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A general organic catalyst for asymmetric addition of stabilized nucleophiles to acyl imines

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Abstract—Cinchona alkaloid-derived thiourea catalysts promote nucleophilic additions to acyl imines for the asymmetric synthesis of secondary amine adducts. The hydroquinine-derived thiourea catalyst efficiently promotes the aza-Henry reaction of nitroalkane with acyl imines, affording β-nitroamines in good yields with enantioselectivities of 90–98% ee and diastereoselectivities up to 97%. The scope of the reaction also includes dimethyl malonate as a nucleophile to access β-amino esters in high enantiopurity. Under the optimized reaction conditions, secondary amine adducts of high enantiopurity are generated based on various aromatic and α,β-unsaturated acyl imines.

1. Introduction

Organocatalysis is an expanding area of research in asymmetric organic synthesis.[1] Catalysts of organic origin are an appealing option versus the metal catalysts often used to achieve high enantio- and diastereoselectivities. Urea and thiourea catalysts, first noted for their catalytic utility in 1988 and widely used since, have been shown to be capable hydrogen bond donors, enabling selectivity in reactions.[2] Their stabilization of reaction components has allowed for the development of many asymmetric urea and thiourea catalyzed transformations, including the Strecker[3] and nitro-Michael reactions,[4] the Morita–Baylis–Hillman reaction,[5] and conjugate addition reactions,[6] to name a few.

Two important and useful organic reactions that have been highly studied are the Mannich[7] and nitro-Mannich[8] (aza-Henry) additions of carbon nucleophiles to electrophilic imines. Utilizing dicarbonyls and nitroalkanes as nucleophiles, respectively, these reactions allow for the formation of secondary amine adducts, which can be easily converted to a variety of synthetically useful products such as α- and β-amino acids, 1,2-diamines, and cyclic amines.[9]

Several systems have been designed to asymmetrically catalyze each separate reaction, with a recent surge in the development of organocatalytic methods to achieve high enantio- and diastereoselectivities.[1c,2e,f,4e,10] List et al. developed the first organocatalyzed direct Mannich reaction, using L-proline to synthesize Mannich products in high enantio- and chemoselectivities.[10] Barbas et al. later extended this work to include other amino acid derivatives.[11] Our laboratory developed the asymmetric Mannich reaction of β-keto esters to acyl imines using cinchona alkaloids, producing enantioenriched dihydropyrimidones and α-amino alcohols.[12] Recently, Deng et al. used a chiral cinchona alkaloid-derived thioureas to promote the reaction of acyl imines with different malonate nucleophiles.[13]

The asymmetric nitro-Mannich reaction using organocatalysts has recently received much attention.[14] Takemoto first used a chiral thiourea with an *N*,*N*-dimethylamino group to enantioselectively catalyze the addition of nitromethane to various *N*-phosphinoylimines, further expanding the reaction scope by enantioselectively adding various nitroalkanes.[14,16] Jørgensen used a chiral copper(II) bisoxazoline complex, combined with cinchona alkaloids, to catalyze the reaction of *p*-methoxyphenylimino ethyl esters with tertiary nitroalkanes to form products in high enantioselectivities (Fig. 1).[15] Using chiral thiourea catalysts in the presence of an external base, Jacobsen and Yoon developed another variation of the nitro-Mannich reaction.[16] Ricci et al. utilized a phase-transfer catalyst to promote the nitro-Mannich reaction of *N*-carbamoyl imines generated from in situ α-amido sulfones.[17] Following this work, they screened a variety of cinchona organocatalysts to catalyze the addition of nitromethane to a variety of protected imines, synthesizing products in satisfactory yields and enantioselectivities.[18]

Due to the previous work completed in our laboratory using cinchona alkaloids as tertiary amine catalysts to asymmetrically catalyze direct Mannich reactions,[10,19] we initially attempted to extend the methodology to the nitro-Mannich

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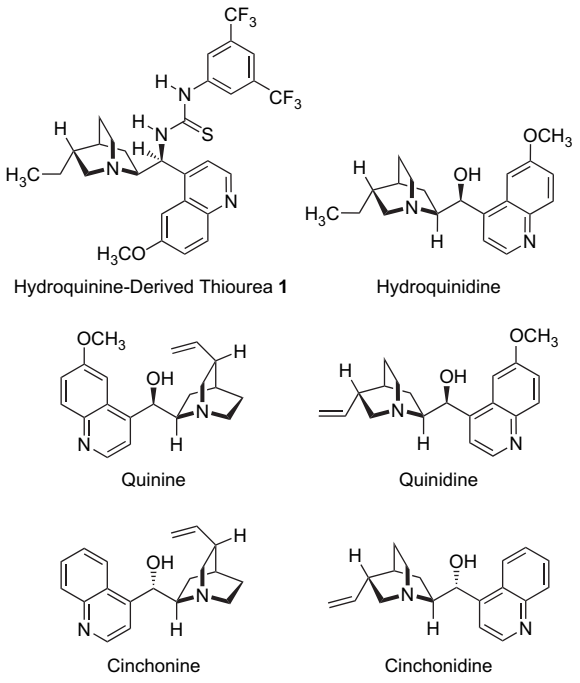


Figure 1. Cinchona alkaloid catalysts.

reaction. In the reactions of benzylidene methyl carbamate, nitromethane, and 10 mol % of a variety of cinchona alkaloids in CH_2Cl_2, we were able to synthesize secondary amine products in high yields (>90%). However, our progress was stymied by low enantioselectivities (<55%). Nevertheless, these preliminary results led us to further investigate the nature of cinchona alkaloids as catalysts, and possible modifications that could lead to greater success.

