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Asymmetric Michael Addition Reaction of 3-Substituted Oxindoles to Nitroolefins Catalyzed by a Chiral Alkyl-Substituted Thiourea Catalyst

Xin Li,[a] Bo Zhang,[b] Zhi-Guo Xi,[b] Sanzhong Luo,[a,*] and Jin-Pei Cheng[a,b,*]

[a] Beijing National Laboratory for Molecular Sciences (BNLMS), CAS Key Laboratory of Molecular Recognition and Function , Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, People's Republic of China
Fax: (+86)-10-6255-4449; e-mail: luosz@iccas.ac.cn

[b] Department of Chemistry and State Key Laboratory of Elementoorganic Chemistry, Nankai University, Tianjin 300071, People's Republic of China

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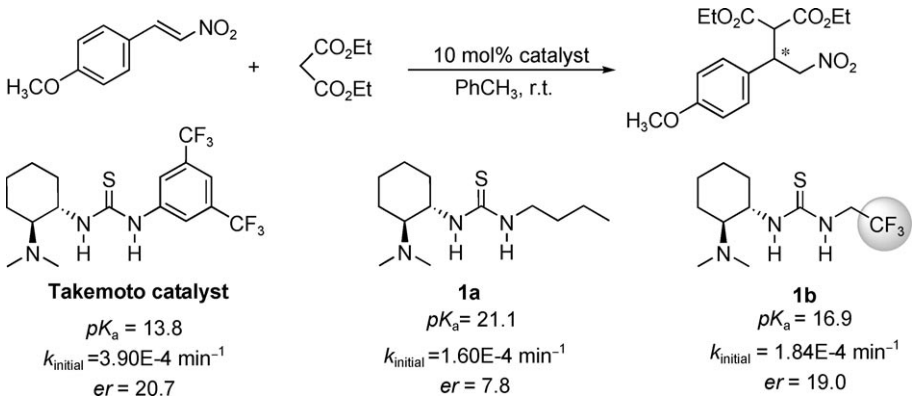
Abstract: A simple alkylthiourea was found to be an effective catalyst for the Michael addition reaction of 3-substituted oxindole to nitroolefins. A number of 3,3′-substituted oxindole derivatives, which have two vicinal quaternary-tertiary chiral centers were synthesized with up to 99% yield, 19:1 *dr* and 98% *ee*.

Keywords: bifunctional thioureas; Michael addition reaction; nitroolefins; organocatalysis; oxindoles

Introduction

With its origin deeply rooted in enzymatic catalysis, small molecular hydrogen bonding catalysis has been evolved as a powerful catalytic motif in asymmetric catalysis over the last ten years.[1] Chiral thiourea represents one such prominent type of asymmetric H-bonding catalyst. In particular, tertiary amine-thioureas, for example, Takemoto's catalyst and Jacobson's catalyst, have enabled a number of chiral C–C bond forming transformations featuring distinctive bifunctional activations of substrates. In the context of numerous impressive catalytic applications, however, the detailed mechanism of thiourea catalysis remains to be disclosed. In addition, the development of simple and new thiourea catalysts is still highly desirable in order to further extend the synthetic applications and to overcome the limitations of current catalysts with respect to both catalytic efficiency and scope. Recently, we have initialized a program for elucidating a systemic electronic activity-stereoselectivity relationship (EASR) of urea/thiourea catalysis, which eventually would be helpful in guiding the design of new catalysts and in understanding the catalytic mechanism.[2]

