

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

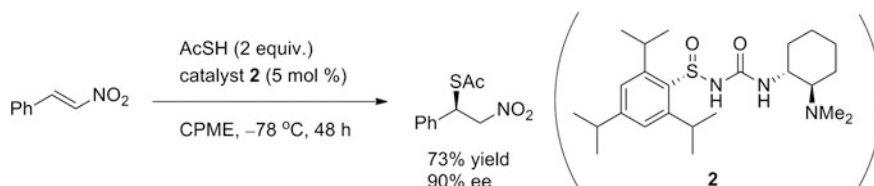
of the most advantageous HB-donating structures due to the suitable positioning of the two N–H protons [23–28]. Since our initial design of bifunctional thiourea catalyst (**1a**) [29–34], my colleagues and I, along with other groups, have used this catalyst in various types of asymmetric reactions [35, 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].

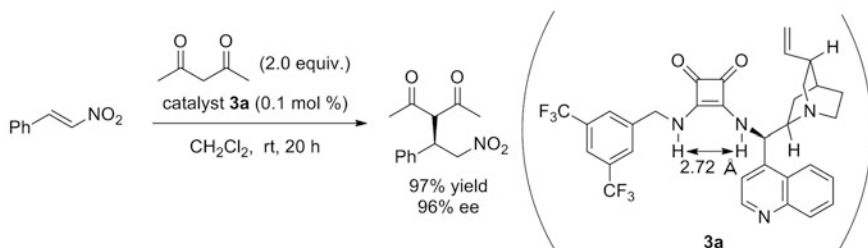
At the same time as my above mentioned studies, Nájera reported the benzimidazole **4a**-catalyzed enantioselective Michael addition of dialkylmalonates and nitroolefins (Scheme 2.3) [39, 40]. The distance between the two acidic protons of **4a** was revealed by crystallographic analysis to be 2.41 Å,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

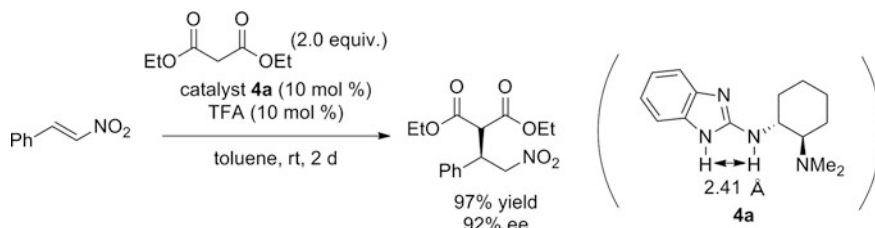
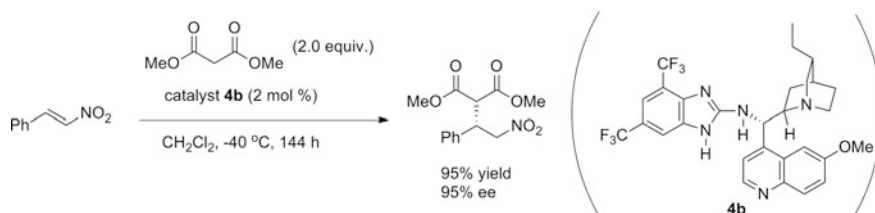
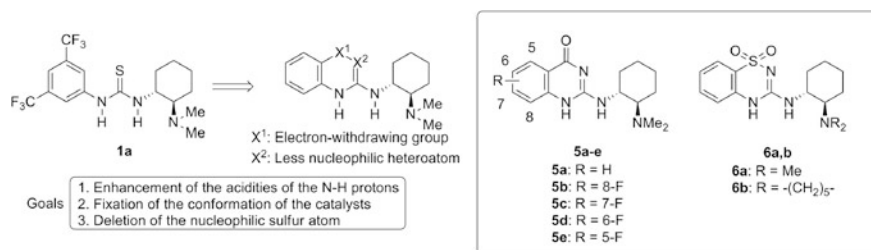
To further develop more efficient double HB-donor catalysts, I designed several novel types of bifunctional catalysts (Fig. 2.1).



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 aminothiurea **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

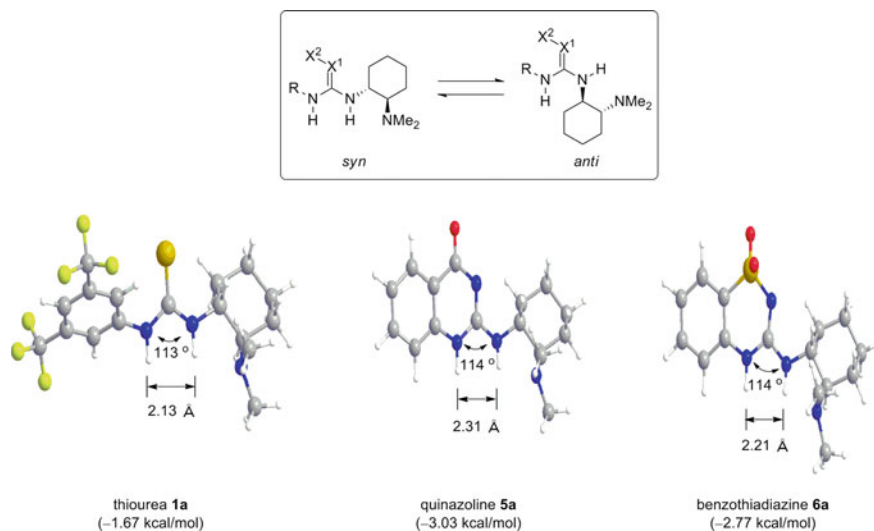
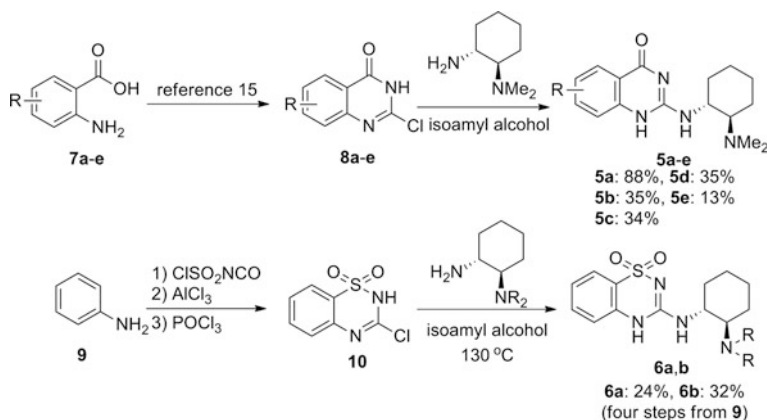


Fig. 2.2 Computational analysis of the ground state of HB donors (the values of the relative energies of the *syn* forms against the *anti* forms are shown in parenthesis)



