Asymmetric Michael addition reaction of 3-substituted-*N*-Boc oxindoles to activated terminal alkenes catalyzed by a bifunctional tertiary-amine thiourea catalyst†

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The current article reports an organocatalytic strategy for the asymmetric catalysis of chiral oxindoles bearing 3-position all-carbon quaternary stereocenters. Accordingly, highly enantioselective Michael addition reactions of 3-substituted oxindoles to terminal alkenes have been developed by utilizing a bifunctional tertiary-amine thiourea catalyst. The reactions accommodate a number of Michael donor compounds (different substituted 3-aryl or methyl oxindoles), and Michael acceptor compounds (vinyl ketones and vinyl sulfones) to give the desired oxindole products with moderate to excellent yields (up to 99%) and moderate to excellent enantioselectivities (up to 91% *ee*).

Introduction

Asymmetric construction of all-carbon quaternary stereocenters has attracted a great deal of effort over recent decades and remains a challenging synthetic task.[1] One particular context is in the synthesis of biologically and pharmaceutically active oxindole alkaloids wherein 3-position quaternary centers are a common structural motif.[2] Accordingly, a number of synthetic transformations such as allylic alkylation, aldol reaction, Heck reaction, Michael addition reaction and cyanoamidation reaction[3–8] have been developed in order to address this synthetic challenge. A straightforward approach for the construction of oxindoles bearing a 3-quaternary center would be the direct Michael addition of 3-substituted oxindoles to terminal activated alkenes (Fig. 1). Though easily conceived, an asymmetric catalytic method for such reactions has not been achieved until recently. Maruoka reported an enantioselective Michael addition reaction of 3-aryloxindoles to methyl vinyl ketone (MVK) catalyzed by a chiral quaternary tetraalkylphosphonium salt.[9] Herein, we present a distinctive organocatalytic approach for the Michael addition of 3-substituted oxindoles to activated terminal alkenes by utilizing the well-proved bifunctional catalytic features of tertiary amine-thiourea catalysts.[10] A number of 3-substituted oxindoles (R_2 = Ar and CH_3) and terminal alkenes (vinyl ketones and vinyl sulfones) are incorporated into this synthetic strategy and the detailed results are presented here.

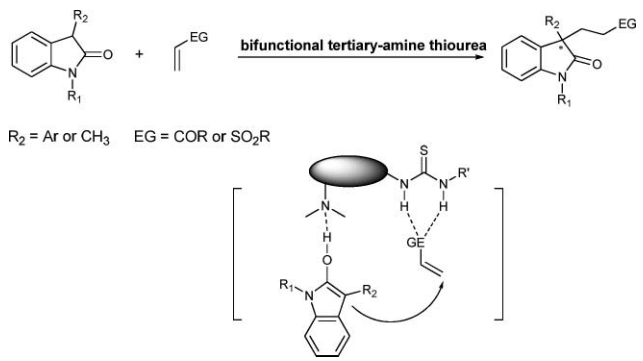

Fig. 1 Strategy of bifunctional tertiary-amine thiourea catalyzed Michael reactions of oxindoles to terminal alkenes.

Results and discussion

Bifunctional tertiary-amine thiourea catalyzed Michael addition reaction of 3-aryl oxindoles to vinyl ketones

The Michael addition reaction of oxindole **1a** to MVK was first selected as our initial testing reaction. And four widely used bifunctional tertiary-amine thiourea catalysts **4a–4d**[11–14] (20 mol%) with different chiral scaffolds were screened in the current model reaction at room temperature. To our delight, all of the chiral thioureas **4a–4d** exhibited high catalytic activity and the Michael addition products were cleanly isolated with quantitative yields (entries 2–5 in Table 1). No reaction was observed in the absence of catalyst (Table 1, entry 1). Among the four types of thiourea catalysts tested, catalyst **4d** was found to give the optimal enantioselectivity (99% yield and 61% *ee*, entry 5 in Table 1). In addition, the racemic product obtained with a simple diamine catalyst **4e** suggested an obvious bifunctional catalytic mode in the current reaction (Table 1, entry 6).

