h**): White solids; mp 76–77 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, $J = 7.5$ Hz, 2H), 7.57 (dd, $J_1 = J_2 = 7.5$ Hz, 1H), 7.47 (dd, $J_1 = J_2 = 7.5$ Hz, 2H), 7.34 (d, $J = 7.5$ Hz, 2H), 7.29 (dd, $J_1 = J_2 = 7.5$ Hz, 2H), 7.21 (dd, $J_1 = J_2 = 7.5$ Hz, 1H), 6.53 (d, $J = 16.0$ Hz, 1H), 6.17 (dd, $J_1 = 16.0$ Hz, $J_2 = 8.0$ Hz, 1H), 3.79-3.70 (m, 2H), 3.27 (dd, $J_1 = 18.3$ Hz, $J_2 = 8.0$ Hz, 1H), 3.17 (dd, $J_1 = 18.3$ Hz, $J_2 = 6.3$ Hz, 1H), 3.23-3.14 (m, 1H), 1.83 (brs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.3, 137.0, 136.9, 133.2, 132.0, 129.7, 128.6, 128.5, 128.2, 127.4, 126.2, 65.6, 41.3, 40.4; IR (KBr) ν 3274, 1691 cm^{-1}; MS (FAB$^+$) 267 (M + H$^+$, 20), 105 (100); HRMS (FAB$^+$) $C_{18}H_{19}O_2$: 267.1385, Found: 267.1391; HPLC [Chiralpak AS-H, hexane/ethanol = 80/20, 0.5 ml/min, $\lambda = 254$ nm, retention times: (major) 25.8 min (minor) 21.5 min, 93 % ee]; $[\alpha]^{29}_D$ + 47.5 (c 1.03, $CHCl_3$, 93 % ee).

(*S*,*E*)-5-(3,4-Dimethoxyphenyl)-3-(hydroxymethyl)-1-phenylpent-4-en-1-one (**20i**): White solids; mp 85–86 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, $J = 8.1$ Hz, 2H), 7.57 (dd, $J_1 = J_2 = 8.1$ Hz, 1H), 7.47 (dd, $J_1 = J_2 = 8.1$ Hz, 2H), 6.89 (s, 1H), 6.88 (d, $J = 8.0$ Hz, 1H), 6.79 (d, $J = 8.0$ Hz, 1H), 6.47 (d, $J = 16.1$ Hz, 1H), 6.02 (dd, $J_1 = 16.1$ Hz, $J_2 = 8.0$ Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.77-3.70 (m, 2H), 3.27 (dd, $J_1 = 17.8$ Hz, $J_2 = 8.6$ Hz, 1H), 3.20-3.13 (m, 2H), 1.82 (dd, $J_1 = J_2 = 5.7$ Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.3, 148.9, 148.7, 137.0, 133.1, 131.7, 130.0, 128.7, 128.1, 127.6, 119.3, 111.1, 108.6,

65.6, 55.9, 55.8, 41.3, 40.5; IR (KBr) ν 3455, 1685 cm^{-1}; MS (FAB^+) 327 ($M + H^+$, 8), 105 (100); HRMS (FAB^+) $C_{20}H_{23}O_4$: 327.1596, Found: 327.1591; HPLC [Chiralcel OD-H, hexane/2-proanol = 80/20, 0.5 ml/min, $\lambda = 254$ nm, retention times: (major) 28.3 min (minor) 34.3 min]; $[\alpha]^{26}_D + 51.9$ (c 1.11, $CHCl_3$, 98 % ee).

(*S*,*E*)-3-(Hydroxymethyl)-1-phenyl-5-p-tolylpent-4-en-1-one (**20j**): White solids; mp 80–81 °C (hexane/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, $J = 7.3$ Hz, 2H), 7.55 (dd, $J_1 = J_2 = 7.3$ Hz, 1H), 7.47 (dd, $J_1 = J_2 = 7.3$ Hz, 2H), 7.22 (d, $J = 8.1$ Hz, 2H), 7.08 (d, $J = 8.1$ Hz, 2H), 6.48 (d, $J = 15.8$ Hz, 1H), 6.10 (dd, $J_1 = 15.8$ Hz, $J_2 = 7.8$ Hz, 1H), 3.76-3.68 (m, 2H), 3.24 (dd, $J_1 = 18.2$ Hz, $J_2 = 8.6$ Hz, 1H), 3.17-3.10 (m, 2H), 2.33 (brs, 1H), 2.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.4, 137.2, 137.0, 134.1, 133.1, 131.9, 129.2, 128.6, 128.5, 128.1, 126.1, 65.6, 41.3, 40.5, 21.1; IR (KBr) ν 3202, 1678, 1596 cm^{-1}; MS (FAB^+) 281 ($M + H^+$, 6), 105 (100); HRMS (FAB^+) $C_{19}H_{20}O$: 264.1509. Found: 264.1501; HPLC [Chiralcel OD-H, hexane/2-propanol = 90/10, 0.5 ml/min, $\lambda = 254$ nm, retention times: (major) 23.9 min (minor) 29.0 min]; $[\alpha]^{26}_D + 40.8$ (c 1.13, $CHCl_3$, 93 % ee).

(*S*,*E*)-5-(4-Chlorophenyl)-3-(hydroxymethyl)-1-phenylpent-4-en-1-one (**20k**): Yellow amorphous; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, $J = 7.5$ Hz, 2H), 7.57 (dd, $J_1 = J_2 = 7.5$ Hz, 1H), 7.47 (dd, $J_1 = J_2 = 7.5$ Hz, 2H), 7.31-7.17 (m, 4H), 6.48 (d, $J = 16.1$ Hz, 1H), 6.15 (dd, $J_1 = 16.1$ Hz, $J_2 = 8.0$ Hz, 1H), 3.82-3.68 (m, 2H), 3.27-3.23 (m, 1H), 3.22-3.12 (m, 2H), 1.61 (brs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.1, 137.0, 135.4, 133.2, 133.0, 130.8, 130.5, 128.7, 128.6, 128.1, 127.4, 65.6, 41.2, 40.3; IR (neat) ν 3444, 1683, 1596 cm^{-1}; MS (FAB^+) 301 ($M + H^+$, 7), 105 (100); HRMS (FAB^+) $C_{18}H_{16}ClO$: 284.0962, Found: 284.0958; HPLC [Chiralcel OD-H, hexane/2-propanol = 90/10, 0.5 ml/min, $\lambda = 254$ nm, retention times: (major) 23.9 min (minor) 29.6 min]; $[\alpha]^{26}_D + 45.7$ (c 1.07, $CHCl_3$, 90 % ee).

(*S*,*E*)-3-(Hydroxymethyl)-1-phenyl-5-(thiophen-3-yl)pent-4-en-1-one (**20l**): Colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, $J = 7.5$ Hz, 2H), 7.57 (dd, $J_1 = J_2 = 7.5$ Hz, 1H), 7.47 (dd, $J_1 = J_2 = 7.5$ Hz, 2H), 7.24 (dd, $J_1 = 5.2$ Hz, $J_2 = 2.9$ Hz, 1H), 7.17 (d, $J = 5.2$ Hz, 1H), 7.10 (d, $J = 2.9$ Hz, 1H), 6.55 (d, $J = 16.0$ Hz, 1H), 6.02 (dd, $J_1 = 16.0$ Hz, $J_2 = 8.1$ Hz, 1H), 3.81-3.67 (m, 2H), 3.26 (dd, $J_1 = 18.3$ Hz, $J_2 = 8.6$ Hz, 1H), 3.20-3.10 (m, 2H), 1.83 (brs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.3, 139.5, 137.0, 133.2, 129.5, 128.7, 128.2, 126.3, 126.0, 124.8, 121.8, 65.6, 41.2, 40.4; IR (neat) ν 3431, 1683, 1597 cm^{-1}; MS (FAB^+) 255 ($M–H_2O$, 7), 105 (100); HRMS (FAB^+) $C_{16}H_{15}OS$: 255.0838, Found: 255.0836; HPLC [Chiralcel OJ-H, hexane/2-propanol = 90/10, 0.5 ml/min, $\lambda = 254$ nm, retention times: (major) 86.8 min (minor) 70.5 min]; $[\alpha]^{31}_D + 14.3$ (c 1.76, $CHCl_3$, 91 % ee).

3.1.3.7 Determination of the Absolute Configuration of 20h

To a solution of **20h** (18.2 mg, 0.0684 mmol) in dry CH_2Cl_2 was added Dess-Martin periodinane (38.7 mg, 0.0913 mmol) at 0 °C. After being stirred at the same

temperature for 1 h, the reaction mixture was quenched with $NaHCO_3$-$Na_2S_2O_3$ solution, extracted with $CHCl_3$, dried over Na_2SO_4 and concentrated in vacuo. Resulting crude aldehyde was directly used for the next reaction. To a solution of crude aldehyde in THF (2.4 mL) was added 2-methyl-2-butene (72.4 μL, 0.684 mmol) and a solution of $NaClO_2$ (18.1 mg, 0.200 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (35.5 mg, 0.228 mmol) in H_2O (2.4 mL) at 0 °C. After being stirred at the same temperature for 26 h the reaction mixture was extracted with EtOAc, dried over Na_2SO_4 and concentrated in vacuo. Resulting crude carboxylic acid was directly used for the next reaction. To a solution of crude carboxylic acid in CH_3CN (1.2 mL) was added morpholine (6.5 μL, 0.0752 mmol) and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (20.7 mg, 0.0750 mmol) at room temperature. After being stirred at the same temperature for 12 h the reaction mixture was extracted with EtOAc, washed with 1NHCl, H_2O, saturated $NaHCO_3$aq, H_2O, brine, dried over Na_2SO_4 and concentrated in vacuo. Resulting crude morpholineamide was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to give **22** (10.8 mg, 45 %) as a yellow solids: ^{1}H NMR and ^{13}C NMR spectra were identical to those reported previously[14]; $[\alpha]_D^{32}$ +68.6 (c = 1.08 in EtOAc); HPLC [Chiralpak AD-H, hexane/2-propanol = 80/20, 0.5 mL/min, λ = 254 nm, retention times: (major) 44.6 min (minor) 40.9 min, 91 % ee].

3.1.3.8 Construction of the Cyclopropane 23

To a solution of **20a** (21.7 mg, 0.0733 mmol) in dry THF (0.4 mL) was added PPh_3 (33.9 mg, 0.129 mmol), DIAD (36.7 μL, 0.137 mmol) and *o*-$NsNH_2$ (27.6 mg, 0.137 mmol) at room temperature. After being stirred at the same temperature for 2 h, the reaction mixture was purified by silica gel column chromatography (hexane/EtOAc = 9/1) to give **23** (14.6 mg, 72 %, dr = 94:6).

((1*S*,2*R*)-2-(4-Methoxystyryl)cyclopropyl)(phenyl)methanone (**23**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8.6 Hz, 2H), 7.56 (dd, $J_1 = J_2$ = 8.6 Hz, 1H), 7.47 (dd, $J_1 = J_2$ = 8.6 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 6.52 (d, J = 15. 5 Hz, 1H), 5.78 (dd, J_1 = 15.5 Hz, J_2 = 9.2 Hz, 1H), 3.80 (s, 3H), 2.80-2.72 (m, 1H), 2.35-2.28 (m, 1H), 1.89-1.76 (m, 1H), 1.33-1.21 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.6, 159.0, 137.9, 132.8, 130.0, 129.8, 128.5, 128.1, 128.0, 127.0, 114.0, 55.3, 29.9, 27.2, 18.5; IR (neat) ν 2929, 1664 cm^{-1}; MS (FAB$^+$) 279 (M + H$^+$, 17), 105 (100); HRMS (FAB$^+$) $C_{19}H_{19}O_2$: 279.1385. Found: 279.1382; $[\alpha]^{30}{}_D$ + 398.1 (c 1.2, $CHCl_3$).

3.1.3.9 Construction of the Bicyclic Compound 25

A mixture of **20a** (33.3 mg, 0.133 mmol) and NBS (33.3 mg, 0.187 mmol) in MeCN (1.0 mL) was stirred at 0 °C for 2 h. After being evporated in vacuo, resulting residue was added *t*-BuOH (1.0 mL) and *t*-BuOK (13.1 mg, 0.117 mmol) at room

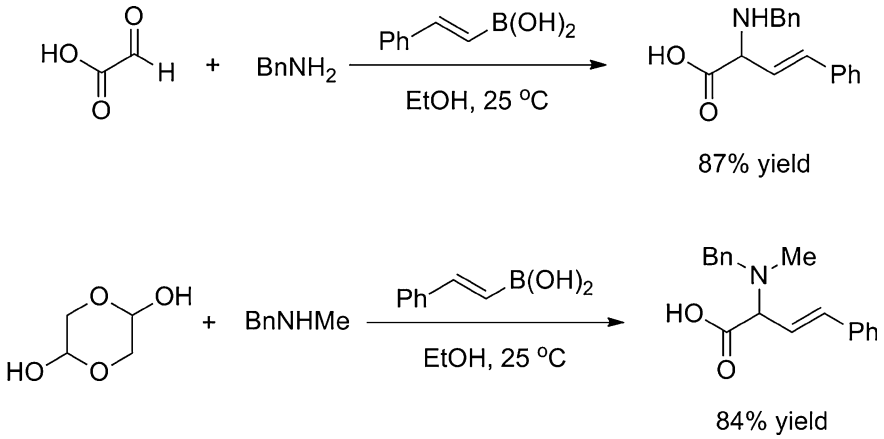
temperature. After being stirred at 50 °C for 10 h, the reaction mixture was extracted with ethyl acetate, dried over Na_2SO_4, evaporated in vacuo, purified by silica gel column chromatography (hexane/EtOAc = 3/1) to give **25** (19.1 mg, 57 %).

((1*S*,2*R*,5*R*,6*R*)-2-(4-Methoxyphenyl)-3-oxabicyclo[3.1.0]hexan-6-yl)(phenyl) methanone (**25**): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.3 Hz, 2H), 7.53 (dd, $J_1 = J_2$ = 7.3 Hz, 1H), 7.40 (dd, $J_1 = J_2$ = 7.3 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 5.13 (d, J = 2.7 Hz, 1H), 4.19 (d, J = 9.0 Hz, 1H), 4.07 (dd, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1H), 3.81 (s, 3H), 2.76 (dd, $J_1 = J_2$ = 3.2 Hz, 1H), 2.59 (ddd, J_1 = 7.1 Hz, J_2 = 3.2 Hz, J_3 = 2.7 Hz, 1H), 2.49 (ddd, J_1 = 7.1 Hz, J_2 = 3.2 Hz, J_3 = 2.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.2, 159.2, 137.5, 132.9, 131.3, 128.5, 128.1, 127.3, 113.8, 80.2, 70.0, 55.3, 35.0, 29.9, 24.2; IR (neat) ν 1664, 1449 cm^{-1}; MS (FAB$^+$) 295 (M + H$^+$, 76), 105 (100); HRMS (FAB$^+$) $C_{19}H_{19}O_3$: (M + H$^+$) 295.1334, Found: 295.1339; $[\alpha]^{27}_D$ − 59.7 (c 0.55, $CHCl_3$).

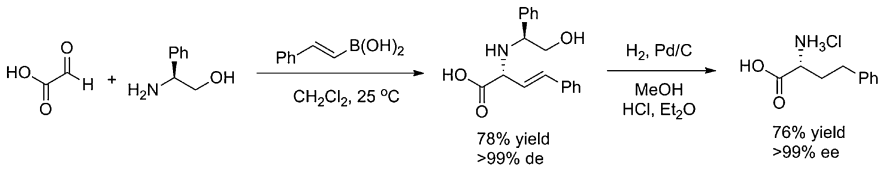
3.2 Asymmetric Petasis Reaction of *N*-aryl-α-Iminoamides and Alkenylboronates

3.2.1 Introduction and Background

Since Petasis first reported the Mannich-type reaction of organoboronic acids, amines and glyoxylic acid or glycolaldehyde, it has been recognized as a powerful synthetic tool for constructing α-amino acid derivatives (Scheme 3.12) [46–49, 50–53].



Scheme 3.12 Petasis reactions of glyoxylic acid or glycolaldehyde for the synthesis of α-amino acid derivatives



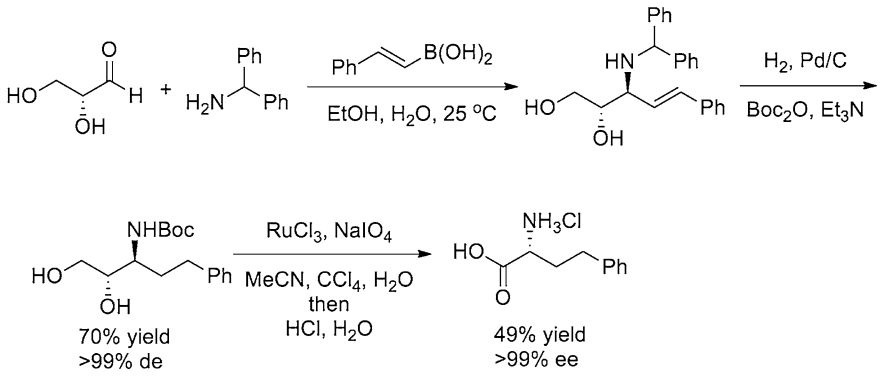
Scheme 3.13 Diastereoselective petasis reaction using a chiral amine

The ultimate goal in the discovery of this reaction is the functionalization or introduction of new chiral centers in a molecule. Until now, three different approaches have been tested for the stereoselective Petasis reaction. The first comprises the use of a chiral amine that can induce a diastereoselective 1,2-addition of organoboronic acids (Scheme 3.13). In this case, enantiomerically pure α-amino acids can be obtained after the deprotection of amine substituent [47].

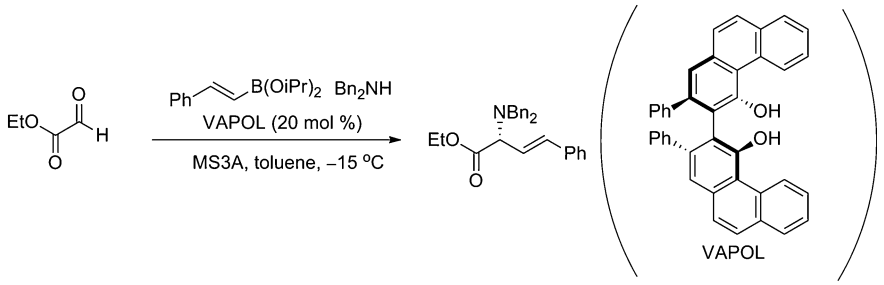
The second approach uses chiral aldehydes as a substrate (Scheme 3.14). This method also often accesses to the synthesis of optically active α-amino acids [48].

The two methods described above, however, have the drawback that a stoichiometric amount of chiral auxiliary is necessary. The third method uses enantioenriched ligands or catalysts which combine with boronic acids to form chiral boronic esters, resulting in the formation of enantiomerically enriched products [54–56]. In this approach, stereoselective reactions can theoretically be achieved with the use of substoichiometric amounts of the chiral components. My colleagues previously reported the asymmetric catalytic Petasis reaction of quinolines and organoboronic acids by using thiourea catalyst **1a** bearing an amino alcohol moiety (Scheme 3.3) [56]. Schaus reported the VAPOL-catalyzed asymmetric Petasis reaction of ethyl glyoxalate, secondary amines and organoboronic acids (Scheme 3.15) [54, 55]. To date, only two examples have been published.