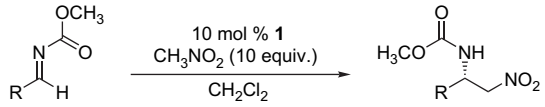
Our attention turned to the cinchona alkaloid-derived thiourea catalyst **1** used by Connon and Soos.[6b,g] Thiourea compounds have often been used in organic chemistry to efficiently enhance reaction rates, and have been known to catalyze nucleophilic addition reactions.[2,6]

2. Results and discussion

The reaction of methyl benzylidenecarbamate **2a** with nitromethane and 10 mol % hydroquinine-derived thiourea **1** in CH_2Cl_2 yielded the corresponding β-nitroamine **3a** in 91% isolated yield and in 93% ee after 24 h at −10 °C (Table 1, entry 1). Compared to the trifluoromethylated thiourea, the dimethyl-substituted catalyst gave **3a** in a comparable yield, yet with lower enantioselectivity (most likely due to the weaker electron-withdrawing capabilities of the methyl groups, affecting the hydrogen-bonding ability of the thiourea portion). In contrast, the cinchona alkaloid-derived thiourea was quite an efficient catalyst for this nitro-Mannich reaction.

The asymmetric nitro-Mannich reaction catalyzed by the hydroquinine-derived thiourea was found to be successful with other imines of varying electronics, both more electron-rich and electron-poor acyl imines (Table 1, entries 2–6). The reactions of electron-rich and electron-poor imine substrates yielded the corresponding β-nitroamines **3b**–**3f** in high enantioselectivities (90–98%) and yields (60–98%).

Table 1. Asymmetric nitro-Mannich additions of nitromethane[a]



2a–f **3a–f**

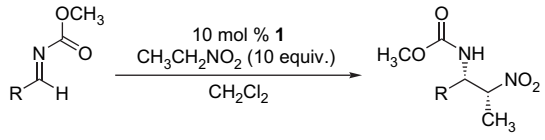
Entry	R	Adduct	Yield (%)[b]	ee (%)[c]
1[d]	**2a**: Ph	**3a**	91	93
2	**2b**: 3-MeC_6H_4	**3b**	98	91
3	**2c**: 3-FC_6H_4	**3c**	98	98
4	**2d**: cinnamyl	**3d**	80	90
5	**2e**: 2-furyl	**3e**	60	92
6	**2f**: 2-furyl-propenyl	**3f**	97	98

[a] Nitro-Mannich additions were carried out using 5 mmol of nitromethane, 0.5 mmol of imine in CH_2Cl_2 (0.5 M) at −10 °C for 48 h under N_2, followed by silica gel flash chromatography.
[b] Isolated yield of nitro-Mannich addition products.
[c] Determined by chiral HPLC analysis.
[d] Reaction was run for 24 h.

While cinchona alkaloid-derived thioureas have previously been utilized to study the nitro-Mannich addition of nitromethane to acyl imines, there has yet to be a thorough investigation using nitroethane as a carbon nucleophile. We attempted to extend the scope of our work by investigating nitroethane additions to the substrates used in Table 1. The same general reaction conditions proved to be useful for nitroethane additions, affording *syn*-addition products of similar yields (73–98%) and enantioselectivities (90–97%) (Table 2, entries 1–6). The nitroethane additions produced β-nitroamines **5a**–**5f** with adjacent stereocenters and established that the alkaloid-derived thiourea also catalyzed with high diastereoselectivity (ranging from 82 to 97%). Lower yields were obtained for the more electrophilic acyl imines **5d** and **5e**; however, there was no compromise in enantio- or diastereoselectivity.

A further expansion of the methodology was investigated upon the enantio- and diastereomeric success of the nitro-Mannich nucleophiles. The Mannich reaction parallels the nitro-Mannich in both the electrophilic substrate (acyl imine) and the nucleophilic additive (carbon nucleophile); it was

Table 2. Asymmetric nitro-Mannich additions of nitroethane[a]

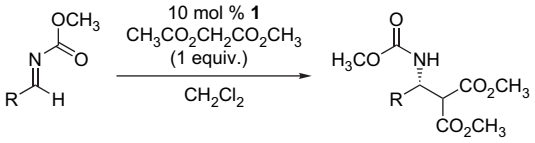


4a–f **5a–f**

Entry	R	Adduct	Yield (%)[b]	ee (%)[c]	de (%)[d]
1[e]	**4a**: Ph	**5a**	96	94	83
2	**4b**: 3-MeC_6H_4	**5b**	98	97	90
3	**4c**: 3-FC_6H_4	**5c**	98	91	97
4	**4d**: cinnamyl	**5d**	80	90	92
5	**4e**: 2-furyl	**5e**	73	97	82
6	**4f**: 2-furyl-propenyl	**5f**	90	97	83

[a] Nitro-Mannich additions were carried out using 5 mmol of nitroethane and 0.5 mmol of imine in CH_2Cl_2 (0.5 M) at −10 °C for 48 h under N_2, followed by silica gel flash chromatography.
[b] Isolated yield of nitro-Mannich addition products.
[c] Determined by chiral HPLC analysis.
[d] Determined by ^{1}H NMR analysis.
[e] Reaction was run for 24 h.