With **4d** as the optimal catalyst, we next examined different solvents. As illustrated in Table 1, the initial selected toluene gave the best result among a range of screened solvents (Table 1, entries 5 and 7–11). The best result was achieved when the reaction was carried out at −60 °C in toluene in the presence of 4 Å molecular sieves (Table 1, entry 14). Under this condition, the yield was almost the same while the *ee* value was improved to 82%.

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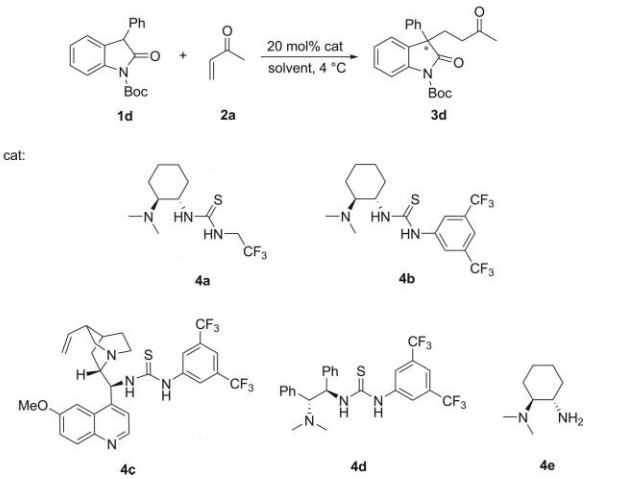
Table 1 Catalyst screening[a]



Entry	Catalysts	Solvent	Time/h	Yield [b](%)	*ee* [c](%)
1	no catalyst	Toluene	24	trace	nd[d]
2	**4a**	Toluene	2	98	40
3	**4b**	Toluene	2	99	45
4	**4c**	Toluene	2	97	37
5	**4d**	Toluene	2	99	61
6	**4e**	Toluene	2	96	rac
7	**4d**	CH_2Cl_2	2	99	56
8	**4d**	$CHCl_3$	2	99	55
9	**4d**	$ClCH_2CH_2Cl$	2	96	58
10	**4d**	Benzene	2	97	58
11	**4d**	THF	2	78	47
12	**4d**[e]	Toluene	2	99	67
13	**4d**[f]	Toluene	36	94	79
14	**4d**[g]	Toluene	36	98	82

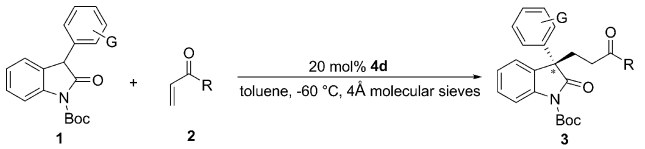
[a] The reaction was carried out on a 0.1 mmol scale in 200 μL solvent at 4 °C, and the molar ratio of oxindole **1d**/**2a** is 1/2. [b] Isolated yield. [c] Determined by HPLC. [d] Not determined. [e] The reaction was carried out on a 0.1 mmol scale in 1 mL toluene with 4 Å molecular sieves at 4 °C, and the molar ratio of oxindole **1d**/**2a** is 1/2. [f] The reaction was carried out on a 0.1 mmol scale in 1 mL toluene at –60 °C, and the molar ratio of oxindole **1d**/**2a** is 1/2. [g] The reaction was carried out on a 0.1 mmol scale in 1 mL toluene with 4 Å molecular sieves at –60 °C, and the molar ratio of oxindole **1d**/**2a** is 1/2.

Under the optimal reaction conditions, the substrate scope was next explored (Table 2). A series of 3-aryl-*N*-Boc oxindoles **1a–1d** (Michael donor compounds) and vinyl ketones **2a–2c** (Michael acceptor compounds) were examined. As summarized in Table 2, vinyl ketones including methyl vinyl ketone (MVK), ethyl vinyl ketone (EVK) and phenyl vinyl ketone (PVK) demonstrated equally good activity in reacting with different substituted 3-aryl-*N*-Boc oxindoles and the reactions generally furnished the desired Michael products in quantitative yields. Inspection of the results in Table 2 suggested similar chiral inductions were normally observed with all three vinyl ketones with slightly better *ee*s in cases of MVK and PVK. The best enantioselectivity (88% *ee*) was obtained in the reaction of MVK and **1c** (Table 1, entry 3).

