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Primary Amine-Thioureas based on *tert*-Butyl Esters of Natural Amino Acids as Organocatalysts for the Michael Reaction

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Abstract: A new class of primary amine-thioureas based on *tert*-butyl esters of (*S*)-α-amino acids and (1*S*,2*S*)-diphenylethylenediamine was synthesized and their activity as catalysts in Michael additions was evaluated. Derivatives based on di-*tert*-butyl aspartate and *tert*-butyl *O*-*tert*-butyl threoninate provided the product of the reaction between *trans*-β-nitrostyrene and acetone in quantitative yield and high enantioselectivity (87–91% *ee*). All the thioureas based on *tert*-butyl esters of amino acids catalyzed the reaction of nitroolefins with acetophenone with high enantioselectivity (92–98% *ee*). Thus, low-cost, commercially available *tert*-butyl esters of natural amino acids are very important chiral building blocks for the construction of novel chiral thioureas able to catalyze asymmetric Michael additions with high enantioselectivity.

Keywords: amino acids; Michael addition; nitroolefins; organocatalysis; thioureas

Introduction

Over the course of the last decade, organocatalysis has emerged as one of the most modern and rapidly growing areas of organic chemistry.[1] Organocatalysts are small organic molecules that do not require special experimental handling conditions, and may be used even in water, thus being considered environmentally friendly catalysts. The most important classes of organocatalysts up to now are proline and proline-derived compounds, MacMillan's imidazolidinones and chiral thioureas.[2] In 1998, Jacobsen reported that urea and thiourea derivatives (like **1**, Figure 1) can be effective asymmetric catalysts for the Strecker reaction.[3] Since then, a variety of chiral thioureas has been used for various asymmetric transformations.[2b,e,o,p,r,s] Takemoto and co-workers developed a thiourea catalyst based on 1,2-*trans*-cyclohexanediamine (**2**, Figure 1) and demonstrated the highly enantioselective Michael addition of 1,3-dicarbonyl compounds to nitroolefins.[4] Most of the known chiral thioureas are bifunctional catalysts containing a tertiary amine group, for example, compound **2**. Only a few examples of chiral thioureas containing a primary amino group have been reported up to now. Tsogoeva has developed catalysts based on 1,2-diphenylethylenediamine or 1,2-cyclohexanediamine, for example, compound **3** (Figure 1), for the nucleophilic addition of ketones to nitroolefins,[5] while Jacobsen presented catalysts based on 1,2-*trans*-cyclo-

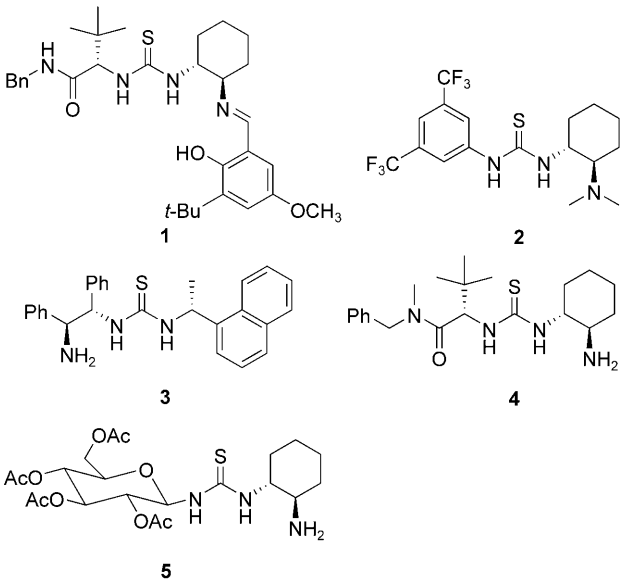


Figure 1. Examples of chiral thiourea catalysts.

hexanediamine (like **4**, Figure 1) for the same reaction as well as for the conjugate addition of α,α-disubstituted aldehydes to nitroolefins.[6] A primary amine-thiourea based on a saccharide (**5**, Figure 1) has been shown to be a highly enantioselective catalyst for the reaction of aromatic ketones with nitroolefins.[7] The aim of the present work was the synthesis of thioureas based on a variety of natural amino acid *tert*-butyl esters bearing a primary amino group and the evaluation of these catalysts in the Michael reaction.

Results and Discussion

The rationale for the design of the catalysts of this work is illustrated in Figure 2. For the construction of the catalyst, apart from the hydrogen bond donor

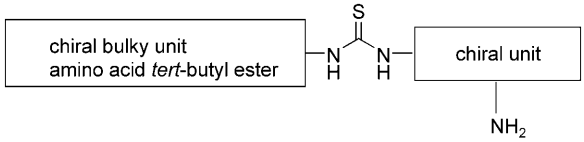
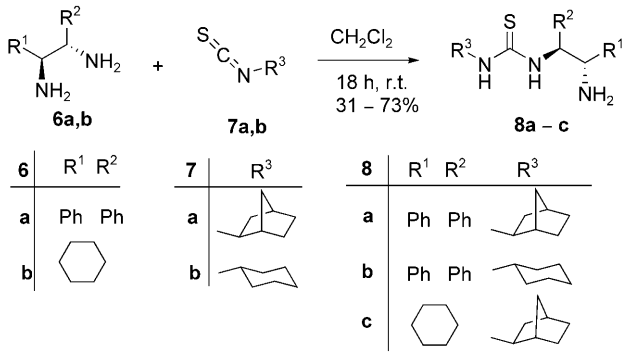


Figure 2. Design of new catalytic thioureas.