Table 3. Asymmetric Mannich additions of dimethyl malonate[a]



6a–f **7a–f**

Entry	R	Adduct	Yield (%)[b]	ee (%)[c]
1[d]	**6a**: Ph	**7a**	98	92
2	**6b**: 3-MeC_6H_4	**7b**	97	86
3	**6c**: 3-FC_6H_4	**7c**	98	90
4	**6d**: cinnamyl	**7d**	97	90
5[e]	**6e**: 2-furyl	**7e**	65	94
6[e]	**6f**: 2-furyl-propenyl	**7f**	96	90

[a] Mannich reactions were carried out using 0.5 mmol of dimethyl malonate and 0.5 mmol of imine in CH_2Cl_2 at −35 °C for 48 h under N_2, followed by silica gel flash chromatography.
[b] Isolated yield of Mannich products.
[c] Determined by chiral HPLC analysis.
[d] Reaction was run for 24 h.
[e] Reactions were run at −50 °C.

believed that this parallel should allow the HQ-derived thiourea to asymmetrically catalyze direct Mannich additions as well. To test this hypothesis, methyl benzylidenecarbamate **6a**, hydroquinine-derived thiourea catalyst, and dimethyl malonate in CH_2Cl_2 were reacted at −35 °C to produce the corresponding Mannich adduct **7a** in 98% yield and 92% ee (Table 3). With this encouraging result, the same substrates were employed in the reaction and similar good results were obtained, with yields ranging from 65 to 98% and enantioselectivities from 86 to 94%. The more electrophilic substrates **6e** and **6f** required lower reaction temperatures to achieve the same levels of enantioselectivity. These results highlight the utility of the cinchona alkaloid-derived thioureas, and the broad range of reaction conditions that may be used.

The relative stereochemistry and absolute stereochemistry of the products obtained were determined via optical rotation comparisons to known literature compounds.[20] The absolute stereochemistry of products **3a**–**3f** and **7a**–**7f** was determined to be (*S*) while the nitroethane addition was determined to be (1*S*,2*R*) by analogy with the corresponding allyl carbamates.

Aside from the reported utilities of the nitro-Mannich additions, we have also developed a method for transforming the Mannich products into their corresponding β-amino esters. Dixon et al. reported a decarboxylation via reflux in toluene for 12 h.[14d] We successfully transformed the malonate addition products to the β-amino esters using microwave irradiation, drastically reducing the previously reported reaction time, with only slight racemization of the resultant ester (Fig. 2).

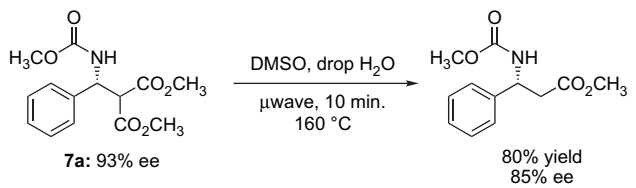


Figure 2. Decarboxylation of Mannich product **7a**.

3. Modeling

Catalyst **1** is capable of promoting the addition of stabilized anions to acyl imines with high levels of enantiodiscrimination. The high degree of selectivity observed in these reactions indicates a catalyst-associated complex with a high degree of coordination.[10a,b] We have developed a model that accounts for the observed diastereo- and enantioselectivity (Fig. 3). We modeled both nitromethane anion and malonate anion complex with thiourea catalyst **1**. A MMFF conformation search[21] identified the lowest energy conformer for each complex with the quinoline ring blocking one face of the nucleophile and the thiourea moiety forming a hydrogen bond with the nucleophile.[21a,22] The aromatic ring of the thiourea forms an edge-face contact with the nucleophile. Modeling of the methyl benzylidenecarbamate *re*-face attack of the nucleophile-catalyst complex provides a model of selectivity for the reactions.[23] The approach of the electrophile places the hydrogen of the energy-minimized *Z*-aldimine in line with the catalyst. Also depicted in Figure 3, the benzylidene aromatic ring forms an edge-face interaction with the thiourea arene. The nitromethane catalyst complex depicted in Figure 3A was modeled with *re*- and *si*-facial attack of the nucleophile. The calculated energy difference between the two binding modes was found to be 1.6 kcal/mol in favor of *si*-facial attack of the nucleophile. While the energy difference is modest, the model is in agreement with the preferred sense of selectivity (Table 2). These models illustrate the important interactions of the nucleophile with the catalyst. They also provide some insight into the factors that result in a selective reaction and how this class of thiourea catalysts is selective for such a wide-range of reactions.

4. Conclusion

In summary, hydroquinine-derived thiourea **1** was found to catalyze nucleophilic additions of nitroalkanes and dimethyl malonate to methyl carbamate acyl imines with good yields and high enantioselectivities. Catalyst **1** is a representative from a class of cinchona alkaloid-derived thiourea catalysts that promote a wide-range of reactions asymmetrically. The generality of these catalysts guarantees their use in the catalytic reaction methodology development. Future work includes the expansion of the methodology to different substrates and investigation of the synthetic utility of the addition products.