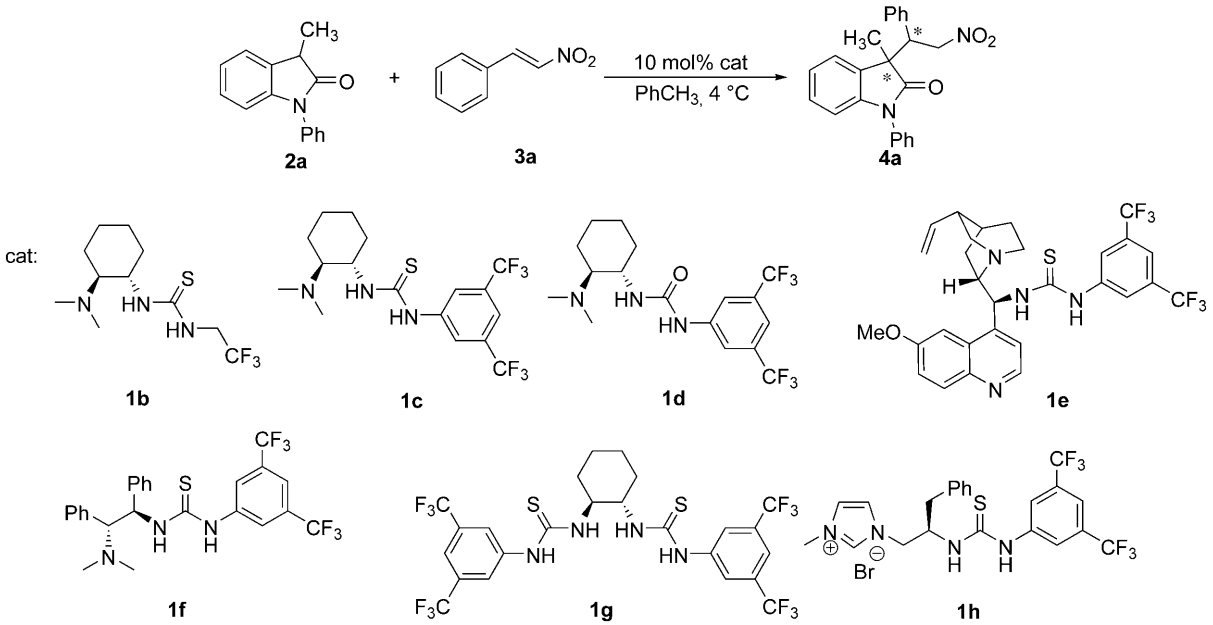


Scheme 1. The identification of a novel alkyl-substituted thiourea catalyst **1b**.

During this study, we noticed that thioureas with alkyl side chains such as **1a**, although less acidic than aromatic thioureas such as Takemoto's catalyst, turned out to be favorable, but as yet largely overlooked catalysts for the typical asymmetric bifunctional catalysis (Scheme 1). An optimal and simple catalyst **1b** was then reached *via* simply electronic tuning of the alkyl side chain, demonstrating comparable performance compared with the well-recognized aromatic thioureas (Scheme 1).

Due to their promising biological profiles and interesting structural features, oxindole alkaloids[3] such as physostigmine, horsfiline, coerulescine, alstonisine chitosenine and strychnofoline have been interesting targets for asymmetric total synthesis and a great deal of asymmetric catalytic reactions, including allylic alkylation,[4] aldol reactions of oxindoles,[5] Heck reaction,[6] Michael addition reaction[7] and cyanoamidation reaction[8] etc., have been developed towards the construction of oxindoles bearing quaternary centers at the 3-positions.[9] However, most of these catalytic methods for the synthesis of oxindoles require the use of transition metals, organocatalytic methods to these valuable structural motifs, especially for the synthesis of 3,3′-substituted oxindoles with two vicinal quaternary-tertiary chiral centers, has been less developed until very recently.[7a] Barbas reported a Takemoto-type aromatic thiourea catalyst for this class of reactions with excellent yields and stereoselectivity.[7a] In this context, it was pleasing to find out that the alkyl-substituted thiourea **1b**, identified from our physical organic studies, was also an optimal catalyst for this challenging quaternary-tertiary C–C bond forming Michael addition reaction, leading to a highly efficient and stereoselective protocol for the synthesis of 3,3′-

Table 1. Screening of different thiourea catalysts.[a]



Entry	Catalyst	Time [h]	Yield[b] [%]	*dr*[c]	*ee*[d] [%]
1	**1b**	**12**	**96**	**4:1**	**85**
2	**1c**	12	93	3:1	69
3	**1d**	12	95	3:1	67
4	**1e**	12	98	3:1	81
5	**1f**	12	92	5:1	−76
6	**1g**	72	nr[e]	nd[f]	nd
7	**1h**	72	nr	nd	nd

[a] The reaction was carried out on a 0.1-mmol scale in 200 μL dry toluene at 4 °C, and the molar ratio of oxindole/nitrostyrene is 1/2.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Determined by HPLC.
[e] No reaction.
[f] Not determined.

oxindole compounds.[11,12] The detailed results from this study are presented herein.

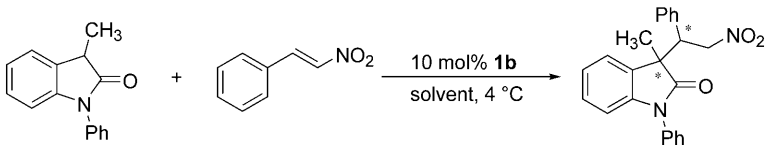
Results and Discussion

The Michael addition reaction of oxindole **2a**, a commercially available compound, to nitrostyrene was selected as our initial test reaction. A variety of bifunctional tertiary amine-thiourea catalysts **1c–1f**, which have been widely applied in a broad range of asymmetric Michael reactions,[13–16] together with catalyst **1b**, were then tested in the model reaction and the results are summarized in Table 1. As shown, all catalysts **1b–1f** exhibited high catalytic activity affording cleanly the desired product **4a** (Table 1, entries 1–5, 92–98% yield). Quite surprisingly, the simply alkylthiourea **1b** gave the best (85%) *ee* among these tested catalysts, suggesting a favorable feature of the alkyl side chain on catalytic performance over that of typical 3,5-bistrifluorophenyl groups usually present in catalysts **1c–1f**. For comparison, monofunctional thiourea catalysts such as **1g** and **1h** have also been examined and no reactions were observed in these cases, proving that the tertiary amine group is indispensable for the present Michael addition reaction.