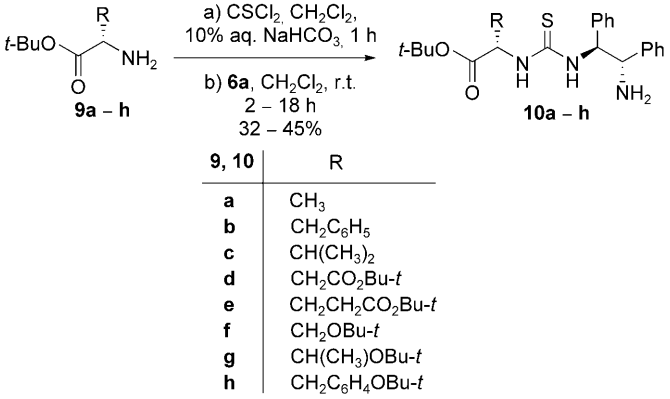
thiourea group, a chiral diamine unit is required to provide the primary amino group ensuring the ability to form an enamine. The chiral environment should be complemented by a bulky unit, or preferably by a commercially available *tert*-butyl ester of a natural amino acid. We have chosen amino acids without side chain functionalities, acidic amino acids where the side chain carboxyl group is protected by the *tert*-butyl ester group, and amino acids bearing a hydroxy functionality in the side chain protected as a *tert*-butyl ether.

(1*S*,2*S*)-1,2-Diphenylethylenediamine (**6a**) and (1*S*,2*S*)-cyclohexanediamine (**6b**) were treated with commercially available *exo*-2-norbornyl isothiocyanate (**7a**) and cyclohexyl isothiocyanate (**7b**) to afford thioureas **8a**–**c** (Scheme 1). A variety of commercially available *tert*-butyl esters of alanine (**9a**), phenylalanine (**9b**), valine (**9c**), aspartic acid (**9d**), glutamic acid (**9e**), serine (**9f**), threonine (**9g**) and tyrosine (**9h**) were converted to the corresponding isothiocyanates by treatment with thiophosgene and reacted with (1*S*,2*S*)-1,2-diphenylethylenediamine (**6a**) to afford chiral thioureas **10a**–**h** (Scheme 2).

The asymmetric Michael addition reaction is one of the most important processes for the synthesis of new C–C and C–X bonds and the application of organocatalysts in this reaction has been intensively studied.[8] In the present work, the conjugate addition of ketones to nitroolefins was explored. Our attention has been focused on two of the most problematic sub-



Scheme 1. Synthesis of catalysts **8a**–**c**.

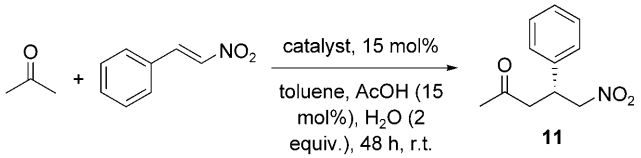


Scheme 2. Synthesis of catalysts **10a**–**h**.

strates for the nitro-Michael addition, namely acetone and acetophenone. Initially, a model reaction between acetone and *trans*-β-nitrostyrene using 15% catalyst loading in the presence of AcOH and water was studied and the results are summarized in Table 1. Both catalysts **8a** and **8b** based on (1*S*,2*S*)-1,2-diphenylethylenediamine afforded the product in quantitative yield and good *ee* (entries 1 and 2, Table 1). However, catalyst **8c** led to low yield and a reduced enantioselectivity (entry 3, Table 1). A comparison between the results obtained using catalysts **8a** and **8c** indicate that the (1*S*,2*S*)-1,2-diphenylethylenediamine moiety leads to better results than the (1*S*,2*S*)-cyclohexanediamine moiety. Thus, for the synthesis of catalysts based on *tert*-butyl esters of amino acids only diamine **6a** was used.

The catalysts **10a** and **10b** based on alanine and phenylalanine produced the product in *ee*s not exceeding 80% (entries 4 and 5, Table 1). However, using the catalyst **10c**, based on valine, the product was isolated in 85% *ee* (entry 6, Table 1), indicating that a more hindered side chain corresponding to valine, in comparison to the less hindered side chains of alanine and phenylalanine, leads to better results. Both catalysts **10d** and **10e**, based on aspartate and glutamate, provided the product in quantitative yields

Table 1. Michael reaction of acetone with *trans*-β-nitrostyrene using thioureas as catalysts.



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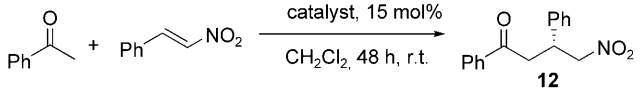
Entry	Catalyst	Yield [%][a]	*ee* [%][b]
1	**8a**	100	84
2	**8b**	100	82
3	**8c**	29	77
4	**10a**	88	73
5	**10b**	42	79
6	**10c**	77	85
7	**10d**	100	91
8	**10e**	100	61
9	**10f**	100	75
10	**10g**	100	87
11	**10h**	89	81

[a] Isolated yield after column chromatography.
[b] The *ee* was determined by HPLC on a Daicel Chiralpak AD-H column.

Table 2. Michael reaction of acetophenone with *trans*-β-nitrostyrene using thioureas as catalysts.



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Entry	Catalyst	Yield [%][a]	*ee* [%][b]
1	**8a**	27	89
2	**8b**	53	88
3	**8c**	traces	–
4	**10b**	37	92
5	**10c**	28	92
6	**10d**	68	95
7	**10f**	51	95
8	**10g**	27	96
9[c]	**10g**	38	94
10	**10h**	34	94

[a] Isolated yield after column chromatography.
[b] The *ee* was determined by HPLC on a Daicel Chiralpak AD-H column.
[c] The reaction was carried out under reflux.