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

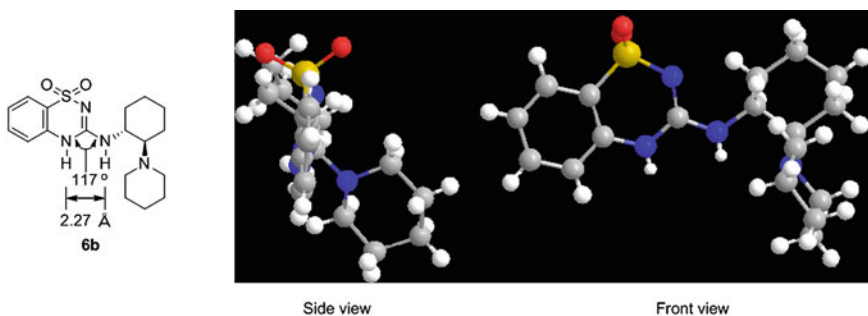
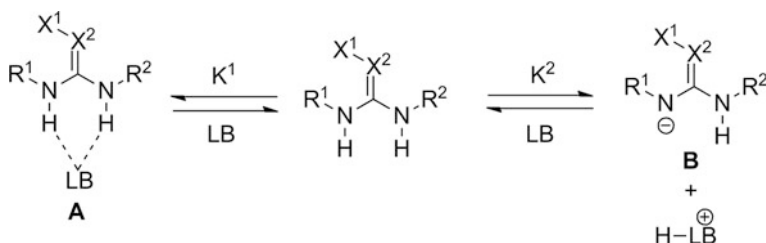


Fig. 2.3 X-ray crystallography of **6b**

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 pK_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

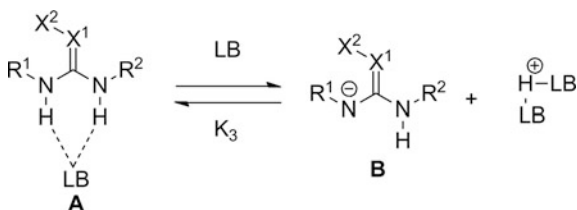
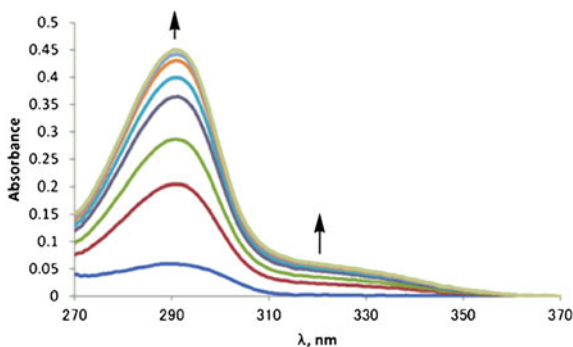


Fig. 2.4 Spectrophotometric titration of **6a** with tetrabutylammonium acetate in DMSO. Arrows show the changes of intensity at increasing TBAOAc concentrations



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 $\Delta\epsilon$ is the difference in molar absorptivity between free **6a** and complexed **6a** [56], I estimated that the association constant K_1^{6a} between free **6a** and the complex of **6a** with TBAC was $1.9 \times 10^3 (\pm 44)$.

$$\text{Abs} = \text{Abs}_0 + 0.5\Delta\epsilon \left[\frac{[\text{RH}]_{\text{T}} + [\text{Cl}^-]_{\text{T}} + 1/K_1}{([\text{RH}]_{\text{T}} + [\text{Cl}^-]_{\text{T}} + 1/K_1)^2 - 4[\text{RH}]_{\text{T}}[\text{Cl}^-]_{\text{T}}} \right]^{0.5} \quad (2.1)$$

The association constants K_1^{1a} and K_1^{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^{1a} and K_1^{5a} were estimated to be $1.2 \times 10^3 (\pm 37)$ and $4.9 \times 10^2 (\pm 18)$, 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

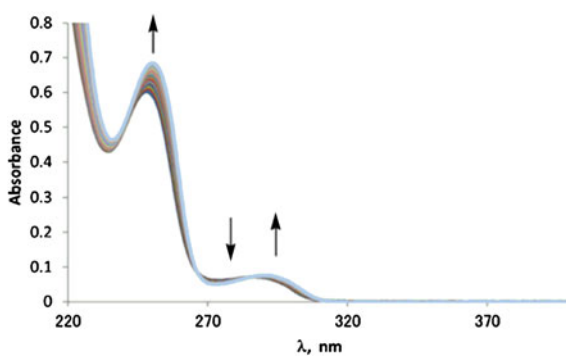


Fig. 2.6 The values of the absorbance at 250 nm in the course of the titration

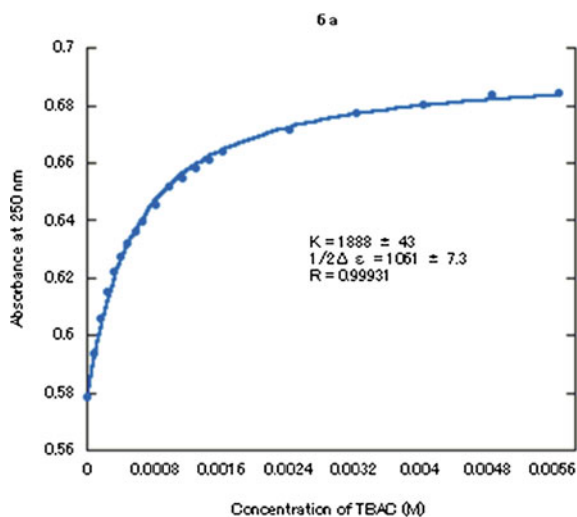


Fig. 2.7 Spectrophotometric titration of **1a** with TBAC in CH_3CN . *Arrows* show the changes of intensity at increasing TBAC concentrations

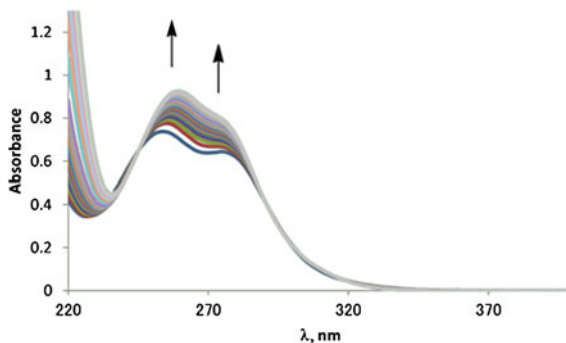


Fig. 2.8 The values of the absorbance at 260 nm in the course of the titration

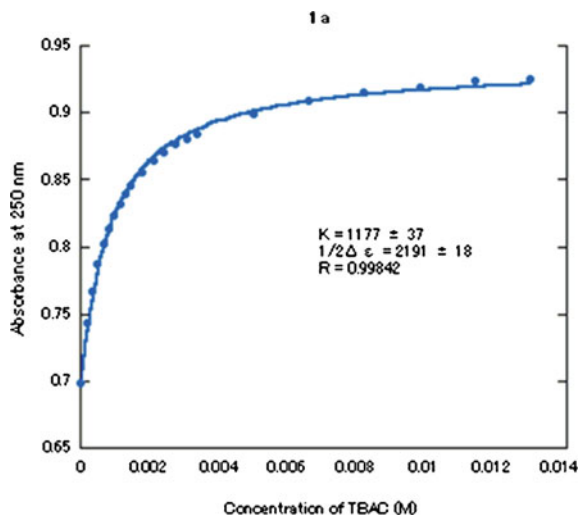
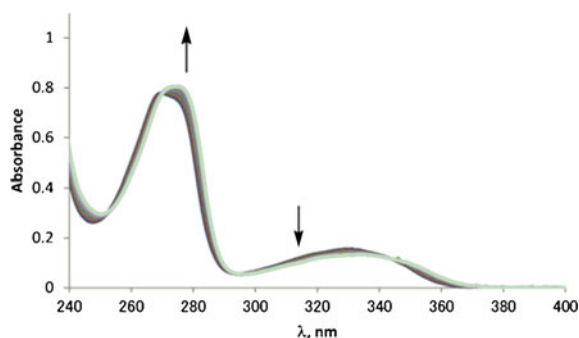