Bifunctional tertiary-amine thiourea catalyzed Michael addition reaction of 3-aryl oxindoles to vinyl sulfones

Vinyl sulfones, which bear two S=O moieties that enable double H-bonding with the N–Hs of thiourea,[15] were next attempted

Table 2 Asymmetric Michael addition reaction of 3-aryl oxindoles to different vinyl ketones[a]

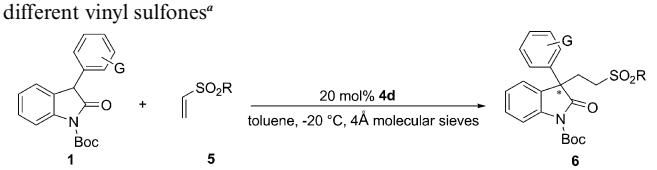


Entry	Terminal alkene	Oxindole	Time/h	Yield [b](%)	*ee* [c](%)
1	**2a**	G = 4-CH_3O (**1a**)	48	**3a**: 92	65
2		4-CH_3 (**1b**)	36	**3b**: 99	81
3		3,5-$(Me)_2$ (**1c**)	36	**3c**: 98	88
4		H (**1d**)	36	**3d**: 98	82(*S*)[d]
5	**2b**	G = 4-CH_3O (**1a**)	72	**3e**: 93	46
6		4-CH_3 (**1b**)	36	**3f**: 99	63
7		3,5-$(Me)_2$ (**1c**)	36	**3g**: 99	76
8		H (**1d**)	36	**3h**: 99	61
9	**2c**	G = 4-CH_3O (**1a**)	60	**3i**: 96	85
10		4-CH_3 (**1b**)	48	**3j**: 99	72
11		3,5-$(Me)_2$ (**1c**)	48	**3k**: 99	60
12		H (**1d**)	48	**3l**: 99	76

[a] The reaction was carried out on a 0.1 mmol scale in 1 mL toluene with 4 Å molecular sieves at –60 °C, and the molar ratio of oxindole **1**/**2** is 1/2. [b] Isolated yield. [c] Determined by HPLC. [d] The absolute configuration of the Michael adduct **3d** was determined to be *S* by comparison with literature.[9]

in the current reaction with the hope that better stereocontrol might be achieved with double H-bonding interactions. Indeed, the reactions of vinyl sulfone provided generally good enantioselectivity (Table 3, 82–91% *ee*), albeit with lower reactivity than those of vinyl ketones. Phenyl vinyl sulfone **5b** demonstrated higher activity than the methyl vinyl sulfone **5a**. Various 3-aromatic substituted oxindoles worked well with vinyl sulfone to give the desired product with yield ranging from 48% to 80%.

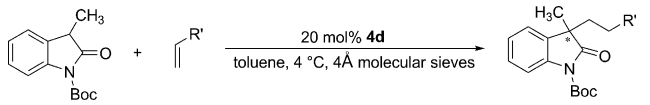
Table 3 Asymmetric Michael addition reaction of 3-aryl oxindoles to different vinyl sulfones[a]



Entry	Terminal alkene	Oxindole	Time/d	Yield [b](%)	*ee* [c](%)
1	SO_2CH_3 **5a**	G = 4-CH_3O	8	trace	nd[d]
2		4-CH_3	8	**6a**: 48	86
3		3,5-$2CH_3$	8	**6b**: 55	87
4		H	6	**6c**: 51	91
5	SO_2Ph **5b**	G = 4-CH_3O	6	**6d**: 60	88
6		4-CH_3	6	**6e**: 75	82
7		3,5-$2CH_3$	6	**6f**: 72	90
8		H	6	**6g**: 80	87

[a] The reaction was carried out on a 0.1 mmol scale in 200 μL toluene with 4 Å molecular sieves at –20 °C, and the molar ratio of oxindole **1**/**5** is 1/3. [b] Isolated yield. [c] Determined by HPLC. [d] Not determined.