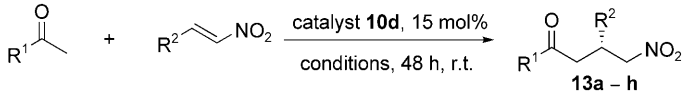
(entries 7 and 8, Table 1). However, the aspartate based catalyst **10d** led to high *ee* (91%, entry 7, Table 1) while, in contrast, the glutamate based catalyst **10e** exhibited a dramatic loss in *ee* (61%, entry 8, Table 1). The addition of one carbon atom between the α-carbon atom and the side chain *tert*-butyl ester group has a detrimental effect on the enantioselectivity. Using derivatives based on serine **10f** and threonine **10g**, the product was isolated in quantitative yields (entries 9 and 10, Table 1), but only in the case of threonine in high *ee* (87%) (entry 10, Table 1). Obviously, the additional stereogenic center in the side chain of threonine positively contributes to the increase of the enantioselectivity. Finally, using the tyrosine derivative **10h**, the product was obtained in high yield and 81% *ee* (entry 11, Table 1). Comparing catalysts **10b** and **10h**, the introduction of a *para-tert*-butoxy group in the phenyl ring efficiently increases the yield from 42% to 89%, however, it only slightly influences the enantioselectivity (entries 5 and 11, Table 1).[9] Attempts to reduce either the loading of catalyst **10d**, or the amount of the nucleophile acetone led to substantial decreases of the reaction yield (data not shown).

The application of organocatalysts in the reaction of aromatic ketones as Michael donors with nitroolefins is described as difficult and limited examples exist in the literature. Only thioureas **4** and **5** based on (1*S*,2*S*)-1,2-cyclohexanediamine have been shown to catalyze this transformation.[6a,7] The reaction between acetophenone and *trans*-β-nitrostyrene was studied in the presence of 15 mol% of our catalysts within 48 h and the results are summarized in Table 2. Catalysts **8a** and **8b** gave the product in high *ee*, but with a low to moderate yield (entries 1 and 2, Table 2). On the contrary, catalyst **8c** failed to catalyze the reaction, indicating that the (1*S*,2*S*)-1,2-diphenylethylenediamine moiety is superior in comparison to (1*S*,2*S*)-cyclohexanediamine.

All the catalysts based on the *tert*-butyl esters of amino acids produced the product in high enantioselectivities (92–96% *ee*), but in variable yields. Phenylalanine, valine, threonine and tyrosine derivatives (**10b**, **10c**, **10g**, **10h**) led to low or moderate yields (entries 4, 5, 8 and 10, Table 2). An increase on the yield from 27% to 38% was observed, when the threonine catalyst **10g** was used under reflux (entries 8 and 9, Table 2). The *ee* value was slightly reduced indicating that the thiourea catalysts based on *tert*-butyl esters of amino acids may work equally well at elevated temperature. Among the aspartate and serine derivatives **10d** and **10f** (entries 6 and 7, Table 2), catalyst **10d**, exhibited the best properties affording the product in 68% yield and 95% *ee*. An attempt to reduce the ratio of *trans*-β-nitrostyrene:acetophenone from 1:10 to 1:5 afforded the product in comparable yield and *ee*, when the catalyst **10f** was applied.

To explore the scope of these transformations, various nitroolefins were studied for their reactions with acetone and acetophenone using the aspartate-based thiourea **10d** as a catalyst and the results are presented in Table 3. The reaction between acetophenone and various nitroolefins took place with high enantioselectivity (95–98% *ee*) (entries 1–4, Table 3). The product was isolated in good yields (61–71%), apart

Table 3. Michael reaction of acetone and acetophenone with various nitroolefins using thioureas as catalysts.



Entry	R^1	R^2	Product	Conditions	Yield [%][a]	*ee* [%][b]
1	Ph	*p*-$MeOC_6H_4$	**13a**	A[c]	43	97
2	Ph	*p*-$NO_2C_6H_4$	**13b**	A[c]	61	96
3	Ph	*p*-FC_6H_4	**13c**	A[c]	71	95
4	Ph	2-furyl	**13d**	A[c]	70	98
5	Me	*p*-$MeOC_6H_4$	**13e**	B[d]	69	91
6	Me	*p*-$NO_2C_6H_4$	**13f**	B[d]	94	88
7	Me	*p*-FC_6H_4	**13g**	B[d]	99	88
8	Me	2-furyl	**13h**	B[d]	94	92

[a] Isolated yield after column chromatography.
[b] The *ee* was determined by HPLC on a Daicel Chiralpak AD-H column.
[c] A: CH_2Cl_2.
[d] B: toluene, AcOH (15 mol%), H_2O (2 equiv).

from the case of an electron-rich nitroolefin (43%, entry 1, Table 3). High enantioselectivity was observed when *p*-OMe-substituted nitroolefin reacted with acetone (entry 5, Table 3), but the yield of the reaction was 69%. When nitroolefins substituted by electron-withdrawing groups were used, the products obtained in high to quantitative yields (94–99%) and high enantioselectivity (88% *ee*) (entries 6 and 7, Table 3). In addition, the product of the reaction between acetone and 2-(2-nitrovinyl)furan was isolated in both high yield and enantioselectivity (entry 8, Table 3).