Fig. 2.9 Spectrophotometric titration of **5a** with TBAC in CH_3CN . Arrows show the changes of intensity at increasing TBAC concentrations

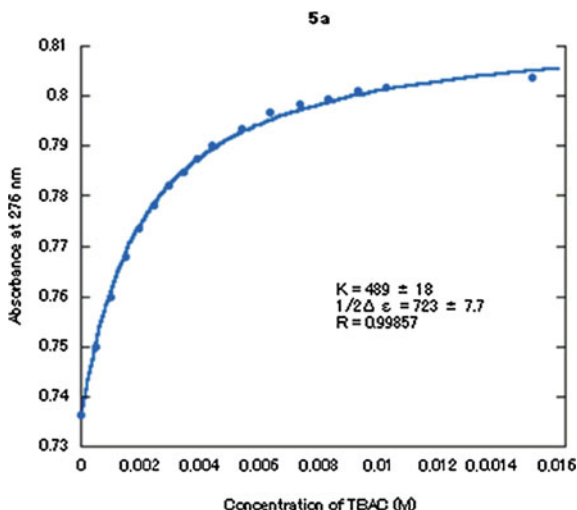


2.1.3 Experimental Section

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. ^1H 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 $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. 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. ($\text{EtOAc/MeOH/Et}_3\text{N} = 97/0/3$ 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; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 8.10 (dd, $J_1 = 7.9 \text{ Hz}$, $J_2 = 1.4 \text{ Hz}$, 1H), 7.52 (ddd, $J_1 = J_2 = 7.9 \text{ Hz}$, $J_3 = 1.4 \text{ Hz}$, 1H), 7.22 (d, $J = 7.9 \text{ Hz}$, 1H), 7.12 (dd, $J_1 = J_2 = 7.9 \text{ Hz}$, 1H), 3.69–3.57 (m, 1H), 2.52 (ddd, $J_1 = J_2 = 10.3 \text{ Hz}$, $J_3 = 2.9 \text{ Hz}$, 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); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$, 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 ($\text{M} + \text{H}^+$, 100); HRMS (FAB^+) Calcd. for $\text{C}_{16}\text{H}_{23}\text{N}_4\text{O}$: 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; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.88 (d, $J = 7.9 \text{ Hz}$, 1H), 7.32–7.20 (m, 1H), 7.04 (ddd, $J_1 = J_2 = 7.9 \text{ Hz}$, $J_3 = 4.6 \text{ Hz}$, 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 ($\text{M} + \text{H}^+$, 100); HRMS (FAB^+) Calcd. for $\text{C}_{16}\text{H}_{21}\text{FN}_4\text{O}$: 305.1778, Found: 305.1766; $[\alpha]_{\text{D}}^{25} = -11.3$ (c 0.95, CHCl_3).

2-[(1*R*, 2*R*)-2-(dimethylamino)cyclohexyl]amino]-7-fluoroquinazolin-4(1*H*)-one (**5c**): Yellow amorphous; ^1H 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 ($\text{M} + \text{H}^+$, 100); HRMS (FAB^+) Calcd. for $\text{C}_{16}\text{H}_{21}\text{FN}_4\text{O}$: 305.1778, Found: 305.1789; $[\alpha]_{\text{D}}^{25} = -36.3$ (c 0.95, CHCl_3).

2-[(1*R*, 2*R*)-2-(dimethylamino)cyclohexyl]amino]-6-fluoroquinazolin-4(1*H*)-one (**5d**): Yellow amorphous; ^1H 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 ($\text{M} + \text{H}^+$, 100); HRMS (FAB^+) Calcd. for $\text{C}_{16}\text{H}_{21}\text{FN}_4\text{O}$: 305.1778, Found: 305.1792; $[\alpha]_{\text{D}}^{25} = -26.9$ (c 0.95, CHCl_3).

2-[(1*R*, 2*R*)-2-(dimethylamino)cyclohexyl]amino]-5-fluoroquinazolin-4(1*H*)-one (**5e**): Yellow amorphous; ^1H 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 ($\text{M} + \text{H}^+$, 100); HRMS (FAB^+) Calcd. for $\text{C}_{16}\text{H}_{21}\text{FN}_4\text{O}$: 305.1778, Found: 305.1779; $[\alpha]_{\text{D}}^{25} = -35.4$ (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 ($\text{CHCl}_3/\text{MeOH}/30\% \text{NH}_3\text{aq} = 85/15/1$) 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); ^1H 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 ($\text{M} + \text{H}^+$, 100); HRMS (FAB^+) Calcd. for $\text{C}_{15}\text{H}_{23}\text{N}_4\text{O}_2\text{S}$: 323.1536, Found: 323.1544; $[\alpha]_{\text{D}}^{25} = 32.6$ ($c = 0.97$, 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; ^1H NMR ($\text{DMSO}-d_6$, 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 ($\text{M} + \text{H}^+$); HRMS (FAB^+) Calcd. for $\text{C}_{18}\text{H}_{27}\text{N}_4\text{O}_2\text{S}$: 363.1854, Found: 363.1857; $[\alpha]_{\text{D}}^{25} = +11$ ($c = 0.32$, 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^{6a} was determined to be 1888 (± 43).

$$\text{Abs} = 0.57873 + 1/2\Delta\epsilon[0.0000540 + m_0 + 1/K^{\text{6a}} - \{(0.0000540 + m_0 + 1/K^{\text{6a}})^2 - 0.000210 \times m_0\}^{0.5}] \quad (2.2)$$

where m_0 is the concentration of TBAC in the sample solution and $\Delta\epsilon$ 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^{1a} was determined to be 1177 (± 37).

$$\text{Abs} = 0.69892 + 1/2\Delta\epsilon[0.0000540 + m_0 + 1/K^{\text{1a}} - \{(0.0000540 + m_0 + 1/K^{\text{1a}})^2 - 0.000210 \times m_0\}^{0.5}] \quad (2.3)$$

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

Titration of TBAC to **5a**

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^{5a} was determined to be 489.0 (± 18).

$$\text{Abs} = 0.73629 + 1/2\Delta\epsilon[0.0000540 + m_0 + 1/K^{\text{5a}} - \{(0.0000540 + m_0 + 1/K^{\text{5a}})^2 - 0.000210 \times m_0\}^{0.5}] \quad (2.4)$$

where m_0 is the concentration of TBAC in the sample solution and $\Delta\epsilon$ 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

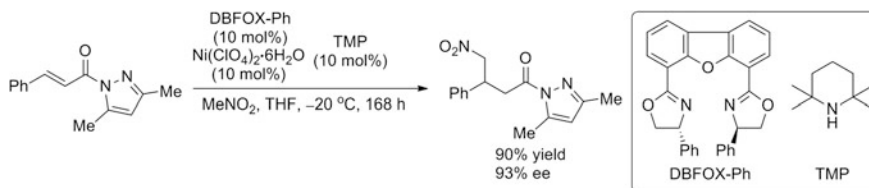
2.2.1 Introduction and Background

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.