So far, not only are there only the two described examples of this reaction, but the substrates are also limited to highly reactive iminium species in both cases.



Scheme 3.14 Diastereoselective petasis reaction using chiral aldehydes

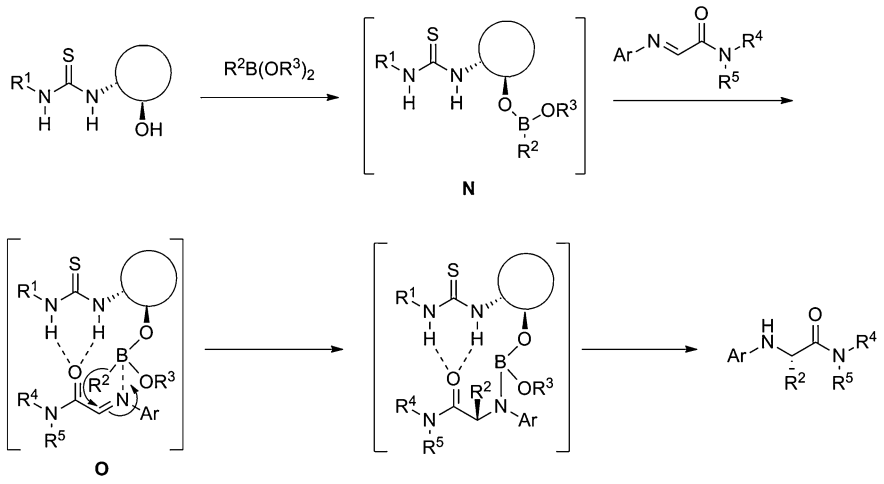


Scheme 3.15 Asymmetric petasis reaction catalyzed by VAPOL

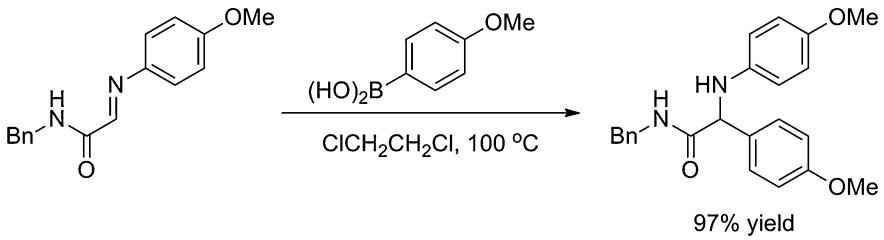
Therefore, it is desirable to develop a catalytic enantioselective Petasis reaction which has a wide scope of substrates.

I planned to use a novel methodology to realize this challenging goal. The hypothesis is outlined in Scheme 3.16. When the thiourea containing a hydroxy group and organoboronic acid are combined, the chiral boronic acid-thiourea species **N** should be formed. It was considered that species **N** would be a suitable component for the Petasis reaction with α-iminocarbonyl compounds. It was predicted that the Lewis acidic boron atom of **N** would coordinate to the nitrogen atom of the imino group and the thiourea moiety would form hydrogen bonds with the carbonyl group. The resulting intermediate **O** would allow for the *quasi*-intramolecular attack of the substituent R^2 from the boron atom to the imino group due to double activation.

In addition, special attention was focused on the use of *N*-aryl-α-iminoamides as the imine substrates. Recently, Li reported the racemic version of this reaction



Scheme 3.16 Mechanistic proposal



Scheme 3.17 Petasis reaction of *N*-aryl-α-iminoamide

(Scheme 3.17) [57]. However, as described above, the enantioselective version of this reaction has not yet been reported.

When these species are used as substrates, *N*-aryl-α-amino acid derivatives would be obtained. It is known that these derivatives possess a variety of interesting biological activities, such as the inhibition of fibrinogen receptor [58, 59], and the replication of hepatitis C virus [60]. They act as glycine antagonists [61] or angiotensin receptor antagonists [62] (Fig. 3.1). In addition, it is known that some compounds of this class are PKC activators [63–65], NMDA receptor antagonists [66, 67], and ACE inhibitors [68]. Others have been shown to have anti-ulcer [69] and cyclosporine receptor-binding activity [70].

In addition, by using *N*-aryl-α-iminoamides bearing a peptide chain at the amide groups, this process could be directly expanded to a novel method for the synthesis of oligopeptides which contain non-natural *N*-aryl amino acid moieties.

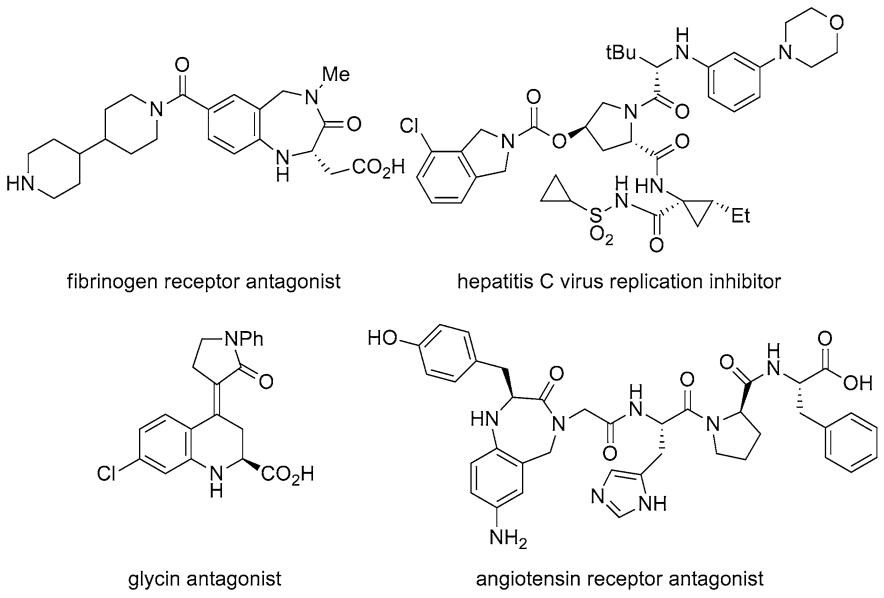


Fig. 3.1 Examples of *N*-aryl amino acid derivatives and their biological activities

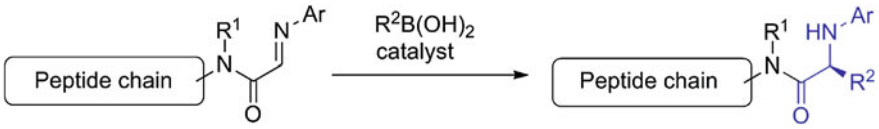


Fig. 3.2 Expansion to the synthesis of oligo peptides

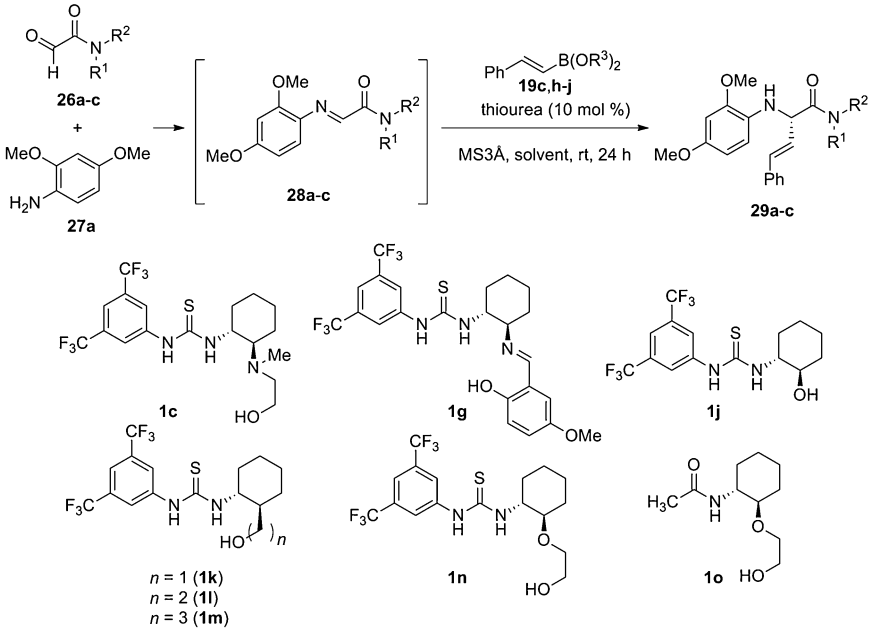
This approach would differ from the classical sequential condensation of amino acid monomers (Fig. 3.2). It is expected that it could be a starting point for synthesizing structurally interesting peptidic compounds or applied to the bio-conjugation of peptides in the future [71–75].

In this section, the first asymmetric Petasis reaction of *N*-aryl-α-iminoamides with the thiourea catalyst to synthesize *N*-aryl amino acid derivatives is decribed. In addition, application of this reaction to the synthesis of oligopeptides is presented.

3.2.2 Results and Discussion

The asymmetric Petasis reaction of iminoamide **28a,** which was readily prepared from **26a** [76] and **27a**, with *trans*-2-phenylvinylboronic acid diisopropyl ester **19h** was initially examined in the presence of 10 mol % of several types of hydroxy thioureas (Table 3.3). When amino alcohol-type thiourea **1c** [56], which had been the best catalyst for the Petasis reaction of quinolines and vinylboronic acids, was used, the desired adduct **29a** was obtained in poor yield and almost racemic form (entry 1). Similarly, iminophenol-type catalyst **1g**, which was described in the previous section, did not give a good result (entry 2). I anticipated that the basic amino and imino groups in catalysts **1c** and **1g** might prevent the boronates from coordinating with the nitrogen atom of **28a**, so other hydroxy-type thioureas that did not contain basic sites were screened. In the case of **1j**, while the ee was improved compared to those of **1c** and **1g**, the chemical yield was still low (entry 3). Next, the homologated thioureas **1k–m** were examined. Although the enantioselectivities were decreased with **1k** and **1l**, the chemical yields were slightly improved through the use of catalysts with a linker between the chiral scaffolds and the hydroxy group. A pronounced increase in yield was observed with the three-carbon linker of thiourea **1m** (entries 4-6). It was assumed that the introduction of another weak Lewis basic site into the carbon linker of the catalyst should result in the effective formation of a complex between the organoboronic acid and the catalyst. When the author tested thiourea **1n**, which contained an ether moiety, an improved result was observed (entry 7). Based on the results of the reaction catalyzed by the corresponding amide **1o**, it became clear that the thiourea moiety was necessary for the catalytic activity (entry 8). For further improvements of the stereoselectivity, the substituents of the amide groups of the substrates were screened. When the *N*-phenyl-*N*-methyl amide **28b** was used, both the yield and

Table 3.3 Optimization of the reaction conditions[a]



Entry	R^1, R^2	**28**	R^3	Catalyst	**29**	Yield (%)[b]	ee (%)[c]
1	Me, Me (**26a**)	**28a**	iPr (**19h**)	**1c**	**29a**	21	1
2	Me, Me (**26a**)	**28a**	iPr (**19h**)	**1g**	**29a**	22	30
3	Me, Me (**26a**)	**28a**	iPr (**19h**)	**1j**	**29a**	18	50
4	Me, Me (**26a**)	**28a**	iPr (**19h**)	**1k**	**29a**	27	12
5	Me, Me (**26a**)	**28a**	iPr (**19h**)	**1l**	**29a**	29	0
6	Me, Me (**26a**)	**28a**	iPr (**19h**)	**1m**	**29a**	51	46
7	Me, Me (**26a**)	**28a**	iPr (**19h**)	**1n**	**29a**	47	74
8	Me, Me (**26a**)	**28a**	iPr (**19h**)	**1o**	**29a**	27	1
9	Ph, Me (**26b**)	**28b**	iPr (**19h**)	**1n**	**29b**	75	86
10	Ph, Et (**26c**)	**28c**	iPr (**19h**)	**1n**	**29c**	74	90
11	Ph, Et (**26c**)	**28c**	H (**19i**)	**1n**	**29c**	72	77
12	Ph, Et (**26c**)	**28c**	Me (**19j**)	**1n**	**29c**	69	88
13	Ph, Et (**26c**)	**28c**	Et (**19c**)	**1n**	**29c**	70	88
14[d]	Ph, Et (**26c**)	**28c**	iPr (**19h**)	**1n**	**29c**	71	62
15[e]	Ph, Et (**26c**)	**28c**	iPr (**19h**)	**1n**	**29c**	8	59
16[f]	Ph, Et (**26c**)	**28c**	iPr (**19h**)	**1n**	**29c**	74	92

[a] Unless otherwise noted, the reactions were conducted with **28** (1.0 equiv.), **19** (1.2 equiv.), **1** (10 mol %) and MS3Å (100 mg/1 mmol of **28**) in toluene at room temperature for 24 h
[b] Yield of isolated product for the two-step process based on **26**
[c] Determined by chiral HPLC analysis
[d] CH_2Cl_2 was used as solvent
[e] THF was used as solvent
[f] Cyclohexane was used as solvent

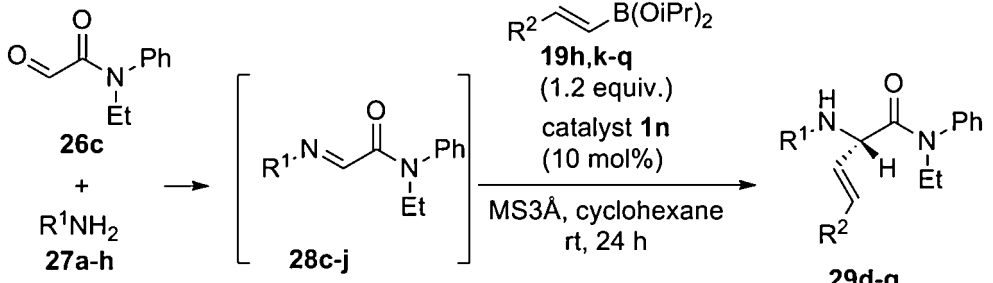
enantioselectivity were further improved and *N*-phenyl-*N*-ethyl amide **28c** was found to be the optimal substrate (entries 9 and 10). With regard to the substituents of the boronic acid esters, boronic acid **19i** gave a diminished enantioselectivity due to the background reaction. Other aliphatic boronates such as **19j** and **19c** gave results similar to those with **19h** (entries 11–13). Next, the author screened the solvents. When CH_2Cl_2 was used as the solvent, the reaction proceeded smoothly as in toluene, but the enantioselectivity was decreased (entry 14). As expected, THF prevented the reaction progression, presumably due to the coordination to the boron atom (entry 15). Cyclohexane, a less-polar solvent than toluene, was found to be the optimal solvent (entry 16). The isomerized product was not observed under any of these conditions.

Next, the scope of the reaction was explored (Table 3.4). As expected, electron-rich vinyl boronates such as **19k** and **19l** gave good results with excellent ee's (entries 1 and 2). In addition, electron-poor **19m** could also be used and the enantioselectivity was still high (entry 3). The position of the substituents in the aromatic ring did not influence the results (entries 4 and 5). Heteroaromatic boronic acid ester **19p** gave the corresponding adduct **29i** in high stereoselectivity (entry 6). In the case of the aliphatic vinyl boronic acid ester **19q**, although the reactivity was lower, the enantioselectivity was maintained at a high level (entry 7). Aryl or alkynyl boronic acids did not react due to their low nucleophilicities. With regard to the aromatic rings at the imine nitrogen atom, electron-rich substrates were preferred, in contrast to copper-catalyzed *N*-arylation reactions (entries 8–12). In addition, derivatives that contained hydroxymethyl or amino groups were also accessible (entries 13 and 14).

Next, the absolute configuration of the adduct was determined (Scheme 3.18). First, conditions for the removal of the electron-rich 2,4-dimethoxybenzene from the nitrogen atom of the Petasis adduct **29c** were screened. Typical procedures for deprotection of the 2,4-dimethoxyphenyl group, such as $PhI(OAc)_2$ [77] or CAN [78, 79] resulted in the decomposition of the substrate. Recently, a mild dearylation procedure, in which periodic acid and water are used, was reported [80]. By using this method, the non-protected amine was obtained from **29c**. Next, carbamate formation and hydrogenolysis afforded the amino acid derivative **30**. Finally, the same compound **30** was synthesized from commercially available (*S*)-homophenylalanine (**31**) in two steps. The comparison of the specific rotations of these compounds suggested that these compounds had the same absolute configuration. Therefore, the author concluded that the absolute configuration of the Petasis adduct **29c** is (*S*).

When 1:1 ratio of **19c** and hydroxy thiourea **1n** were mixed in toluene, **19c** immediately exchanged an ethoxy group for the hydroxy thiourea at room temperature, thereby liberating EtOH. Equilibrium between **1n**, **19c**, and the complex was quickly reached (<5 min), and the composition of the mixture did not change with time. Similar results were seen with **1m** and **19c**. Therefore, it was concluded that the ether moiety of **1n** does not serve to accelerate the formation of the thiourea-boronate complex.