Table 4 Asymmetric Michael addition reaction of 3-methyl-*N*-Boc oxindole to different terminal alkenes[a]



Entry	Terminal alkene	Time/h	Yield [b](%)	*ee* [c](%)
1	**2a**	72	**8a**: 90	22
2	**2b**	72	**8b**: 99	17
3	**2c**	72	**8c**: 99	48
4	**5a**	168	**8d**: trace	nd[d]
5	**5b**	96	**8e**: 48	84

[a] The reaction was carried out on a 0.1 mmol scale in 200 μL toluene with 4 Å molecular sieves at 4 °C, and the molar ratio of oxindole/terminal alkene is 1/2. [b] Isolated yield. [c] Determined by HPLC. [d] Not determined.

Bifunctional tertiary-amine thiourea catalyzed Michael addition reaction of 3-methyl oxindole to terminal alkenes

In addition to the 3-aromatic substituted oxindoles, 3-alkyl substituted oxindoles such as oxindole **7** have also been examined in the reactions and the results were summarized in Table 4. The reactions with vinyl ketones proceeded smoothly to give the desired Michael products in excellent yields, however, only low enantioselectivities were obtained in these cases (Table 4, entries 1–3). In accordance with previous observations, the vinyl sulfones reacted sluggishly with oxindole **7**, but good *ee* (84%) could still be achieved in the reaction of phenyl vinyl sulfone **5b** and oxindole (Table 4, entry 5).

Conclusion

In summary, we have presented highly enantioselective Michael addition reactions of 3-substituted oxindoles to terminal alkenes using a bifunctional tertiary-amine thiourea organocatalyst. This study provided a rather mild procedure for the synthesis of multifunctional chiral oxindole compounds bearing all carbon-substituted quaternary stereocenters with moderate to excellent enantioselectivities. The reaction scope is substantial and a number of 3-aryl or methyl oxindoles could be successfully applied in current studied Michael addition system.

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). Elemental analysis was obtained from thermoQuest (Flash 1112EA, ITALY). Mass spectra were obtained using electron ionization (EI) mass spectrometer. Catalysts **4a**,[11] **4b**,[12] **4c**,[13] **4d**[14] and **4e**[16] were synthesized from the literature methods. Michael products **3a**, **3b**, **3d** and **3h** were known compounds.[9]

General experimental procedure for Michael reaction of 1 and 2

To a stirred solution of 3-aryl-*N*-Boc oxindole **1** (0.1 mmol) and vinyl ketones **2** (2.0 equiv.) in dry toluene (1 mL) was added thiourea-catalyst (0.2 equiv.) at −60 °C with 4 Å molecular sieves. After the reaction completed, the reaction solution was concentrated *in vacuo* and the crude was purified by flash chromatography to afford the product.

3c. The Michael product was synthesized according to the general procedure as white solid in 98% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (1H, d, J = 8.51 Hz), 7.37 (1H, td, J = 8.51, 1.65 Hz), 7.23–7.15 (2H, m), 6.89 (3H, s), 2.77–2.68 (1H, m), 2.51–2.25 (8H, m), 2.11–2.01 (4H, m), 1.63 (9H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 207.12, 176.69, 149.30, 139.77, 139.38, 138.20, 130.82, 129.45, 128.57, 124.74, 124.65, 115.21, 84.56, 55.80, 38.74, 31.63, 29.96, 28.11, 21.43 ppm; HRMS (EI$^+$): calcd. for [$C_{25}H_{29}NO_4$] 407.2097; found 407.2101. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 9), 1.0 mL min^{-1}; t_R = 4.3 min (major), 5.3 min (minor).

3e. The Michael product was synthesized according to the general procedure as white solid in 93% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (1H, d, J = 8.23 Hz), 7.40–7.34 (1H, m), 7.24–7.16 (4H, m), 6.83 (2H, d, J = 9.06 Hz), 3.76 (3H, s), 2.76–2.66 (1H, m), 2.52–2.43 (1H, m), 2.37–2.14 (3H, m), 2.07–1.97 (1H, m), 1.63 (9H, s), 0.95 (3H, t, J = 7.14 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.80, 176.77, 159.08, 149.30, 139.85, 131.53, 130.56, 128.62, 128.13, 124.76, 124.68, 115.27, 114.07, 84.55, 55.39, 55.25, 37.48, 35.94, 31.92, 28.09, 7.63 ppm; HRMS (EI$^+$): calcd. for [$C_{25}H_{29}NO_5$] 423.2046; found 423.2049. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 9), 1.0 mL min^{-1}; t_R = 7.8 min (major), 11.7 min (minor).