With alkylthiourea **1b** as the optimal catalyst, the reaction was further optimized by screening different solvents (Table 2). Highly polar solvents such as DMSO, DMF and methanol were not applicable leading to totally depleted activity (Table 2, entries 1 and 2) or low enantioselectivity (Table 2, entry 3). The reactions generally proceeded smoothly in less polar solvent such as CH_2Cl_2, $CHCl_3$, $ClCH_2CH_2Cl$, C_6H_6 and $PhCH_3$. Among a number of solvents examined, CH_2Cl_2 was the optimal one, furnishing the best enantioselectivity (Table 2, entry 7, 98% yield, *dr* = 4:1, 91% *ee*). When the reaction was conducted with catalyst **1b** in CH_2Cl_2 at −40 °C, the yield and *dr* value were retained, and the *ee* value could be further improved to 93% (Table 2, entry 13).

With the optimal conditions in hand, the substrate scope was next explored with different nitroolefins, including twelve substituted nitrostyrenes and two alkyl nitroolefins. As shown in Table 3, the reactions worked well with nitrostyrenes bearing either electron-withdrawing or electron-donating groups to give the desired adducts with high yield (90–99%), moderate diastereoselectivities and excellent enantioselectivities (92–96% *ee*) (Table 3, entries 1–10). Slightly lower enantioselectivities were observed with 4-nitronitrostyrene (entry 11, 92% yield and 78% *ee*) and 3-nitronitrostyrene (entry 12, 94% yield and 80% *ee*), probably due to the interference of additional nitro groups on the stereocontrolling H-bonding interactions. Alkyl nitroolefins were also good substrates for the catalysis of **1b**. In these cases, the desired products were obtained with excellent yields (95–96%) and

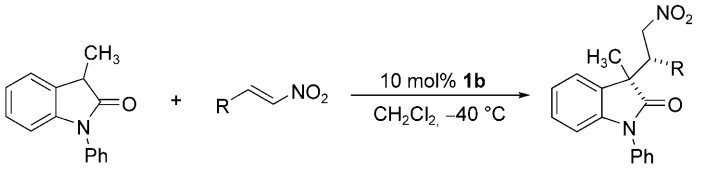
Table 2. Screening of solvents.[a]



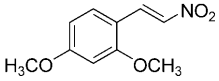
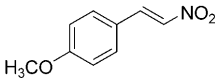
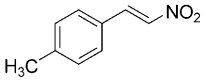
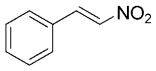
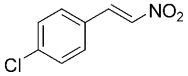
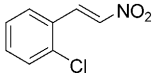
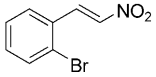
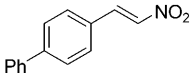
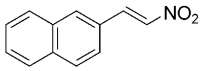
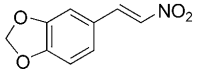
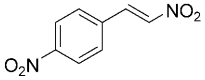
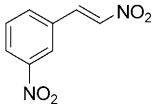
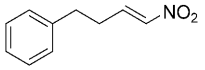
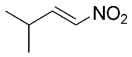
Entry	Solvent	Time [h]	Yield[b] [%]	*dr*[c]	*ee*[d] [%]
1	DMSO	12	trace	nd[e]	nd
2	DMF	12	trace	nd	nd
3	CH_3OH	12	81	4:1	45
4	Et_2O	12	20	4:1	88
5	CH_3CN	12	85	5:1	79
6	Ethyl acetate	12	79	4:1	80
7	**CH_2Cl_2**	**12**	**98**	**4:1**	**91**
8	$CHCl_3$	12	97	3:1	77
9	$ClCH_2CH_2Cl$	12	96	4:1	90
10	THF	12	94	5:1	89
11	C_6H_6	12	95	3:1	75
12	$PhCH_3$	12	96	4:1	85
13	**CH_2Cl_2**	**48**	**96**	**4:1**	**93**[f]

[a] The reaction was carried out on a 0.1-mmol scale in 200 μL different solvent at 4 °C, and the molar ratio of oxindole/nitrostyrene is 1/2.
[b] Isolated yield.
[c] Determined by ^1H NMR.
[d] Determined by HPLC.
[e] Not determined.
[f] Conducted at −40 °C.

Table 3. Asymmetric Michael addition reaction of 3-methyl-*N*-phenyloxindole to different nitroolefins.[a]



