JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

# Catalytic Asymmetric Construction of Vicinal Tetrasubstituted Stereocenters by the Mannich Reaction of Linear α-Substituted Monothiomalonates with Isatin *N*-Boc Ketimines

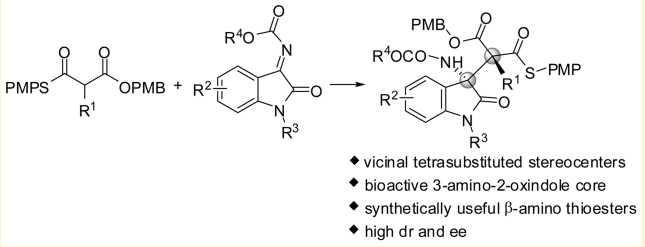
Teng Liu,[†,§] Weiwei Liu,[†,§] Xiaonian Li,[‡] Fangzhi Peng,*[,†] and Zhihui Shao*[,†]

[†]Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming 650091, China

[‡]Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, China

Supporting Information

**ABSTRACT:** A highly diastereo- and enantioselective method for the construction of vicinal tetrasubstituted stereocenters through the first catalytic asymmetric Mannich reaction of linear α-substituted MTMs with isatin *N*-Boc ketimines has been developed. This protocol provides atom-economic synthesis of less accessible 3-aminooxindoles bearing vicinal tetrasubstituted stereocenters. Notably, it also constitutes the first example of stereoselective synthesis of β-amino thioesters bearing vicinal tetrasubstituted stereocenters.




## INTRODUCTION

Stereoselective construction of vicinal tetrasubstituted stereocenters is of great importance,[1] because such structural motifs are present in numerous natural products and bioactive compounds.[2] However, although substrate-directed diastereoselective methods for the generation of vicinal tetrasubstituted stereocenters have been well documented, catalytic asymmetric approaches to construct these highly congested stereochemical dyads remain a formidable challenge due to low reactivity caused by steric repulsion and the introduction of requisite diastereocontrol. To date, only a few catalytic asymmetric approaches have been reported to generate contiguous tetrasubstituted stereocenters via a single synthetic operation. Among these approaches, cycloadditions[3] and alkylation reactions[4] are most commonly used. In recent years, the catalytic asymmetric nucleophilic 1,2-addition of trisubstituted carbon nucleophiles to ketones and ketimines[5] has emerged as a potential method for constructing vicinal tetrasubstituted stereocenters because of its atom economy[6] and incorporation of the alcohol or amine functionality. However, the reported examples generally employ cyclic nucleophiles or both vicinal tetrasubstituted stereocenters are formed at a constrained cycle. To address these limitations, we initiated studies investigating the catalytic asymmetric Mannich reaction of ketimines employing linear α-substituted monothiomalonates to construct challenging vicinal tetrasubstituted stereocenters.

A new class of linear trisubstituted carbon nucleophiles, α-substituted monothiomalonates (MTMs), have recently introduced by Wennemers.[7a] The synthetic potential of α-substituted MTMs has been demonstrated in the asymmetric Michael addition of nitroolefins.[7] Very recently, Wennemers and co-workers disclosed the first asymmetric 1,2-addition of α-substituted MTMs to aldimines (Scheme 1a).[8] This reaction provides an elegant method for the enantioselective synthesis of β-amino thioesters, which are important building blocks for the synthesis of bioactive molecules. However, they noted that although α-substituted MTMs reacted smoothly with *N*-Cbz-protected aldimines, this class of nucleophiles did not react with the corresponding *N*-Boc-protected aldimines because of steric restraints.[8] Thus, it is not surprising that there are no reports challenging the difficulty involved in the enantioselective addition of α-substituted MTMs to ketimines, even though such a reaction, if successful, would provide an attractive atom-economic method for vicinal tetrasubstituted stereocenters. Compared to aldimines, ketimines are typically less reactive due to steric restraints. Additionally, this process is complicated further because a second vicinal tetrasubstituted center is present in the synthetic target. However, the importance of enantioenriched β-amino thioesters bearing contiguous tetrasubstituted stereocenters combined with the virtual absence of reports for their stereoselective synthesis encouraged our exploration of this unprecedented Mannich reaction[9] of linear α-substituted MTMs with *N*-Boc ketimines. Here, isatin *N*-Boc ketimines were chosen as the substrates because the resulting β-amino thioesters have a 3-aminooxindole backbone, which is the core structure in numerous natural products and bioactive molecules.[10,11]