The thiourea catalysts of the present study, combining the (1*S*,2*S*)-diphenylethylenediamine unit and a *tert*-butyl ester of (*S*)-amino acid catalyze the reaction of either acetone or acetophenone with *trans*-nitroolefins producing the (*R*)-enantiomer. In particular, the products of the reactions with *trans*-β-nitrostyrene were obtained in 100% yield and 91% *ee* and 68% yield and 95% *ee*, respectively, when the catalyst **10d** based on aspartate was used. As reported in the literature, the (*S*)-enantiomer of the addition products between either acetone or acetophenone with *trans*-β-nitrostyrene were produced, when catalyst **4** was used.[6a] Using the saccharide thiourea **5**, the (*S*)-enantiomer product of the reaction between acetophenone and *trans*-β-nitrostyrene was obtained in 60% yield and 97% *ee*.[7] On the contrary, application of catalyst **3** in the reaction of acetone with *trans*-β-nitrostyrene produced the (*R*)-enantiomer in 98% yield and 91% *ee*.[5a] It should be noticed that proline produces the product of the reaction between acetone and *trans*-β-nitrostyrene in very low *ee* (7%).[10] We and others have demonstrated that homoprolyltetrazole[11] or homoprolylsulfonamides[12] may substantially increase the *ee* to 42% and 48%, respectively. However, these results are by far inferior to those obtained by thioureas. In addition, to our knowledge proline or proline-derivatives have not been reported to catalyze the reaction between acetophenone and *trans*-β-nitrostyrene. Thus, primary amine-thioureas based on *tert*-butyl esters of α-amino acids represent a new class of thiourea catalysts, which efficiently catalyze "difficult" Michael additions. Comparing the various amino acid side chains, it is obvious that the existence of a second *tert*-butyl ester group or a *tert*-butyl ether group at the β-carbon atom of the amino acid has a profound effect on enantioselectivity. Barbas and coworkers have recently shown that *O*-*tert*-butyl-L-threonine is an efficient organocatalyst of *anti*-Mannich and *syn*-aldol reactions.[13] After the experimental part of this work had been finished, it was reported that self-assemblies from α-amino acids and alkaloid derivatives may efficiently catalyze direct nitro-Michael reactions.[14] In addition, a new class of dehydroabietic amine-substituted primary amine-thiourea catalysts was shown to catalyze the conjugated addition of various heterocycles-bearing ketones to nitroalkenes with excellent enantioselectivity.[15]

A bifunctional mechanism involving hydrogen bonding and enamine formation has been proposed to explain the enantioselectivity observed in Michael additions catalyzed by thioureas **3**, **4** and **5**.[5a,6a,7] A joint experimental-theoretical study showed that only one oxygen atom of the nitro group was bound to the thiourea moiety.[5b] A similar model may be proposed for the catalysts of the present study (Figure 3). The thiourea functionality interacts through hydrogen bonding with the nitro group enhancing the electrophilicity of nitroolefin, while the primary amine activates the ketone through the formation of an enamine intermediate.

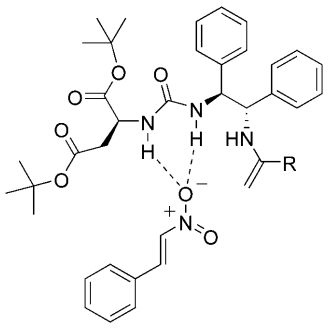


Figure 3. Proposed transition state model for the reaction of ketones with *trans*-β-nitrostyrene.

Conclusions

In conclusion, in the present work new thioureas based on *tert*-butyl esters of natural amino acids bearing a primary amino group were easily synthesized and their activity as catalysts in "difficult" Michael additions was evaluated. In particular, the derivative based on di-*tert*-butyl aspartate affords the product of the reaction of nitroolefins with either acetophenone or acetone in high to quantitative yields and in high enantioselectivity (88–98% *ee*). Thus, low-cost, commercially available *tert*-butyl esters of natural amino acids proved to be very important chiral building blocks to construct novel chiral thiourea catalysts.

Experimental Section

General Remarks

Flash chromatography was performed on silica gel (Merck Kieselgel 60 F_{254} 230–400 mesh). TLC was performed on aluminum backed silica plates (0.2 mm, 60 F_{254}) which were developed using standard visualizing agents: UV fluorescence (254 and 366 nm), phosphomolybdic acid/Δ, anisaldehyde/Δ. Melting points were determined on a Büchi 530 hot-stage apparatus and are not corrected. ^{1}H NMR spectra were recorded at 200 MHz on a Varian Mercury instrument. Chemical shifts (δ_H) are quoted in parts per million (ppm), referenced to the appropriate solvent peak. ^{13}C NMR spectra were recorded at 50 MHz on a Varian Mercury instrument. Chemical shifts (δ_c) are quoted in parts per million (ppm), referenced to the appropriate solvent peak. ^{19}F NMR spectra were recorded at 188 MHz on a Varian Mercury instrument. Chemical shifts (δ_F) are quoted in parts per million (ppm), referenced to trifluoroacetic acid as an internal standard. Chiral HPLC analyses were performed using an Agilent 1100 Series apparatus and a Daicel Chiralpak column (AD-H) using hexane/2-propanol as eluent. The configuration of the Michael addition products has been assigned by comparison to literature data.

General Procedure for the Synthesis of Compounds 8a–c

To a stirring solution of (1,*S*,2*S*)-diphenylethylenediamine (0.15 g, 0.71 mmol) in dichloromethane (7 mL), a solution of the appropriate isothiocyanate (0.71 mmol) in dichloromethane (15 mL) was added over a period of 15 min at room temperature and the reaction mixture was left stirring for 18 h. The solvent was evaporated and the crude product was purified using flash column chromatography eluting with various mixtures of CH_2Cl_2:MeOH.

1-[(1*S*,2*S*)-2-Amino-1,2-diphenylethyl]-3-(bicyclo[2.2.1]-hept-2-yl)thiourea (8a): White solid; yield: 73%; mp 82–83 °C; $[\alpha]_D^{25}$: −59.9 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.42–7.01 (m, 11 H), 6.29–6.08 (m, 1 H), 5.21 (br s, 1 H), 4.37 (br s, 1 H), 3.78–3.49 (m, 1 H), 2.38–2.11 (m, 2 H), 1.92–1.65 (m, 4 H), 1.59–1.42 (m, 2 H), 1.38–0.99 (m, 4 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 180.7, 141.9, 140.1, 129.0, 128.9, 128.8, 128.0, 126.9, 126.8, 64.2, 60.4, 57.4, 42.7, 40.6, 36.0 35.7, 28.3, 26.6; HR-MS: *m/z* = 366.2002, calcd. for $C_{22}H_{27}N_3S$ ($M+H^+$): 366.2004.