Table 3.4 Scope of boronates and anilines[a]



27a: R^1 = 2,4-$(MeO)_2C_6H_3$
27b: R^1 = 4-$MeOC_6H_4$
27c: R^1 = 2-$MeOC_6H_4$
27d: R^1 = 4-Me
27e: R^1 = C_6H_5
27f: R^1 = 2,3-$Me_2C_6H_3$
27g: R^1 = 2-$(TBSOCH_2)C_6H_4$
27h: R^1 = 3-$(BocNH)C_6H_4$

19h: R^2 = C_6H_5
19k: R^2 = 4-$MeOC_6H_4$
19l: R^2 = 4-MeC_6H_4
19m: R^2 = 4-ClC_6H_4
19n: R^2 = 3-$MeOC_6H_4$
19o: R^2 = 3-MeC_6H_4
19p: R^2 = 3-thienyl
19q: R^2 = Cy

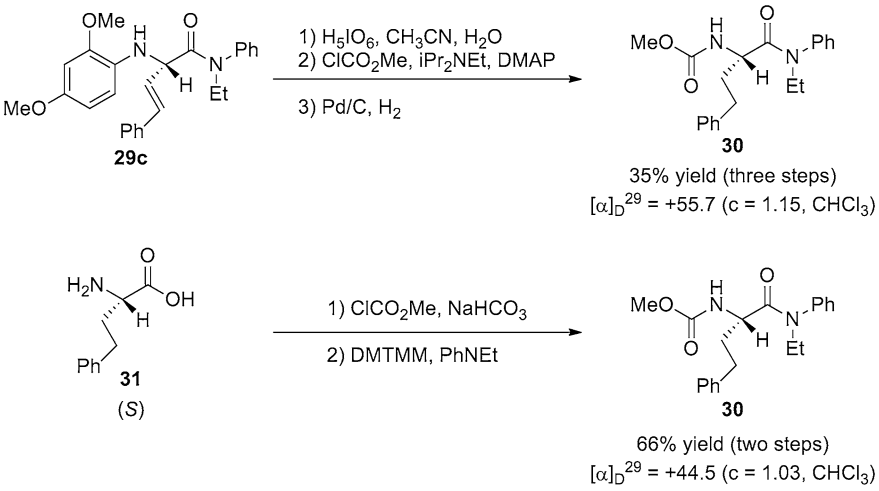
Entry	27	28	19	Time (h)	29	Yield (%)[b]	ee (%)[c]
1	**27a**	**28a**	**19k**	**24**	**29d**	77	87
2	**27a**	**28a**	**19l**	**24**	**29e**	76	90
3	**27a**	**28a**	**19m**	**24**	**29f**	65	90
4	**27a**	**28a**	**19n**	**24**	**29g**	69	89

(continued)

Table 3.4 (continued)

Entry	27	28	19	Time (h)	29	Yield (%)[b]	ee(%)[c]
5	**27a**	**28a**	**19o**	**24**	**29h**	86	93
6	**27a**	**28a**	**19p**	24	**29i**	77	89
7	**27a**	**28a**	**19q**	24	**29j**	53	80
8	**27b**	**28b**	**19h**	48	**29k**	62	82
9	**27c**	**28c**	**19h**	48	**29l**	77	86
10	**27d**	**28d**	**19h**	48	**29m**	78	87
11	**27e**	**28e**	**19h**	48	**29n**	58	84
12	**27f**	**28f**	**19h**	48	**29o**	56	90
13	**27g**	**28g**	**19h**	72	**29p**	63	82
14	**27h**	**28h**	**19h**	72	**29q**	54	90

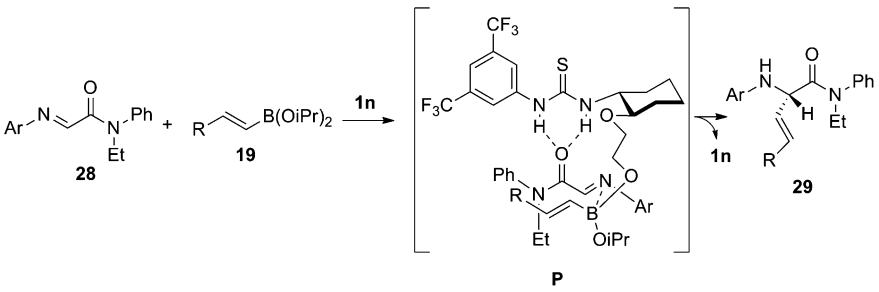
[a] The reactions were conducted with **28** (1.0 equiv.), **19** (1.2 equiv.), **1n** (10 mol %), and MS3Å (100 mg/1 mmol of **28**) in cyclohexane at room temperature
[b] Yield of isolate product for the two step process based on **26**
[c] Determined by chiral HPLC analysis



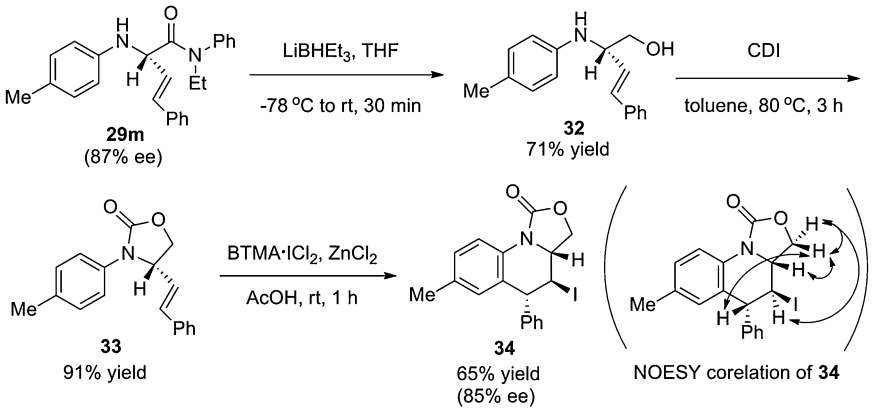
Scheme 3.18 Determination of the absolute configuration of the adduct

The possible reaction pathway is shown in Scheme 3.19. The boron atom first coordinates to the nitrogen atom of the imine moiety, and the thiourea moiety forms a hydrogen-bond with the amide carbonyl oxygen to form the complex **P**. It was assumed that the higher enantioselectivity of **1n** is a result of the additional dipole moment introduced by the oxygen in the alcohol chain. The dipole moments of the carbon–oxygen bonds in the $ROCH_2CH_2OH$ subunit should align themselves so that the overall dipole moment is minimized. This limits the number of possible conformations of the transition state as compared to, for example, catalyst **1m**.

Next the conversion of the obtained *N*-aryl amino acid derivatives to pharmacologically important heterocyclic structures was investigated (Scheme 3.20). The amide moiety of **29m** could be reduced to amino alcohol **32** with $LiBHEt_3$ [81], and then converted to the corresponding oxazolidinone **33**. When **33** was treated with benzyltrimethylammonium dichloroiodate (BTMA ICl_2) and $ZnCl_2$ [82], intramolecular iodoarylation occurred to give the tricyclic dihydroquinoline



Scheme 3.19 Possible reaction pathway

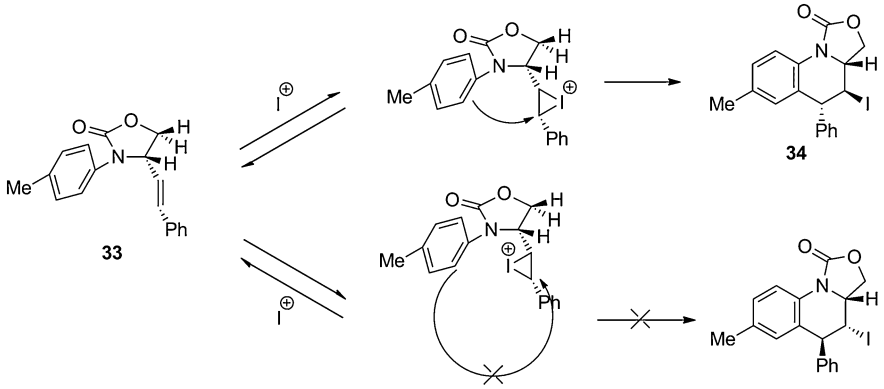


Scheme 3.20 Synthesis of tetrahydroquinoline

derivative **34,** which would be a valuable pharmacophore [83–86], as a single diastereoisomer without significant loss of the enantiomeric excess.

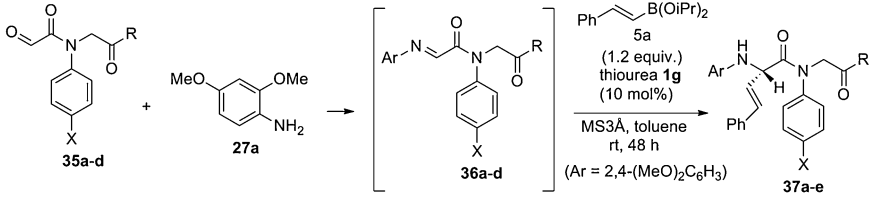
The diastereoselectivity of this reaction can be explained as follows. When the olefin moiety of **33** reacts with BTMA ICl_2, two possible diastereomers of the iodinium intermediate should be produced. However, this step would be reversible and in only one of the diastereomers is the phenyl ring in the proper position to attack the iodonium, thereby producing the single diastereomer **34** under kinetic control (Scheme 3.21).

Finally, this reaction was applied to the modification of peptide compounds (Table 3.5). The reaction of **36a** with **19h** proceeded to give the Gly-(styrylglycine) compound **37a** in 82 % ee. Substrate **36b** containing a 4-bromophenyl group on the amide nitrogen atom could also be converted to the corresponding adduct **37b**, which could be used for further elaboration of the chemical structure based on the bromine atom (entry 2). Next, the synthesis of tripeptides was examined. When **36c**



Scheme 3.21 Rationalization of the diastereoselectivity

Table 3.5 Application in the peptide modification[a]



Entry	R	X	35	36	37	Yield (%)[b]	ee (%)[c]	dr[d]
1	-OMe	OMe	**35a**	**36a**	**37a**	67	82	–
2	-OMe	Br	**35b**	**36b**	**37b**	71	92	–
3	-(*L*)-Ala-OMe	OMe	**35c**	**36c**	**37c**	58	–	85:15
4	-(*D*)-Ala-OMe	OMe	(*ent*)-**35c**	(*ent*)-**36c**	**37d**	57	–	89:11
5	-(*L*)-Phe-OMe	OMe	**35d**	**36d**	**37e**	60	–	88:12

[a] The reactions were conducted with **36** (1.0 equiv.), **19 h** (1.2 equiv.), **1n** (10 mol %) and MS3Å (100 mg/1 mmol of **36**) in toluene at room temperature for 48 h

[b] Yield of isolated product for the two step process based on **35**

[c] Determined by chiral HPLC analysis

[d] Determined by ^{1}H NMR analysis

was used, the desired tripeptide **37c** was obtained in good diastereoselectivity (entry 3). Use of the enantiomeric substrate *ent*-**36c** gave the other diastereoisomer of **37c** as the major product (entry 4). Therefore, the stereoselectivity of this process is controlled by the catalyst. In addition, **36d**, which contains a more bulky amino acid unit than **36c**, could be converted to the corresponding tripeptide **37e** (entry 5). In all of these cases, isomerization of the olefin moieties was not observed. Although this methodology has been applied only to the synthesis of peptides bearing a glycine unit as a second amino acid residue from the *N*-terminus at this time, this method would be an efficient way to install styryl glycine units, which are readily isomerized under normal peptide condensation conditions into peptides [87, 88].

In conclusion, I developed a novel thiourea catalyst **1n** and applied it to the first asymmetric Petasis reaction of α-iminoamides. This method is not limited to the synthesis of simple monomers of α-amino acid derivatives, but is also applicable to the synthesis of peptide oligomers which are difficult to prepare by the classical sequential elongation of peptide chains.

3.2.3 Experimental Section

3.2.3.1 General

All non-aqueous reactions were carried out under a positive atmosphere of argon in dried glassware unless otherwise noted. Solvents were dried and distilled according to standard protocols. Materials were obtained from commercial suppliers and used without further purification except when otherwise noted. All melting points were determined on YANAGIMOTO micro melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 or 400 MHz, and at 125 or 100 MHz, respectively; Tetramethylsilane (TMS) was used as an internal standard. IR spectra were recorded on a JASCO FT/IR-4100 Fourier-transform infrared spectrometer. Low and High resolution mass spectra were obtained by EI or FAB method. Optical rotations were recorded on a JASCO P-2200 polarimeter with a path length of 1 cm; concentrations are quoted in grams per 100 mL. $[\alpha]_D$ values are measured in 10^{-1} deg cm^2g^{-1}. Enantiomeric excess was determined by high performance liquid chromatography (HPLC) analysis.

The organoboronates **19c**, **h–q** were prepared according to the literature procedure [87, 88].

3.2.3.2 Experimental Procedure for the Synthesis of the Catalysts 1k, l, m

The catalysts **1k–m** were prepared from (1*R*,2*R*)-2-aminocyclohexanecarboxylic acid [89].

{(1*R*,2*R*)-2-aminocyclohexyl}methanol: To a mixture of (1*R*,2*R*)-2-aminocyclohexanecarboxylic acid[24] (2.42 g, 16.9 mmol) in THF was added $LiAlH_4$ (1.02 g, 26.8 mmol) at 0 °C and stirred at 60 °C for 1 h. Then the reaction mixture was cooled to 0 °C, and distilled water (1.0 mL), 3 N NaOH (1.0 mL) and distilled water (3.0 mL) were added. The resulting precipitate was removed by filtration through Celite and the filtrate was concentrated in vacuo to afford {(1*R*,2*R*)-2-aminocyclohexyl}methanol (2.19 g, quant). This compound was used without further purification.

3.2.3.3 Preparation of 1k

A mixture of {(1*R*,2*R*)-2-aminocyclohexyl}methanol (151 mg, 1.17 mmol) and bis(trifluoromethyl)phenylisothiocyanate (0.213 mL, 1.17 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 1 h. Then the reaction mixture was concentrated and purified by silica gel column chromatography (hexane/EtOAc = 2/1 to 1/1) to afford the hydroxy-thiourea **1k** (319 mg, 68 % yield): White solids; mp 64–65 °C (Hexane/EtOAc); ^{1}H NMR (500 MHz, DMSO) δ 9.89 (s, 1H), 8.21 (s, 2H), 8.17 (d, J = 8.3 Hz, 1H), 7.71 (s, 1H), 4.40-4.30 (m, 1H), 4.06-3.97 (m, 1H), 3.50-3.40 (m, 1H), 3.32-3.24 (m, 1H), 2.04-1.98 (m, 1H), 1.94-1.86 (m, 1H), 1.72-1.62 (m, 2H), 1.51-1.42 (m, 1H), 1.29-1.09 (m, 4H); ^{13}C NMR (126 MHz, DMSO) δ 179.9, 142.3, 130.5 (q, J = 34.9 Hz), 123.5 (q, J = 274 Hz), 122.0, 115.8, 63.2, 54.4, 44.9, 32.0, 28.9, 25.1 One carbon peak was missing due to overlapping; IR (ATR) ν 3270, 2978, 2921, 1562, 1383, 1278, 1236 cm^{-1}; MS (FAB^+) 401 ($M + H^+$, 100); Anal. Calcd. for $C_{16}H_{18}F_6N_2OS$: C, 48.00; H, 4.53; N, 7.00; Found: C, 47.94; H, 4.24; N, 6.96; $[\alpha]^{28}_D$ − 31.3 (c 1.07, $CHCl_3$).

3.2.3.4 Preparation of 1l

To a mixture of {(1*R*,2*R*)-2-aminocyclohexyl}methanol (1.01 g, 7.82 mmol) and Et_3N (2.18 mL, 15.6 mmol) in THF (20 mL) was added Ac_2O (1.48 mL, 15.7 mmol) at 0 °C and stirred at room temperature for 8 h. Then NaOHaq (2.0 M, 50 mL) was added and stirred for additional 5 h. After that, the solvent was removed by evaporation, extracted with EtOAc, dried over Na_2SO_4, evaporated in vacuo to give the crude product as amorphous solids. It was recrystallized from hexane and EtOAc to obtain the desired product *N*-{(1*R*,2*R*)-2-(hydroxymethyl)cyclohexyl}acetamide (482 mg, 36 %). White solids; mp 123-124 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59 (s, 1H), 3.94 (s, 1H), 3.72-3.64 (m, 1H), 3.65 (dd, J_1 = 11.8 Hz, J_2 = 3.2 Hz, 1H), 3.32 (d, J = 11.8 Hz, 1H), 2.02 (s, 3H), 1.94-1.86 (m, 1H), 1.81-1.76 (m, 2H), 1.69-1.62 (m, 1H), 1.56 (ddd, $J_1 = J_2$ = 12.5 Hz, J_3 = 3.7 Hz, 1H), 1.39-1.16 (m, 3H), 1.11 (dd, J_1 = 10.6 Hz, J_2 = 10.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2,

63.4, 49.0, 46.7, 33.0, 28.7, 25.5, 25.4, 23.1; IR (ATR) *v* 3288, 2924, 2857, 1652, 1635, 1558, 1236 cm^{-1}; MS (FAB^+) 172 ($M + H^+$, 100); Anal. Calcd. for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18; Found: C, 62.83; H, 10.09; N, 8.04; $[\alpha]^{28}{}_D$ − 14.3 (c 1.00, $CHCl_3$).

To a mixture of *N*-{(1*R*,2*R*)-2-(hydroxymethyl)cyclohexyl}acetamide (188 mg, 1.10 mmol) in CH_2Cl_2 (5.0 mL) was added Dess-Martin periodinane (487 mg, 1.15 mmol) at 0 °C and stirred at the same temperature for 30 min. Then the reaction mixture was extracted with $CHCl_3$, washed with $Na_2S_2O_3$aq and purified by silica gel column chromatography (EtOAc) to obtain the desired product *N*-{(1*R*,2*R*)-2-formylcyclohexyl}acetamide (128 mg, 69 %). White amorphous solids; ^1H NMR (500 MHz, $CDCl_3$) δ 9.53 (d, $J = 4.3$ Hz, 1H), 6.01 (d, $J = 6.9$ Hz, 1H), 4.14-4.03 (m, 1H), 2.15-2.08 (m, 1H), 2.03-1.97 (m, 1H), 1.95 (s, 3H), 1.85-1.77 (m, 3H), 1.57-1.47 (m, 1H), 1.45-1.36 (m, 1H), 1.30-1.20 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.5, 169.7, 56.7, 47.4, 32.0, 25.3, 24.5, 23.7, 23.2; IR (ATR) *v* 3291, 2980, 2922, 1729, 1638, 1236 cm^{-1}; MS (FAB^+) 170 ($M + H^+$, 100); HRMS (FAB^+) Calcd. for $C_9H_{16}NO_2$: 170.1182, Found: 170.1181; $[\alpha]^{26}{}_D$ − 14.1 (c 1.13, $CHCl_3$).

To a mixture of (methoxymethylene)triphenylphosphonium chloride (493 mg, 1.44 mmol) in THF (4.0 mL) was added NaHMDS (1.0 M THF solution, 1.44 mL, 1.44 mmol) at −20 °C and stirred at the same temperature for 15 min. Then *N*-{(1*R*,2*R*)-2-formylcyclohexyl}acetamide (128 mg, 0.755 mmol) in THF (4.0 mL) was added and stirred at the same temperature for 15 min. After that the reaction mixture was quenched with NH_4Claq, extracted with EtOAc, dried over Na_2SO_4, evaporated in vacuo and filtered through short silica gel column to afford the mixture of the corresponding methyl enol ether (*E*:*Z* = 4:1) and triphenylphosphine oxide. These compounds were difficult to separate and the mixture was used without further purification.

A solution of this crude mixture in HCO_2H (0.9 mL) and H_2O (0.1 mL) was stirred at room temperature for 15 min. Then the reaction mixture was cooled to 0 °C, disacidified with $NaHCO_3$aq, extracted with EtOAc, dried over Na_2SO_4, evaporated in vacuo to afford the aldehyde. It was directly used in next step.

To the solution of this aldehyde in THF (2.0 mL) was added $NaBH_4$ (28.1 mg, 0.739 mmol) at 0 °C and stirred at room temperature for 30 min. Then the reaction mixture was quenched with NH_4Claq, extracted with EtOAc, dried over Na_2SO_4, evaporated in vacuo to afford the corresponding alcohol. This alcohol was dissolved in 5N HCl (2.0 mL) and stirred at 100 °C for 9 h. Then the reaction mixture was cooled to 0 °C, basified with 5 N NaOH (pH > 9), extracted with $CHCl_3$, dried over Na_2SO_4 and evaporated in vacuo to afford the corresponding amine. Then the mixture of this amine and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.138 mL, 0.755 mmol) in CH_2Cl_2 (2.0 mL) was stirred at room temperature for 1 h. Then the reaction mixture was purified by silica gel column chromatography (hexane/EtOAc = 2/1 to 1/1) to afford the thiourea **1l** (24.1 mg, 8 % from *N*-{(1*R*,2*R*)-2-formylcyclohexyl}acetamide). Colorless amorphous; ^1H NMR (500 MHz,$CHCl_3$) δ 8.31 (s, 1H), 7.84 (s, 2H), 7.65 (s, 1H), 6.65 (d, $J = 7.7$ Hz, 1H),

4.24-4.02(m,1H),3.80-3.55(m,2H),2.44-2.20(m,1H),1.84-1.66(m,5H),1.55-1.10(m, 6H); ^{13}CNMR(126 MHz,$CDCl_3$)δ180.0,139.4,132.4,123.6,122.9(q,J = 272 Hz), 118.7,60.4,58.3,39.4,35.2,32.7,31.6,25.2,24.7; IR (ATR) ν3298,3060,2928,2858, 1725, 1604, 1277 cm^{-1}; MS (FAB^+) 415 (M + H^+, 100); HRMS (FAB^+) calcd for $C_{17}H_{21}F_6N_2OS$:415.1279,Found:415.1278; $[\alpha]^{25}_D$ + 11.2(c 1.83,$CHCl_3$).