6 – 19

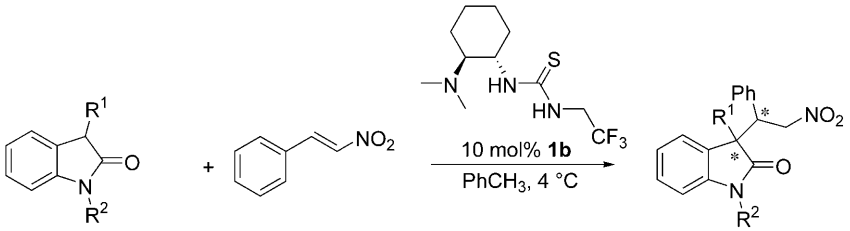
Entry	Nitroolefin	Time [h]	Product: Yield[b] [%]	*dr*[c]	*ee*[d] [%]
1		72	**6**: 93	3:1	96
2		72	**7**: 92	4:1	95
3		48	**8**: 99	5:1	95
4		48	**9**: 96	4:1	93
5		48	**10**: 95	3:1	92
6		48	**11**: 95	3:1	95
7		48	**12**: 98	2:1	96
8		60	**13**: 90	4:1	94
9		48	**14**: 97	4:1	94
10		60	**15**: 91	5:1	95
11		72	**16**: 92	2:1	78
12		72	**17**: 94	3:1	80
13		54	**18**: 95	3:1	98
14		48	**19**: 96	3:1	98

[a] The reaction was carried out on a 0.1-mmol scale in 200 μL dry CH_2Cl_2 at −40 °C, and the molar ratio of oxindole/nitroolefin is 1/2.
[b] Isolated yield.
[c] Determined by ^1H NMR or weight.
[d] Determined by HPLC.

enantioselectivities (98% *ee*) (Table 3, entries 13 and 14).

To further illustrate the synthetic utility of the current reactions, other oxindoles derivatives have also been examined in the reaction (Table 4). Not quite unexpectedly, the reaction with 3-phenyl-substituted oxindole **2b** proceeded very fast, but without any chiral induction (Table 4, entry 1) at 4 °C. Improved

Table 4. Screening of different oxindole compounds.[a]



2b: R^1= Ph, R^2 = Boc
2c: R^1 = CH_3, R^2 = Boc
2d: R^1 = CH_3, R^2 = CH_3

20 – **22**

Entry	R^1	R^2	Time [h]	Product: Yield[b] [%]	*dr*[c]	*ee*[d] [%]
1	Ph	Boc	2	**20**: 99	1:1	rac
2[e]	Ph	Boc	8	**20**: 94	3:1	53
3	CH_3	Boc	12	**21**: 94	9:1	74
4[e]	CH_3	Boc	72	**21**: 96	19:1	89
5	CH_3	CH_3	12	**22**: 93	3:1	54
6[e]	CH_3	CH_3	96	**22**: 65	3:1	68

[a] The reaction was carried out on a 0.1-mmol scale in 200 μL dry toluene at 4 °C, and the molar ratio of oxindole/nitrostyrene is 1/2.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Determined by HPLC.
[e] Reaction in CH_2Cl_2 at −40 °C.

stereoselectivity could be obtained when the reaction was conducted at −40 °C (Table 4, entry 2). Under the optimized conditions, the reactions with other *N*-substituted oxindoles such as **2c** and **2d** worked very well (Table 4, entries 3–6). Inspired by the work of Barbas,[7a] we examined the reaction *N*-Boc protected oxindole **2c**. To our delight, the reaction furnished the desired product in high yield with much improved diastereoselectivity (19:1 *dr*) and good enantioselectivity (89% *ee*), results comparable with those of Barbas' aromatic thiourea catalyst[17] (Table 4, entry 4).

The X-ray crystal structure of product **12** was determined (Figure 1), which proved the (1*S*,2*S*) relative and absolute configurations of the major product. The

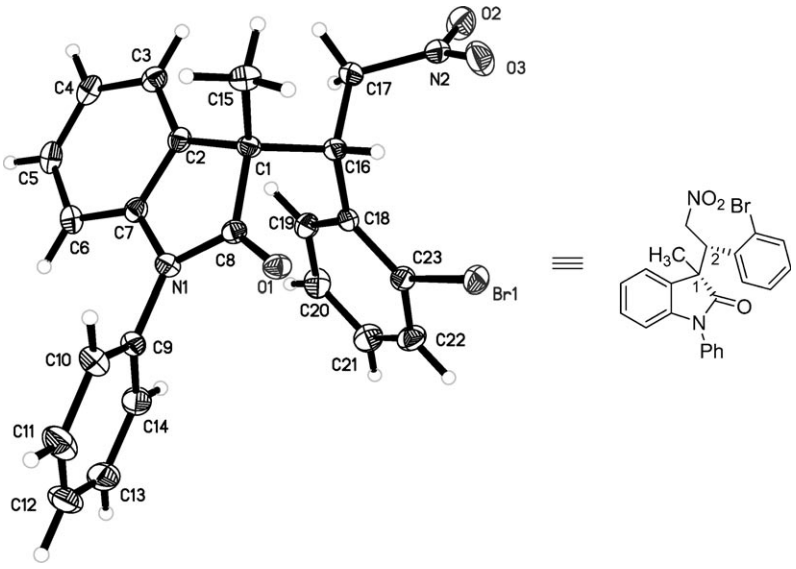


Figure 1. X-ray crystal structure of **12**.

configurations of other *syn*-Michael products can therefore be deduced.