1-[(1*S*,2*S*)-2-Amino-1,2-diphenylethyl]-3-cyclohexylthiourea[16] **(8b):** White solid; yield: 65%; $[\alpha]_D^{25}$: −57.0 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 5.8 Hz, 1 H), 7.31–7.05 (m, 10 H), 6.13 (d, *J* = 6.2 Hz, 1 H), 5.11 (br s, 1 H), 4.24 (d, *J* = 5.8 Hz, 1 H), 4.01–3.72 (m, 1 H), 2.08 (br s, 2 H), 1.98–1.76 (m, 2 H), 1.67–1.46 (m, 2 H), 1.41–0.89 (m, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 180.8, 141.8, 139.6, 129.1, 128.9, 128.8, 128.0, 127.0, 126.9, 64.2, 60.7, 53.3, 32.8, 25.6, 24.7, 24.6.

1-[(1*S*,2*S*)-2-Aminocyclohexyl]-3-(bicyclo[2.2.1]hept-2-yl)thiourea (8c): Colourless oil; yield: 31%; $[\alpha]_D^{25}$: −35.2 (*c* 1, CH_3OH). ^{1}H NMR (200 MHz, CD_3OD): δ = 4.56–4.39 (m, 1 H), 4.08–3.91 (m, 1 H), 3.28–2.98 (m, 1 H), 2.37–2.24 (m, 2 H), 2.19–1.97 (m, 2 H), 1.91–1.69 (m, 4 H), 1.61–1.11 (m, 10 H); ^{13}C NMR (50 MHz, CD_3OD): δ = 182.3, 57.5, 55.5, 55.3, 42.2, 39.5, 35.9 35.2, 31.6, 30.0, 28.1, 26.1, 24.5, 23.8; HR-MS: *m/z* = 268.1844, calcd. for $C_{14}H_{25}N_3S$ ($M+H^+$): 268.1847.

General Procedure for the Synthesis of Compounds 10a–h

To a stirring solution of amino acid *tert*-butyl ester hydrochloride (1.0 mmol) in dichloromethane (5 mL), a saturated aqueous solution of $NaHCO_3$ (5 mL) was added at 0 °C and left stirring vigorously for 10 min. The stirring was stopped and thiophosgene (0.1 mL, 1.05 mmol) was added to the organic layer (bottom layer) *via* syringe. The reaction mixture was stirred vigorously at room temperature for 1 h. The two layers were separated and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated to afford the isothiocyanate of sufficient purity to be used in the subsequent step. A solution of the isothiocyanate in dichloromethane (15 mL) was added to a stirring solution of (1,*S*,2*S*)-diphenylethylenediamine (0.21 g, 1.0 mmol) in dichloromethane (10 mL) over a period of 15 min at room temperature and the reaction mixture was left stirring until the consumption of the isothiocyanate (2–18 h). The solvent was evaporated and the crude product was purified using flash column chromatography eluting with various mixtures of $CHCl_3$:MeOH or CH_2Cl_2:MeOH.

(*S*)-*tert*-Butyl 2-{3-[(1*S*,2*S*)-2-amino-1,2-diphenylethyl]-thioureido}propanoate (10a): Colourless oil; yield: 35%; $[\alpha]_D^{25}$: −14.8 (*c* 0.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.71 (m, 1H), 7.32–7.12 (m, 11H), 6.72 (m, 1H), 4.74 [qu (ap), *J* = 7.0 Hz, 1H], 4.29 (d, *J* = 6.2 Hz, 1H), 3.12 (br s, 2H), 1.39 (s, 9H), 1.23 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 182.0, 172.8, 141.0, 139.1, 129.0, 128.9, 128.8, 128.1, 128.0, 127.2, 82.2, 63.9, 61.0, 53.9, 28.2, 18.7; HR-MS: *m/z* = 400.2057, calcd. for $C_{22}H_{29}N_3O_2S$ ($M+H^+$): 400.2059.

(*S*)-*tert*-Butyl 2-{3-[(1*S*,2*S*)-2-amino-1,2-diphenylethyl]-thioureido}-3-phenylpropanoate (10b): White solid; yield: 32%; mp 92–94 °C; $[\alpha]_D^{25}$: +21.6 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 4.8 Hz, 1H), 7.34–7.06 (m, 15H), 6.86 (br s, 1H), 6.57 (d *J* = 6.6 Hz, 1H), 5.21–5.12 (m, 1H), 4.27 (d, *J* = 4.8 Hz, 1H), 3.14 (dd, *J* = 17.0 and 6.2 Hz, 1H), 3.02 (dd, *J* = 17.0 and 6.6 Hz, 1H), 1.73 (br s, 2H), 1.39 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 181.3, 170.6, 141.4, 139.1, 136.1, 129.4, 128.9, 128.5, 128.1, 126.6, 126.5, 82.3, 63.9, 60.6, 58.3, 37.9, 27.9; HR-MS: *m/z* = 476.2371, calcd. for $C_{28}H_{33}N_3O_2S$ ($M+H^+$): 476.2372.

(*S*)-*tert*-Butyl 2-{3-[(1*S*,2*S*)-2-amino-1,2-diphenylethyl]-thioureido}-3-methylbutanoate (10c): Colourless oil; yield: 33%; $[\alpha]_D^{25}$: −3.2 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 5.2 Hz, 1H), 7.36–7.11 (m, 10H), 6.34 (d, *J* = 6.6 Hz, 1H), 4.89–4.63 (m, 2H), 4.20 (d, *J* = 5.2 Hz, 1H), 2.12–1.97 (m, 1H), 1.88 (br s, 2H), 1.40 (s, 9H), 0.62 (d, *J* = 7.0 Hz, 3H), 0.56 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 181.6, 170.9, 141.5, 138.7, 128.9, 128.5, 128.1, 127.8, 126.8, 126.6, 81.9, 64.0, 62.8, 60.7, 31.3, 27.9, 17.7, 17.6; HR-MS: *m/z* = 428.2365, calcd. for $C_{24}H_{33}N_3O_2S$ ($M+H^+$): 428.2372.