To a solution of {(1*R*,2*R*)-2-aminocyclohexyl}methanol (863 mg, 6.69 mmol) in THF (60 mL) was added Boc_2O (2.20 g, 10.1 mmol) at room temperature and stirred at the same temperature for 14 h. Then the solvent was removed by evaporation and purified by silica gel column chromatography (hexane/EtOAc = 2/1) to obtain the desired product *tert*-Butyl {(1*R*,2*R*)-2-(hydroxymethyl)cyclohexyl}carbamate (1.04 g, 68 %). White solids; mp 96–97 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 6.22 (s, 1H), 3.83 (dd, $J_1 = J_2 = 5.2$ Hz, 1H), 3.44 (ddd, $J_1 = 10.3$ Hz, $J_2 = 5.8$ Hz, $J_3 = 5.2$ Hz, 1H), 3.27 (ddd, $J_1 = 10.3$ Hz, $J_2 = 5.2$ Hz, $J_3 = 3.9$ Hz, 1H), 3.13-3.04 (m, 1H), 1.85-1.76 (m, 2H), 1.68-1.61 (m, 2H), 1.41-1.38 (m, 1H), 1.39 (s, 9H), 1.33-1.28 (m, 1H), 1.24-1.04 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.0, 79.9, 63.7, 49.7, 47.4, 33.4, 28.7, 28.3, 25.61, 25.59; IR (ATR) ν 3396, 3288, 1674, 1161 cm^{-1}; MS (FAB^+) 230 (M + H^+, 45), 174 (100); Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 62.85; H, 10.11; N, 6.11; Found: C, 62.56; H, 9.93; N, 6.01; $[\alpha]^{25}_D$ − 9.5 (c 1.34, $CHCl_3$).

To a mixture of *tert*-Butyl {(1*R*,2*R*)-2-(hydroxymethyl)cyclohexyl}carbamate (500 mg, 2.18 mmol) in CH_2Cl_2 (20 mL) was added Dess-Martin periodinane (924 mg, 2.18 mmol) at room temperature and stirred at the same temperature for 4 h. Then the reaction mixture was extaracted with $CHCl_3$, washed with $Na_2S_2O_3$aq and purified by silica gel column chromatography (hexane/EtOAc = 5/1) to obtain the desired product *tert*-Butyl {(1*R*,2*R*)-2-formylcyclohexyl}carbamate (448 mg, 90 %). White solids; mp 68–69 °C (hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (s, 1H), 4.78 (d, J = 8.6 Hz, 1H), 3.61-3.45 (m, 1H), 2.15-2.08 (m, 1H), 2.05-1.98 (m, 1H), 1.84-1.73 (m, 3H), 1.54-1.31 (m, 2H), 1.42 (s, 9H), 1.27-1.18 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.5, 155.1, 79.4, 56.8, 48.9, 32.3, 28.2, 25.3, 24.5, 23.7; IR (ATR) ν 3345, 2979, 2921, 1722, 1699, 1236 cm^{-1}; MS (FAB^+) 228 (M + H^+, 68), 172 (100); HRMS (FAB^+) Calcd.. for $C_{12}H_{22}NO_3$: 228.1600, Found: 228.1600; $[\alpha]^{27}_D$ + 19.4 (c 1.04, $CHCl_3$).

(*E*)-Methyl 3-[(1*S*,2*R*)-2-{(tert-butoxycarbonyl)amino}cyclohexyl]acrylate: A mixture of *tert*-Butyl {(1*R*,2*R*)-2-formylcyclohexyl}carbamate (448 mg, 1.97 mmol) and methyl 2-(triphenylphosphoranylidene)acetate (990 mg, 2.96 mmol) in toluene (20 mL) was stirred under the reflux condition for 12 h. Then the solvent was removed by evaporation and the residue was purified by silica gel column chromatography (hexane/EtOAc = 5/1) to afford (*E*)-Methyl 3-[(1*S*,2*R*)-2-{(tert-butoxycarbonyl)amino}cyclohexyl]acrylate (507 mg, 91 %). White solids; mp 85–86 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (dd, $J_1 = 15.8$ Hz, $J_2 = 8.9$ Hz, 1H), 5.83 (d, $J = 15.8$ Hz, 1H), 4.52 (d, $J = 6.6$ Hz, 1H), 3.71 (s, 3H), 3.41-3.26 (m, 1H), 2.06-1.94 (m, 2H), 1.80-1.69 (m, 3H), 1.40 (s, 9H), 1.36-1.11 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 155.1, 151.0, 121.0, 79.0, 52.7, 51.2, 48.1, 33.1, 31.2, 28.1, 25.0, 24.7; IR (ATR) ν

3362, 2977, 2922, 1724, 1688, 1236 cm^{-1}; MS (FAB^+) 284 ($M + H^+$, 20), 228 (100); HRMS (FAB+) Calcd. for $C_{10}H_{16}NO_2$: 182.1181, Found: 182.1180; $[\alpha]^{25}_D$ +6.0 (c 1.02, $CHCl_3$).

A mixture of (*E*)-Methyl 3-[(1*S*,2*R*)-2-{(tert-butoxycarbonyl)amino}cyclohexyl]acrylate (507 mg, 1.79 mmol) and Pd/C (10 %, 190 mg) in MeOH (20 mL) was stirred at room temperature under the 1 atom of hydrogen atmosphere for 4 h. Then the catalyst was removed by filtration through Celite and the filtrate was concentrated in vacuo to afford the reduced product. This product was used without further purification.

$LiBH_4$ (78.0 mg, 3.58 mmol) was added to the crude product dissolved in THF (10 mL) at 0 °C and stirred at room temperature for 4 h. Then the reaction was quenched with NH_4Claq, extracted with $CHCl_3$, dried over Na_2SO_4 and evaporated in vacuo to afford the *N*-Boc protected amino alcohol. This product was used without further purification.

The amino alcohol was dissolved in dioxane (12 mL) and 4M HCl (dioxane solution) was added at 0 °C. After stirred at room temperature for 15 h, the reaction mixture was basified with NaOHaq, extracted with chloroform, dried over Na_2SO_4 and evaporated in vacuo to obtain the primary amino alcohol. This product was used without further purification.

A mixture of aminoalcohol and 3,5-bis(trifluoromethyl)phenylisothiocyanate (0.340 mL, 1.87 mmol) in CH_2Cl_2 (5.0 mL) was stirred at room temperature for 2 h. Then the solvent was removed by evaporation, and the residues was purified by silica gel column chromatography (hexane/EtOAc = 1/1) to afford the desired hydroxy-thiourea **1m** (644 mg, 1.50 mmol, 84 % from (*E*)-Methyl 3-[(1*S*,2*R*)-2-{(tert-butoxycarbonyl)amino}cyclohexyl]acrylate). Colorless amorphous; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.82 (s, 2H), 7.70 (s, 1H), 6.14 (s, 1H), 4.21-4.08 (m, 1H), 3.72-3.61 (m, 2H), 2.28-2.19 (m, 1H), 1.92-1.86 (m, 1H), 1.81-1.64 (m, 5H), 1.55-1.44 (m, 1H), 1.43-1.26 (m, 3H), 1.21-1.08 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.8, 139.8, 132.3, 123.1, 122.8 (q, J = 273 Hz), 118.3, 62.4, 58.0, 42.1, 32.7, 30.5, 29.0, 28.4, 25.1, 24.8; IR (ATR) ν 3262, 2980, 2922, 1546, 1469, 1236 cm^{-1}; MS (FAB^+) 429 ($M + H^+$, 100); HRMS (FAB^+) Calcd. for $C_{18}H_{23}F_6N_2OS$: 429.1435, Found: 429.1434; $[\alpha]^{27}_D$ + 43.4 (c 1.08, $CHCl_3$).

3.2.3.5 Experimental Procedure for the Synthesis of the Catalyst 1n and 1o

To a mixture of (1*R*,2*R*)-2-[{(*S*)-1-phenylethyl}amino]cyclohexanol [90] (4.32 g, 19.7 mmol) and Et_3N (3.30 mL, 23.6 mmol) in THF (50 mL) was added AcCl (1.68 mL) at 0 °C and stirred at the same temperature for 2 h. Then NaOHaq (1.2 M, 30 mL) was added and stirred for additional 1 h. After that, the solvent was removed by evaporation, extracted with EtOAc, dried over Na_2SO_4, evaporated in vacuo to give the crude product as amorphous solids. It was recrystallized

from hexane and EtOAc to obtain N-{(1*R*,2*R*)-2-hydroxycyclohexyl}-N-{(*S*)-1-phenylethyl}acetamide (2.76 g, 54 %). White solids; mp 105-106 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 7.53 (d, $J = 8.0$ Hz, 2H), 7.23 (dd, $J_1 = J_2 = 8.0$ Hz, 2H), 7.14 (dd, $J_1 = J_2 = 8.0$ Hz, 1H), 4.67 (br, 1H), 3.58 (br, 2H), 3.00 (br, 2H), 1.95 (br, 4H), 1.80-1.74 (m, 1H), 1.72-1.68 (m, 1H), 1.67 (d, $J = 6.9$ Hz, 3H), 1.64-1.56 (m, 1H), 1.31-1.16 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 128.5, 128.2, 126.9, 126.5, 69.7, 65.7, 53.7, 35.4, 33.5, 29.7, 25.3, 24.0, 19.9; IR (ATR) ν 3362, 2932, 1612, 1440 cm^{-1}; MS (FAB^{+}) 262 (M + H^{+}, 100); Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36; Found: C, 73.34; H, 8.91; N, 5.34; $[\alpha]^{25}_{D}$ − 27.8 (c 1.05, $CHCl_3$).

A solution of N-{(1*R*,2*R*)-2-hydroxycyclohexyl}-N-{(*S*)-1-phenylethyl}acetamide (1.39 g, 5.32 mmol) in THF (10 mL) was added NaH (442 mg, 11.0 mmol) at 0 °C. Then, the reaction mixture was warmed to room temperature for 5 min. A resulting suspension was cooled to 0 °C, added allyl bromide (0.952 mL, 11.0 mmol) and KI (1.18 g, 7.11 mmol) and stirred at room temperature. After 8 h, the mixture was extracted with EtOAc, dried over Na_2SO_4, evaporated in vacuo and purified by silica gel column chromatography (hexane/EtOAc = 2/1 to 1/1) to obtain *N*-{(1*R*,2*R*)-2-(Allyloxy)cyclohexyl}-*N*-{(*S*)-1-phenylethyl}acetamide (1.36 g, 85 %). Colorless oil; ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 7.38 (d, $J = 7.5$ Hz, 2H), 7.19 (dd, $J_1 = J_2 = 7.5$ Hz, 2H), 7.11 (dd, $J_1 = J_2 = 7.5$ Hz, 1H), 5.72 (ddd, $J_1 = 17.8$ Hz, $J_2 = 10.3$ Hz, $J_3 = 5.2$ Hz, 1H), 5.10 (dd, $J_1 = 17.8$ Hz, $J_2 = 1.6$ Hz, 1H), 5.01 (dd, $J_1 = 10.3$ Hz, $J_2 = 1.8$ Hz, 1H), 4.77-4.46 (m, 1H), 3.87 (dd, $J_1 = 12.6$ Hz, $J_2 = 4.6$ Hz, 1H), 3.74-3.56 (m, 2H), 3.55-3.41 (m, 1H), 2.46 (s, 3H), 2.19-2.07 (m, 1H), 2.01-1.84 (m, 1H), 1.82-1.72 (m, 1H), 1.70-1.65 (m, 2H), 1.63 (d, $J = 6.9$ Hz, 3H), 1.31-1.22 (m, 1H), 1.16 (dddd, $J_1 = J_2 = 13.2$ Hz, $J_3 = J_4 = 3.5$ Hz, 1H), 1.09-0.96 (m, 1H); ^{13}C NMR (126 MHz, DMSO, 100 °C) δ 169.3, 135.2, 126.9, 126.3, 114.6, 76.1, 67.5, 40.1, 39.9, 39.8, 39.6, 39.4, 30.6, 29.7, 24.6, 23.1, 19.3; IR (ATR) ν 3065, 2933, 1636, 1435 cm^{-1}; MS (EI^{+}) 301 (M^{+}, 2), 105 (100); Anal. Calcd. for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65; Found: C, 75.82; H, 9.10; N, 4.53; $[\alpha]^{25}_{D}$ + 27.7 (c 1.10, $CHCl_3$).

N-{(1*R*,2*R*)-2-(Allyloxy)cyclohexyl}-*N*-{(*S*)-1-phenylethyl}acetamide (7.65 g, 25.4 mmol) was dissolved in dichloromethane (80 mL) and methanol (20 mL). The solution was purged with O_3 at −78 °C until the solution turned blue. The excess O_3 was removed by purging oxygen at −78 °C. To the mixture was added $NaBH_4$ (1.44 g, 38.1 mmol) at −78 °C, and stirring was continued at −78 °C to room temperature under argon atmosphere overnight. Then the reaction mixture was quenched with NH_4Claq, evaporated in vacuo, extracted with EtOAc, dried over Na_2SO_4, evaporated in vacuo to afford the alcohol compound. This crude product was used without further purification. It was dissolved in THF and NaH (60 %, 1.24 g, 31.0 mmol) was added at 0 °C. After stirring at room temperature for 10 min, it was cooled to 0 °C, BnBr (3.71 mL, 31.0 mmol) and KI (5.52 g, 33.3 mmol) were added and stirred at 50 °C for 24 h. Then the reaction mixture was quenched with NH_4Claq, evaporated in vacuo, extracted with EtOAc, dried over

Na_2SO_4, evaporated in vacuo and purified by silica gel column chromatography (hexane/EtOAc = 3/1 to 1/1) to afford *N*-[(1*R*,2*R*)-2-{2-(Benzyloxy)ethoxy}cyclohexyl]-*N*-{(*S*)-1-phenylethyl}acetamide (7.67 g, 77 % from *N*-{(1*R*,2*R*)-2-(Allyloxy)cyclohexyl}-*N*-{(*S*)-1-phenylethyl}acetamide). Yellow oil; ^{1}H NMR (500 MHz, DMSO) δ 7.42-7.02 (m, 10H), 4.47 (q, J = 6.3 Hz, 1H), 4.46 (s, 2H), 3.66-3.57 (m, 2H), 3.47-3.38 (m, 2H), 3.23-3.15 (m, 1H), 2.99-2.93 (m, 1H), 2.25-2.19 (m, 1H), 2.04 (s, 3H), 1.85-1.79 (m, 1H), 1.72-1.56 (m, 3H), 1.64 (d, J = 6.3 Hz, 3H), 1.34-1.26 (m, 1H), 1.21-1.05 (m, 2H); ^{13}C NMR (126 MHz, $CHCl_3$) δ 171.1, 142.9, 138.4, 138.2, 128.3, 128.2, 128.1, 127.7, 127.6, 127.52, 127.47, 127.3, 126.4, 125.8, 77.3, 76.9, 73.1, 73.0, 69.5, 69.3, 66.7, 63.3, 53.1, 30.7, 25.5, 25.3, 24.6, 24.2, 24.0, 23.7, 20.1; IR (ATR) ν 2978, 2921, 1642, 1235, 1088 cm^{-1}; MS (FAB$^+$) 396 (M + H$^+$, 31), 105 (100); Anal. Calcd. for $C_{25}H_{33}NO_3$: C, 75.91; H, 8.41; N, 3.54; Found: C, 76.04; H, 8.69; N, 3.58; $[\alpha]^{22}_D$ + 16.5 (c 1.00, $CHCl_3$).

A solution of *N*-[(1*R*,2*R*)-2-{2-(Benzyloxy)ethoxy}cyclohexyl]-*N*-{(*S*)-1-phenylethyl}acetamide (3.40 g, 8.60 mmol) in HCO_2H (16 mL) was heated to 100 °C in sealed tube for 12 h. After that the reaction mixture was evaporated in vacuo and purified by silica gel column chromatography (EtOAc) to afford *N*-[(1*R*,2*R*)-2-{2-(Benzyloxy)ethoxy}cyclohexyl]acetamide (1.53 g, 61 %). White solids; mp 79–80 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 5.96 (s, 1H), 4.60 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 3.79 (ddd, J_1 = 9.3 Hz, $J_2 = J_3$ = 3.5 Hz, 1H), 3.67 (ddd, $J_1 = J_2$ = 8.1 Hz, J_3 = 2.9 Hz, 1H), 3.63-3.54 (m, 3H), 3.19 (ddd, $J_1 = J_2$ = 10.3 Hz, J_3 = 4.0 Hz, 1H), 2.36-2.27 (m, 1H), 2.09-2.00 (m, 1H), 1.81 (s, 3H), 1.77-1.72 (m, 1H), 1.63-1.58 (m, 1H), 1.36-1.18 (m, 3H), 1.06 (dd, J_1 = 21.2 Hz, J_2 = 3.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 137.9, 128.4, 127.8, 127.6, 81.0, 73.2, 70.2, 67.5, 53.7, 31.3, 30.4, 24.1, 24.0, 23.4; IR (ATR) ν 3286, 2978, 2919, 1648, 1234, 1090; MS (FAB$^+$) 292 (M + H$^+$, 100); HRMS (FAB$^+$) Calcd. for $C_{17}H_{26}NO_3$: 292.1913, Found: 292.1904; $[\alpha]^{25}_D$ + 19.9 (c 1.09, $CHCl_3$).