3f. The Michael product was synthesized according to the general procedure as colorless oil in 99% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (1H, d, J = 7.96 Hz), 7.39–7.33 (1H, m), 7.24–7.09 (6H, m), 2.78–2.68 (1H, m), 2.55–2.45 (1H, m), 2.38–2.14 (6H, m), 2.10–1.99 (1H, m), 1.63 (9H, s), 0.95 (3H, t, J = 7.14 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.80, 176.69, 149.29, 139.84, 137.48, 136.57, 130.61, 129.41, 128.61, 126.82, 124.75, 124.70, 115.25, 84.53, 55.75, 37.46, 35.46, 31.77, 28.09, 20.91, 7.64 ppm; HRMS (EI$^+$): calcd. for [$C_{25}H_{29}NO_4$] 407.2097; found 407.2101. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 9), 1.0 mL min^{-1}; t_R = 6.0 min (major), 8.7 min (minor).

3g. The Michael product was synthesized according to the general procedure as white solid in 99% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (1H, d, J = 7.96 Hz), 7.39–7.33 (1H, m), 7.23–7.15 (2H, m), 6.89 (3H, m), 2.78–2.68 (1H, m), 2.54–2.44 (1H, m), 2.37–2.16 (9H, m), 2.08–1.98 (1H, m), 1.64 (9H, s), 0.95 (3H, t, J = 7.14 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.89, 176.73, 149.31, 139.78, 139.43, 138.18, 130.81, 129.43,

128.54, 124.74, 124.71, 124.66, 115.19, 84.54, 55.92, 37.43, 35.95, 31.74, 28.11, 21.43, 7.65 ppm; Anal. Calcd. for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C, 73.83; H, 7.47; N, 3.14. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 9), 1.0 mL min^{-1}; t_R = 4.2 min (major), 5.2 min (minor).

3i. The Michael product was synthesized according to the general procedure as white solid in 96% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (1H, d, J = 8.23 Hz), 7.81–7.78 (2H, m), 7.53–7.19 (10H, m), 6.85–6.82 (2H, m), 3.76 (3H, s), 2.97–2.83 (2H, m), 2.67–2.55 (2H, m), 1.64 (9H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.80, 176.81, 159.12, 149.33, 139.84, 136.60, 133.07, 131.50, 130.61, 128.70, 128.51, 128.19, 128.01, 124.74, 115.35, 114.11, 84.56, 55.52, 55.26, 33.86, 32.60, 28.12 ppm; Anal. Calcd. for $C_{29}H_{29}NO_5$: C, 73.87; H, 6.20; N, 2.97. Found: C, 72.76; H, 6.21; N, 2.87. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (2-propanol : hexane = 1 : 49), 1.0 mL min^{-1}; t_R = 16.1 min (minor), 23.9 min (major).

3j. The Michael product was synthesized according to the general procedure as white solid in 99% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (1H, d, J = 8.23 Hz), 7.81–7.78 (2H, m), 7.50 (1H, t, J = 7.14 Hz), 7.41–7.33 (3H, m), 7.25–7.10 (6H, m), 2.98–2.84 (2H, m), 2.70–2.57 (2H, m), 2.30 (3H, s), 1.63 (9H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.81, 176.72, 149.33, 139.83, 137.52, 136.61, 136.54, 133.07, 130.66, 129.46, 128.68, 128.51, 128.01, 126.87, 124.76, 124.72, 115.32, 84.55, 55.88, 33.84, 32.44, 28.12, 20.94 ppm; Anal. Calcd. for $C_{29}H_{29}NO_4$: C, 76.46; H, 6.42; N, 3.07. Found: C, 76.58; H, 6.49; N, 2.93. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 9), 1.0 mL min^{-1}; t_R = 7.6 min (minor), 8.7 min (major).