(*S*)-Di-*tert*-butyl 2-{3-[(1*S*,2*S*)-2-amino-1,2-diphenylethyl]-thioureido}succinate (10d): Colourless oil; yield: 44%; $[\alpha]_D^{25}$: +18.5 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 6.6 Hz, 1H), 7.38–7.11 (m, 11H), 6.91 (br s, 1H), 5.19–5.08 (m, 1H), 4.29 (d, *J* = 4.8 Hz, 1H), 2.79 (dd, *J* = 17.4 and 4.2 Hz, 1H), 2.69 (dd, *J* = 17.4 and 4.4 Hz, 1H), 1.81 (br s, 2H), 1.39 (s, 9H), 1.31 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 182.1, 170.7, 170.2, 141.9, 139.7, 129.0, 128.9, 128.8, 127.9, 126.9, 126.8, 82.4, 81.4, 64.0, 60.8, 54.8, 37.7, 28.2, 28.1; HR-MS: *m/z* = 500.2575, calcd. for $C_{27}H_{37}N_3O_4S$ ($M+H^+$): 500.2583.

(*S*)-Di-*tert*-butyl 2-{3-[(1*S*,2*S*)-2-amino-1,2-diphenylethyl]-thioureido}pentanedioate (10e): Colourless oil; yield: 38%; $[\alpha]_D^{25}$: −23.4 (*c* 0.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 6.2 Hz, 1H), 7.33–7.12 (m, 10H), 6.53 (d, *J* = 7.0 Hz, 1H), 4.89–4.76 (m, 2H), 4.24 (d, *J* = 6.2 Hz, 1H), 2.05–1.69 (m, 6H), 1.41 (s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 181.8, 172.3, 171.5, 141.8, 139.1, 129.1, 128.9, 128.8, 128.2, 128.0, 127.0, 82.6, 80.7, 64.2, 61.0, 57.4, 30.8, 28.3, 28.2, 27.7; HR-MS: *m/z* = 514.2729, calcd. for $C_{28}H_{39}N_3O_4S$ ($M+H^+$): 514.2740.

(*S*)-*tert*-Butyl 2-{3-[(1*S*,2*S*)-2-amino-1,2-diphenylethyl]-thioureido}-3-*tert*-butoxypropanoate (10f): Colourless oil; yield: 34%; $[\alpha]_D^{25}$: +13.7 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.51 (d, *J* = 5.2 Hz, 1H), 7.31–7.16 (m, 11H), 6.61 (d, *J* = 6.6 Hz, 1H), 5.12–4.97 (m, 1H), 4.25 (d, *J* = 5.2 Hz, 1H), 3.62 (dd, *J* = 8.8 and 3.0 Hz, 1H), 3.46–3.31 (m, 1H), 1.84 (br s, 2H), 1.45 (s, 9H), 0.91 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 181.5, 169.4, 141.6, 138.9, 128.8, 128.5, 127.8, 127.7, 126.7, 126.6, 81.6, 72.7, 63.7, 62.2, 60.6, 58.7, 27.9, 27.0; HR-MS: *m/z* = 472.2633, calcd. for $C_{26}H_{37}N_3O_3S$ ($M+H^+$): 472.2634.

(2*S*,3*R*)-*tert*-Butyl 2-{3-[(1*S*,2*S*)-2-amino-1,2-diphenylethyl]thioureido}-3-*tert*-butoxybutanoate (10g): Colourless oil; yield: 45%; $[\alpha]_D^{25}$: +8.2 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 5.6 Hz, 1H), 7.31–7.07 (m, 11H), 6.57 (d, *J* = 8.4 Hz, 1H), 4.78 (d, *J* = 6.2 Hz, 1H), 4.22 (d, *J* = 5.6 Hz, 1H), 4.10–4.00 (m, 1H), 1.86 (br s, 2H), 1.39 (s, 9H), 1.03 (s, 9H), 0.72 (br s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 182.4, 169.9, 141.6, 138.8, 128.8, 128.4, 127.9, 127.7, 126.8, 126.7, 81.6, 73.6, 66.2, 64.1, 64.0, 60.7, 28.6, 27.9, 20.1; HR-MS: *m/z* = 486.2788, calcd. for $C_{27}H_{39}N_3O_3S$ ($M+H^+$): 486.2790.

(*S*)-*tert*-Butyl 2-{3-[(1*S*,2*S*)-2-amino-1,2-diphenylethyl]-thioureido}-3-(4-*tert*-butoxyphenyl)propanoate (10h): Colourless oil; yield: 32%; $[\alpha]_D^{25}$: +13.2 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 6.6 Hz, 1H), 7.33–6.98 (m, 12H), 6.97–6.70 (m, 3H), 6.51 (d *J* = 6.6 Hz, 1H), 5.18–5.02 (m, 1H), 4.24 (d, *J* = 4.4 Hz, 1H), 3.17–2.85 (m, 2H), 1.82 (br s, 2H), 1.29 (s, 9H), 1.27 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 181.2, 170.5, 153.9, 141.4, 139.0, 131.0, 130.1, 129.8, 128.9, 128.5, 128.0, 127.7, 126.6, 123.8, 82.2, 78.2, 63.8, 60.6, 58.7, 37.3, 28.3, 27.9; HR-MS: *m/z* = 548.2937, calcd. for $C_{32}H_{41}N_3O_3S$ ($M+H^+$): 548.2947.

General Procedure for the Michael Reaction Between Acetone and Nitroolefins

To a stirring solution of catalyst (0.03 mmol) in toluene (1 mL), acetic acid (2 μL, 0.03 mmol) and H_2O (8 μL, 0.40 mmol) were added. Nitroolefin (0.2 mmol) was added following by acetone (0.15 mL, 2.0 mmol). The reaction mixture was left stirring for 48 h. The solvent was evaporated and the crude product was purified using flash column chromatography eluting with a mixture of petroleum ether (40–60 °C)/EtOAc (70:30) to afford the product.