A mixture of *N*-[(1*R*,2*R*)-2-{2-(Benzyloxy)ethoxy}cyclohexyl]acetamide (647 mg, 2.22 mmol) and 6N HCl (22 mL) was stirred at reflux condition for 12 h. Then the reaction mixture was cooled to 0 °C, basified with 6 N NaOH, extracted with $CHCl_3$, dried over Na_2SO_4 and evaporated in vacuo to afford the primary amino alcohol. To a solution of this compound in CH_2Cl_2 was added bis(trifluoromethyl)phenylisothiocyanate (0.402 mL, 2.22 mmol) at room temperature. The stirring was continued for 1 h and then the resulting mixture was purified by silica gel column chromatography (hexane/EtOAc = 1/1 to 1/2) to obtain the desired hydroxythiourea **1n** (311 mg, 33 % from *N*-[(1*R*,2*R*)-2-{2-(Benzyloxy)ethoxy}cyclohexyl]acetamide). White solids; mp 141–142 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.67 (s, 1H), 8.15 (s, 2H), 7.60 (s, 1H), 6.43 (s, 1H), 3.91-3.77 (m, 3H), 3.70-3.48 (m, 2H), 3.22 (dt, J_1 = 10.2 Hz, J_2 = 4.3 Hz, 1H), 2.31-2.12 (m, 2H), 1.86-1.75 (m, 3H), 1.42-1.10 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.3, 141.1, 131.5 (q, J = 27.6 Hz), 123.3, 123.1 (q, J = 274.0 Hz), 117.7, 84.4, 70.5, 61.6, 59.1, 31.7, 30.3, 24.3, 23.5; IR (ATR) ν 3392, 2927, 1645, 1174 cm^{-1}; MS

(FAB$^+$) 431 (M + H$^+$, 100); Anal. Calcd. for $C_{17}H_{20}F_6N_2O_2S$: C, 47.44; H, 4.68; N, 6.51; Found: C, 47.04; H, 4.53; N, 6.33; $[\alpha]^{26}_D$ − 61.3 (c 1.00, $CHCl_3$).

A mixture of *N*-[(1*R*,2*R*)-2-{2-(Benzyloxy)ethoxy}cyclohexyl]acetamide (110 mg, 0.378 mmol) and Pd/C (10 %, 72.4 mg) in MeOH (2.0 mL) was stirred at room temperature under the 1 atom of hydrogen atmosphere for 24 h. Then the catalyst was removed by filtration through Celite and the filtrate was concentrated in vacuo to afford the acetoamide **1o** (74.8 mg, 98 %). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (s, 1H), 3.79-3.65 (m, 4H), 3.45 (ddd, $J_1 = 7.2$ Hz, $J_2 = J_3 = 4.6$ Hz, 1H), 3.14 (ddd, $J_1 = J_2 = 9.7$ Hz, $J_3 = 4.6$ Hz, 1H), 2.16-2.03 (m, 2H), 1.99 (s, 3H), 1.77-1.72 (m, 1H), 1.66-1.61 (m, 1H), 1.39-1.11 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 81.0, 69.6, 61.9, 53.2, 31.4, 30.5, 24.1, 23.9, 23.3; IR (ATR) ν 3288, 2979, 2920, 1635, 1236 cm^{-1}; MS (FAB$^+$) 202 (M + H$^+$, 100); HRMS (FAB$^+$) Calcd. for $C_{10}H_{20}NO_3$: 202.1443, Found: 202.1444; $[\alpha]^{27}_D$ + 20.6 (c 1.41, $CHCl_3$).

3.2.3.6 Typical Procedure for the Synthesis of the Glyoxylamides 26

The glyoxylamide **26** were prepared from N-monoalkyl anilines via two steps.

To a mixture of N-ethylaniline (10.7 g, 88.3 mmol) and K_2CO_3 (27.7 g, 200 mmol) in THF (200 mL) was added acryloyl chloride (8.61 mL, 106 mmol) at 0 °C and stirred at the same temperature for 10 min. Then the reaction mixture was extracted with EtOAc, washed with $NaHCO_3$aq, H_2O, 1 N HCl, H_2O and brine, dried over Na_2SO_4, evaporated in vacuo and purified by silica gel column chromatography (hexane/EtOAc = 1/2) to afford N-ethyl-N-phenylacrylamide (15.4 g, 99 %). Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, $J_1 = J_2 = 7.5$ Hz, 2H), 7.36 (dd, $J_1 = J_2 = 7.5$ Hz, 1H), 7.17 (d, $J = 7.5$ Hz, 2H), 6.36 (d, $J = 16.9$ Hz, 1H), 5.99 (dd $J_1 = 16.9$ Hz, $J_2 = 10.0$ Hz, 1H), 5.49 (d, $J = 10.0$ Hz, 1H), 3.84 (q, $J = 7.2$ Hz, 2H), 1.15 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.9, 141.5, 129.3, 128.7, 128.1, 127.5, 127.0, 44.1, 12.7; IR (ATR) ν 2978, 1676, 1615, 1412 cm^{-1}; MS (FAB$^+$) 176 (M + H$^+$, 100); HRMS (FAB$^+$) Calcd. for $C_{11}H_{14}NO$: 176.1075, Found: 176.1077.

A procedure similar to that described for the preparation of *N*-ethyl-*N*-phenylacrylamide afforded *N*-Methyl-*N*-phenylacrylamide. White solids; mp 75-76 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, $J_1 = J_2 = 7.5$ Hz, 2H), 7.34 (dd, $J_1 = J_2 = 7.5$ Hz, 1H), 7.18 (d, $J = 7.5$ Hz, 2H), 6.37 (d, $J = 16.7$ Hz, 1H), 6.07 (dd $J_1 = 16.7$ Hz, $J_2 = 10.0$ Hz, 1H), 5.52 (d, $J = 10.0$ Hz, 1H), 3.36 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.7, 143.3, 129.5, 128.4, 127.5, 127.3, 127.2, 37.3; IR (ATR) ν 3053, 1656, 1614, 1425 cm^{-1}; MS (FAB$^+$) 162 (M + H$^+$, 100); Anal. Calcd. for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69; Found: C, 74.53; H, 6.99; N, 8.63.

N-Ethyl-*N*-phenylacrylamide (15.4 g, 87.9 mmol) was dissolved in dichloromethane (200 mL) and methanol (50 mL). The solution was purged with O_3 at −78 °C until the solution turned blue. The excess O_3 was removed by purging

oxygen at −78 °C. To the mixture was added PPh_3 (23.6 g, 90.0 mmol) at −78 °C, and stirring was continued at −78 °C to room temperature under argon atmosphere overnight. Then the reaction mixture was concentrated in vacuo and purified by distillation (118 °C/0.8 mmHg) to afford the glyoxylamide **26c** (9.37 g, 60 %). Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33 (s, 1H), 7.50-7.36 (m, 3H), 7.19 (d, J = 7.2 Hz, 2H), 3.87 (q, J = 7.2 Hz, 2H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.8, 161.7, 138.8, 129.8, 129.6, 127.4, 44.5, 12.4; IR (KBr) ν 3393, 1657, 1595, 1496 cm^{-1}; MS (FAB^+) 178 ($M + H^+$, 100); HRMS (FAB^+) Calcd. for $C_{10}H_{12}NO_2$: 178.0868, Found: 178.0868. This compound is sensitive to air and moisture. It was sealed and protected under argon and stored in a freezer.

N-Methyl-2-oxo-*N*-phenylacetamide (**26b**): A procedure similar to that described for the preparation of **26c** afforded **26b.** Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (s, 1H), 7.44 (dd, $J_1 = J_2$ = 7.2 Hz, 2H), 7.39 (dd, $J_1 = J_2$ = 7.2 Hz, 1H), 7.20 (d, J = 7.2 Hz, 2H), 3.41 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.6, 162.3, 140.5, 129.9, 128.5, 126.3, 37.1; IR (ATR) ν 3395, 1656, 1595, 1496 cm^{-1}; MS (FAB^+) 164 ($M + H^+$, 100); HRMS (FAB^+) Calcd. for $C_9H_{10}NO_2$: 164.0712, Found 164.0711.

3.2.3.7 Typical Procedure for the Asymmetric Petasis reaction

A mixture of *N*-ethyl-*N*-phenyl glyoxylamide **26c** (84.1 mg, 0.475 mmol), 2,4-dimethoxyaniline **27a** (72.7 mg, 0.475 mmol) and Na_2SO_4 (67.5 mg, 0.475 mmol) in toluene (2.0 mL) was stirred at room temperature for 1 h. After that, the mixture was filtered and the filtrate was evaporated in vacuo to afford the imine **28c** and used without further purifications. A mixture of **28c**, **19h** (132 mg, 0.570 mmol), MS3Å (47.5 mg) and thiourea catalyst **1n** (20.4 mg, 0.0475 mmol) in cyclohexane (9.5 mL) was stirred under argon atmosphere at room temperature. After 24 h, the reaction mixture was directly purified by silica gel column chromatography (hexane/EtOAc = 2/1) to obtain the desired product **29c** (146 mg, 74 % yield in two steps, 92 % ee).

(*S*,*E*)-2-{(2,4-Dimethoxyphenyl)amino}-*N*,*N*-dimethyl-4-phenylbut-3-enamide (**29a**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 7.2 Hz, 2H), 7.29 (dd $J_1 = J_2$ = 7.2 Hz, 2H), 7.22 (dd, $J_1 = J_2$ = 7.2 Hz, 1H), 6.68 (d, J = 15.8 Hz, 1H), 6.50 (d, J = 8.3 Hz, 1H), 6.45 (d, J = 2.6 Hz, 1H), 6.35 (dd, J_1 = 8.3 Hz, J_2 = 2.6 Hz, 1H), 6.19 (dd, J_1 = 15.8 Hz, J_2 = 7.2 Hz, 1H), 5.20 (s, 1H), 4.91 (d, J = 7.2 Hz, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 3.16 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 152.3, 148.6, 136.2, 133.0, 130.6, 128.5, 127.9, 126.5, 125.7, 111.3, 103.5, 99.2, 56.8, 55.7, 36.9, 36.1; IR (KBr) ν 3317, 2979, 1651, 1236 cm^{-1}; MS (FAB^+) 341 ($M + H^+$, 52), 268 (100); HRMS (FAB^+) Calcd. for $C_{20}H_{25}N_2O_3$: 341.1865, Found: 341.1870; HPLC [Chiralpak AD-H, hexane/2-propanol = 80/20, 1.0 ml/min, λ = 254 nm, retention times: (major) 23.1 min (minor) 15.2 min]; $[\alpha]^{31}{}_D$ +58.4 (c 1.32, $CHCl_3$, 74 % ee).

(*S*,*E*)-2-{(2,4-Dimethoxyphenyl)amino}-*N*-methyl-*N*,4-diphenylbut-3-enamide (**6b**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.39 (m, 3H), 7.34-7.18 (m, 7H), 6.43 (d, $J = 2.3$ Hz, 1H), 6.26 (dd $J_1 = 9.2$, $J_2 = 2.3$ Hz, 1H), 6.19 (d, $J = 9.2$ Hz, 1H), 6.18 (d, $J = 15.5$ Hz, 1H), 6.03 (dd, $J_1 = 15.5$ Hz, $J_2 = 7.2$ Hz, 1H), 5.04 (s, 1H), 4.66 (d, $J = 7.2$ Hz, 1H), 3.81 (s, 3H), 3.70 (s, 3H), 3.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 152.3, 148.6, 142.9, 136.3, 133.1, 130.2, 129.7, 128.4, 127.8, 127.7, 126.4, 126.2, 111.7, 103.4, 99.1, 56.9, 55.6, 55.4, 37.9; IR (KBr) ν 3396, 2980, 2922, 1660, 1595, 1517 cm^{-1}; MS (FAB^+) 402 (M^+, 18), 268 (100); HRMS (FAB^+) Calcd. for $C_{25}H_{26}N_2O_3$: 402.1943, Found: 402.1943; HPLC [Chiralpak AD-H, hexane/2-propanol = 80/20, 1.0 ml/min, $\lambda = 254$ nm, retention times: (major) 13.1 min (minor) 9.7 min]; $[\alpha]^{29}{}_D$ + 17.8 (c 1.91, $CHCl_3$, 86 % ee).

(*S*,*E*)-2-{(2,4-Dimethoxyphenyl)amino}-*N*-ethyl-*N*,4-diphenylbut-3-enamide (**29c**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.41 (m, 3H), 7.29-7.18 (m, 7H), 6.42 (d, $J = 2.6$ Hz, 1H), 6.25 (dd $J_1 = 8.6$ Hz, $J_2 = 2.6$ Hz, 1H), 6.18 (d, $J = 8.6$ Hz, 1H), 6.17 (d, $J = 16.1$ Hz, 1H), 6.01 (dd, $J_1 = 16.1$ Hz, $J_2 = 7.5$ Hz, 1H), 5.02 (s, 1H), 4.57 (d, $J = 7.5$ Hz, 1H), 3.89 (qd, $J_1 = 20.6$ Hz, $J_2 = 7.2$ Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 3.68 (qd, $J_1 = 20.6$ Hz, $J_2 = 7.2$ Hz, 1H), 1.12 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 152.3, 148.7, 141.2, 136.4, 136.1, 133.2, 129.6, 129.0, 128.44, 128.40, 127.7, 126.5, 126.3, 111.8, 103.4, 99.1, 57.2, 55.6, 55.4, 44.8, 12.9; IR (ATR) ν 3404, 2978, 2921, 1659, 1518, 1232 cm^{-1}; MS (FAB^+) 417 ($M + H^+$, 22), 268 (100); Anal. Calcd. for $C_{26}H_{28}N_2O_3$: C, 74.97; H, 6.78; N, 6.73; Found: C, 74.96; H, 7.02; N, 6.55: HPLC [Chiralpak AD-H, hexane/2-propanol = 80/20, 1.0 mL/min, $\lambda = 254$ nm, retention times: (major) 10.3 min (minor) 7.6 min]; $[\alpha]^{27}{}_D$ + 21.8 (c = 1.00 in $CHCl_3$, 92 % ee).

(*S*,*E*)-2-{(2,4-Dimethoxyphenyl)amino}-*N*-ethyl-4-(4-methoxyphenyl)-*N*-phenylbut-3-enamide (**29d**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.44 (m, 3H), 7.22 (d, $J = 6.9$ Hz, 2H), 7.18 (d, $J = 8.3$ Hz, 2H), 6.81 (d, $J = 8.3$ Hz, 2H), 6.42 (d, $J = 2.3$ Hz, 1H), 6.25 (dd $J_1 = 8.3$ Hz, $J_2 = 2.3$ Hz, 1H), 6.18 (d, $J = 8.3$ Hz, 1H), 6.11 (d, $J = 15.8$ Hz, 1H), 5.86 (dd, $J_1 = 15.8$ Hz, $J_2 = 7.7$ Hz, 1H), 4.99 (s, 1H), 4.54 (d, $J = 7.7$ Hz, 1H), 3.88 (qd, $J_1 = 20.9$ Hz, $J_2 = 6.9$ Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.70 (s, 3H), 3.68 (qd, $J_1 = 20.9$ Hz, $J_2 = 6.9$ Hz, 1H), 1.11 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 159.3, 152.2, 148.6, 141.2, 132.7, 130.3, 129.5, 129.2, 129.0, 128.3, 127.7, 124.0, 113.8, 111.7, 103.4, 99.1, 57.2, 55.7, 55.4, 55.3, 44.7, 12.9; IR (ATR) ν 3366, 2978, 2920, 1654, 1236 cm^{-1}; MS (FAB^+) 446 (M^+, 24), 298 (100); HRMS (FAB^+) Calcd. for $C_{27}H_{30}N_2O_4$: 446.2206, Found: 446.2207; HPLC [Chiralpak AD-H, hexane/2-propanol = 80/20, 1.0 ml/min, $\lambda = 254$ nm, retention times: (major) 17.5 min (minor) 11.1 min]; $[\alpha]^{26}{}_D$ + 8.4 (c 1.34, $CHCl_3$, 87 % ee).

(*S*,*E*)-2-{(2,4-Dimethoxyphenyl)amino}-*N*-ethyl-*N*-phenyl-4-(*p*-tolyl)but-3-enamide (**29e**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.42 (m, 3H), 7.22-7.19 (m, 2H), 7.14 (d, $J = 8.0$ Hz, 2H), 7.08 (d, $J = 8.0$ Hz, 2H), 6.41 (d, $J = 2.6$ Hz, 1H), 6.25 (dd $J_1 = 8.6$ Hz, $J_2 = 2.6$ Hz, 1H), 6.17 (d, $J = 8.6$ Hz,

1H), 6.12 (d, $J = 16.1$ Hz, 1H), 5.95 (dd, $J_1 = 16.1$ Hz, $J_2 = 7.2$ Hz, 1H), 5.01 (s, 1H), 4.55 (d, $J = 7.2$ Hz, 1H), 3.87 (qd, $J_1 = 20.9$ Hz, $J_2 = 7.2$ Hz, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 3.69 (qd, $J_1 = 20.9$ Hz, $J_2 = 7.2$ Hz, 1H), 2.23 (s, 3H), 1.12 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 152.3, 148.6, 141.2, 137.6, 133.6, 133.1, 130.3, 129.6, 129.1, 129.0, 128.4, 126.4, 125.2, 111.8, 103.4, 99.1, 57.2, 55.7, 55.4, 44.8, 21.2, 12.9; IR (ATR) ν 3382, 2967, 2923, 1654, 1206 cm^{-1}; MS (FAB$^+$) 431 (M + H$^+$, 7), 282 (100); HRMS (FAB$^+$) Calcd. for $C_{27}H_{31}N_2O_3$: 431.2335, Found: 431.2334; HPLC [Chiralpak AD-H, hexane/2-propanol = 80/20, 1.0 ml/min, $\lambda = 254$ nm, retention times: (major) 14.7 min (minor) 8.4 min]; $[\alpha]^{26}{}_D$ + 13.6 (c 1.91, $CHCl_3$, 90 % ee).

(*S*,*E*)-4-(4-Chlorophenyl)-2-{(2,4-dimethoxyphenyl)amino}-*N*-ethyl-*N*-phenylbut-3-enamide (**29f**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.40 (m, 3H), 7.26-7.14 (m, 6H), 6.43 (d, $J = 2.3$ Hz, 1H), 6.25 (dd $J_1 = 8.9$ Hz, $J_2 = 2.3$ Hz, 1H), 6.15 (d, $J = 8.9$ Hz, 1H), 6.13 (d, $J = 16.1$ Hz, 1H), 5.98 (dd, $J_1 = 16.1$ Hz, $J_2 = 7.5$ Hz, 1H), 5.03 (s, 1H), 4.56 (d, $J = 7.5$ Hz, 1H), 3.91 (qd, $J_1 = 20.9$ Hz, $J_2 = 7.5$ Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 3.66 (qd, $J_1 = 20.9$ Hz, $J_2 = 7.5$ Hz, 1H), 1.18 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.0, 170.3, 152.4, 148.7, 141.1, 134.9, 131.8, 130.1, 129.6, 128.9, 128.6, 128.5, 127.7, 127.0, 111.7, 103.4, 99.2, 57.1, 55.6, 55.4, 44.8, 12.9; IR (ATR) ν 3214, 2921, 1659, 1236 cm^{-1}; MS (FAB$^+$) 451 (M + H$^+$, 100); HRMS Calcd. for $C_{26}H_{28}ClN_2O_3$: 451.1788, Found: 451.1784: HPLC [Chiralpak AD-H, hexane/2-propanol = 80/20, 1.0 ml/min, $\lambda = 254$ nm, retention times: (major) 14.7 min (minor) 10.9 min]; $[\alpha]^{27}{}_D$ + 1.3 (c 1.45, $CHCl_3$, 90 % ee).