5. Experimental

5.1. General procedure for nitro-Mannich addition of nitroalkanes to acyl imines

5.1.1. Synthesis of product 3a: ((*S*)-2-nitro-1-phenylethyl)-carbamic acid methyl ester. To an oven-dried reaction vessel under argon were added acyl imine **2a** and thiourea catalyst **1** in CH_2Cl_2, (0.5 M). The mixture was cooled to −10 °C and then nitromethane (10 equiv) was added. The reaction was run to completion (24 h) and the crude mixture was run through a silica gel plug, eluted with ethyl acetate (5 mL). The filtrate was concentrated under

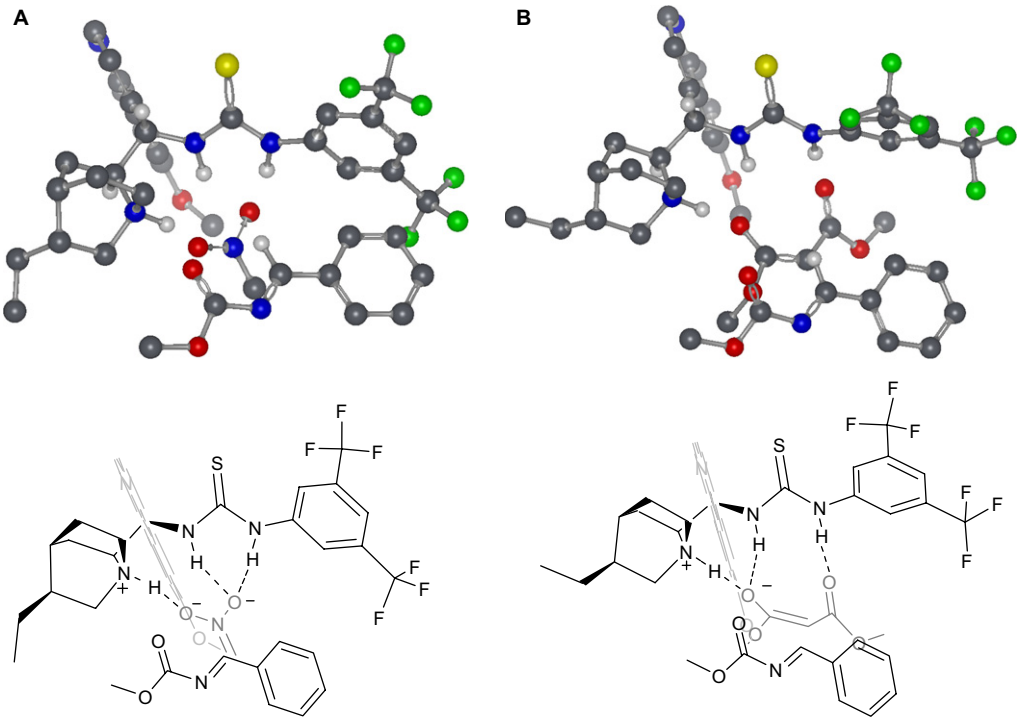


Figure 3. Proposed catalytically active thiourea **1** complexes (MMFF) approaching the *re*-face of methyl benzylidenecarbamate. (A) Nitromethane complex. (B) Malonate complex.

reduced pressure and the crude product was purified by flash chromatography over silica gel (eluted with 15–30% ethyl acetate in hexanes) to afford the nitro-Mannich adduct.

5.2. General procedure for Mannich addition of dimethyl malonate to acyl imines

5.2.1. Synthesis of product 7a: 2-((*R*)-methoxycarbonyl-amino-phenyl-methyl)-malonic acid dimethyl ester. To an oven-dried reaction vessel under argon were added acyl imine **2a** and thiourea catalyst **1** in CH_2Cl_2 (0.5 M). The mixture was cooled to −35 °C and dimethyl malonate (1 equiv) was added. The reaction was run to completion (24 h) and the crude mixture was run through a silica gel plug, eluted with ethyl acetate (5 mL). The filtrate was concentrated under reduced pressure and the crude product was purified by flash chromatography over silica gel (eluted with 15–30% ethyl acetate in hexanes) to afford the Mannich adduct.

Please refer to table footnotes for specific reaction times and temperature of each respective product.

5.2.2. Compound 3a: ((*S*)-2-nitro-1-phenyl-ethyl)-carbamic acid methyl ester. Yield: 0.102 g (91%), white solid; ee: 93%; HPLC analysis, t_R minor: 9.72 min, t_R major: 15.91 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.28 (m, 5H), 5.42 (m, 2H), 4.84 (br s, 1H), 4.70 (m, 1H), 3.69 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 156.2, 136.7, 129.1, 128.7, 126.3, 78.6, 53.1, 52.6; IR (thin film, cm^{-1}): 3322, 2954, 1686, 1534, 1256, 1049; HRMS (*m*/*z*) $(M+Na)^+$ calculated for $C_{10}H_{12}N_2O_4Na$: 247.0695, found: 247.0695; $[\alpha]_D^{23}$ +26.7 (*c* 1.00, $CHCl_3$).