(*R*)-5-Nitro-4-phenylpentan-2-one[6a] **(11):** White solid; yield: 100%; mp 120–122 °C; $[\alpha]_D^{25}$: −2.2 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.38–7.14 (m, 5H), 4.69 (dd, *J* = 12.3 and 7.0 Hz, 1H), 4.59 (dd, *J* = 12.3 and 7.6 Hz, 1H), 4.07–3.92 (m, 1H), 2.91 (d, *J* = 7.0 Hz, 2H), 2.11 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 205.4, 138.8, 129.0, 127.8, 127.3, 79.4, 46.1, 39.0, 30.3; 91% *ee* measured on chiral HPLC using a Daicel Chiralpak AD-H column, eluting with a mixture of hexane:2-propanol (94:6), flow rate 1 mL min^{-1}, retention time: 11.92 (major) and 11.08 (minor).

(*R*)-4-(4-Methoxyphenyl)-5-nitropentan-2-one[6a] **(13e):** White solid; yield: 69%; mp 93–95 °C; $[\alpha]_D^{25}$: +5.2 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.69 (dd, *J* = 12.3 and 6.8 Hz, 1H), 4.59 (dd, *J* = 12.3 and 7.8 Hz, 1H), 4.04–3.91 (m, 1H), 3.78 (s, 3H), 2.93 (d, *J* = 7.0 Hz, 2H), 2.11 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 205.4, 159.1, 130.6, 128.4, 114.3, 79.7, 55.5, 46.2, 38.4, 30.4; 91% *ee* measured on chiral HPLC using a Daicel Chiralpak AD-H column, eluting with a mixture of hexane:2-propanol (94:6), flow rate 1 mL min^{-1}, retention time: 20.52 (major) and 18.17 (minor).

(*R*)-4-(4-Nitro-phenyl)-5-nitropentan-2-one (13f): Yellow oil; yield: 94%; $[\alpha]_D^{25}$: −1.9 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 4.77 (dd, *J* = 12.8 and 6.5 Hz, 1H), 4.65 (dd, *J* = 12.8 and 8.0 Hz, 1H), 4.21–4.07 (m, 1H), 2.94 (d, *J* = 7.0 Hz,

2H), 2.16 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=204.4, 147.3, 146.3, 128.6, 124.2, 78.5, 45.6, 38.6, 30.3; HR-MS: m/z=275.0638, calcd. for $C_{11}H_{12}N_2O_5$ ($M+Na^+$): 275.0644. 88% *ee* measured on chiral HPLC using a Daicel Chiralpak AD-H column, eluting with a mixture of hexane:2-propanol (85:15), flow rate 1 mL min^{-1}, retention time: 22.62 (major) and 16.65 (minor). The stereochemistry has been tentatively assigned by comparison to analogous compound **11**.

(*R*)-4-(4-Fluorophenyl)-5-nitro-pentan-2-one (13g): White solid; yield: 99%; $[\alpha]_D^{25}$: +2.4 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.29–7.11 (m, 2H), 7.06–6.93 (m, 2H), 4.67 (dd, *J*=12.4 and 6.7 Hz, 1H), 4.55 (dd, *J*=12.4 and 7.9 Hz, 1H), 4.11–3.89 (m, 1H), 2.88 (d, *J*=7.0 Hz, 2H), 2.11 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=205.1, 162.1 (d, *J*=246.8 Hz), 134.5 (d, *J*=3.3 Hz), 129.0 (d, *J*=8.1 Hz), 115.9 (d, *J*=21.5 Hz), 79.4, 46.1, 38.3, 30.4; ^{19}F NMR (188 MHz, $CDCl_3$): δ=−48.4 (m, 1F,); HR-MS: m/z= 248.0698, calcd. for $C_{11}H_{12}FNO_3$ ($M+Na^+$): 248.0699. 88% *ee* measured on chiral HPLC using a Daicel Chiralpak AD-H column, eluting with a mixture of hexane:2-propanol (94:6), flow rate 1 mL min^{-1}, retention time: 17.17 (major) and 15.12 (minor). The stereochemistry has been tentatively assigned by comparison to analogous compound **11**.

(*R*)-4-Furan-5-nitropentan-2-one[6a] **(13h):** White solid; yield: 94%; mp 53–55 °C; $[\alpha]_D^{25}$: −7.2 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.34 (dd, *J*=1.8 and 0.7 Hz, 1H), 6.30 (dd, *J*=3.2 and 1.8 Hz, 1H), 6.14 (d, *J*=3.2 Hz, 1H), 4.71 (dd, *J*=12.6 and 6.6 Hz, 1H), 4.65 (dd, *J*=12.6 and 6.6 Hz, 1H), 4.22–4.04 (m, 1H), 3.00 (dd, *J*=16.7 and 5.2 Hz, 1H), 2.88 (dd, *J*=16.7 and 6.0 Hz, 1H), 2.18 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=205.1, 151.6, 142.3, 110.4, 107.0, 77.0, 43.4, 32.8, 30.2; 92% *ee* measured on chiral HPLC using a Daicel Chiralpak AD-H column, eluting with a mixture of hexane:2-propanol (94:6), flow rate 1 mL min^{-1}, retention time: 14.04 (major) and 12.09 (minor).

General Procedure for the Michael Reaction between Acetophenone and Nitroolefins

To a stirring solution of catalyst (0.03 mmol) in dichloromethane (1 mL), nitroolefin (0.2 mmol) was added following by acetophenone (0.23 mL, 2.0 mmol). The reaction mixture was left stirring for 48 h. The solvent was evaporated and the crude product was purified using flash column chromatography eluting with a mixture of petroleum ether (40–60 °C)/EtOAc (80:20) to afford the product.