(*S*,*E*)-2-{(2,4-Dimethoxyphenyl)amino}-*N*-ethyl-4-(3-methoxyphenyl)-*N*-phenylbut-3-enamide (**29g**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.44 (m, 3H), 7.25-7.18 (m, 3H), 6.83 (d, $J = 7.8$ Hz, 1H), 6.81-6.76 (m, 2H), 6.42 (d, $J = 2.6$ Hz, 1H), 6.25 (dd $J_1 = 8.6$ Hz, $J_2 = 2.6$ Hz, 1H), 6.17 (d, $J = 8.6$ Hz, 1H), 6.13 (d, $J = 15.8$ Hz, 1H), 6.00 (dd, $J_1 = 15.8$ Hz, $J_2 = 7.5$ Hz, 1H), 5.04 (s, 1H), 4.56 (d, $J = 7.5$ Hz, 1H), 3.88 (qd, $J_1 = 20.1$ Hz, $J_2 = 7.2$ Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.71 (s, 3H), 3.69 (qd, $J_1 = 20.1$ Hz, $J_2 = 7.2$ Hz, 1H), 1.12 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 160.0, 152.3, 148.7, 137.8, 133.1, 130.2, 129.6, 129.4, 129.0, 128.5, 128.4, 126.6, 119.2, 113.5, 111.7, 111.6, 103.5, 99.2, 57.2, 55.7, 55.5, 55.2, 44.8, 12.9; IR (ATR) ν 2978, 2920, 1654, 1236 cm^{-1}; MS (FAB$^+$) 447 (M + H$^+$, 8), 298 (100); HRMS (FAB$^+$) Calcd. for $C_{27}H_{31}N_2O_4$: 447.2284, Found: 447.2287; HPLC [Chiralpak AD-H, hexane/2-propanol = 80/20, 1.0 ml/min, $\lambda = 254$ nm, retention times: (major) 10.4 min (minor) 7.7 min]; $[\alpha]^{27}{}_D$ + 18.8 (c 1.04, $CHCl_3$, 89 % ee).

(*S*,*E*)-2-{(2,4-Dimethoxyphenyl)amino}-*N*-ethyl-*N*-phenyl-4-(*o*-tolyl)but-3-enamide (**29 h**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.42 (m, 3H), 7.35-7.31 (m, 1H), 7.28-7.21 (m, 2H), 7.14-7.06 (m, 3H), 6.42 (d, $J = 2.6$ Hz, 1H), 6.41 (d, $J = 15.8$ Hz, 1H), 6.26 (dd $J_1 = 8.6$ Hz, $J_2 = 2.6$ Hz, 1H), 6.21 (d, $J = 8.6$ Hz, 1H), 5.90 (dd, $J_1 = 15.8$ Hz, $J_2 = 7.5$ Hz, 1H), 4.58 (d, $J = 7.5$ Hz, 1H), 3.85 (qd, $J_1 = 20.6$ Hz, $J_2 = 7.2$ Hz, 1H), 3.84 (s, 1H), 3.82 (s, 3H), 3.72 (qd, $J_1 = 20.6$ Hz, $J_2 = 7.2$ Hz, 1H), 3.71 (s, 3H), 2.19 (s, 3H), 1.13

(t, $J = 7.2$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 152.4, 148.8, 141.3, 140.4, 135.5, 135.4, 131.1, 130.1, 129.6, 128.9, 128.4, 127.6, 127.5, 126.0, 125.7, 112.2, 103.5, 99.1, 57.4, 55.7, 55.4, 44.8, 19.7, 12.9; IR (ATR) ν 2978, 2921, 1660, 1518, 1236 cm^{-1}; MS (FAB^+) 431 ($M + H^+$, 100); HRMS Calcd. for $C_{27}H_{31}N_2O_3$: 431.2335, Found: 431.2337; HPLC [Chiralpak AD-H, hexane/2-propanol = 80/20, 1.0 ml/min, $\lambda = 254$ nm, retention times: (major) 8.9 min (minor) 7.0 min]; $[\alpha]^{27}{}_D$ + 13.6 (c 1.00, $CHCl_3$, 93 % ee).

(*S*,*E*)-2-{(2,4-Dimethoxyphenyl)amino}-*N*-ethyl-*N*-phenyl-4-(thiophen-3-yl) but-3-enamide (29**i**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56-7.41 (m, 3H), 7.22-7.18 (m, 3H), 7.11 (d, $J = 4.9$ Hz, 1H), 7.04 (d, $J = 2.3$ Hz, 1H), 6.42 (d, $J = 2.6$ Hz, 1H), 6.25 (dd $J_1 = 8.1$ Hz, $J_2 = 2.6$ Hz, 1H), 6.20 (d, $J = 15.8$ Hz, 1H), 6.16 (d, $J = 8.6$ Hz, 1H), 5.87 (dd, $J_1 = 15.8$ Hz, $J_2 = 7.5$ Hz, 1H), 5.00 (s, 1H), 4.51 (d, $J = 7.5$ Hz, 1H), 3.89 (qd, $J_1 = 20.7$ Hz, $J_2 = 6.9$ Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 3.68 (qd, $J_1 = 20.7$ Hz, $J_2 = 6.9$ Hz, 1H), 1.12 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 152.3, 148.6, 141.2, 139.1, 130.2, 129.6, 128.9, 128.4, 127.3, 126.1, 125.9, 125.0, 122.4, 111.7, 103.4, 99.1, 57.0, 55.7, 44.7, 12.9; IR (ATR) ν 3366, 2976, 2920, 1658, 1595, 1236 cm^{-1}; MS (FAB^+) 423 ($M + H^+$, 23), 274 (100); HRMS (FAB^+) Calcd. for $C_{24}H_{27}N_2O_3S$: 423.1742, Found: 423.1739; HPLC [Chiralpak AD-H, hexane/2-propanol = 80/20, 1.0 ml/min, $\lambda = 254$ nm, retention times: (major) 14.7 min (minor) 10.9 min]; $[\alpha]^{27}{}_D$ + 9.3 (c 2.40, $CHCl_3$, 89 % ee).

(*S*,*E*)-4-Cyclohexyl-2-{(2,4-dimethoxyphenyl)amino}-*N*-ethyl-*N*-phenylbut-3-enamide (**29j**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.39 (m, 3H), 7.18 (d, $J = 7.5$ Hz, 2H), 6.41 (d, $J = 2.6$ Hz, 1H), 6.26 (dd $J_1 = 8.6$ Hz, $J_2 = 2.6$ Hz, 1H), 6.15 (d, $J = 8.6$ Hz, 1H), 5.24-5.18 (m, 2H), 4.82 (s, 1H), 4.33 (d, $J = 5.5$ Hz, 1H), 3.81 (m, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.69 (m, 1H), 1.86 (dd, $J_1 = 10.6$ Hz, $J_2 = 9.2$ Hz, 1H), 1.71-1.58 (m, 5H), 1.28-1.15 (m, 3H), 1.10 (t, $J = 7.2$ Hz, 3H), 1.04-0.91 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 152.2, 148.7, 144.2, 140.9, 129.4, 129.0, 128.2, 124.0, 111.9, 103.4, 99.9, 99.1, 57.2, 55.7, 44.6, 40.5, 32.6, 32.4, 26.1, 25.9, 12.9; IR (ATR) ν 2978, 2922, 1650, 1236 cm^{-1}; MS (FAB^+) 422 (M^+, 30), 274 (100); HRMS (FAB +) Calcd. for $C_{26}H_{34}N_2O_3$: 422.2569, Found: 422.2568; HPLC [Chiralpak AD-H, hexane/2-propanol = 90/10, 1.0 ml/min, $\lambda = 254$ nm, retention times: (major) 9.3 min (minor) 7.3 min]; $[\alpha]^{27}{}_D$ + 16.7 (c 0.90, $CHCl_3$, 80 % ee).

(*S*,*E*)-*N*-Ethyl-2-{(4-methoxyphenyl)amino}-*N*,4-diphenylbut-3-enamide (**29k**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.47 (m, 3H), 7.31-7.20 (m, 7H), 6.71 (d, $J = 8.9$ Hz, 2H), 6.47 (d, $J = 8.9$ Hz, 2H), 6.18 (d, $J = 16.1$ Hz, 1H), 5.99 (dd, $J_1 = 16.1$ Hz, $J_2 = 7.4$ Hz, 1H), 4.59 (s, 1H), 4.53 (d, $J = 7.4$ Hz, 1H), 3.89 (qd, $J_1 = 20.8$ Hz, $J_2 = 7.2$ Hz, 1H), 3.71 (s, 3H), 3.66 (qd, $J_1 = 20.8$ Hz, $J_2 = 7.2$ Hz, 1H), 1.11 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 152.4, 141.0, 140.3, 136.3, 133.3, 129.7, 128.9, 128.53, 128.48, 127.8, 126.5, 126.0, 115.7, 114.7, 57.9, 55.7, 44.8, 12.9; IR (KBr) ν 3366, 2976, 2921, 1654, 1236 cm^{-1}; MS (FAB^+) 446 ($M + H^+$, 24), 298 (100); HRMS (FAB +) Calcd.. for $C_{27}H_{27}N_2O_4$: 446.2206, Found: 446.2207; HPLC [Chiralpak AD-H, hexane/

2-propanol = 80/20, 1.0 ml/min, $\lambda = 254$ nm, retention times: (major) 46.2 min (minor) 22.7 min]; $[\alpha]^{26}_{D}$ + 34.6 (c 1.55, $CHCl_3$, 81 % ee).

(*S*,*E*)-*N*-Ethyl-2-{(2-methoxyphenyl)amino}-*N*,4-diphenylbut-3-enamide (**29l**): Colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.43 (m, 3H), 7.32-7.18 (m, 7H), 6.75 (d, $J = 8.1$ Hz, 1H), 6.70 (dd $J_1 = J_2 = 8.1$ Hz, 1H), 6.62 (dd, $J_1 = J_2 = 8.1$ Hz, 1H), 6.23 (d, $J = 8.1$ Hz, 1H), 6.17 (d, $J = 15.8$ Hz, 1H), 5.99 (dd, $J_1 = 15.8$ Hz, $J_2 = 7.5$ Hz, 1H), 5.43 (d, $J = 7.5$ Hz, 1H), 4.64 (dd, $J_1 = J_2 = 7.5$ Hz, 1H), 3.93 (qd, $J_1 = 20.6$ Hz, $J_2 = 7.2$ Hz, 1H), 3.86 (s, 3H), 3.66 (qd, $J_1 = 20.6$ Hz, $J_2 = 7.2$ Hz, 1H), 1.13 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 147.3, 141.1, 136.3, 133.2, 129.7, 129.0, 128.4, 127.7, 126.5, 125.9, 120.8, 116.9, 114.0, 110.7, 109.5, 98.9, 56.4, 55.4, 44.9, 12.9; IR (ATR) ν 3401, 2980, 1654, 1236 cm^{-1}; MS (FAB^+) 387 ($M + H^+$, 81), 238 (100); HRMS (FAB^+) Calcd. for $C_{25}H_{27}N_2O_2$: 387.2073, Found: 387.2072; HPLC [Chiralcel OD-3, hexane/2-propanol = 90/10, 1.0 ml/min, $\lambda = 254$ nm, retention times: (major) 8.0 min (minor) 5.5 min]; $[\alpha]^{26}_{D}$ + 13.0 (c 1.46, $CHCl_3$, 86 % ee).

(*S*,*E*)-*N*-ethyl-*N*,4-diphenyl-2-(*p*-tolylamino)but-3-enamide (**29m**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.43 (m, 3H), 7.30-7.19 (m, 7H), 6.91 (d, $J = 8.3$ Hz, 2H), 6.40 (d, $J = 8.3$ Hz, 2H), 6.18 (d, $J = 16.1$ Hz, 1H), 5.97 (dd, $J_1 = 16.1$ Hz, $J_2 = 7.2$ Hz, 1H), 4.75 (s, 1H), 4.59 (d, $J = 7.2$ Hz, 1H), 3.91 (qd, $J_1 = 20.7$ Hz, $J_2 = 7.2$ Hz, 1H), 3.66 (qd, $J_1 = 20.7$ Hz, $J_2 = 7.2$ Hz, 1H), 2.18 (s, 3H), 1.20 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 143.9, 141.0, 136.3, 133.3, 129.7, 129.6, 129.0, 128.52, 128.45, 127.8, 126.9, 126.5, 125.9, 114.0, 57.0, 44.8, 20.4, 12.9; IR (ATR) ν 3366, 2975, 2921, 1654, 1236 cm^{-1}; MS (FAB^+) 371 ($M + H^+$, 100); HRMS (FAB^+) Calcd. for $C_{25}H_{27}N_2O$: 371.2123, Found: 371.2123; HPLC [Chiralpak AD-H, hexane/2-propanol = 80/20, 1.0 ml/min, $\lambda = 254$ nm, retention times: (major) 28.5 min (minor) 15.1 min]; $[\alpha]^{29}_{D}$ + 41.5 (c 1.83, $CHCl_3$, 87 % ee).

(*S*,*E*)-*N*-Ethyl-*N*,4-diphenyl-2-(phenylamino)but-3-enamide (**29n**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.43 (m, 3H), 7.31-7.18 (m, 7H), 7.09 (dd, $J_1 = J_2 = 7.4$ Hz, 2H), 6.66 (dd, $J_1 = J_2 = 7.4$ Hz, 1H), 6.48 (d, $J = 7.4$ Hz, 2H), 6.17 (d, $J = 16.1$ Hz, 1H), 5.96 (dd $J_1 = 16.1$ Hz, $J_2 = 7.2$ Hz, 1H), 4.92 (s, 1H), 4.63 (d, $J = 7.2$ Hz, 1H), 3.93 (qd, $J_1 = 20.6$ Hz, $J_2 = 7.2$ Hz, 1H), 3.65 (qd, $J_1 = 20.6$ Hz, $J_2 = 7.2$ Hz, 1H), 1.13 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 146.2, 141.0, 136.2, 133.4, 129.7, 129.1, 129.0, 128.6, 128.5, 127.8, 126.5, 125.7, 117.7, 113.7, 56.6, 44.9, 12.9; IR (ATR) ν 3399, 2978, 2921, 1654, 1602, 1236 cm^{-1}; MS (FAB^+) 357 ($M + H^+$, 72), 208 (100); HRMS (FAB^+) Calcd. for $C_{24}H_{25}N_2O$: 357.1967, Found: 357.1966; HPLC [Chiralpak AD-H, hexane/2-propanol = 80/20, 1.0 ml/min, $\lambda = 254$ nm, retention times: (major) 28.0 min (minor) 14.7 min]; $[\alpha]^{26}_{D}$ + 33.0 (c 1.13, $CHCl_3$, 84 % ee).

(*S*,*E*)-2-{(2,3-Dimethylphenyl)amino}-*N*-ethyl-*N*,4-diphenylbut-3-enamide (**29o**): Colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.47 (m, 3H), 7.32-7.18 (m, 7H), 6.85 (dd $J_1 = J_2 = 7.7$ Hz, 1H), 6.55 (d, $J = 7.7$ Hz, 1H), 6.17 (d, $J = 16.6$ Hz, 1H), 6.14 (d, $J = 7.7$ Hz, 1H), 5.97 (dd, $J_1 = 16.6$ Hz, $J_2 = 6.9$ Hz, 1H), 4.93 (d, $J = 7.2$ Hz, 1H), 4.64 (dd, $J_1 = 7.2$ Hz, $J_2 = 6.9$ Hz,

1H), 3.93 (qd, $J_1 = 19.8$ Hz, $J_2 = 7.5$ Hz, 1H), 3.65 (qd, $J_1 = 19.8$ Hz, $J_2 = 7.5$ Hz, 1H), 2.26 (s, 3H), 2.15 (s, 3H), 1.13 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6, 144.2, 141.0, 136.7, 136.3, 133.1, 129.7, 129.0, 128.5, 128.4, 127.7, 126.5, 125.8, 121.2, 120.0, 109.2, 57.0, 45.0, 20.7, 12.9, 12.7; IR (ATR) ν 3424, 2980, 2920, 1654, 1236 cm^{-1}; MS (FAB^+) 385 ($M + H^+$, 25), 236 (100); HRMS (FAB +) Calcd. for $C_{26}H_{29}N_2O$: 385.2280, Found: 385.2282; HPLC [Chiralpak AD-H, hexane/2-propanol = 80/20, 1.0 ml/min, $\lambda = 254$ nm, retention times: (major) 8.1 min (minor) 6.4 min]; $[\alpha]^{29}_D$ + 13.4 (c 1.00, $CHCl_3$, 90 % ee).

(*S*,*E*)-2-{(2-[{(*tert*-Butyldimethylsilyl)oxy}methyl]phenyl)amino}-*N*-ethyl-*N*,4-diphenylbut-3-enamide (**29p**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.44 (m, 3H), 7.30-7.19 (m, 7H), 7.07 (d, $J = 7.2$ Hz, 1H), 7.00 (dd $J_1 = J_2 = 7.2$ Hz, 1H), 6.60 (dd, $J_1 = J_2 = 7.2$ Hz, 1H), 6.23 (d, $J = 7.2$ Hz, 1H), 6.21 (d, $J = 15.8$ Hz, 1H), 6.00 (dd, $J_1 = 15.8$ Hz, $J_2 = 7.2$ Hz, 1H), 5.75 (d, $J = 7.7$ Hz, 1H), 4.78 (d, $J = 12.3$ Hz, 1H), 4.67 (d, $J = 12.3$ Hz, 1H), 4.66 (dd, $J_1 = 7.7$ Hz, $J_2 = 7.2$ Hz, 1H), 3.94 (qd, $J_1 = 20.7$ Hz, $J_2 = 7.2$ Hz, 1H), 3.66 (qd, $J_1 = 20.7$ Hz, $J_2 = 7.2$ Hz, 1H), 1.12 (t, $J = 7.2$ Hz, 3H), 0.94 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 145.1, 141.2, 136.4, 133.0, 129.7, 129.0, 128.5, 128.42, 128.36, 128.1, 127.7, 126.5, 126.0, 125.5, 116.5, 111.0, 64.5, 56.3, 44.8, 25.9, 18.3, 12.9, −5.20, −5.22; IR (ATR) ν 2980, 2921, 1669, 1236 cm^{-1}; MS (FAB^+) 501 ($M + H^+$, 60), 353 (100); HRMS (FAB^+) Calcd. for $C_{31}H_{41}N_2O_2Si$: 501.2937, Found: 501.2933; HPLC [Chiralpak IC, hexane/2-propanol = 95/5, 0.5 ml/min, $\lambda = 254$ nm, retention times: (major) 9.7 min (minor) 9.0 min]; $[\alpha]^{27}_D$ + 1.9 (c 1.27, $CHCl_3$, 82 % ee).