Conclusions

We have presented a highly enantioselective Michael addition reaction of 3-methyl-*N*-phenyloxindole to nitroolefins by a simple alkyl-substituted bifunctional tertiary amine-thiourea organocatalyst. The reaction scope is substantial and a number of aryl- or alkyl-nitroolefins could be successfully applied to give multifunctional chiral oxindole compounds bearing an adjacent all carbon-substituted quaternary stereocenter and a tertiary stereocenter with good to excellent enantioselectivities. And our current work is actively under way to expand the use of this alkyl-substituted bifunctional thiourea catalyt **1b** to other valuable transformations.

Experimental Section

General Remarks

Commercial reagents were used as received, unless otherwise stated. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, br = broad. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Mass spectra were obtained using electron ionization (EI) mass spectrometer. The Michael product **21** is a known compound.[7a,b]

Catalyst **1b** was synthesized by a literature method.[18] **1b:** $[\alpha]_D^{25}$: −64.8° (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00 (br, 1H), 4.32 (d, J = 4.67 Hz, 2H), 3.84 (br, 1H), 2.53 (s, 1H), 2.37 (s, 6H), 2.27 (s, 1H), 1.96–1.72 (m, 3H), 1.36–1.18 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 183.50, 128.60, 124.91, 121.21, 66.28, 54.91, 44.83, 38.91, 31.74, 23.17, 23.08, 21.17; HR-MS (EI$^+$): m/z = 283.1328, calcd. for $[C_{11}H_{20}F_3N_3S]$: 283.1330.

General Experimental Michael Reaction Procedure

To a stirred solution of 3-methyl-*N*-phenyloxindole (0.1 mmol) and nitroolefin (2.0 equiv.) in dry CH_2Cl_2 (200 μL) was added thiourea catalyst (0.1 equiv.) at −40 °C. After the reaction was completed, the reaction solution was concentrated under vacuum and the crude material was purified by flash chromatography to afford the product.

Compound 6: The Michael product was synthesized according to the general procedure as a white solid; overall yield: 93%. $[\alpha]_D^{25}$: +52.0° (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (t, J = 7.68 Hz, 2H), 7.38 (t, J = 7.68 Hz, 1H), 7.22–7.14 (m, 3H), 7.08–6.98 (m, 3H), 6.72 (d, J = 7.96 Hz, 1H), 6.41–6.35 (m, 2H), 5.09–4.94 (m, 2H), 4.54 (s, 1H), 3.78 (s, 3H), 3.54 (s, 3H), 1.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 178.06, 160.57, 159.16, 143.18, 134.18, 131.99, 129.56, 128.30, 128.13, 126.59, 123.95, 122.75, 116.03, 109.29, 104.18, 98.78, 75.64, 55.45, 55.33, 50.27, 20.32; HR-MS (EI$^+$): m/z = 432.1689, calcd. for $[C_{25}H_{24}N_2O_5]$: 432.1685. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol:hexane = 1:4), 1.0 mL min^{-1}; t_R = 11.7 min (minor), 16.5 min (major).

Compound 7: The Michael product was synthesized according to the general procedure as a white solid; overall yield: 92%. $[\alpha]_D^{25}$: −41.0° (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 3H), 7.19–7.13 (m, 2H), 7.10–7.05 (m, 1H), 6.78–6.68 (m, 4H), 6.59 (d, J = 8.78 Hz, 2H), 6.52 (d, J = 7.47 Hz, 1H), 5.09–5.03 (m, 1H), 4.87 (t, J = 11.56 Hz, 1H), 3.97 (dd, J = 4.67, 11.53 Hz, 1H), 3.65 (s, 3H), 1.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 177.55, 159.51, 143.82, 133.82, 130.16, 129.88, 129.51, 128.85, 128.23, 126.66, 126.52, 123.72, 122.92, 113.54, 109.69, 76.27, 55.25, 51.10, 49.96, 20.60; HR-MS (EI$^+$): m/z = 402.1583, calcd. for $[C_{24}H_{22}N_2O_4]$: 402.1580. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol:hexane = 1:4), 1.0 mL min^{-1}; t_R = 16.1 min (minor), 31.8 min (major).

Compound 8: The Michael product was synthesized according to the general procedure as a white solid; overall yield: 99%. $[\alpha]_D^{25}$: −11.0° (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 3H), 7.18–7.12 (m, 2H), 7.08–7.03 (m, 1H), 6.85 (d, J = 7.96 Hz, 2H), 6.71 (d, J = 7.14 Hz, 2H), 6.65 (d, J = 7.96 Hz, 2H), 6.5 (d, J = 7.68 Hz, 1H), 5.08–5.03 (m, 1H), 4.87 (t, J = 11.25 Hz, 1H), 3.96 (dd, J = 4.67, 11.25 Hz, 1H), 2.18 (s, 3H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 177.50, 143.86, 137.98, 133.84, 131.64, 130.17, 129.48, 128.82, 128.77, 128.67, 128.22, 126.54, 123.73, 122.89, 109.65, 76.22, 50.99, 50.31, 20.98, 20.59; HR-MS (EI$^+$): m/z = 386.1634, calcd. for $[C_{24}H_{22}N_2O_3]$: 386.1630. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol:hexane = 1:4), 1.0 mL min^{-1}; t_R = 9.5 min (minor), 20.0 min (major).