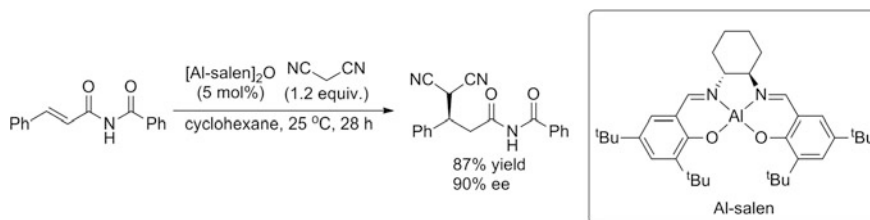
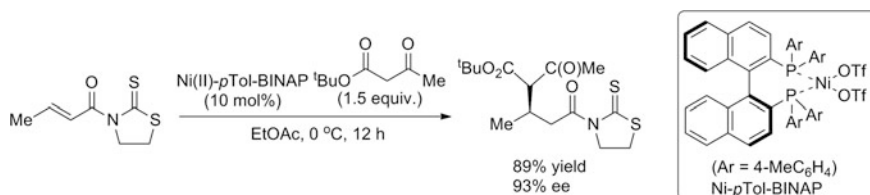
Jacobsen et al. reported the Al–salen-catalyzed Michael reaction of α,β -unsaturated imides and malononitrile or methylcyanomalonate (Scheme 2.9) [88, 89]. They also achieved the construction of a chiral piperidine structure by using the Michael adducts they obtained.

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 aminothiurea **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-pTol-BINAP catalyzed asymmetric Michael reaction

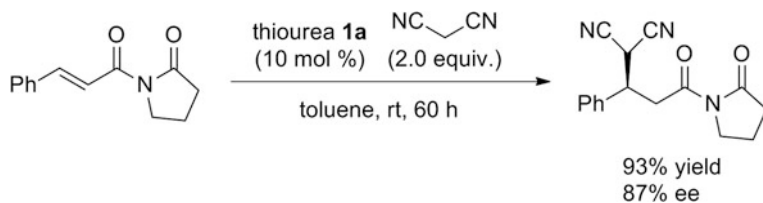
However, the reaction suffered from low reactivities, and more reactive reaction systems are needed. I expected that different HB donors would possess the different reactivities in this asymmetric reaction due to their different HB-donating abilities. In addition, the imides derived from benzamides are 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

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

methoxybenzimidide **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-methylbenzimidide **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 ₆ H ₄	OMe	11f	CH ₂ (CN) ₂	rt	7	12f	99	92
2	4-MeOC ₆ H ₄	OMe	11g	CH ₂ (CN) ₂	rt	24	12g	92	90
3	3-furyl	OMe	11h	CH ₂ (CN) ₂	rt	31	12h	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 ₂ Me	80	52	12l ^d	94	82 ^c
8	4-FC ₆ H ₄	OMe	11f	CH ₂ (CN)CO ₂ Me	80	48	12m ^d	91	85 ^c
9	Me	OMe	11j	CH ₂ (CN)CO ₂ Me	rt	87	12n ^d	90	92 ^c
10	TBSO(CH ₂) ₅	OMe	11k	CH ₂ (CN)CO ₂ Me	rt	137	12o ^d	96	92 ^c
11	Ph	OMe	11c	MeNO ₂	60	168	12p	56	87
12	4-FC ₆ H 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

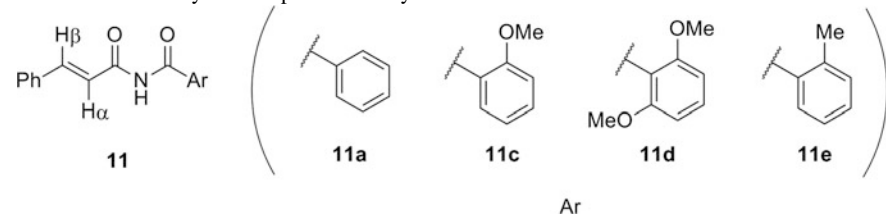
^e The ee values were estimated from ee of the decarboxylated nitrile

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).

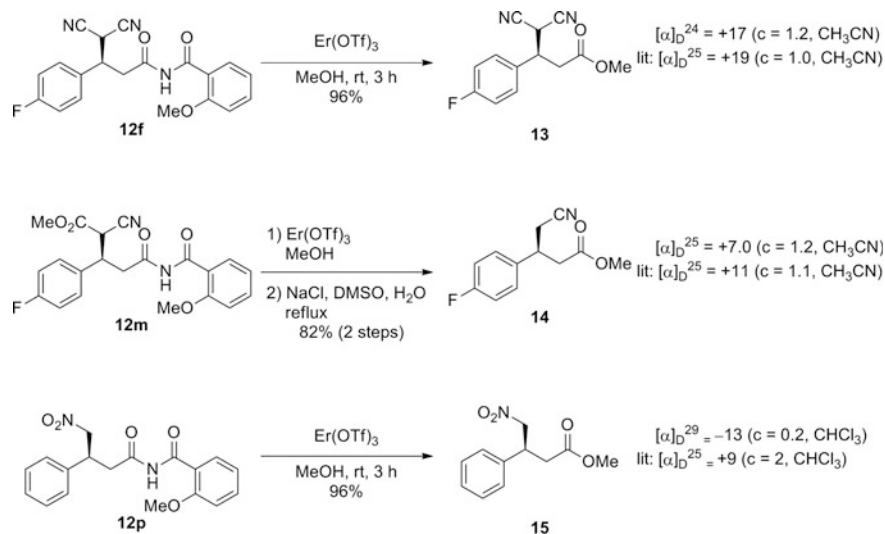
The absolute configurations of the Michael adducts obtained were determined as follows (Scheme 2.12). Treatment of **12f** with MeOH in the presence of a catalytic amount of $\text{Er}(\text{OTf})_3$ produced the corresponding methyl ester **13** [88] ($[\alpha]_{\text{D}}^{24} = +17$; c 1.2, CH_3CN) 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 ($[\alpha]_{\text{D}}^{25} = +7.0$; c 1.1, CH_3CN). The same treatment of **12p** gave the corresponding methyl ester **15** [96] ($[\alpha]_{\text{D}}^{29} = -13$; 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 ^1H 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 ^1H NMR signals such as the vinylic protons (H_α and H_β) 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** ($3391\text{--}3405\text{ cm}^{-1}$). 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-methoxybenzimidide **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	^1H NMR (CDCl_3 , 0.015 M)	IR (CHCl_3 , 0.01 M)
11a	8.59 (NH) 7.86 (H α) 7.95 (H β)	3405 (N–H) 1680 (C=O) 1619 (C=C)
11c	10.30 (NH) 7.86 (H α) 7.91 (H β)	3330 (N–H) 1671 (C=O) 1619 (C=C)
11d	8.19 (NH) 7.75 (H α) 7.89 (H β)	3393 (N–H) 1679 (C=O) 1620 (C=C)
11e	8.21 (NH) 7.76 (H α) 7.94 (H β)	3391 (N–H) 1680 (C=O) 1618 (C=C)