(*R*)-4-Nitro-1,3-diphenylbutan-1-one[7] **(12):** White solid; yield: 68%; mp 91–93 °C; $[\alpha]_D^{25}$: +23.1 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.98–7.85 (m, 2H), 7.62–7.21 (m, 8H), 4.84 (dd, *J*=12.5 and 6.7 Hz, 1H), 4.68 (dd, *J*=12.5 and 7.8 Hz, 1H), 4.31–4.04 (m, 1H), 3.50 (dd, *J*=17.7 and 6.4 Hz, 1H), 3.40 (dd, *J*=17.7 and 7.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=196.8, 139.1, 136.4, 133.5, 129.1, 128.7, 128.0, 127.9, 127.4, 79.5, 41.5, 39.3. 96% *ee* measured on chiral HPLC using a Daicel Chiralpak AD-H column, eluting with a mixture of hexane:2-propanol (90:10), flow rate 1 mL min^{-1}, retention time: 21.07 (major) and 15.45 (minor).

(*R*)-3-(4-Methoxyphenyl)-4-nitro-1-phenylbutan-1-one[6a,7] **(13a):** White solid; yield: 43%; mp 70–72 °C; $[\alpha]_D^{25}$: +21.6 (*c* 0.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.98–7.85 (m, 2H), 7.61–7.48 (m, 3H), 7.19 (d, *J*=8.7 Hz, 2H), 6.85 (d, *J*=8.7 Hz, 2H), 4.80 (dd, *J*=12.3 and 6.7 Hz, 1H), 4.63 (dd, *J*=12.3 and 7.9 Hz, 1H), 4.24–4.07 (m, 1H), 3.77 (s, 3H), 3.44 (dd, *J*=16.5 and 6.5 Hz, 1H), 3.37 (dd, *J*=16.5 and 6.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=197.0, 159.0, 136.4, 133.5, 131.0, 128.7, 128.5, 128.0, 114.4, 79.8, 55.2, 41.6, 38.6. 97% *ee* measured on chiral HPLC using a Daicel Chiralpak AD-H column, eluting with a mixture of hexane:2-propanol (80:20), flow rate 1 mL min^{-1}, retention time: 21.13 (major) and 15.54 (minor).

(*R*)-4-Nitro-3-(4-nitrophenyl)-1-phenylbutan-1-one[17] **(13b):** Yellow solid; yield: 61%; mp 104–105 °C; $[\alpha]_D^{25}$: +32.9 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.20 (d, *J*=8.8 Hz, 2H), 7.90 (dd, *J*=8.3 and 1.2 Hz, 2H), 7.61–7.42 (m, 5H), 4.88 (dd, *J*=12.8 and 6.4 Hz, 1H), 4.73 (dd, *J*=12.8 and 8.2 Hz, 1H), 4.43–4.27 (m, 1H), 3.49 (d, *J*=7.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=195.9, 147.5, 146.5, 135.9, 133.9, 128.9, 128.6, 128.0, 124.2, 78.8, 41.0, 38.9. 96% *ee* measured on chiral HPLC using a Daicel Chiralpak AD-H column, eluting with a mixture of hexane:2-propanol (80:20), flow rate 1 mL min^{-1}, retention time: 42.34 (major) and 25.09 (minor). The stereochemistry has been tentatively assigned by comparison to analogous compound **12**.

(*R*)-3-(4-Fluorophenyl)-4-nitro-1-phenylbutan-1-one[18] **(13c):** Yellow oil; yield: 71%; $[\alpha]_D^{25}$: +23.7 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.93 (d, *J*=7.0 and 1.6 Hz, 2H), 7.62–7.41 (m, 3H), 7.32–7.21 (m, 2H), 7.07–6.92 (m, 2H), 4.82 (dd, *J*=12.5 and 6.6 Hz, 1H), 4.65 (dd, *J*=12.5 and 8.0 Hz, 1H), 4.40–4.15 (m, 1H), 3.47 (dd, *J*=18.0 and 6.8 Hz, 1H), 3.38 (dd, *J*=18.0 and 7.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=196.6, 162.2 (d, *J*=246.8 Hz), 136.3, 134.8 (d, *J*=3.4 Hz), 133.6, 129.1 (d, *J*=8.2 Hz), 128.8, 128.0, 116.0 (d, *J*=21.5 Hz), 79.6, 41.5, 38.6; ^{19}F NMR (188 MHz, $CDCl_3$): δ=−47.8 (1F, m). 95% *ee* measured on chiral HPLC using a Daicel Chiralpak AD-H column, eluting with a mixture of hexane:2-propanol (90:10), flow rate 1 mL min^{-1}, retention time: 26.03 (major) and 18.55 (minor).

(*R*)-3-Furan-2-yl-4-nitro-1-phenylbutan-1-one[7] **(13d):** Colourless oil; yield: 70%; $[\alpha]_D^{25}$: +11.6 (*c* 1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.99–7.91 (m, 2H), 7.65–7.41 (m, 3H), 7.35–7.31 (m, 1H), 6.32–6.26 (m, 1H), 6.18 (d, *J*=3.3 Hz, 1H), 4.81 (dd, *J*=11.6 and 5.4 Hz, 1H), 4.73 (dd, *J*=11.6 and 6.0 Hz, 1H), 4.41–4.26 (m, 1H), 3.53 (dd, *J*=17.7 and 6.1 Hz, 1H), 3.41 (dd, *J*=17.7 and 7.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=196.8, 152.2, 142.6, 136.5, 133.9, 129.0, 128.4, 110.7, 107.4, 77.6, 39.2, 33.4. 98% *ee* measured on chiral HPLC using a Daicel Chiralpak AD-H column, eluting with a mixture of hexane:2-propanol (90:10), flow rate 1 mL min^{-1}, retention time: 17.28 (major) and 14.21 (minor).

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