Compound 9: The Michael product was synthesized according to the general procedure as a white solid; overall yield: 96%. $[\alpha]_D^{25}$: +10.0° (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.45 (m, 2H), 7.41 −7.36 (m, 1H), 7.33–7.30 (m, 1H), 7.13–7.07 (m, 7H), 7.03–7.00 (m, 2H), 6.51–6.48 (m, 1H), 5.34–5.26 (m, 1H), 5.17–5.11 (m, 1H), 4.06 (dd, J = 4.67, 10.70 Hz, 1H), 1.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 177.81, 142.65, 134.99, 133.90, 131.91, 129.59, 128.61, 128.27, 128.04, 127.92, 126.34, 123.42, 123.07, 109.44, 75.23, 50.89, 21.92; HR-MS (EI$^+$): m/z = 372.1478, calcd. for $[C_{23}H_{20}N_2O_3]$: 372.1474 The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol:hexane = 1:4), 1.0 mL min^{-1}; t_R = 9.4 min (minor), 23.5 min (major).

Compound 10: The Michael product was synthesized according to the general procedure as a white solid; overall yield: 95%. $[\alpha]_D^{25}$: +19.0° (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 3H), 7.19–7.14 (m, 2H), 7.10–7.01 (m, 3H), 6.74–6.70 (m, 4H), 6.53 (d, J = 7.14 Hz, 1H), 5.07–5.01 (m, 1H), 4.85 (t, J = 12.35 Hz, 1H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 177.17, 143.74, 134.32, 133.62, 133.27, 130.16, 129.63, 129.12, 128.37, 128.31, 126.34, 123.64, 123.14, 109.89, 75.89, 50.88, 50.04, 20.72; HR-

MS (EI$^+$): m/z = 406.1088, calcd. for [$C_{23}H_{19}N_2O_3Cl$]: 406.1084. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol:hexane = 1:4), 1.0 mL min^{-1}; t_R = 13.2 min (minor), 27.9 min (major).

Compound 11: The Michael product was synthesized according to the general procedure as a white solid; overall yield: 95%. $[\alpha]_D^{25}$: +72.0° (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.41 (m, 2H), 7.36–7.30 (m, 3H), 7.21–7.13 (m, 5H), 7.05–6.97 (m, 2H), 6.71 (d, J = 7.68 Hz, 1H), 4.84–4.79 (m, 3H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 177.50, 143.13, 136.42, 133.94, 133.37, 131.44, 130.05, 129.71, 129.33, 128.89, 128.36, 126.82, 126.51, 126.24, 123.59, 123.50, 109.69, 75.76, 49.57, 44.32, 20.87; HR-MS (EI$^+$): m/z = 406.1087, calcd. for [$C_{23}H_{19}N_2O_3Cl$]: 406.1084. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol:hexane = 1:4), 1.0 mL min^{-1}; t_R = 7.3 min (minor), 8.0 min (major).

Compound 12: The Michael product was synthesized according to the general procedure as a white solid; overall yield: 98%. $[\alpha]_D^{25}$: +92.3° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.40 (m, 5H), 7.32–7.23 (m, 4H), 7.20–7.03 (m, 3H), 6.80 (d, J = 7.96 Hz, 1H), 4.92–4.82 (m, 3H), 1.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 177.62, 143.13, 135.10, 133.99, 133.45, 131.61, 129.74, 129.65, 129.07, 128.89, 128.40, 128.40, 127.91, 127.56, 126.55, 123.74, 123.57, 109.70, 75.86, 49.56, 47.10, 20.93; HR-MS (EI$^+$): m/z = 450.0584 and 452.0561, calcd. for [$C_{23}H_{19}BrN_2O_3$]: 450.0579 and 452.0559. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (2-propanol:hexane = 1:9), 1.0 mL min^{-1}; t_R = 12.3 min (minor), 31.9 min (major).

Compound 13: The Michael product was synthesized according to the general procedure as a white solid; overall yield: 90%. $[\alpha]_D^{25}$: −23.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.48 (m, 2H), 7.44–7.40 (m, 2H), 7.36–7.30 (m, 6H), 7.27–7.22 (m, 2H), 7.20–7.15 (m, 1H,), 6.89 (d, J = 7.96 Hz, 2H), 6.76–6.73 (m, 2H), 6.55 (d, J = 7.68 Hz, 1H), 5.22–5.16 (m, 1H), 5.02 (t, J = 12.90 Hz, 1H), 4.14 (dd, J = 4.67, 11.25 Hz, 1H), 1.69 (s, 3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 177.36, 143.98, 141.25, 140.52, 133.72, 133.67, 129.87, 129.54, 128.17, 128.98, 128.81, 128.28, 127.46, 127.01, 126.81, 126.51, 123.71, 122.99, 109.75, 76.04, 51.18, 50.41, 20.53; HR-MS (EI$^+$): m/z = 448.1791, calcd. for [$C_{29}H_{24}N_2O_3$]: The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol:hexane = 1:4), 1.0 mL min^{-1}; t_R = 14.1 min (minor), 29.3 min (major).