5.2.3. Compound 3b: ((*S*)-2-nitro-1-*m*-tolyl-ethyl)-carbamic acid methyl ester. Yield: 0.035 g (98%), white solid; ee: 91%; HPLC analysis, t_R minor: 4.16 min, t_R major: 9.58 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25–7.06 (m, 5H), 5.38 (m, 1H), 4.82 (br s, 1H), 4.70 (m, 2H), 3.68 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 156.1, 138.8, 136.6, 129.4, 128.9, 127.0, 123.2, 78.5, 76.6, 53.1, 52.4. 21.3; IR (thin film, cm^{-1}): 3316, 3025, 2956, 1702, 1554, 1454, 1378, 1261, 1060, 913, 781; HRMS calcd for $(M+H)^+$ $C_{11}H_{14}N_2O_4$: 238.0948, found 239.1031; $[\alpha]_D^{23}$ −9.4 (*c* 1.10, $CHCl_3$).

5.2.4. Compound 3c: ((*S*)-1-(3-fluoro-phenyl)-2-nitro-ethyl)-carbamic acid methyl ester. Yield: 0.036 g (98%), light yellow solid; ee: 98%; HPLC analysis, t_R minor: 8.56 min, t_R major: 13.55 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.22 (m, 2H), 7.08–6.92 (m, 3H), 6.14 (d, *J*=8.4 Hz, 1H), 5.54 (br s, 1H), 5.37 (m, 2H), 5.09 (m, 1H), 3.69 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 164.3, 161.2, 155.9, 130.1, 122.3, 117.6, 113.7, 83.7, 55.6, 53.7; IR (thin film, cm^{-1}): 3659, 3323, 2924, 1705, 1595, 1533, 1354, 1258, 1058, 775; HRMS calcd for $(M+H)^+$ $C_{10}H_{11}N_2O_4$: 242.0697, found: 243.0781; $[\alpha]_D^{23}$ +13.9 (*c* 1.00, $CHCl_3$).

5.2.5. Compound 3d: ((*E*)-(*S*)-1-nitromethyl-3-phenyl-allyl)-carbamic acid methyl ester. Yield: 0.029 g (80%), light yellow solid; ee: 90%; HPLC Analysis, t_R minor: 9.27 min, *t* major: 17.92 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.19 (m, 5H), 6.63 (d, *J*=6.8 Hz, 1H), 6.14 (dd, *J*=6.4, 6.8 Hz, 1H), 5.38 (br s, 1H), 4.96–4.94 (m, 1H), 4.70–4.60 (m, 2H), 3.71 (s, 3H); ^{13}C NMR

(75.0 MHz, $CDCl_3$): δ 156.0, 133.7, 128.6, 128.41, 127.9, 127.1, 126.5, 123.3, 80.9, 52.7, 51.4; IR (thin film, cm^{-1}): 3325, 2955, 2926, 1717, 1550, 1520, 1449, 1538, 1246, 1065, 969, 748; HRMS calcd for $(M+H)^+$ $C_{12}H_{14}N_2O_4$: 250.0954, found: 251.1032; $[\alpha]_D^{23}$ +38.9 (*c* 0.77, $CHCl_3$).

5.2.6. Compound 3e: ((*R*)-1-furan-2-yl-2-nitro-ethyl)-carbamic acid methyl ester. Yield: 0.039 g (60%), orange solid; ee: 92%; HPLC analysis, t_R minor: 9.04 min, t_R major: 9.92 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J*=1.6 Hz, 1H), 6.33 (dd, *J*=3.4, 1.6 Hz, 1H), 6.30 (d, *J*=2.8 Hz, 1H), 5.49 (m, 1H), 5.43 (br s, 1H), 4.86 (dd, *J*=16.0, 8.0 MHz, 1H), 4.72 (dd, *J*=13.2, 5.6 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 156.0, 149.0, 143.0, 110.7, 107.9, 76.3, 52.7, 47.5; IR (thin film, cm^{-1}): 3311, 3127, 2954, 2933, 1702, 1553, 1265; HRMS (*m*/*z*) $(M+Na)^+$ calculated for $C_8H_{10}N_2O_5Na$: 237.0644, found: 237.0487; $[\alpha]_D^{23}$ +30.3 (*c* 0.60, $CHCl_3$).

5.2.7. Compound 3f: ((*S*)-3-furan-2-yl-1-nitromethyl-allyl)-carbamic acid methyl ester. Yield: 0.035 g (97%), yellow solid; ee: 98%; HPLC analysis, t_R minor: 12.55 min, t_R major: 18.37 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J*=2.0 Hz, 1H), 6.45 (d, *J*=16.0 Hz, 1H), 6.35 (dd, *J*=3.2, 2.0 Hz, 1H), 6.28 (d, *J*=3.2 Hz, 1H), 6.07 (dd, *J*=16.0, 6.4 Hz, 1H), 5.25 (br s, 1H), 4.92 (m, 1H), 4.66 (m, 1H), 4.59 (dd, *J*=12.8, 4.8 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 156.0, 151.0, 142.7, 121.9, 121.5, 111.5, 109.9, 78.0, 52.6, 51.0; IR (thin film, cm^{-1}): 3313, 2956, 2924, 2853, 1700, 1550, 1378, 1256; HRMS (*m*/*z*) $(M+Na)^+$ calculated for $C_{10}H_{12}N_2O_5Na$: 263.0800, found: 263.0644; $[\alpha]_D^{23}$ +36.9 (*c* 1.00, $CHCl_3$).