The catalytic asymmetric nucleophilic 1,2-addition to isatin-derived ketimines has received increasing attention[12,13] because of the importance of 3-aminooxindoles. However, despite remarkable advances, most reports generate 3-aminooxindole

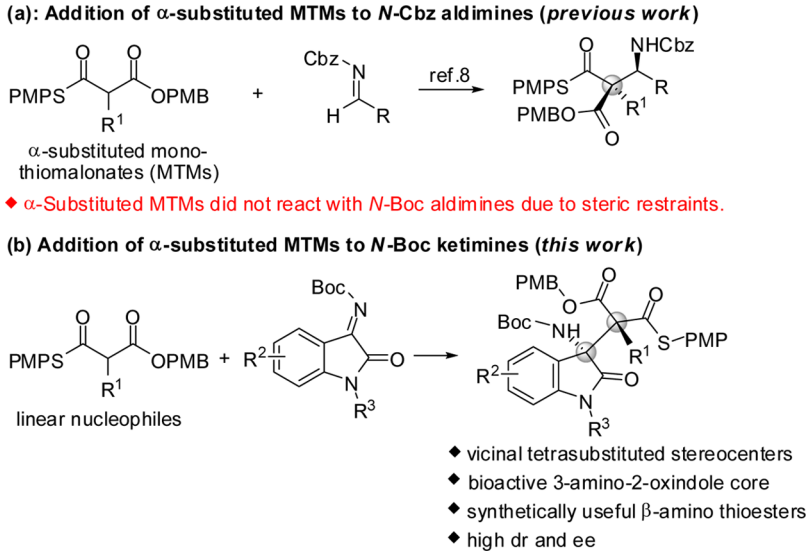
**Received:** February 9, 2015
**Published:** April 21, 2015





DOI: 10.1021/acs.joc.5b00302
J. Org. Chem. 2015, 80, 4950−4956

**Scheme 1. Construction of Tetrasubstituted Stereogenic Centers in the Addition of α-Substituted MTMs to Imines**




products containing a single stereocenter[12] with only a few examples furnishing products containing vicinal quaternary and tertiary stereocenters with good stereoselectivities.[13] Catalytic asymmetric nucleophilic 1,2-additions to isatin-derived ketimines targeting 3-aminooxindoles bearing vicinal tetrasubstituted stereocenters are rare. During the preparation of our manuscript, Feng et al. reported a metal-catalyzed asymmetric addition of linear silyl ketene imine to isatin-derived ketimine.[14] However, despite its elegance, to achieve high diastereo-and enantioselectivity, lower temperature (−45 °C) was required. To date, the organocatalytic asymmetric nucleophilic 1,2-additions of linear nucleophiles to isatin-derived ketimines targeting 3-aminooxindoles bearing vicinal tetrasubstituted stereocenters remains to be developed.

## RESULTS AND DISCUSSION

We began our study by evaluating a variety of bifunctional tertiary amine−thiourea organocatalysts[15] (Figure 1) for the model reaction of **1a** and **2a** at room temperature, and the results are summarized in Table 1. It was found that the catalyst structures have remarkable effects on the stereochemical results. Using quinine-derived thiourea **I**, product **3a** was obtained with high enantioselectivity (98% ee) but moderate diastereoselectivity (5:1 dr) (entry 1). However, the use of cinchonine-derived thiourea **II** provided product **3a** with poor diastereo- and enantioselectivity (1:1 dr and 25% ee) (entry 2). Diphenylethane-1,2-diamine derived tertiary amine thiourea **III** gave poor enantioselectivity (19% ee) and moderate diastereoselectivity (4:1 dr) (entry 3). When cyclohexane-1,2-diamine-derived tertiary amine thiourea **IV** was used, the desired product was obtained in 98% yield with 99% ee and >20:1 dr (entry 4). This is useful as both enantiomers of the product could be obtained with excellent enantioselectivity values. To gain further insights into the effects of the catalyst structure on the reaction, we examined cyclohexane-1,2-diamine-derived tertiary amine thiourea catalysts **V** and **VI**. Interestingly, bulky catalyst **V** gave poor diastereo- and enantioselectivity (entry 5) whereas catalyst **VI** bearing multiple hydrogen bond donors afforded good enantioselectivity but moderate diastereoselectivity (entry 6). Then, solvent effects were examined. Whereas the solvents had little influence on enantioselectivity, they had remarkable effects on diastereoselectivity (entries 4 and 7−9). Ultimately, toluene proved to be the optimal solvent (entry 4).