3k. The Michael product was synthesized according to the general procedure as white solid in 99% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 (1H, d, J = 8.23 Hz), 7.81–7.78 (2H, m), 7.50 (1H, t, J = 7.14 Hz), 7.41–7.33 (3H, m), 7.25–7.18 (2H, m), 6.94–6.89 (3H, m), 2.97–2.84 (2H, m), 2.68–2.56 (2H, m), 2.26 (6H, s), 1.64 (9H, m) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.91, 176.77, 149.35, 139.76, 139.39, 138.24, 136.61, 133.08, 130.86, 129.48, 128.61, 128.52, 128.03, 124.77, 124.72, 115.27, 84.56, 56.06, 33.81, 32.44, 28.14, 21.46 ppm; Anal. Calcd. for $C_{30}H_{31}NO_4$: C, 76.73; H, 6.65; N, 2.98. Found: C, 74.61; H, 6.64; N, 2.93. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (2-propanol : hexane = 1 : 49), 1.0 mL min^{-1}; t_R = 7.9 min (minor), 8.8 min (major).

3l. The Michael product was synthesized according to the general procedure as white solid in 99% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (1H, d, J = 8.23 Hz), 7.81–7.78 (2H, m), 7.51 (1H, t, J = 7.14 Hz), 7.41–7.20 (10H, m), 2.99–2.85 (2H, m), 2.72–2.58 (2H, m), 1.64 (9H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.75, 176.60, 149.28, 139.84, 139.49, 136.59, 133.09, 130.46, 128.77, 128.52, 128.01, 127.75, 127.01, 124.79, 115.35, 84.64, 56.17, 33.81, 32.51, 28.12 ppm; HRMS (EI$^+$): calcd. for [$C_{28}H_{27}NO_4$] 441.1940; found 441.1944. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 9), 1.0 mL min^{-1}; t_R = 7.4 min (minor), 8.1 min (major).

General experimental procedure for Michael reaction of 1 and 5

To a stirred solution of 3-aryl-*N*-Boc oxindole **1** (0.1 mmol) and vinyl sulfones **5** (3.0 equiv.) in dry toluene (200 μL) was added thiourea-catalyst (0.2 equiv.) at –20 °C with 4 Å molecular sieves. After the reaction completed, the reaction solution was concentrated *in vacuo* and the crude was purified by flash chromatography to afford the product.

6a. The Michael product was synthesized according to the general procedure as white solid in 48% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (1H, d, J = 8.23 Hz), 7.42–7.35 (1H, m), 7.26–7.12 (6H, m), 2.98–2.86 (5H, m), 2.79–2.59 (2H, m), 2.31 (3H, s), 1.63 (9H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.89, 148.94, 139.57, 138.08, 135.10, 129.72, 129.35, 129.23, 126.62, 125.10, 124.50, 115.59, 84.99, 55.02, 50.57, 40.62, 30.49, 28.07, 20.92 ppm; HRMS (EI$^+$): calcd. for [$C_{23}H_{27}NO_5S$] 429.1610; found 429.1613. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 9), 1.0 mL min^{-1}; t_R = 13.3 min (minor), 16.1 min (major).

6b. The Michael product was synthesized according to the general procedure as white solid in 55% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 (1H, d, J = 7.96 Hz), 7.42–7.36 (1H, m), 7.26–7.24 (2H, m), 6.92–6.90 (3H, m), 2.97–2.87 (5H, m), 2.79–2.58 (2H, m), 2.27 (6H, s), 1.64 (9H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.95, 148.94, 139.52, 138.60, 138.03, 129.88, 129.49, 129.18, 125.12, 124.51, 124.42, 115.54, 85.00, 55.20, 50.56, 40.61, 30.46, 28.09, 21.44 ppm; Anal. Calcd. for $C_{23}H_{27}NO_5S$: C, 64.31; H, 6.34; N, 3.26. Found: C, 64.67; H, 6.62; N, 3.10. 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 = 7.4 min (minor), 8.1 min (major).