Compound 14: The Michael product was synthesized according to the general procedure as a white solid; overall yield: 97%. $[\alpha]_D^{25}$: −91.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.51 Hz, 1H), 7.80–7.71 (m, 2H), 7.53–7.41 (m, 2H), 7.31–7.16 (m, 5H), 7.11–7.00 (m, 2H), 7.88 (d, J = 7.14 Hz, 1H), 6.63–6.59 (m, 3H), 5.32–5.26 (m, 1H), 5.20–5.15 (m, 1H), 5.09–5.01 (m, 1H), 1.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 177.45, 143.74, 133.81, 133.72, 132.56, 131.43, 130.72, 129.44, 128.85, 128.45, 128.08, 126.52, 126.29, 125.82, 124.43, 124.31, 123.82, 123.42, 122.95, 109.60, 76.61, 50.40, 42.70, 20.70; HR-MS (EI$^+$): m/z = 422.1635, calcd. for [$C_{27}H_{22}N_2O_3$]: 422.1630. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol:hexane = 1:4), 1.0 mL min^{-1}; t_R = 8.7 min (minor), 9.8 min (major).

Compound 15: The Michael product was synthesized according to the general procedure as a white solid; overall yield: 91%. $[\alpha]_D^{25}$: −15.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.33 (m, 3H), 7.27–7.12 (m, 3H), 6.95 (d, J = 7.68 Hz, 2H), 6.67–6.58 (m, 2H), 6.41–6.34 (m, 2H), 5.86 (d, J = 5.69 Hz, 2H), 5.11–5.06 (m, 1H), 4.89 (t, J = 12.60 Hz, 1H), 4.00 (dd, J = 4.39, 11.25 Hz, 1H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 177.47, 147.47, 147.31, 143.72, 133.85, 130.18, 129.59, 128.95, 128.34, 128.27, 126.41, 123.65, 123.04, 122.71, 109.76, 108.95, 107.91, 101.06, 76.31, 50.90, 50.35, 20.81; HR-MS (EI$^+$): m/z = 416.1375, calcd. for [$C_{24}H_{20}N_2O_5$]: 416.1372. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol:hexane = 1:4), 1.0 mL min^{-1}; t_R = 13.9 min (minor), 36.2 min (major).

Compound 16: The Michael product was synthesized according to the general procedure as a white solid; overall yield: 92%. $[\alpha]_D^{25}$: −8.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.51 Hz, 2H), 7.43–7.34 (m, 3H), 7.30–7.26 (m, 2H), 7.23–7.18 (m, 1H), 7.10 (d, J = 8.51 Hz, 2H), 6.82 (d, J = 7.14 Hz, 2H), 6.65 (d, J = 7.68 Hz, 1H), 5.17–5.11 (m, 1H), 5.00 (t, J = 12.90 Hz, 1H), 4.22 (dd, J = 4.39, 11.25 Hz, 1H), 1.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 176.77, 147.80, 143.46, 142.23, 133.35, 129.93, 129.72, 129.47, 129.21, 128.53, 125.99, 123.59, 123.48, 123.19, 110.16, 75.52, 50.66, 50.23, 21.12. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol:hexane = 1:4), 1.0 mL min^{-1}; t_R = 24.6 min (minor), 45.2 min (major).

Compound 17: The Michael product was synthesized according to the general procedure as a white solid; overall yield: 94%. $[\alpha]_D^{25}$: +44° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (td, J = 1.92, 7.41 Hz, 1H), 7.65 (s, 1H), 7.44–7.35 (m, 5H), 7.33–7.21 (m, 3H), 6.82 (d, J = 7.14 Hz, 2H), 6.65–6.62 (m, 1H), 5.17–5.11 (m, 1H), 5.05–4.97 (m, 1H), 4.23 (dd, J = 4.39, 11.25 Hz, 1H), 1.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 176.85, 147.76, 143.36, 137.07, 135.94, 133.38, 129.70, 129.57, 129.14, 128.48, 126.06, 123.61, 123.29, 122.98, 110.10, 75.59, 50.63, 50.13, 21.03. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol:hexane = 1:4), 1.0 mL min^{-1}; t_R = 13.0 min (minor), 29.5 min (major).