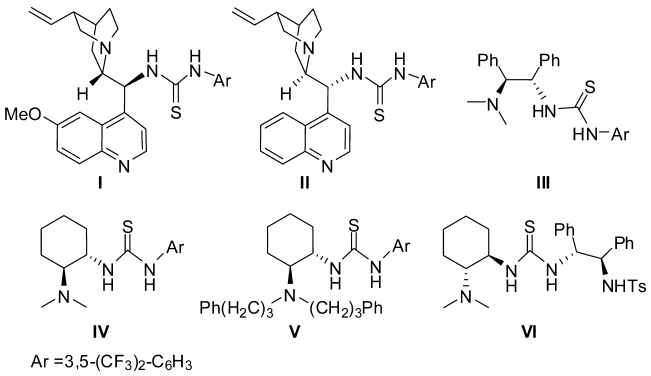
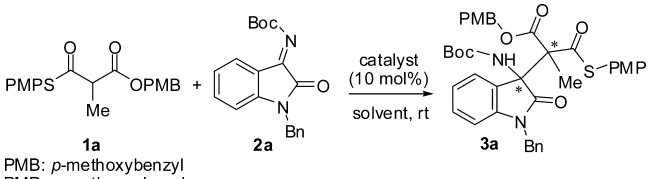



**Figure 1.** Structures of catalysts screened in this study.

**Table 1. Optimization of the Reaction Conditions**[a]




PMB: *p*-methoxybenzyl
PMP: *p*-methoxyphenyl

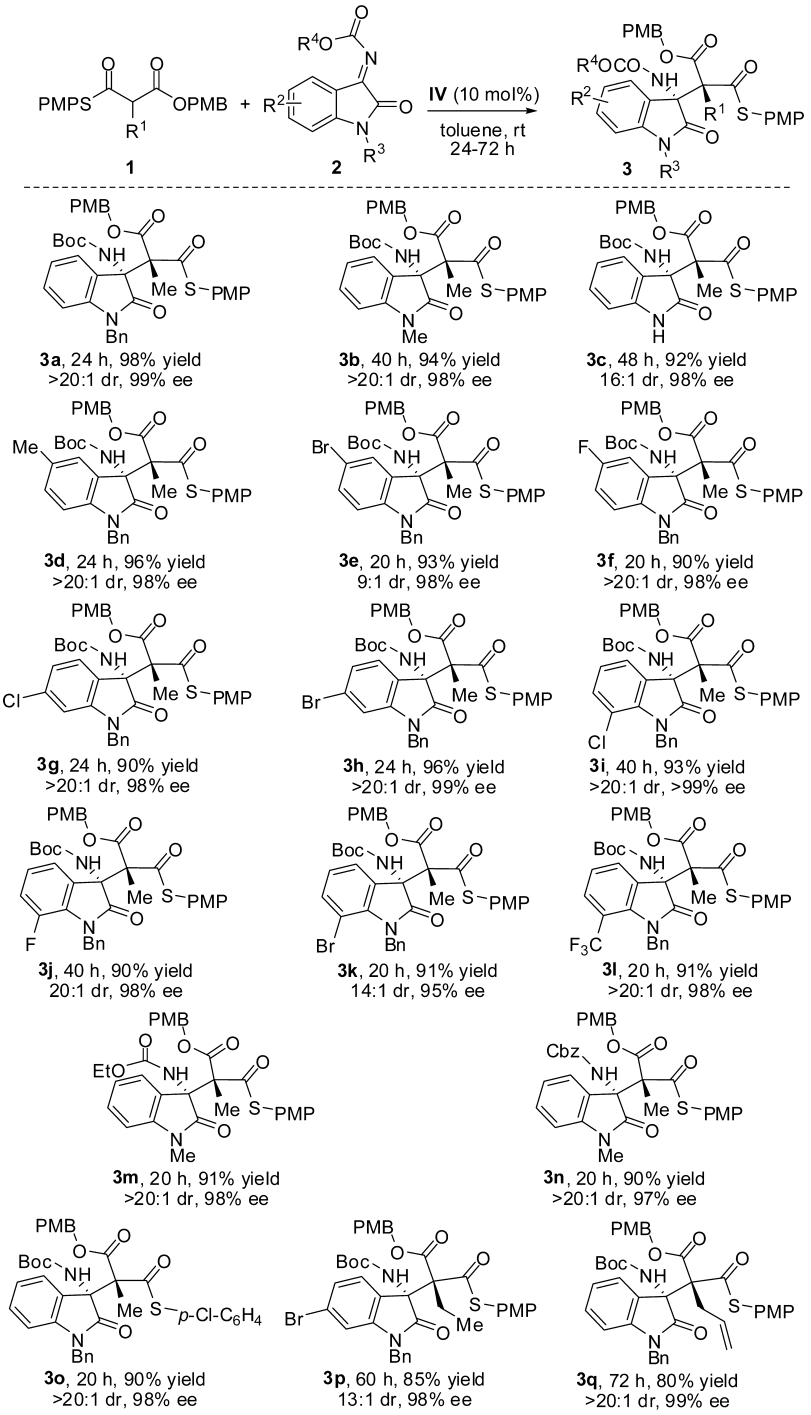
| entry | catalyst | solvent | time (h) | yield (%)[b] | dr[c] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **I** | toluene | 40 | 75 | 5:1 | 98 |
| 2 | **II** | toluene | 48 | 70 | 1:1 | −25 |
| 3 | **III** | toluene | 48 | 82 | 4:1 | −19 |
| 4 | **IV** | toluene | 20 | **98** | **>20:1** | **−99** |
| 5 | **V** | toluene | 48 | 68 | 2:1 | −7 |
| 6 | **VI** | toluene | 66 | 85 | 4:1 | 92 |
| 7 | **IV** | $CHCl_3$ | 70 | 92 | 6:1 | 96 |
| 8 | **IV** | MeCN | 72 | 75 | 4:1 | 92 |
| 9 | **IV** | EtOAc | 60 | 95 | 7:1 | 95 |

[a]Reactions was performed with **1a** (0.11 mmol) and **2a** (0.1 mmol) in the presence of catalyst (10 mol %) at room temperature. [b]Isolated yield. [c]Determined by chiral HPLC.



DOI: 10.1021/acs.joc.5b00302
J. Org. Chem. 2015, 80, 4950−4956

**Scheme 2. Substrate Scope**




Upon the optimized conditions being determined, the substrate scope was investigated. The Mannich reaction with a range of isatin-derived *N*-Boc ketimines proceeded smoothly to provide the products in excellent yields and diastereo- and enantioselectivities (Scheme 2, **3a**–**l**). The ketimines, with potecting groups such as Cbz and $CH_3CH_2OCO$-, also worked very well (**3m** and **3n**).[16] Notably, the ketimine without the substituted group at the 1-position could also react well with $\alpha$-methyl-substituted MTM to afford Mannich product **3c** in 92% yield with 16:1 dr and 98% ee. Other MTMs bearing ethyl and allyl substituents at the $\alpha$-position were also tolerated well, and the products **3p** and **3q** were obtained in high yields with diastereoselectivities of 13:1 to >20:1 and enantioselectivities of 98 to >99% ee. MTM with a *p*-chlorophenyl thioester also worked well to provide product **3o** in 90% yield with >20:1 dr and 98% ee.