**Scheme 2.12** Determination of the absolute configuration

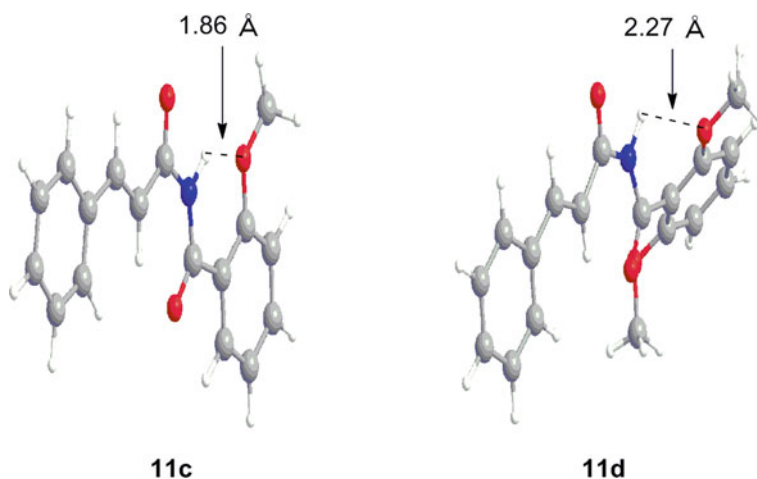


Fig. 2.11 Computational analysis of the ground states of the imides **11c** and **11d**

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 ^1H 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 $\ln([\mathbf{11c}]/[\mathbf{11c}_0])$ 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

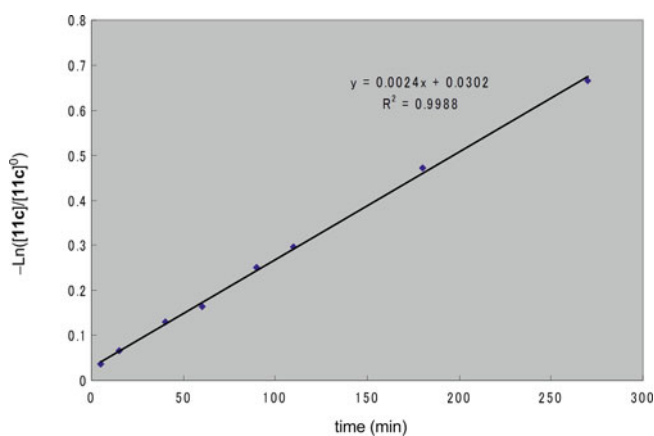


Fig. 2.12 Kinetic studies on the Michael reaction of malononitrile to imide **11c** in the presence of **1a**

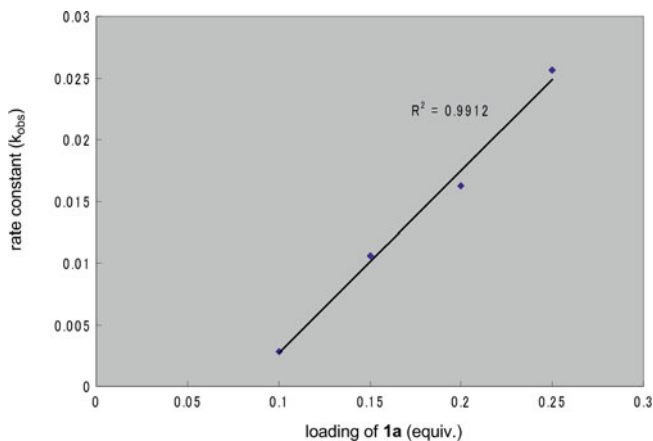


Fig. 2.13 Kinetic studies on the Michael reaction of malononitrile to imide **11c** in the presence of **1a**

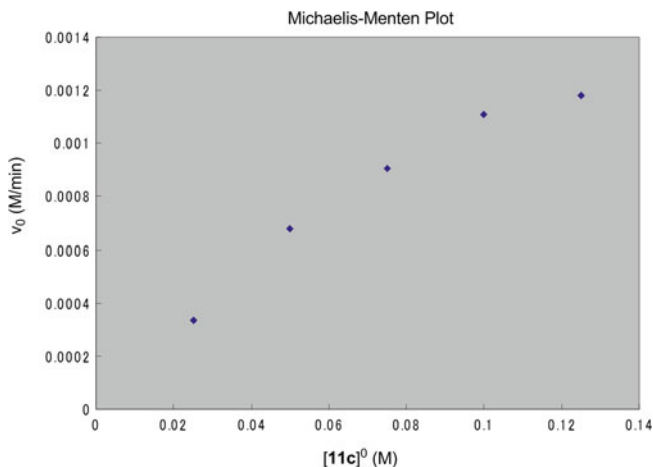


Fig. 2.14 Michaelis–Menten plot of the Michael addition

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

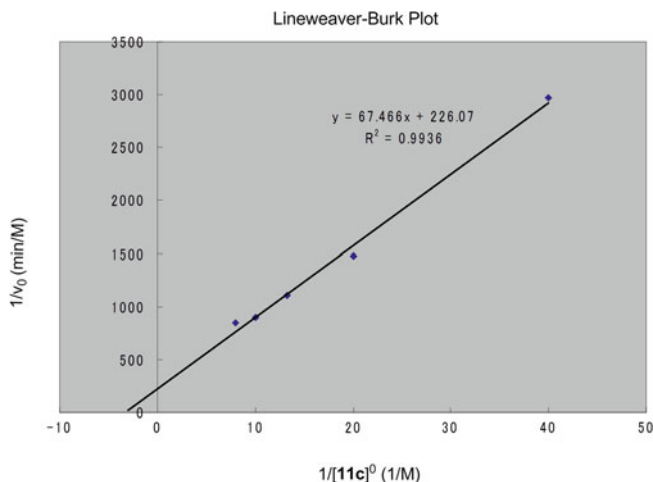
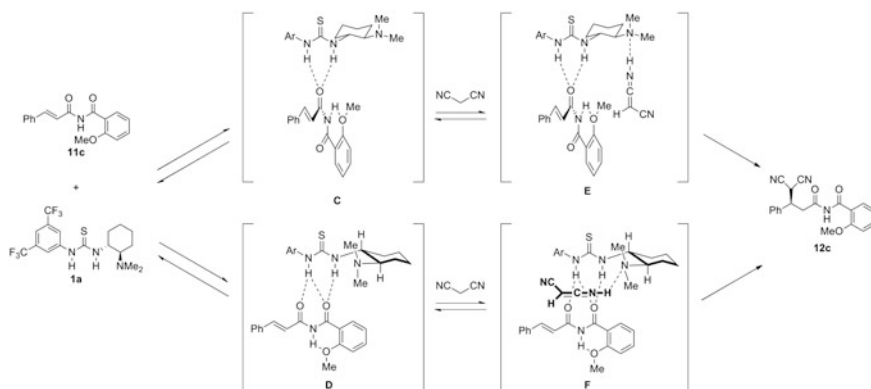