(*S*,*E*)-*tert*-Butyl {3-([1-{ethyl(phenyl)amino}-1-oxo-4-phenylbut-3-en-2-yl]amino)phenyl}carbamate (**29q**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.43 (m, 3H), 7.31-7.18 (m, 7H), 6.98 (dd, $J_1 = 8.1$ Hz, $J_2 = 8.0$ Hz, 1H), 6.65 (s, 1H), 6.59 (d, $J = 8.0$ Hz, 1H), 6.30 (s, 1H), 6.17 (d, $J = 16.1$ Hz, 1H), 6.14 (d, $J = 8.1$ Hz, 1H), 5.95 (dd $J_1 = 16.1$ Hz, $J_2 = 7.2$ Hz, 1H), 4.91 (s, 1H), 4.61 (d, $J = 7.2$ Hz, 1H), 3.94 (qd, $J_1 = 20.3$ Hz, $J_2 = 7.2$ Hz, 1H), 3.63 (qd, $J_1 = 20.3$ Hz, $J_2 = 7.2$ Hz, 1H), 1.94 (s, 9H), 1.12 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.1, 160.7, 147.0, 144.2, 141.0, 139.2, 133.4, 129.7, 129.6, 129.1, 128.53, 128.47, 127.8, 126.5, 125.5, 124.3, 108.5, 87.1, 56.7, 44.9, 28.3, 12.9; IR (ATR) ν 3561, 3352, 2923, 1725, 1656, 1236 cm^{-1}; MS (FAB^+) 472 ($M + H^+$, 12), 73 (100); HRMS (FAB^+) Calcd. for $C_{29}H_{34}N_3O_3$: 472.2600, Found: 472.2600; HPLC [Chiralpak AD-H, hexane/2-propanol = 70/30, 1.0 ml/min, $\lambda = 254$ nm, retention times: (major) 22.1 min (minor) 16.9 min]; $[\alpha]^{29}_D$ + 24.0 (c 1.12, $CHCl_3$, 90 % ee).

3.2.3.8 Determination of the Absolute Configuration of the Petasis Adduct

Interconversion of the Petasis Adduct to the Reference Compound

(*S*)-Methyl [1-{ethyl(phenyl)amino}-1-oxo-4-phenylbutan-2-yl]carbamate (**30**): To a solution of **29c** (131 mg, 0.315 mmol) in CH_3CN (3 mL) and H_2O (3 mL) was added H_5IO_6 (88.4 mg, 0.388 mmol) at room temperature and stirred at the room temperature for 2 h Then the reaction mixture was passed through the short silica gel column ($CHCl_3$/MeOH = 10/1) and resulting amine was used without further purification.

To a solution of amine, iPr_2NEt (54.9 μL, 0.315 mmol) and DMAP (17.2 mg, 0.141 mmol) in THF (3 mL) was added methylchloroformate (24.3 μL, 0.315 mmol) at 0 °C and stirred at room temperature. After 13 h, the reaction mixture was extracted with EtOAc, washed with 1N HCl, H_2O, $NaHCO_3$aq, dried over Na_2SO_4 and evaporated in vacuo to afford the corresponding methylcarbamate. This product was used without further purification.

A mixture of the methylcarbamate and Pd/C (30.0 mg) in MeOH was stirred at 50 °C under the hydrogen atmosphere (1 atm) for 3 h. After that, the mixture was passed through Celite, evaporated in vacuo and purified by silica gel column chromatography (hexane/EtOAc = 2/1) to afford **30** (37.5 mg, 35 % from **29c**): Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.32 (m, 3H), 7.21-7.11 (m, 4H), 6.98 (d, J = 7.2 Hz, 2H), 5.50 (d, J = 8.6 Hz, 1H), 4.35-4.28 (m, 1H), 3.88 (qd, J_1 = 20.3 Hz, J_2 = 6.9 Hz, 1H), 3.66 (s, 3H), 3.58 (qd, J_1 = 20.3 Hz, J_2 = 6.9 Hz, 1H), 2.58-2.51 (m, 1H), 2.42-2.32 (m, 1H), 1.85-1.69 (m, 2H), 1.10 (t, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.0, 171.7, 156.6, 140.8, 140.7, 140.6, 129.8, 128.3, 128.2, 125.8, 52.1, 51.3, 44.6, 34.7, 31.4, 12.8; IR (ATR) ν 3304, 2977, 2923, 1722, 1649, 1237 cm^{-1}; MS (FAB$^+$) 341 (M + H$^+$, 100); HRMS (FAB +) Calcd. for $C_{20}H_{25}N_2O_3$: 341.1865, Found: 341.1866; $[\alpha]^{29}_D$ + 55.7 (c 1.15, $CHCl_3$).

Preparation of the Sample for Reference

To a mixture of commercially available (*S*)-2-amino-5-phenylpentanoic acid (38.8 mg, 0.217 mmol) and $NaHCO_3$ (56.6 mg, 0.674 mmol) in THF (1.0 mL) and H_2O (1.0 mL) was added methylchloroformate (20.1 μL, 0.260 mmol) at room temperature and stirred at the same temperature. After 4 h, the reaction mixture was extracted with EtOAc, dried over Na_2SO_4 and evaporated in vacuo to afford the methylcarbamate. This product was used without further purification.

To a solution of mathylcarbamate in CH_3CN (1.0 mL) were added DMTMM (105 mg) and PhNHEt (35.1 μL, 0.326 mmol) and stirred at room temperature for 32 h. Then the reaction mixture was extracted with EtOAc, washed with 1N HCl, H_2O, $NaHCO_3$aq, brine, dried over Na_2SO_4, evaporated in vacuo and purified by

silica gel column chromatography (hexane/EtOAc = 2/1) to afford **30** (49.1 mg, 66 % from (S)-2-amino-5-phenylpentanoic acid): $[\alpha]_{D^{29}}$ + 44.5 (c = 1.03 in $CHCl_3$).

3.2.3.9 Interconversion to the Tetrahydroquinoline 34

(*S*,*E*)-4-Phenyl-2-(*p*-tolylamino)but-3-en-1-ol (**32**): To a solution of **29m** (89.0 mg, 0.240 mmol) in THF (1.0 mL) was added $LiBHEt_3$ (1.0 M THF solution, 0.528 mL, 0.528 mmol) slowly at −78 °C and stirred at room temperature. After 30 min, the reaction mixture was quenched with NH_4Claq, extracted with EtOAc, dried over Na_2SO_4, evaporated in vacuo and purified by silica gel column chromatography (hexane/EtOAc = 4/1 to 1/1) to afford the aminoalcohol **32** (43.3 mg, 71 %) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J = 7.5 Hz, 2H), 7.29 (dd $J_1 = J_2$ = 7.5 Hz, 2H), 7.22 (dd, $J_1 = J_2$ = 7.5 Hz, 1H), 6.98 (d, J = 8.6 Hz, 2H), 6.63 (d, J = 8.6 Hz, 2H), 6.63 (d, J = 14.9 Hz, 1H), 6.15 (dd, J_1 = 14.9 Hz, J_2 = 6.0 Hz, 1H), 4.13 (ddd, J_1 = 6.6 Hz, J_2 = 6.0 Hz, J_3 = 4.6 Hz, 1H), 3.84 (dd, J_1 = 11.0 Hz, J_2 = 4.6 Hz, 1H), 3.68 (dd, J_1 = 11.0 Hz, J_2 = 6.6 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.9, 136.4, 132.1, 129.7, 128.5, 128.1, 127.7, 127.4, 126.4, 114.2, 65.2, 57.9, 20.4; IR (ATR) ν 3384, 2919, 1519, 1236 cm^{-1}; MS (FAB$^+$) 254 (M + H$^+$, 100); HRMS (FAB$^+$) Calcd. for $C_{17}H_{20}NO$: 254.1545, Found: 254.1544: $[\alpha]^{25}{}_D$ + 68.5 (c 1.18, $CHCl_3$).

(*S*,*E*)-4-Styryl-3-(*p*-tolyl)oxazolidin-2-one (**33**): To a solution of **32** (43.3 mg, 0.172 mmol) in toluene (1.5 mL) was added carbonyldiimidazole (55.7 mg, 0.343 mmol) at room temperature and stirred at 80 °C. After 3 h, the reaction mixture was purified by silica gel column chromatography (hexane/EtOAc = 2/1) to afford the oxazolidinone **33** (43.7 mg, 91 %) as a brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.24 (m, 7H), 7.14 (d, J = 8.0 Hz, 2H), 6.63 (d, J = 15.8 Hz, 1H), 6.10 (dd, J_1 = 15.8 Hz, J_2 = 8.3 Hz, 1H), 4.97 (ddd, J_1 = 8.6 Hz, J_2 = 8.3 Hz, J_3 = 6.6 Hz, 1H), 4.63 (dd, $J_1 = J_2$ = 8.6 Hz, 1H), 4.17 (dd, J_1 = 8.6 Hz, J_2 = 6.6 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.8, 135.2, 135.1, 134.9, 134.3, 129.5, 128.7, 128.5, 126.7, 125.6, 121.8, 67.3, 59.7, 20.8; IR (ATR) ν 2919, 1748, 1515, 1397, 1206 cm^{-1}; MS (FAB$^+$) 280 (M + H$^+$, 100); HRMS (FAB$^+$) Calcd. for $C_{18}H_{18}NO_2$: 280.1338, Found: 280.1336; $[\alpha]^{28}{}_D$ + 106.1 (c 1.00, $CHCl_3$).

(3a*R*,4*S*,5*R*)-4-Iodo-7-methyl-5-phenyl-3,3a,4,5-tetrahydro-1H-oxazolo[3,4-a]quinolin-1-one (**34**): To a solution of **33** (31.2 mg, 0.112 mmol) in AcOH (0.6 mL) were added BTMA·ICl_2 (53.7 mg, 0.154 mmol) and $ZnCl_2$ (33.0 mg, 0.242 mmol) at room temperature and stirred at the same temperature for 1 h. Then the reaction mixture was extracted with EtOAc, dried over Na_2SO_4, evaporated in vacuo and purified by silica gel column chromatography (hexane/EtOAc = 3/1) to afford the tetrahydroquinoline **34** (29.7 mg, 65 %) as white solids. mp 209–210 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02

(d, $J = 8.6$ Hz, 1H), 7.41-7.34 (m, 3H), 7.16 (dd $J_1 = 7.8$ Hz, $J_2 = 1.8$ Hz, 2H), 7.06 (d, $J = 8.6$ Hz, 1H), 6.46 (s, 1H), 4.67-4.59 (m, 2H), 4.47 (d, $J = 10.9$ Hz, 1H), 4.27 (dddd, $J_1 = 11.5$ Hz, $J_2 = 10.9$ Hz, $J_3 = 4.6$ Hz, $J_4 = 4.0$ Hz, 1H), 4.17-4.11 (m, 1H), 2.13 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0, 141.7, 134.0, 131.6, 130.3, 129.1, 128.8, 128.7, 127.8, 127.4, 118.4, 68.8, 60.0, 54.9, 36.6, 20.8; IR (ATR) ν 2901, 1741, 1705, 1503, 1390 cm^{-1}; MS (FAB$^+$) 406 (M + H$^+$, 100); Anal. Calcd. for $C_{18}H_{16}INO_2$: C, 53.35; H, 3.98; N, 3.46; Found: C, 53.12; H, 3.78; N, 3.51; HPLC [Chiralcel OD-3, hexane/2-propanol = 90/10, 1.0 ml/min, $\lambda = 254$ nm, retention times: (major) 13.1 min (minor) 10.8 min]; $[\alpha]^{27}{}_D$ + 56.5 (c 1.24, $CHCl_3$, 85 % ee).

Typical Procedure for the synthesis of **35** and Petasis reaction of these compounds.

Dipeptide precursors **35a** and **35b** were prepared from N-arylglycine methylesters via two steps similar as that of **26c**. Tripeptide precursor **35c** and *ent*-**35c** were prepared from (*S*) or (*R*)-methyl 2-(2-bromoacetamido)propanoate and **35d** were prepared from (*S*)-methyl 2-(2-bromoacetamido)-3-phenylpropanoate, respectively.

A procedure similar to that described for the preparation of *N*-ethyl-*N*-phenylacrylamide afforded Methyl 2-{*N*-(4-methoxyphenyl)acrylamido}acetate. Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, $J = 8.6$ Hz, 2H), 6.91 (d, $J = 8.6$ Hz, 2H), 6.39 (dd $J_1 = 16.9$ Hz, $J_2 = 2.0$ Hz, 1H), 6.11 (dd, $J_1 = 16.9$ Hz, $J_2 = 10.4$ Hz, 1H), 5.58 (dd, $J_1 = 10.4$ Hz, $J_2 = 2.0$ Hz, 1H), 4.43 (s, 3H), 3.83 (s, 3H), 3.74 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 166.1, 159.1, 134.6, 129.1, 128.3, 127.6, 114.6, 55.4, 52.0, 51.3; IR (ATR) ν 2953, 1749, 1657, 1510, 1247 cm^{-1}; MS (FAB$^+$) 250 (M + H$^+$, 100); HRMS (FAB$^+$) Calcd. for $C_{13}H_{16}NO_4$: 250.1079, Found: 250.1078.

A procedure similar to that described for the preparation of *N*-ethyl-*N*-phenylacrylamide afforded Methyl 2-{*N*-(4-bromophenyl)acrylamido}acetate. Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, $J = 8.3$ Hz, 2H), 7.21 (d, $J = 8.3$ Hz, 2H), 6.42 (dd, $J_1 = 16.8$ Hz, $J_2 = 1.7$ Hz, 1H), 6.09 (dd, $J_1 = 16.8$ Hz, $J_2 = 10.3$ Hz, 1H), 5.61 (dd, $J_1 = 10.3$ Hz, $J_2 = 1.7$ Hz, 1H), 4.44 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 165.7, 141.1, 132.8, 129.8, 129.2, 127.4, 122.1, 52.3, 51.1; IR (ATR) ν 3065, 2981, 1742, 1663, 1236 cm^{-1}; MS (FAB$^+$) 298 (M + H$^+$, 100); HRMS (FAB$^+$) Calcd. for $C_{12}H_{13}BrNO_3$: 298.0079, Found: 298.0081.

Methyl 2-{*N*-(4-methoxyphenyl)-2-oxoacetamido}acetate (**35a**): Methyl 2-{*N*-(4-methoxyphenyl)acrylamido}acetate (550 mg, 2.21 mmol) was dissolved in dichloromethane (16 mL) and methanol (4 mL). The solution was purged with O_3 at −78 °C until the solution turned blue. The excess O_3 was removed by purging oxygen at −78 °C. To the mixture was added PPh_3 (23.6 g, 90.0 mmol) at −78 °C, and stirring was continued at −78 °C to room temperature under argon atmosphere overnight. Then the reaction mixture was concentrated in vacuo, extracted with EtOAc, dried over Na_2SO_4 and evaporated in vacuo to afford the hydrated aldehyde. This compound was dissolved in toluene (10 mL) and heated to 130 °C with Dean-

Stark apparatus. Resulting solution was concentrated in vacuo to afford the aldehyde **35a** (528.1 mg, 95 %). This compound is sensitive to air and moisture. It was sealed and protected under argon and stored in a freezer. Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (s, 1H), 7.25 (d, $J = 8.9$ Hz, 2H), 6.93 (d, $J = 8.9$ Hz, 2H), 4.46 (s, 2H), 3.82 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.4, 178.8, 168.3, 162.4, 159.9, 128.7, 115.1, 55.5, 52.5, 51.3; IR (ATR) ν 2959, 2918, 1750, 1660, 1211 cm^{-1}; MS (FAB^+) 252 ($M + H^+$, 31), 136 (100); HRMS (FAB^+) Calcd. for $C_{12}H_{14}NO_5$: 252.0872, Found: 252.0874.

Methyl 2-{*N*-(4-bromophenyl)-2-oxoacetamido}acetate (**35b**): A procedure similar to that described for the preparation of **35a** afforded **35b.** Yellow amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.55 (d, $J = 8.6$ Hz, 2H), 7.21 (d, $J = 8.6$ Hz, 2H), 4.46 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.7, 168.0, 162.1, 138.7, 133.0, 128.9, 122.9, 52.5, 51.2; IR (ATR) ν 2980, 2920, 1770, 1757, 1236 cm^{-1}; MS (FAB^+) 300 ($M + H^+$, 18), 136 (100); HRMS (FAB^+) Calcd.. for $C_{11}H_{11}^{81}BrNO_4$: 301.9856, Found: 301.9849.

(*S*,*E*)-Methyl 2-[2-{(2,4-dimethoxyphenyl)amino}-*N*-(4-methoxyphenyl)-4-phenylbut-3-enamido]acetate (**37a**): A procedure similar to that described for the preparation of **29c** afforded **37a.** Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, $J = 8.3$ Hz, 2H), 7.29-7.19 (m, 5H), 6.94 (d, $J = 8.6$ Hz, 2H), 6.43 (d, $J = 2.3$ Hz, 1H), 6.34 (d, $J = 16.1$ Hz, 1H), 6.31 (dd $J_1 = 8.6$ Hz, $J_2 = 2.3$ Hz, 1H), 6.27 (d, $J = 8.6$ Hz, 1H), 6.04 (dd, $J_1 = 16.1$ Hz, $J_2 = 7.2$ Hz, 1H), 4.94 (s, 1H), 4.70 (d, $J = 7.2$ Hz, 1H), 4.43 (d, $J = 17.2$ Hz, 1H), 4.32 (d, $J = 17.2$ Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.72 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 169.3, 159.6, 152.4, 148.6, 136.4, 134.3, 133.5, 130.3, 129.8, 128.4, 127.7, 126.5, 125.6, 114.7, 111.6, 103.5, 99.2, 56.7, 55.7, 55.5, 55.4, 52.2, 51.8; IR (ATR) ν 3392, 2923, 1750, 1665, 1511, 1206 cm^{-1}; MS (FAB^+) 490 ($M + H^+$, 34), 268 (100); HRMS (FAB^+) Calcd. for $C_{28}H_{31}N_2O_6$: 490.2104, Found: 490.2101; HPLC [Chiralpak AD-H, hexane/2-propanol = 80/20, 1.0 ml/min, $\lambda = 254$ nm, retention times: (major) 17.2 min (minor) 12.2 min]; $[\alpha]^{26}_D$ + 5.5 (c 1.09, $CHCl_3$, 82 % ee).

(*S*,*E*)-Methyl 2-[*N*-(4-bromophenyl)-2-{(2,4-dimethoxyphenyl)amino}-4-phenylbut-3-enamido]acetate (**37b**): A procedure similar to that described for the preparation of **29c** afforded **37b.** Yellow amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, $J = 8.3$ Hz, 2H), 7.34-7.21 (m, 7H), 6.43 (d, $J = 2.3$ Hz, 1H), 6.32 (d, $J = 16.0$ Hz, 1H), 6.30 (dd $J_1 = 8.6$ Hz, $J_2 = 2.6$ Hz, 1H), 6.26 (d, $J = 8.6$ Hz, 1H), 6.04 (dd, $J_1 = 16.0$ Hz, $J_2 = 7.2$ Hz, 1H), 4.87 (s, 1H), 4.67 (d, $J = 7.2$ Hz, 1H), 4.42 (d, $J = 17.2$ Hz, 1H), 4.32 (d, $J = 17.2$ Hz, 1H), 3.81 (s, 3H), 3.723 (s, 3H), 3.719 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 169.0, 152.6, 148.7, 140.7, 136.2, 133.9, 132.9, 130.4, 130.0, 128.5, 127.9, 126.6, 125.3, 122.8, 111.8, 103.5, 99.2, 57.1, 55.7, 55.5, 52.3, 51.5; IR (ATR) ν 2974, 2922, 1750, 1670, 1517, 1236 cm^{-1}; MS (FAB^+) 539 ($M + H^+$, 21), 268 (100); HRMS (FAB^+) Calcd. for $C_{27}H_{27}BrN_2O_5$: 538.1103, Found: 538.1107; HPLC [Chiralpak AD-H, hexane/2-propanol = 80/20, 1.0 ml/min, $\lambda = 254$ nm, retention times: (major) 15.8 min (minor) 10.9 min]; $[\alpha]^{25}_D$ 3.6 (c 1.05, $CHCl_3$, 92 % ee).