The absolute and relative configurations of all of the Mannich products (**3**) were unambiguously assigned on the basis of X-ray crystallographic analysis of **3h** (Figure 2).[17]

On the basis of the X-ray structure of **3h** and the work by Wennemers,[8] a proposed stereochemical model is illustrated in Figure 3. It involves coordination of the MTM to the urea moiety of the catalyst[18] and addition of the MTM enolate from the *Re* face to the *Re* face of the imine (Figure 3, left). An



DOI: 10.1021/acs.joc.5b00302
*J. Org. Chem.* 2015, 80, 4950–4956

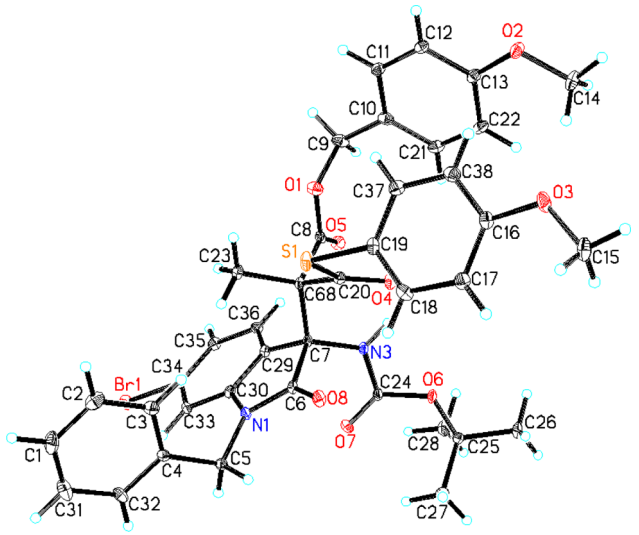



**Figure 2.** X-ray crystal structure of **3h** (displacement ellipsoids are drawn at the 30% probability level).

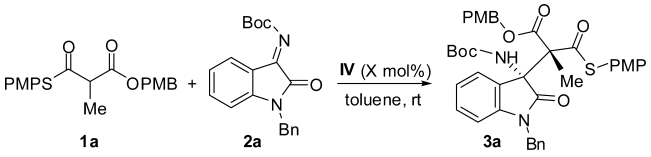
alternative *Si*−*Si* face approach is less likely due to unfavorable steric interactions (Figure 3, right).

Encouraged by the unexpected high efficiency of this asymmetric Mannich process, we further examined reactions with low catalyst loading, and the results are summarized in Table 2. When the catalyst loading was decreased from 10 to 2 mol %, remarkably high yield (94%) and excellent diastereo- and enantioselectivity (>20:1 dr and >99% ee) were still obtained, although a long reaction time was necessary (entries 1−3). However, a further decrease in the catalyst loading to 1 mol % led to a drop in diastereoselectivity (10:1 dr) albeit in excellent enantioselectivity (>99% ee) and high yield (92%) (entry 4).

## CONCLUSION

In summary, we have developed a highly diastereo- and enantioselective method for the construction of vicinal tetrasubstituted stereocenters through the first Mannich reaction of linear $\alpha$-substituted MTMs with isatin *N*-Boc ketimines. The catalyst structure had a remarkable influence on the stereoselectivity. By using cyclohexane-1,2-diamine-derived tertiary amine-thiourea catalyst **IV**, less accessible chiral 3-aminooxindoles bearing vicinal tetrasubstituted stereocenters were obtained in an atom-economic manner in high yields (up to 98% yield) and remarkably high stereoselectivities (up to >20:1 dr and 99% ee). The present reaction also constitutes the first example of stereoselective synthesis of $\beta$-amino thioesters bearing vicinal tetrasubstituted stereocenters.

**Table 2. Reaction with Low Catalyst Loading**[a]




| entry | *X* (mol %) | time (h) | yield (%)[b] | dr[c] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | 10 | 20 | 98 | >20:1 | 99 |
| 2 | 5 | 47 | 97 | >20:1 | >99 |
| 3 | 2 | 96 | 94 | >20:1 | >99 |
| 4 | 1 | 96 | 92 | 10:1 | >99 |

[a]The reactions was performed with **1a** (0.11 mmol) and **2a** (0.1 mmol) in the presence of **IV** (X mol %) at room temperature. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

## EXPERIMENTAL SECTION

$^1$H and $^{13}$C NMR spectra were recorded at 300 and 400 MHz, respectively, on a spectrophotometer. Chemical shifts ($\delta$) are expressed in ppm, and *J* values are given in Hz. The enantiomeric excess was determined by chiral HPLC with *n*-hexane and *i*-propanol as eluents. High resolution mass spectrometry (HRMS) was recorded on a spectrometer using a time-of-flight (TOF) analyzer. Optical rotations were measured on a polarimeter. All chemicals and solvents were used as received without further purification unless otherwise stated. Flash column chromatography was performed on silica gel (200−300 mesh).