6c. The Michael product was synthesized according to the general procedure as white solid in 51% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (1H, d, J = 8.23 Hz), 7.43–7.26 (8H, m), 2.99–2.62 (7H, m), 1.64 (9H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.77, 148.89, 139.60, 138.08, 129.32, 129.14, 129.05, 128.20, 126.76, 125.14, 124.56, 115.63, 82.08, 55.31, 50.55, 40.64, 30.53, 28.07 ppm; HRMS (EI$^+$): calcd. for [$C_{22}H_{25}NO_5S$] 415.1453; found 415.1457. 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 = 26.4 min (minor), 36.3 min (major).

6d. The Michael product was synthesized according to the general procedure as colorless oil in 60% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91–7.82 (3H, m), 7.69–7.53 (3H, m), 7.37 (1H, td, J = 7.96, 1.37 Hz), 7.23–7.09 (4H, m), 6.80 (2H, d, J = 8.78 Hz), 3.76 (3H, s), 3.12–3.02 (1H, m), 2.88–2.67 (2H, m), 2.55–2.45 (1H, m), 1.60 (9H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.72, 159.33, 148.95, 139.60, 138.60, 133.88, 129.90, 129.39, 129.30, 129.14, 128.11, 128.04, 124.93, 124.47, 115.58, 114.30, 84.88, 55.28, 54.59, 51.87, 30.93, 28.05 ppm; HRMS (EI$^+$): calcd. for [$C_{28}H_{29}NO_6S$] 507.1716; found 507.1720. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 9), 1.0 mL min^{-1}; t_R = 19.4 min (minor), 21.3 min (major).

6e. The Michael product was synthesized according to the general procedure as white solid in 75% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91–7.82 (3H, m), 7.69–7.53 (3H, m), 7.37

(1H, td, J = 7.96, 1.37 Hz), 7.22–7.08 (6H, m), 3.12–3.02 (1H, m), 2.90–2.69 (2H, m), 2.55–2.45 (1H, m), 2.29 (3H, s), 1.60 (9H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.63, 148.94, 139.59, 138.60, 137.97, 135.03, 133.87, 129.64, 129.38, 129.11, 128.12, 126.67, 124.93, 124.45, 115.55, 84.87, 54.94, 51.85, 30.79, 28.05, 20.91 ppm; *Anal.* Calcd. for $C_{28}H_{29}NO_5S$: C, 68.41; H, 5.95; N, 2.85. Found: C, 67.44; H, 5.97; N, 2.66. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 9), 1.0 mL min^{-1}; t_R = 13.3 min (minor), 16.2 min (major).

6f. The Michael product was synthesized according to the general procedure as white solid in 72% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91–7.82 (3H, m), 7.69–7.53 (3H, m), 7.36 (1H, td, J = 7.96, 1.37 Hz), 7.22–7.07 (2H, m), 6.89 (1H, s), 6.78 (2H, s), 3.13–3.03 (1H, m), 2.91–2.70 (2H, m), 2.54–2.45 (1H, m), 2.22 (6H, s), 1.61 (9H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.66, 148.97, 139.53, 138.65, 138.51, 137.85, 133.86, 129.79, 129.56, 129.38, 129.04, 128.10, 124.92, 124.50, 124.47, 115.50, 84.87, 55.10, 51.82, 30.75, 28.07, 21.41 ppm; Anal. Calcd. for $C_{29}H_{31}NO_5S$: C, 68.89; H, 6.18; N, 2.77. Found: C, 68.04; H, 6.18; N, 2.60. 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 = 12.0 min (minor), 16.5 min (major).

6g. The Michael product was synthesized according to the general procedure as white solid in 80% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84–7.75 (3H, s), 7.60 (1H, t, J = 7.14 Hz), 7.49 (2H, t, J = 7.41 Hz), 7.31 (1H, td, J = 7.96, 1.37 Hz), 7.22–7.12 (6H, m), 7.05–7.03 (1H, d, J = 7.41 Hz), 3.06–2.93 (1H, m), 2.82–2.65 (2H, m), 2.54–2.42 (1H, m), 1.54 (9H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.52, 148.89, 139.60, 138.54, 137.99, 133.93, 129.41, 129.22, 129.13, 128.97, 128.12, 126.82, 125.00, 124.52, 115.61, 84.97, 55.22, 51.82, 30.84, 28.06 ppm; Anal. Calcd. for $C_{27}H_{27}NO_5S$: C, 67.90; H, 5.70; N, 2.93. Found: C, 67.82; H, 5.71; N, 2.73. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 9), 1.0 mL min^{-1}; t_R = 11.3 min (minor), 13.8 min (major).