Fig. 2.15 Lineweaver–Burk plot of the Michael reaction



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-methoxybenzimidides **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. ^1H 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. $[\alpha]_{\text{D}}$ values are measured in $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. 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 HCl(aq, 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); ^1H NMR (500 MHz, $\text{DMSO}-d_6$) 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, $\text{DMSO}-d_6$) 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 $\text{C}_{18}\text{H}_{11}\text{F}_6\text{NO}_2$: 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); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 (CHCl₃) ν 3230, 3021, 1671, 1619, 1479, 1341 cm⁻¹; Anal. Calcd. for C₁₇H₁₅NO₃: 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); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 (CHCl₃) ν 3393, 3021, 2942, 2841, 2360, 1717, 1678, 1619, 1597, 1475, 1340, 1257 cm⁻¹; Anal. Calcd. for C₁₈H₁₇NO₄: 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); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 (CHCl₃) ν 3691, 3391, 2398, 1712, 1681, 1619, 1337 cm⁻¹; Anal. Calcd. for C₁₇H₁₅NO₂: 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); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 (CHCl₃) ν 3396, 3018, 1701 cm⁻¹; MS (EI⁺) 317 (M⁺, 4), 105 (100); HRMS (EI⁺) Calcd. for C₁₉H₁₅N₃O₂: 317.1164, Found: 317.1160; HPLC [Chiralcel AD-H, hexane/2-

propanol = 70/30, 0.5 mL/min, λ = 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; ^1H 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 ($\text{M} + \text{H}^+$, 100); HRMS (FAB^+) Calcd. for $\text{C}_{21}\text{H}_{14}\text{F}_6\text{N}_3\text{O}_2$: 454.0990; Found: 454.0991; HPLC [Chiralcel OD-H, hexane/2-propanol = 80/20, 0.3 mL/min, λ = 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; ^1H 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 ($\text{M} + \text{H}^+$, 42), 135 (100); HRMS (FAB^+) Calcd. for $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_3$: 348.1348, Found: 348.1352; HPLC [Chiralcel OD-H, hexane/2-propanol = 70/30, 0.5 mL/min, λ = 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; ^1H 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 ($\text{M} + \text{H}^+$, 35), 165 (100); HRMS (FAB^+) Calcd. for $\text{C}_{21}\text{H}_{20}\text{N}_3\text{O}_4$: 378.1454; Found: 378.1449; HPLC [Chiralcel OD-H, hexane/2-propanol = 70/30, 0.5 mL/min, λ = 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; ^1H 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 $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_2$: 332.1399, Found: 332.1404; HPLC [Chiralcel OD, hexane/2-propanol = 80/20, 0.5 mL/min, λ = 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/EtOAc); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) δ 168.0, 163.7, 157.8, 135.3, 133.1, 121.9, 119.4, 111.8, 56.2, 45.4; IR (CHCl₃) ν 3540, 3313, 3026, 2956, 1750, 1726, 1687, 1600, 1479, 1292 cm⁻¹; Anal. Calcd. for C₁₀H₁₀ClNO₃: 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-oxoethylphosphonic acid diethylester (1.92 g, 91 %). Yellow oil; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 (CHCl₃) ν 3320, 3001, 1750, 1710, 1684, 1601, 1479, 1215 cm⁻¹; MS (FAB⁺) 330 (M + H⁺, 87), 135 (100); HRMS (FAB⁺) Calcd. for C₁₄H₂₁NO₆P: 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 H₂O and then acidified by 1 N HCl, the resulting mixture was extracted with CHCl₃. The extract was dried over MgSO₄, 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); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 (CHCl₃) ν 3329, 3022, 1696, 1670, 1599, 1508, 1480, 1223 cm⁻¹; Anal. Calcd. for C₁₇H₁₄FNO₃: 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); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 (CHCl₃) ν 3331, 3009, 2360, 1694, 1668, 1599, 1510, 1479, 1216 cm⁻¹; Anal. Calcd. for C₁₈H₁₇NO₄: 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); ¹H 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); ¹³C 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 C₁₅H₁₃NO₄: 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); ¹H 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); ¹³C 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 C₁₄H₁₀FNO₃: 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; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 (CHCl₃) ν 3330, 3017, 1739, 1670, 1479 cm⁻¹; MS (FAB⁺) 220 (M + H⁺, 100); HRMS (FAB⁺) Calcd. for C₁₂H₁₄NO₃: 220.0974, Found: 290.0967.

(*E*)-*N*-[(*tert*-Butyldimethylsilyloxy)-oct-2-enoyl]-2-methoxybenzamide (**11k**): Yellow oil; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 (CHCl₃) ν 3331, 2933, 1699, 1673, 1600, 1479, 1347 cm⁻¹; MS (FAB⁺) 406 (M + H⁺, 54), 135 (100); HRMS (FAB⁺) Calcd. for C₂₂H₃₆NO₄Si: 406.2414, Found: 406.2421.

(3*R*)-*N*-[4,4-Dicyano-3-(4-fluorophenyl)butyryl]-2-methoxybenzamide (**12f**): Colorless amorphous; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 (CHCl₃) ν 3314, 2360, 1710, 1683, 1604, 1514, 1478, 1243 cm⁻¹; MS (FAB⁺) 366 (M + H⁺, 92), 135 (100); HRMS (FAB⁺) Calcd. for C₂₀H₁₇FN₃O₃: 366.1254, Found: 366.1248; 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]; [α]_D²⁸ = +10.2 (c 1.00, CHCl₃, 92 % ee).

(3*R*)-*N*-[4,4-Dicyano-3-(4-methoxyphenyl)butyryl]-2-methoxybenzamide (**12g**): Colorless amorphous; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) 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 (CHCl₃) ν 3316, 3024, 1709, 1683, 1514, 1479, 1217 cm⁻¹; MS (FAB⁺) 378 (M + H⁺, 87), 135 (100); HRMS (FAB⁺) Calcd. for C₂₁H₂₀N₃O₄: 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]; [α]_D²⁴ = +11.0 (c 1.21, CHCl₃, 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); ¹³C 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 C₁₈H₁₅N₃O₄: 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]; [α]_D²³ = -8.5 (c 1.2, CHCl₃, 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 ($\text{M} + \text{H}^+$, 100); HRMS (FAB $^+$): Calcd. for $\text{C}_{17}\text{H}_{13}\text{FN}_3\text{O}_3$: 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]; $[\alpha]_{\text{D}}^{23} = -7.5$ (c 1.0, CHCl_3 , 95 % ee).

(3R)-N-[4,4-Dicyano-3-methylbutyryl]-2-methoxybenzamide (**12j**): Yellow oil; ^1H 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 ($\text{M} + \text{H}^+$, 64), 135 (100); HRMS (FAB $^+$) Calcd. for $\text{C}_{15}\text{H}_{16}\text{N}_3\text{O}_3$: 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]; $[\alpha]_{\text{D}}^{20} = -23.3$ (c 1.61, CHCl_3 , 90 % ee).

(3R)-N-[(8-*tert*-Buthyldimethylsilanyloxy)-3, 3-dicyanomethyloctanoyl]-2-methoxybenzamide (**12k**): Yellow oil; ^1H 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 ($\text{M} + \text{H}^+$, 56), 135 (100); HRMS (FAB $^+$) Calcd. for $\text{C}_{25}\text{H}_{38}\text{N}_3\text{O}_4\text{Si}$: 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]; $[\alpha]_{\text{D}}^{28} = -25.9$ (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 μ L, 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 **12i** (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-methoxybenzoylamino)-5-oxo-3-phenylpentanoic acid methyl ester (**12i**): Colorless oil; ¹H NMR (500 MHz, CDCl₃) (3:2 mixture of diastereomers, 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); ¹³C NMR (126 MHz, CDCl₃) 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 (CHCl₃) ν 3316, 2360, 1753, 1710, 1680, 1476 cm⁻¹; MS (FAB⁺) 381 (M + H⁺, 50), 135 (100); HRMS (FAB⁺) Calcd. for C₂₁H₂₁N₂O₅: 381.1450, Found: 381.1448; $[\alpha]_D^{22} = -3.18$ (c 1.99, CHCl₃).