5.2.8. Compound 5a: ((1*S*,2*R*)-2-nitro-1-phenyl-propyl)-carbamic acid methyl ester. Yield: 0.107 g (96%), white solid; ee: 94%, de: 83%; HPLC analysis, t_R minor: 18.82 min, t_R major: 23.16 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=90:10, 1.5 mL/min]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.32 (m, 3H), 7.22–7.20 (m, 2H), 5.72 (br s, 1H, minor), 5.49 (br s, 1H, major), 5.22 (dd, *J*=9.0, 5.8 Hz, 1H, major), 5.13 (s, 1H, minor), 4.92 (m, 1H), 3.67 (s, 3H), 1.52 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 156.2, 136.2, 128.9, 128.7, 126.7, 85.5, 57.8, 52.5, 15.1; IR (thin film, cm^{-1}): 3311, 2924, 2853, 1691, 1544, 1291, 1018; HRMS (*m*/*z*) $(M+Na)^+$ calculated for $C_{11}H_{14}N_2O_4Na$: 261.0954, found: 261.0851; $[\alpha]_D^{23}$ +40.1 (*c* 1.00, $CHCl_3$).

5.2.9. Compound 5b: ((1*S*,2*R*)-2-nitro-1-*m*-tolyl-propyl)-carbamic acid methyl ester. Yield: 0.037 g (98%), white solid; ee: 97%, de: 90%; HPLC analysis, t_R minor: 11.91 min, t_R major: 19.11 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26–7.21 (m, 2H), 7.13–7.11 (m, 1H), 7.03–6.98 (m, 2H), 5.42 (m, 1H), 4.18 (m, 1H), 4.89 (br s, 1H), 3.67 (s, 3H), 2.32 (s, 3H), 1.51 (d, *J*=6.4 Hz, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 156.1, 138.5, 129.2, 128.7, 128.5, 126.8, 123.6, 85.57, 57.7, 52.7, 21.3, 21.2; IR (thin film, cm^{-1}): 3326, 2954, 2857, 1732, 1547, 1449, 1355, 1243, 1027, 913, 783, 731; HRMS calcd for $(M+H)^+$ $C_{12}H_{16}N_2O_4$: 252.1105, found: 253.1188; $[\alpha]_D^{23}$ +17.9 (*c* 0.86, $CHCl_3$).

5.2.10. Compound 5c: ((1*S*,2*R*)-1-(3-fluoro-phenyl)-2-nitro-propyl)-carbamic acid methyl ester. Yield: 0.037 g (98%), light yellow solid; ee: 91%, de: 97%; HPLC analysis, t_R minor: 9.92 min, t_R major: 14.12 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.22 (m, 2H), 7.04–6.93 (m, 3H), 5.50 (br s, 1H), 5.22 (m, 1H), 4.89 (m, 1H), 3.68 (s, 3H), 1.53 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 164.5, 161.2, 156.2, 130.6, 122.5, 115.6, 114.1, 85.3, 57.3, 52.7, 15.1; IR (thin film, cm^{-1}): 3316, 3067, 2955, 1703, 1593, 1550, 1452, 1357, 1248, 1026, 877, 786; HRMS calcd for $(M+H)^+$ $C_{11}H_{13}FN_2O_4$: 256.0854; found: 257.0938; $[\alpha]_D^{23}$ +51.0 (*c* 0.90, $CHCl_3$).

5.2.11. Compound 5d: ((*E*)-(*S*)-1-((*R*)-1-nitro-ethyl)-3-phenyl-allyl)-carbamic acid methyl ester. Yield: 0.032 g (80%), light yellow solid; ee: 90%, de: 92%; HPLC analysis, t_R minor: 12.30 min, t_R major: 21.25 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.09–6.91 (m, 5H), 6.37 (d, *J*=16.4 Hz, 1H), 5.81 (dd, *J*=7.2, 7.6 Hz, 1H), 5.04 (br s, 1H), 4.59 (m, 1H), 4.44 (m, 1H), 3.46 (s, 3H), 1.31 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 156.2, 135.9, 132.4, 128.5, 127.2, 126.6, 126.9, 85.1, 55.3, 52.5, 29.6; IR (thin film, cm^{-1}): 3323, 2954, 2927, 1731, 1547, 1519, 1296, 1247, 1197, 1049, 968, 744; HRMS calcd for $(M+H)^+$ $C_{13}H_{16}N_2O_4$: 263.1110, found: 264.1010; $[\alpha]_D^{23}$ +58.6 (*c* 0.52, $CHCl_3$).