Compound 18: The Michael product was synthesized according to the general procedure as colorless oil; overall yield: 95%. $[\alpha]_D^{25}$: +53.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57–7.52 (m, 2H), 7.46–7.37 (m, 3H), 7.29–7.19 (m, 5H), 7.14–7.10 (m, 2H), 6.85 (d, J = 7.68 Hz, 1H), 4.65–4.59 (m, 1H), 4.49–4.42 (m, 1H), 3.05–2.97 (m, 1H), 2.71–2.54 (m, 2H), 2.06–1.95 (m, 1H), 1.77–1.64 (m, 1H), 1.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 178.14, 143.16, 140.95, 134.13, 131.43, 129.71, 128.64, 128.52, 128.32, 126.51, 126.20, 123.42, 109.91, 49.96, 44.04, 33.98, 30.92, 22.19; HR-MS (EI$^+$): m/z = 400.1790, calcd. for [$C_{25}H_{24}N_2O_3$]: 400.1787. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol:hexane = 1:4), 1.0 mL min^{-1}; t_R = 10.8 min (minor), 17.6 min (major).

Compound 19: The Michael product was synthesized according to the general procedure as colorless oil; overall yield: 96%. $[\alpha]_D^{25}$: +40.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR

(300 MHz, $CDCl_3$): $\delta = 7.57–7.52$ (m, 2H), 7.45–7.38 (m, 3H), 7.28–7.22 (m, 2H), 7.14–7.09 (m, 1H), 6.85 (d, $J = 7.68$ Hz, 1H), 4.61–4.55 (m, 1H), 4.36–4.30 (m, 1H), 3.05–2.97 (m, 1H), 1.61–1.50 (m, 4H), 1.44–1.35 (m, 1H), 1.29–1.19 (m, 1H), 0.89 (q, $J = 6.31$, 11.53 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 178.23$, 143.21, 134.19, 131.49, 129.71, 128.53, 128.25, 126.48, 123.46, 123.29, 109.79, 50.11, 42.33, 37.92, 25.91, 23.47, 22.01, 21.64; HR-MS (EI^+): $m/z =$ 352.1790, calcd. for $[C_{21}H_{24}N_2O_3]$: 352.1787. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (2-propanol:hexane = 1:19), 1.0 mL min^{-1}; $t_R =$ 8.9 min (minor), 15.8 min (major).

Compound 20: The Michael product was synthesized as a white solid; overall yield: 99%. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 8.23$ Hz, 1H), 7.63–7.60 (m, 2H), 7.45–7.32 (m, 6H), 7.17–7.12 (m, 1H), 7.09–7.03 (m, 3H), 6.78 (d, $J = 7.41$ Hz, 2H), 5.00–4.86 (m, 2H), 4.75 (dd, $J =$ 1.65, 11.25 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.85$, 148.30, 141.02, 135.44, 132.85, 129.65, 129.27, 128.89, 128.80, 128.64, 128.40, 128.04, 127.90, 126.60, 125.19, 125.73, 124.22, 115.72, 84.24, 75.83, 60.14, 50.89, 28.10, 27.87; HR-MS (EI^+): $m/z = 458.1845$, calcd. for $[C_{27}H_{26}N_2O_5]$: 458.1842. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol:hexane = 1:19), 1.0 mL min^{-1}; $t_R = 7.2$ min (minor), 8.2 min (major), racemic.

Compound 22: The Michael product was synthesized as yellow oil; overall yield: 65%. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.27–7.14$ (m, 3H), 7.11–7.09 (m, 3H), 7.04 (d, $J =$ 7.41 Hz, 1H), 7.00–6.96 (m, 2H), 6.61–6.58 (m, 1H), 5.15–5.07 (m, 1H), 4.98–4.91 (m, 1H), 3.98 (dd, $J = 4.67$, 10.98 Hz, 1H), 3.05 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 178.49$, 142.61, 134.95, 131.71, 128.50, 128.39, 127.89, 127.84, 123.43, 122.59, 108.11, 75.37, 50.60, 26.02, 21.79; HR-MS (EI^+): $m/z = 310.1321$, calcd. for $[C_{18}H_{18}N_2O_3]$: 310.1317. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol:hexane = 3:97), 0.5 mL min^{-1}; $t_R = 24.5$ min (minor), 25.7 min (major).

X-Ray Crystallographic Determination of Compound 12

Single crystals of enantiopure **12** suitable for X-ray analysis were obtained by recrystallization from *i*-PrOH/hexane at room temperature. Crystal data for **12**: $C_{23}H_{19}BrN_2O_3$ (451.31), orthorhombic, space group: $P2(1)2(1)2(1)$, $a =$ 9.839(2), $b = 10.575(2)$, $c = 19.779(4)$ Å, $U = 2057.9(7)$ Å^3, $Z = 4$, specimen $0.41 \times 0.39 \times 0.33$ mm^3, $T = 173(2)$ K, absorption coefficient: 2.024 mm^{-1}, reflections collected: 16670, independent reflections: 4649 [$R_{int} = 0.0421$], refinement by full-matrix least-squares on F^2, data/restraints/parameters 4649/0/262, goodness-of-fit on $F^2 = 1.127$, final R indices [$I > 2\sigma(I)$] $R1 = 0.0341$, $wR2 = 0.0782$, R indices (all data) $R1 =$ 0.0365, $wR2 = 0.0795$, largest diff. peak and hole 0.295 and −0.280eÅ^{-3}. CCDC 739992 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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