(3*S*)-2-Cyano-3-phenylpentanedioic acid dimethyl ester: To a stirred solution of **12i** (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; ¹H NMR (500 MHz, CDCl₃) (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); ¹³C NMR (126 MHz, CDCl₃) 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 (CHCl₃) ν 3028, 2956, 2252, 1747, 1454, 1439, 1266 cm⁻¹; MS (FAB⁺) 262 (M + H⁺, 67), 154 (100); HRMS (FAB⁺) Calcd. for C₁₄H₁₆NO₄: 262.1079, Found: 262.1082; $[\alpha]_D^{20} = +7.80$ (c 1.44, CHCl₃).

(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/H₂O (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; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (126 MHz, CDCl₃) δ 171.5, 140.4, 129.0, 127.9, 127.0, 117.9, 51.9, 38.7, 37.9, 24.2; IR (CHCl₃) ν 3026, 2360, 1733,

1438, 1216 cm^{-1} ; MS (FAB⁺) 204 (M + H⁺, 94), 154 (100); HRMS (FAB⁺) Calcd. for C₁₂H₁₄NO₂: 204.1025, Found: 204.1027; HPLC [Chiralcel OD-H, hexane/2-propanol = 90/10, 0.3 mL/min, λ = 254 nm, retention times: (major) 63.4 min, (minor) 52.8 min] $[\alpha]_{\text{D}}^{21}$ = +16.3 (c 1.00, CHCl₃, 82 % ee).

(3*S*)-2-Cyano-3-(4-fluorophenyl)-5-(2-methoxybenzoylamino)-5-oxo-pentanoic acid methyl ester (**12m**): Colorless amorphous; ¹H NMR (500 MHz, CDCl₃) (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); ¹³C NMR (126 MHz, CDCl₃) 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 (CHCl₃) ν 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 C₂₁H₂₀FN₂O₅: 399.1356, Found: 399.1358; $[\alpha]_{\text{D}}^{22}$ = –5.86 (c 2.97, CHCl₃).

(3*S*)-4-Cyano-3-(4-fluorophenyl)butanoic acid methyl ester (**14**) [88]: $[\alpha]_{\text{D}}^{25}$ = +6.68 (c 1.12, CH₃CN, 85 % ee); HPLC [Chiralcel OJ-H, hexane/ethanol = 85/15, 0.5 mL/min, λ = 254 nm, retention times: (major) 89.1 min, (minor) 37.3 min].

(3*S*)-2-Cyano-5-(2-methoxybenzoylamino)-3-methyl-5-oxo-pentanoic acid methyl ester (**12n**): Colorless oil; ¹H NMR (500 MHz, CDCl₃) (3:2 mixture of diastereomers, 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); ¹³C NMR (126 MHz, CDCl₃) 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 (CHCl₃) ν 3323, 3023, 2360, 2252, 1749, 1709, 1684, 1480 cm^{-1} ; MS (FAB⁺) 319 (M + H⁺, 100); HRMS (FAB⁺) Calcd. for C₁₆H₁₉N₂O₅: 319.1294, Found: 319.1295; $[\alpha]_{\text{D}}^{27}$ = –3.90 (c 1.11, CHCl₃).

(3*S*)-2-Cyano-3-methylpentanedioic acid dimethyl ester: Colorless oil; ¹H NMR (500 MHz, CDCl₃) (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); ¹³C NMR (126 MHz, CDCl₃) 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 (CHCl₃) ν 3028, 2955, 1747, 1439 cm^{-1} ; MS (FAB⁺) 200 (M + H⁺, 12), 154 (100); HRMS (FAB⁺) Calcd. for C₉H₁₄NO₄: 200.0923, Found: 200.0926; $[\alpha]_{\text{D}}^{23}$ = –17.0 (c 1.17, CHCl₃).

(3*S*)-4-Cyano-3-methylbutanoic acid methyl ester: Colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 3.70 (s, 3H), 2.49–2.35 (m, 5H), 1.16 (d, $J = 5.8$ Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 172.1, 118.2, 51.8, 39.4, 27.4, 23.8, 19.4; IR (CHCl₃) ν 3025, 2251, 1734 cm^{-1} ; MS (CI⁺) 142 (M + H⁺, 100); HPLC [Chiralcel AS-H, hexane/2-propanol = 90/10, 0.5 mL/min, λ = 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-methoxybenzoylamino)-2-oxoethyl] octanoic acid methyl ester (**12o**): Colorless oil; ^1H NMR (500 MHz, CDCl_3) (3:2 mixture of diastereomers, 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 ($\text{M} + \text{H}^+$, 28); HRMS (FAB⁺) Calcd. for $\text{C}_{26}\text{H}_{41}\text{N}_2\text{O}_6\text{Si}$: 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; ^1H 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 ($\text{M} + \text{H}^+$, 100); HRMS (FAB⁺) Calcd. for $\text{C}_{13}\text{H}_{22}\text{NO}_5$: 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; ^1H 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 ($\text{M} + \text{H}^+$, 98), 154 (100); HRMS (FAB⁺) Calcd. for $\text{C}_{11}\text{H}_{20}\text{NO}_3$: 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/ $\text{EtOAc} = 4/1$) to afford desired product (39.5 mg, 90 %). Colorless oil; ^1H 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 ($\text{M} + \text{H}^+$, 40), 105 (100); HRMS (FAB^+) Calcd. for $\text{C}_{18}\text{H}_{24}\text{NO}_4$: 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]; $[\alpha]_{\text{D}}^{22} = -4.92$ (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); ^1H 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 $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_5$: 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]; $[\alpha]_{\text{D}}^{29} = -46.0$ (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); ^1H 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 $\text{C}_{18}\text{H}_{17}\text{FN}_2\text{O}_3$: 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]; $[\alpha]_{\text{D}}^{23} = -30.2$ (c 1.03, CHCl_3 , 86 % ee).

(3*S*)-2-Methoxy-*N*-(3-methyl-4-nitro-butyl)benzamide (**12r**): White solids; mp 82–83 °C (hexane/EtOAc); ^1H 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 ($\text{M} + \text{H}^+$, 71), 135 (100); HRMS (FAB^+) Calcd. for $\text{C}_{13}\text{H}_{17}\text{N}_2\text{O}_5$: 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]; $[\alpha]_{\text{D}}^{26} = +2.88$ (c 1.09, CHCl_3 , 83 % ee).

(3*S*)-*N*-[8-(*tert*-Butyldimethylsilyloxy]-3-nitromethyloctanoyl]-2-methoxybenzamide (**12s**): Colorless oil; ^1H 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 ($\text{M} + \text{H}^+$, 10), 135 (100); HRMS (FAB^+) Calcd. for $\text{C}_{23}\text{H}_{39}\text{N}_2\text{O}_6\text{Si}$: 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]; $[\alpha]_{\text{D}}^{22} = -6.89$ (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 $\text{Er}(\text{OTf})_3$ (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; $[\alpha]_{\text{D}}^{24} = +17.3$ (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 $\text{Er}(\text{OTf})_3$ (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; $[\alpha]_{\text{D}}^{29} = -13.3$ (c 0.21, CHCl_3).