5.2.12. Compound 5e: ((1*R*,2*R*)-1-furan-2-yl-2-nitro-propyl)-carbamic acid methyl ester. Yield: 0.025 g (73%), light yellow solid; ee: 97%, de: 82%; HPLC analysis, t_R minor: 7.38 min, t_R major: 8.18 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J*=1.2 Hz, 1H), 6.31 (dd, *J*=3.4, 1.8 Hz, 1H), 6.27 (d, *J*=3.2 Hz, 1H), 5.55 (br s, 1H, minor), 5.45 (br s, 1H, major), 5.35 (dd, *J*=9.0, 6.0 Hz, 1H, major), 5.27 (br m, 1H, minor), 5.04 (m, 1H, minor), 4.88 (m, 1H, major), 3.70 (s, 3H), 1.57 (d, *J*=9.2 Hz, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 156.1, 148.7, 143.0, 110.6, 108.6, 84.2, 52.8, 52.1, 15.3; IR (thin film, cm^{-1}): 3310, 2955, 2924, 1701, 1550, 1235, 1013, 743; HRMS (*m*/*z*) $(M+Na)^+$ calcd for $C_9H_{12}N_2O_5Na$: 251.0487, found: 251.0644; $[\alpha]_D^{23}$ +49.6 (*c* 0.50, $CHCl_3$).

5.2.13. Compound 5f: ((*S*)-3-furan-2-yl-1-((*R*)-1-nitro-ethyl)-allyl)-carbamic acid methyl ester. Yield: 0.065 g (90%), yellow oil; ee: 97%, de: 83%; HPLC analysis, t_R minor: 22.91 min, t_R major: 30.38 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=95:5, 1.5 mL/min]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J*=1.6 Hz, 1H), 6.43 (d, *J*=16.0 Hz, 1H), 6.35 (dd, *J*=3.2, 2.0 Hz, 1H), 6.27 (d, *J*=3.6 Hz, 1H), 5.98 (dd, *J*=15.6, 7.6 Hz, 1H), 5.26 (d, *J*=8.4 Hz, 1H), 4.79 (m, 1H), 4.67 (m, 1H), 3.69 (s, 3H), 1.56 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 156.1, 151.1, 142.6, 123.0, 121.4, 111.4, 108.8, 85.0, 56.0, 52.6, 15.9; IR (thin film, cm^{-1}): 3375, 2958, 2921, 2850, 1709, 1550, 1259, 733; HRMS (*m*/*z*) $(M+Na)^+$ calcd for $C_{11}H_{14}N_2O_5Na$: 277.0746, found: 277.0800; $[\alpha]_D^{23}$ +5.3 (*c* 1.00, $CHCl_3$).

5.2.14. Compound 7a: 2-((*R*)-methoxycarbonylamino-phenyl-methyl)-malonic acid dimethyl ester. Yield: 0.145 g (98%), white solid; ee: 92%; HPLC analysis, t_R

minor: 12.42 min, t_R major: 15.11 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.26 (m, 5H), 6.36 (d, J=8.0 Hz, 1H), 5.48 (m, 1H), 3.90 (d, J=5.6 Hz, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 168.6, 167.6, 156.5, 139.3, 128.9, 128.0, 126.4, 56.7, 54.1, 53.2, 52.8, 52.5; IR (thin film, cm^{-1}): 3274, 2954, 2924, 1754, 1739, 1688, 1550, 1434, 1290, 1263, 1149; HRMS (*m*/*z*) (M+Na)$^+$ calcd for $C_{14}H_{17}NO_6Na$: 318.0954, found: 318.0954; $[\alpha]_D^{23}$ −1.4 (*c* 1.00, $CHCl_3$).

5.2.15. Compound 7b: 2-((*R*)-methoxycarbonylamino-*m*-tolyl-methyl)-malonic acid dimethyl ester. Yield: 0.045 g (97%), white solid; ee: 86%; HPLC analysis, t_R minor: 9.21 min, t_R major: 11.57 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.17 (m, 3H), 7.07–7.06 (m, 2H), 6.36 (d, J=7.2 Hz, 1H), 5.46 (br s, 1H), 3.88 (br s, 1H), 3.74 (s, 3H), 3.64 (s, 3H), 3.63 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 168.2, 167.2, 156.2, 138.9, 138.2, 128.5, 128.4, 126.8, 123.0, 56.3, 53.8, 52.8, 52.4, 52.1, 21.3; IR (thin film, cm^{-1}): 3287, 2955, 2926, 1748, 1693, 1545, 1438, 1354, 1293, 1194, 1149, 1049, 1013, 913, 786; HRMS calcd for (M+H)$^+$ $C_{17}H_{21}NO_6$: 335.1369, found 336.2093; $[\alpha]_D^{23}$ −1.7 (*c* 1.10, $CHCl_3$).

5.2.16. Compound 7c: 2-((*R*)-(3-fluoro-phenyl)-methoxycarbonylamino-methyl)-malonic acid dimethyl ester. Yield: 0.092 g (98%), light yellow solid; ee: 90%; HPLC analysis, t_R minor: 16.67 min, t_R major: 20.19 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.24 (m, 2H), 7.06–6.91 (m, 3H), 6.42 (d, J=8.4 Hz, 1H), 5.48 (d, J=4.4 Hz, 1H), 3.89 (d, J=1.3 Hz, 1H), 3.72 (s, 3H), 3.63 (s, 6H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 168.9, 167.4, 164.5, 161.2, 142.1, 130.2, 122.0, 114.7, 113.5, 63.7, 62.3, 52.8, 52.5; IR (thin film, cm^{-1}): 3316, 3067, 2955, 1703, 1593, 1550, 1452, 1357, 1248, 1026, 877, 786; HRMS calcd for (M+H)$^+$ $C_{16}H_{18}FNO_6$: 339.1118, found: 340.0278; $[\alpha]_D^{23}$ −15.4 (*c* 1.46, $CHCl_3$).