To a mixture of (*S*)-methyl 2-(2-bromoacetamido)propanoate (2.30 g, 10.3 mmol) and K_2CO_3 (1.61 g, 11.6 mmol) in CH_3CN (30 mL) was added *p*-anisidine (1.43 g, 11.6 mmol) at room temperature and stirred at the same temperature for 48 h. Then the reaction mixture was evaporated in vacuo, extracted with EtOAc, dried over Na_2SO_4, evaporated in vacuo and purified by silica gel column chromatography (hexane/EtOAc = 1/2) to afford (*S*)-Methyl 2-[2-{(4-methoxyphenyl)amino}acetamido]propanoate (1.78 g, 65 %). White amorphous solids; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (s, 1H), 6.79 (d, J = 8.9 Hz, 2H), 6.59(d, J = 8.9 Hz, 2H), 4.65 (td, J_1 = 7.5 Hz, J_2 = 7.2 Hz, 1H), 3.78-3.74 (m, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 4.08 (s, 1H), 1.38 (d, J = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 170.6, 153.1, 141.2, 114.8, 114.5, 55.6, 52.4, 49.7, 47.6, 18.1; IR (ATR) ν 3365, 2979, 2922, 1742, 1654, 1235 cm^{-1}; MS (FAB$^+$) 266 (M^+, 100); HRMS (FAB +) Calcd. for $C_{13}H_{19}N_2O_4$: 267.1345, Found: 267.1346; $[\alpha]^{28}{}_D$ + 11.8 (c 1.06, $CHCl_3$).

A procedure similar to that described for the preparation of (*S*)-Methyl 2-[2-{(4-methoxyphenyl)amino}acetamido]propanoate afforded (*R*)-Methyl 2-[2-{(4-methoxyphenyl)amino}acetamido]propanoate. NMR spectrum of this compound was identical to that of its enantiomer. $[\alpha]^{27}{}_D$ − 11.6 (c 1.41, $CHCl_3$).

A procedure similar to that described for the preparation of (*S*)-methyl 2-[2-{(4-methoxyphenyl)amino}acetamido]propanoate afforded (*S*)-methyl 2-[2-{(4-methoxyphenyl)amino}acetamido]-3-phenylpropanoate. Colorles amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.23-7.14 (m, 3H), 6.94 (d, J = 7.2 Hz, 2H), 6.77 (d, J = 8.9 Hz, 2H), 6.51 (d, J = 8.9 Hz, 2H), 4.93 (td J_1 = 7.8 Hz, J_2 = 6.3 Hz, 1H), 3.70 (s, 1H), 3.79-3.64 (m, 1H), 3.76 (s, 3H), 3.70 (s, 3H), 3.07 (dd, J_1 = 14.7 Hz, J_2 = 7.8 Hz, 1H), 3.04 (dd, J_1 = 14.7 Hz, J_2 = 6.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 170.6, 153.1, 141.0, 135.5, 129.1, 128.5, 127.0, 114.8, 114.4, 55.7, 52.5, 52.3, 49.4, 37.9; IR (ATR) ν 3372, 2922, 1743, 1663, 1513, 1236 cm^{-1}; MS (FAB$^+$) 342 (M^+, 92), 136 (100); HRMS (FAB$^+$) Calcd. for $C_{19}H_{23}N_2O_4$: 342.1658, Found: 342.1658; $[\alpha]^{29}{}_D$ + 68.0 (c 1.05, $CHCl_3$).

A procedure similar to that described for the preparation of *N*-Ethyl-*N*-phenylacrylamide afforded (*S*)-Methyl 2-2-{*N*-(4-methoxyphenyl)acrylamido}acetamido propanoate. Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 6.3 Hz, 1H), 6.91 (d, J = 8.6 Hz, 2H), 6.42 (dd, J_1 = 16.8 Hz, J_2 = 1.7 Hz, 1H), 6.11 (dd, J_1 = 16.8 Hz, J_2 = 10.3 Hz, 1H), 5.59 (dd, J_1 = 10.3 Hz, J_2 = 1.7 Hz, 1H), 4.59 (qd, J_1 = 7.5 Hz, J_2 = 6.3 Hz, 1H), 4.54 (d, J = 15.2 Hz, 1H), 4.21 (d, J = 15.2 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 1.44 (d, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 168.3, 159.3, 134.6, 128.9, 128.7, 127.7, 114.9, 55.5, 54.3, 52.4, 48.0, 18.2; IR (ATR) ν 3307, 2921, 1744, 1649, 1510, 1219 cm^{-1}; MS (FAB$^+$) 321 (M + H$^+$, 21), 136 (100); HRMS (FAB$^+$) Calcd. for $C_{16}H_{21}N_2O_5$: 321.1450, Found: 321.1449; $[\alpha]^{30}{}_D$ +45.6 (c 0.88, $CHCl_3$).

A procedure similar to that described for the preparation of *N*-Ethyl-*N*-phenylacrylamide afforded (*R*)-Methyl 2-2-{*N*-(4-methoxyphenyl)acrylamido}

acetamido propanoate. NMR spectrum of this compound was identical to that of its enantiomer. $[\alpha]^{27}_{D}$ − 51.0 (c 1.23, $CHCl_3$).

A procedure similar to that described for the preparation of *N*-Ethyl-*N*-phenylacrylamide afforded (*S*)-Methyl 2-[2-{*N*-(4-methoxyphenyl)acrylamido}acetamido]-3-phenylpropanoate. Yellow amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.24 (m, 3H), 7.13 (d, $J = 6.3$ Hz, 2H), 6.94 (s, 1H), 6.91 (d, $J = 8.6$ Hz, 2H), 6.82 (d, $J = 8.6$ Hz, 2H), 6.43 (dd, $J_1 = 16.8$ Hz, $J_2 = 2.1$ Hz, 1H), 6.03 (dd, $J_1 = 16.8$ Hz, $J_2 = 10.3$ Hz, 1H), 5.60 (dd, $J_1 = 10.3$ Hz, $J_2 = 2.1$ Hz, 1H), 4.85 (ddd, $J_1 = J_2 = 7.2$ Hz, $J_3 = 5.5$ Hz, 1H), 4.36 (d, $J = 15.2$ Hz, 1H), 4.27 (d, $J = 15.2$ Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.20 (dd, $J_1 = 13.9$ Hz, $J_2 = 5.5$ Hz, 1H), 3.04 (dd, $J_1 = 13.9$ Hz, $J_2 = 7.2$ Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 168.4, 166.7, 159.2, 135.9, 134.4, 129.3, 128.8, 128.7, 128.6, 127.7, 127.0, 114.8, 55.5, 54.3, 53.2, 52.3, 37.8; IR (ATR) ν 3319, 2919, 1745, 1685, 1659, 1220 cm^{-1}; MS (FAB^+) 397 ($M + H^+$, 69), 136 (100); HRMS (FAB^+) Calcd. for $C_{22}H_{25}N_2O_5$: 397.1763, Found: 397.1765: $[\alpha]^{30}_{D}$ + 7.5 (c 1.06, $CHCl_3$).

(*S*)-Methyl 2-[2-{*N*-(4-methoxyphenyl)-2-oxoacetamido}acetamido]propanoate (**35c**): A procedure similar to that described for the preparation of **35a** afforded **35c.** Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.27 (d, $J = 8.9$ Hz, 2H), 6.92 (d, $J = 8.9$ Hz, 2H), 6.69 (s, 1H), 4.59 (dq, $J_1 = 7.5$ Hz, $J_2 = 7.2$ Hz, 1H), 4.46 (d, $J = 15.5$ Hz, 1H), 4.31 (d, $J = 15.5$ Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 1.42 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.4, 173.0, 166.6, 162.3, 159.7, 131.9, 128.5, 115.0, 55.4, 53.3, 52.4, 48.1, 17.9; IR (ATR) ν 3327, 2977, 2919, 1773, 1743, 1236 cm^{-1}; MS (FAB^+) 323 ($M + H^+$, 71), 136 (100); HRMS (FAB^+) Calcd. for $C_{15}H_{19}N_2O_5$: 323.1243, Found: 323.1243; $[\alpha]^{28}_{D}$ + 8.0 (c 1.02, $CHCl_3$).

(*R*)-Methyl 2-[2-{*N*-(4-methoxyphenyl)-2-oxoacetamido}acetamido]propanoate (*ent*-**35c**): A procedure similar to that described for the preparation of **35a** afforded *ent*-**35c.** NMR spectrum of this compound was identical to that of **35c**. $[\alpha]^{28}_{D}$ − 8.1 (c 1.24, $CHCl_3$).

(*S*)-Methyl 2-[2-{N-(4-methoxyphenyl)-2-oxoacetamido}acetamido]-3-phenylpropanoate (**35d**): A procedure similar to that described for the preparation of **35a** afforded **35d.** Yellow amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.31-7.11 (m, 5H), 7.04 (d, $J = 8.9$ Hz, 2H), 6.86 (d, $J = 8.9$ Hz, 2H), 6.50 (d, $J = 8.0$ Hz, 1H), 4.86 (dd, $J_1 = 6.6$ Hz, $J_2 = 5.2$ Hz, 1H), 4.36 (d, $J = 15.2$ Hz, 1H), 4.28 (d, $J = 15.2$ Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.21 (dd, $J_1 = 13.9$ Hz, $J_2 = 5.2$ Hz, 1H), 3.06 (dd, $J_1 = 13.9$ Hz, $J_2 = 6.6$ Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.1, 171.6, 166.7, 162.4, 159.9, 135.6, 131.7, 129.3, 128.6, 128.4, 127.1, 115.1, 55.5, 53.8, 53.3, 52.4, 37.6; IR (ATR) ν 3324, 2979, 2919, 1773, 1749, 1236 cm^{-1}; MS (FAB^+) 399 ($M + H^+$, 24), 136 (100); HRMS (FAB^+) Calcd. for $C_{21}H_{23}N_2O_6$: 399.1556, Found: 399.1555; $[\alpha]^{28}_{D}$ + 43.1 (c 1.32, $CHCl_3$).

(*S*)-methyl 2-(2-[(*S*,*E*)-2-{(2,4-dimethoxyphenyl)amino}-*N*-(4-methoxyphenyl)-4-phenylbut-3-enamido]acetamido)propanoate (**37c**): A procedure similar to that described for the preparation of **29c** afforded **37c.** Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.20 (m, 7H), 6.95 (d, $J = 8.9$ Hz, 2H), 6.68 (d, $J = 7.5$ Hz, 1H), 6.43 (d, $J = 2.0$ Hz, 1H), 6.36 (d, $J = 15.8$ Hz, 1H), 6.31 (dd, $J_1 = 8.1$ Hz, $J_2 = 2.0$ Hz, 1H), 6.28 (d, $J = 8.1$ Hz, 1H), 6.10 (dd, $J_1 = 15.8$ Hz, $J_2 = 7.2$ Hz, 1H), 4.91 (s, 1H), 4.72 (d, $J = 7.2$ Hz, 1H), 4.54 (qd, $J_1 = J_2 = 7.5$ Hz, 1H), 4.47 (d, $J = 15.5$ Hz, 1H), 4.14 (d, $J = 15.5$ Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 1.28 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 168.0, 159.7, 158.2, 148.8, 136.2, 134.1, 134.0, 129.43, 129.38, 128.5, 128.4, 128.0, 126.6, 125.2, 115.0, 111.8, 103.6, 99.3, 56.9, 55.60, 55.57, 55.5, 54.6, 52.4, 47.9, 17.9; IR (ATR) ν 3328, 2980, 1743, 1662, 1236 cm^{-1}; MS (FAB^+) 562 ($M + H^+$, 30), 268 (100); HRMS (FAB^+) Calcd. for $C_{31}H_{35}N_3O_7$: 561.2475, Found: 561.2473; $[\alpha]^{25}_D + 3.6$ (c 1.18, $CHCl_3$).

(*R*)-methyl 2-(2-[(*S*,*E*)-2-{(2,4-dimethoxyphenyl)amino}-*N*-(4-methoxyphenyl)-4-phenylbut-3-enamido]acetamido)propanoate (**37d**): A procedure similar to that described for the preparation of **29c** afforded **37d.** Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.20 (m, 7H), 6.95 (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 7.2$ Hz, 1H), 6.44 (d, $J = 2.0$ Hz, 1H), 6.39 (d, $J = 16.0$ Hz, 1H), 6.29 (dd, $J_1 = 8.6$ Hz, $J_2 = 2.0$ Hz, 1H), 6.26 (d, $J = 8.6$ Hz, 1H), 6.12 (dd, $J_1 = 16.0$ Hz, $J_2 = 7.2$ Hz, 1H), 4.93 (s, 1H), 4.73 (d, $J = 7.2$ Hz, 1H), 4.52 (qd, $J_1 = J_2 = 7.2$ Hz, 1H), 4.50 (d, $J = 15.2$ Hz, 1H), 4.09 (d, $J = 15.2$ Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.72 (s, 3H), 3.66 (s, 3H), 1.30 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 172.9, 168.0, 159.7, 152.6, 148.7, 136.3, 134.1, 133.7, 130.1, 129.3, 128.4, 127.9, 126.6, 125.5, 114.9, 111.9, 103.5, 99.3, 56.8, 55.63, 55.55, 55.5, 52.3, 47.9, 18.0; IR (ATR) ν 3345, 2979, 1741, 1653, 1236 cm^{-1}; MS (FAB^+) 562 ($M + H^+$, 30), 268 (100); HRMS (FAB^+) Calcd. for $C_{31}H_{35}N_3O_7$: 561.2475, Found: 561.2473; $[\alpha]^{24}_D -23.8$ (c 1.10, $CHCl_3$).

(*S*)-methyl 2-(2-[(*S*,*E*)-2-{(2,4-dimethoxyphenyl)amino}-*N*-(4-methoxyphenyl)-4-phenylbut-3-enamido]acetamido)-3-phenylpropanoate (**37e**): A procedure similar to that described for the preparation of **29c** afforded **37e.** Yellow amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.35-7.20 (m, 9H), 7.01 (d, $J = 8.0$ Hz, 2H), 6.91 (d, $J = 8.0$ Hz, 2H), 6.61 (d, $J = 7.5$ Hz, 1H), 6.44 (s, 1H), 6.32 (d, $J = 15.8$ Hz, 1H), 6.30-6.24 (m, 2H), 6.07 (dd $J_1 = 15.8$ Hz, $J_2 = 7.2$ Hz, 1H), 4.92 (s, 1H), 4.77 (ddd, $J_1 = J_2 = 7.2$ Hz, $J_3 = 5.5$ Hz, 1H), 4.70 (d, $J = 7.2$ Hz, 1H), 4.41 (d, $J = 15.8$ Hz, 1H), 4.10 (d, $J = 15.8$ Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.712 (s, 3H), 3.708 (s, 3H), 3.09 (dd, $J_1 = 13.9$ Hz, $J_2 = 5.5$ Hz, 1H), 2.80 (dd, $J_1 = 13.9$ Hz, $J_2 = 7.2$ Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 171.7, 168.1, 159.7, 152.5, 148.7, 136.2, 135.8, 134.03, 133.98, 130.2, 129.3, 129.2, 128.6, 128.5, 128.0, 127.0, 126.6, 125.2, 114.9, 111.6, 103.6, 99.3, 56.9, 55.60, 55.55, 55.5, 54.6, 53.3, 52.3, 37.6; IR (ATR) ν 3327, 2978, 2921, 1743, 1662, 1513, 1236 cm^{-1}; MS (FAB^+) 638

($M + H^+$, 44), 268 (100); HRMS (FAB^+) Calcd. for $C_{37}H_{40}N_3O_7$: 638.2866, Found: 638.2864; $[\alpha]^{24}_D$ + 11.4 (c 1.79, $CHCl_3$).

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Chapter 4
Conclusion

Abstract The contents in this thesis are summarized in this chapter. I developed novel asymmetric bifunctional organocatalysts based on the previously developed amino thiourea catalyst. One of them is the development of the quinazoline and benzothiadiazine catalysts, which could be used as novel HB donors. I succeeded in developing the first asymmetric organocatalytic Michael reaction of α,β-unsaturated carboxylic acid derivatives and several activated methylene compounds. In addition, it was found that the highly enantioselective hydrazination of activated methylene compounds occurred in the presence of the novel quinazoline catalysts. The other content is the development of the novel hydroxy thiourea catalysts. Both catalysts could be applied to asymmetric reactions involving the organoboronic acids, which could not be utilized under the conditions of the previous amino thiourea catalysts.

In this thesis, I developed novel asymmetric bifunctional organocatalysts based on the previously developed amino thiourea catalyst **1a** (Fig. 4.1).

I developed the quinazoline and benzothiadiazine catalysts **5** and **6**, which could be used as novel HB donors. The structures and the abilities of HB donation varied among these catalysts. I succeeded in developing the first asymmetric organocatalytic Michael reaction of α,β-unsaturated carboxylic acid derivatives and several activated methylene compounds by using the amino thiourea **1a**. In addition, it was found that the highly enantioselective hydrazination of activated methylene compounds occurred in the presence of the novel quinazoline catalysts **5**. From these results, it was revealed that the HB donors which possess the strongest capacity for HB donation are not always the best catalysts for asymmetric reactions.

In addition, I developed the novel thiourea catalysts **1g** and **1n** bearing the hydroxy groups. Both catalysts could be applied to asymmetric reactions involving the organoboronic acids, which could not be utilized under the conditions of the previous amino thiourea catalysts. By using the iminophenol-type catalyst **1g**,

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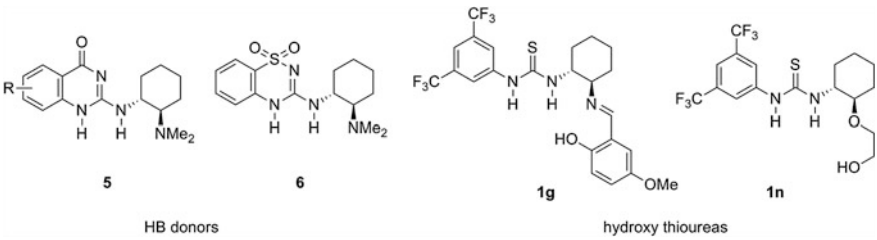

Fig. 4.1 Novel HB donor catalysts

I developed the Michael reaction of organoboronic acids to γ-hydroxyenones. Furthermore, the alcohol thiourea **1n** was used for the first asymmetric catalytic Petasis reaction of α-iminoamides.

Curriculum Vitae

Tsubasa Inokuma was born in Okayama in 1983. He studied Chemistry at Kyoto University and obtained BSc (2005) and MSc (2007) degree at Kyoto University under the guidance of Prof. Yoshiji Takemoto. In 2008, during his PhD course, he became an assistant professor at Kyoto University. He obtained PhD degree at Kyoto University in 2011 under the supervision of Prof. Yoshiji Takemoto. Since 2012, he has been working as a postdoctoral fellow in Barbas laboratory at The Scripps Research Institute. His research interests are development of novel catalytic reaction and bioconjugation methods.

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