2.3 Asymmetric Hydrazination of Activated Methylene Compounds Catalyzed by HB Donors

2.3.1 Introduction and Background

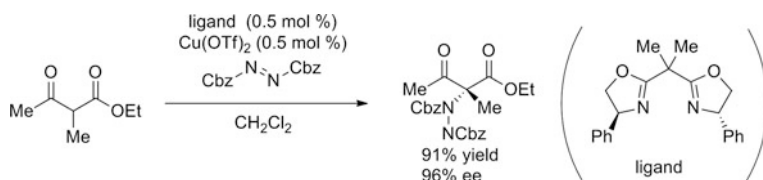
The hydrazination of 1,3-dicarbonyl compounds with azodicarboxylates is a valuable method for installing an amino group. When 2-monosubstituted 1,3-dicarbonyl compounds are used as nucleophiles, the resulting products possess α -amino acid moieties bearing quaternary stereogenic centers. These derivatives 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].

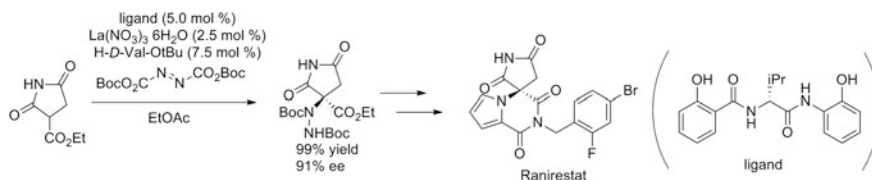
Shibasaki succeeded in developing a lanthanum-catalyzed variation of this reaction that was used in the synthesis of Ranirestat [104], which is a highly potent aldose reductase inhibitor (Scheme 2.15) [110–116].

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].

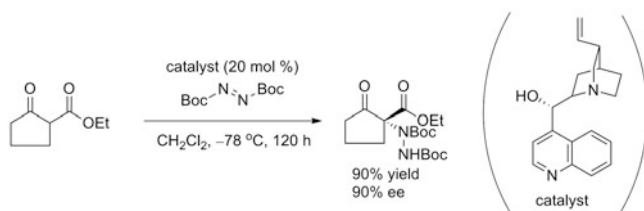
Recently, Rawal's group reported that squaramide **3b** is an effective catalyst for this reaction in terms of the substrate scope and stereoselectivity (Scheme 2.17) [118].



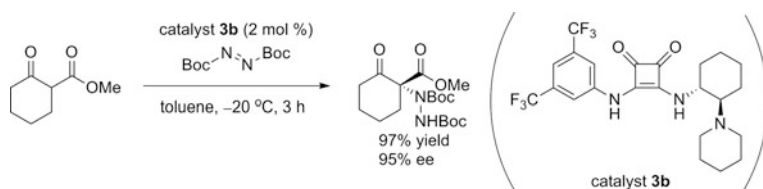
Scheme 2.14 (S)-Ph-BOX-Cu(OTf)₂-catalyzed hydrazination of 1,3-dicarbonyl compound



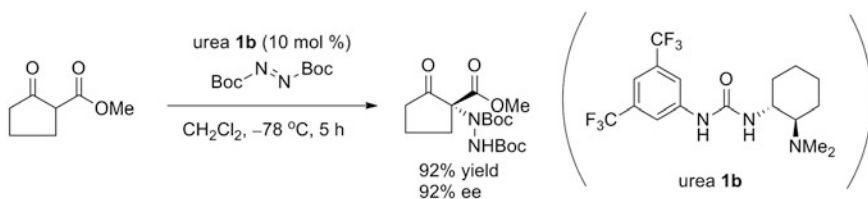
Scheme 2.15 La/Amide-catalyzed hydrazination of 1,3-dicarbonyl compound



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



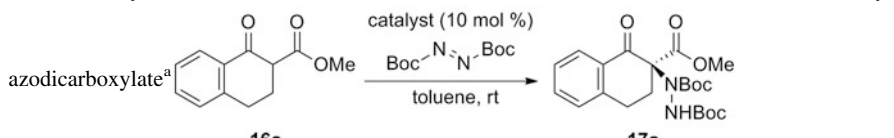
Scheme 2.17 Squaramide-catalyzed hydrazination of 1,3-dicarbonyl compounds



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


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 $-40\text{ }^{\circ}\text{C}$

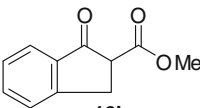
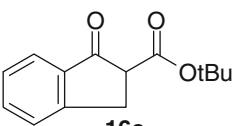
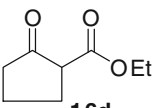
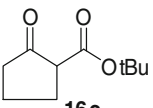
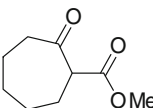
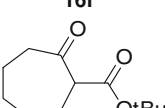
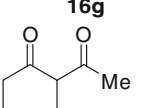
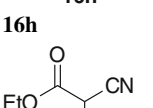
2.3.2 Results and Discussion

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 $-20\text{ }^{\circ}\text{C}$ [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 azodicarboxylate by using **5b** or **1b**^a

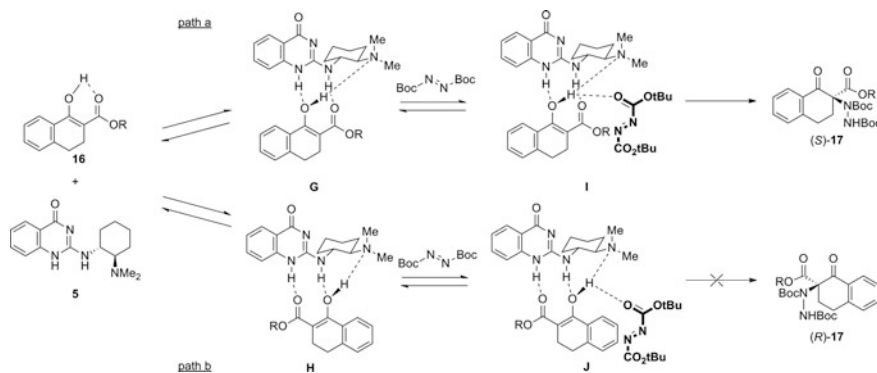
16b-i		17b-i				
Entry	16	Catalyst	Temp.	Time (h)	17	Yield (%) ^b ee (%) ^c
1	 16b	5b	−78 °C	5	17b	94 91
2	 16c	1b	−78 °C	4	17c	93 90
3	 16d	5b	−40 °C	8	17d	99 92
4	 16e	1b	−78 °C	15	17e	96 91
5	 16f	5b	rt	78	17f	86 81
6	 16g	1b	−40 °C	48	17g	90 90
7	 16h	5b	−78 °C	16	17h	87 94
8	16h	1b	−78 °C	3	17h	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. ^1H 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. $[\alpha]_{\text{D}}$ values are measured in $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. 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 $\rightarrow$ 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**): ^1H 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, λ = 254 nm, retention times: (major) 15.5 min, (minor) 18.2 min].

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

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