5.2.17. Compound 7d: 2-((*E*)-(*S*)-1-methoxycarbonylamino-3-phenyl-allyl)-malonic acid dimethyl ester. Yield: 0.046 g (97%), light yellow solid; ee: 90%; HPLC analysis, t_R minor: 9.18 min, t_R major: 11.35 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.22 (m, 5H), 6.57 (d, J=16.0 Hz, 1H), 6.18 (dd, J=6.8, 6.8 Hz, 1H), 5.86 (br s, 1H), 5.02 (m, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 168.2, 156.2, 136.0, 132.4, 128.5, 127.9, 126.6, 125.9, 55.3, 52.8, 52.6, 52.3; IR (thin film, cm^{-1}): 3376, 2955, 2854, 1735, 1511, 1442, 1354, 1240, 1197, 1069, 1034, 970, 785; HRMS calcd for (M)$^+$ $C_{16}H_{19}NO_6$: 321.1212, found: 321.1110; $[\alpha]_D^{23}$ +4.5 (*c* 0.66, $CHCl_3$).

5.2.18. Compound 7e: 2-((*R*)-furan-2-yl-methoxycarbonylamino-methyl)-malonic acid dimethyl ester. Yield: 0.022 g (65%), light yellow oil; ee: 94%; HPLC analysis, t_R minor: 5.96 min, t_R major: 6.57 min [Chiralcel OD chiral column, hexanes:IPA=90:10, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (dd, J=1.8, 0.6 Hz, 1H), 6.28 (dd, J=3.4, 1.8 Hz, 1H), 6.21 (dd, J=3.2, 1.2 Hz, 1H), 6.09 (d, J=8.8 Hz, 1H), 5.56 (dd, J=9.4, 4.2 Hz, 1H), 4.02 (d, J=4.8 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 168.1, 167.0, 156.3, 151.8, 142.2, 110.5, 106.9, 53.8, 53.0, 52.7, 52.4, 48.7; IR (thin film, cm^{-1}): 3357, 2923, 2852, 1725, 1503, 1436, 1230, 1147; HRMS (*m*/*z*) (M+Na)$^+$ calcd for $C_{12}H_{15}NO_7Na$: 308.0746, found: 308.0746; $[\alpha]_D^{23}$ +12.7 (*c* 1.00, $CHCl_3$).

5.2.19. Compound 7f: 2-((*S*)-3-furan-2-yl-1-methoxycarbonylamino-allyl)-malonic acid dimethyl ester. Yield: 0.033 g (96%), a yellow oil; ee: 97%; HPLC analysis, t_R minor: 12.16 min, t_R major: 24.21 min [(*R*,*R*)-Whelk-O 1 column, hexanes:IPA=85:15, 1.5 mL/min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J=1.6 Hz, 1H), 6.40 (d, J=15.2 Hz, 1H), 6.33 (dd, J=3.2, 2.0 Hz, 1H), 6.23 (d, J=3.2 Hz, 1H), 6.09 (dd, J=15.4, 6.6 Hz, 1H), 5.85 (d, J=10.4 Hz, 1H), 4.99 (br s, 1H), 3.74 (s, 6H), 3.66 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 167.3, 151.4, 142.1, 124.2, 124.2, 120.4, 111.2, 108.8, 55.0, 52.6, 52.4, 52.1; IR (thin film, cm^{-1}): 3379, 2956, 2852, 1724, 1511, 1436, 1232, 729; HRMS (*m*/*z*) (M+Na)$^+$ calcd for $C_{12}H_{15}NO_7Na$: 334.0903, found: 334.0903; $[\alpha]_D^{23}$ +5.6 (*c* 1.00, $CHCl_3$).

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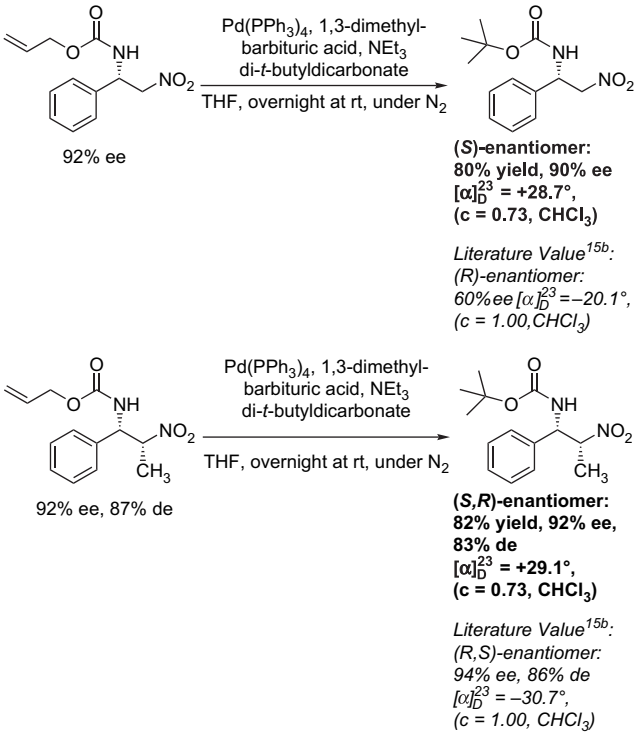

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