General experimental procedure for Michael reaction of 7 and 2 (or 5)

To a stirred solution of 3-methyl-*N*-Boc oxindole **5** (0.1 mmol) and terminal alkene (2.0 equiv.) in dry toluene (200 μL) was added thiourea-catalyst (0.2 equiv.) at 4 °C with 4 Å molecular sieves. After the reaction completed, the reaction solution was concentrated *in vacuo* and the crude was purified by flash chromatography to afford the product.

8a. The Michael product was synthesized according to the general procedure as white solid in 90% overall yield.^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (1H, d, J = 8.23 Hz), 7.33–7.27 (1H, m), 7.18–7.16 (2H, m), 2.35–1.95 (7H, m), 1.66 (9H, s), 1.43 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 207.25, 178.75, 149.28, 139.01, 132.16, 128.26, 124.71, 122.57, 115.04, 84.48, 47.72, 38.48, 32.47, 29.89, 28.11, 24.70 ppm; HRMS (EI$^+$): calcd. for [$C_{18}H_{23}NO_4$] 317.1627; found 317.1630. 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 = 5.3 min (minor), 5.7 min (major).

8b. The Michael product was synthesized according to the general procedure as colorless oil in 99% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (1H, d, J = 8.23 Hz), 7.33–7.27 (1H, m), 7.17–7.16 (2H, m), 2.33–2.10 (5H, m), 2.02–1.92 (1H, m), 1.66 (9H, s), 1.43 (3H, s), 0.94 (3H, t, J = 7.41 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 209.96, 178.79, 149.28, 139.01, 132.18, 128.22, 124.67, 122.65, 115.01, 84.45, 47.83, 37.19, 35.89, 32.54, 28.11, 24.72, 7.62 ppm; HRMS (EI$^+$): calcd. for [$C_{19}H_{25}NO_4$] 331.1784; found 331.1787. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (2-propanol : hexane = 1 : 49), 1.0 mL min^{-1}; t_R = 7.9 min (minor), 9.1 min (major).

8c. The Michael product was synthesized according to the general procedure as white solid in 99% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79–7.70 (3H, m), 7.46–7.41 (1H, m), 7.34–7.29 (2H, m), 7.25–7.08 (3H, m), 2.85–2.74 (1H, m), 2.53–2.42 (1H, m), 2.35–2.12 (2H, m), 1.59 (9H, m), 1.40 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.94, 178.82, 149.33, 139.01, 136.59, 133.05, 132.28, 128.50, 128.30, 127.98, 124.75, 122.60, 115.09, 84.47, 47.93, 33.51, 33.08, 28.14, 24.85 ppm; Anal. Calcd. for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 72.47; H, 6.67; N, 3.54. The enantiomeric excess was determined by HPLC with an OD-H column at 210 nm (2-propanol : hexane = 1 : 49), 1.0 mL min^{-1}; t_R = 9.6 min (minor), 10.5 min (major).

8e. The Michael product was synthesized according to the general procedure as yellow oil in 48% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85–7.80 (3H, m), 7.69–7.53 (3H, m), 7.34–7.29 (1H, m), 7.21–7.10 (2H, m), 2.98 (1H, td, J = 13.45, 4.94 Hz), 2.76 (1H, td, J = 13.45, 4.94 Hz), 2.34–2.10 (2H, m), 1.64 (9H, s), 1.41 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.61, 148.93, 138.85, 138.67, 133.86, 130.93, 129.36, 128.79, 128.05, 125.03, 122.40, 125.30, 84.82, 51.64, 47.17, 31.16, 28.08, 24.45 ppm; HRMS (EI$^+$): calcd. for [$C_{22}H_{25}NO_5S$] 415.1453; found 415.1457. The enantiomeric excess was determined by HPLC with an AD-H column at 210 nm (2-propanol : hexane = 1 : 9), 1.0 mL min^{-1}; t_R = 11.0 min (minor), 12.6 min (major).

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