**General Procedure for the Catalytic Asymmetric Mannich Reactions of $\alpha$-Substituted MTMs 1 with Isatin *N*-Boc Ketimines 2.** To a solution of *N*-Boc ketimines **2** (0.1 mmol) and catalyst **IV** (0.01 mmol, 0.1 equiv) in toluene (0.25 mL) was added $\alpha$-substituted MTMs **1** (0.11 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature until the reaction was complete (monitored by TLC). The solvent was removed under reduced pressure, and the crude product was purified by flash silica gel chromatography (ethyl acetate/petroleum ether = 1:5) to afford product **3**.

*(R)-4-Methoxybenzyl 2-((R)-1-Benzyl-3-((tert-butoxycarbonyl)-amino)-2-oxoindolin-3-yl)-3-((4-methoxyphenyl)thio)-2-methyl-3-oxopropanoate (**3a**).* White solid (70.4 mg, 98% yield). Mp 154−156 °C. $[\alpha]_D^{20}$ −9.6 (*c* 1.0 $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.36 (d, *J* = 7.2 Hz, 2H), 7.25−7.21 (m, 2H), 7.18−7.13 (m, 5H), 7.07 (t, *J* = 8 Hz, 1H), 7.01−6.99 (m, 2H), 6.85−6.78 (m, 5H), 6.58 (d, *J* = 7.6 Hz, 1H), 5.05 (m, 2H), 4.92−4.88 (m, 1H), 4.77−4.74 (m, 1H), 3.75

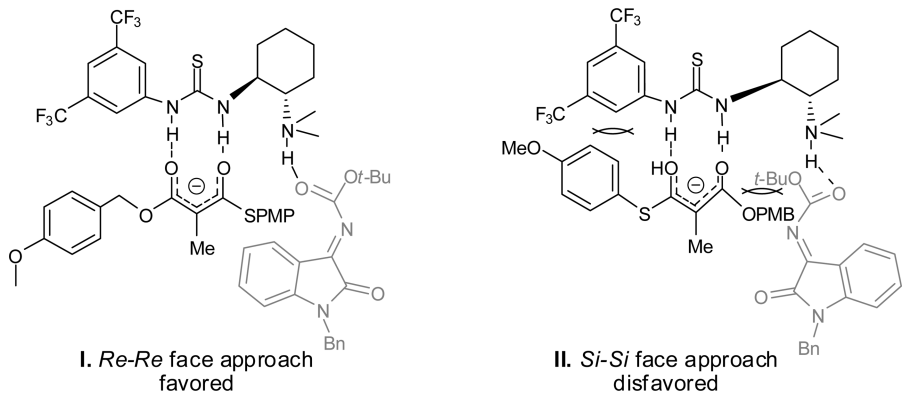



**Figure 3.** Proposed stereochemical model.



DOI: 10.1021/acs.joc.5b00302
J. Org. Chem. 2015, 80, 4950−4956

(s, 3H), 3.73 (s, 3H), 1.49 (s, 3H), 1.17 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 196.3, 173.8, 168.1, 161.0, 159.8, 153.8, 144.2, 136.5, 135.9, 130.3, 129.3, 128.7, 127.8, 127.5, 126.9, 124.2, 122.6, 117.6, 115.0, 113.9, 108.9, 79.9, 68.0, 65.6, 63.1, 55.4, 55.3, 44.6, 28.2, 15.8. HRMS (ESI-TOF): calcd for $C_{39}H_{40}N_2O_8SNa$ $[M + Na]^+$, 719.2397; found, 719.2398. HPLC (Chiralcel OD-H, *i*-propanol/*n*-hexane = 10:90, flow rate = 0.5 mL/min, λ = 254 nm): $t_{minor}$ = 30.1 min, $t_{major}$ = 44.0 min.

*(R)-4-Methoxybenzyl 2-((R)-3-((tert-Butoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)-3-((4-methoxyphenyl)thio)-2-methyl-3-oxopropanoate (**3b**).* White solid (60.4 mg, 94% yield). Mp 159−161 °C. $[\alpha]_D^{20}$ +10.6 (*c* 1.0 $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.22−7.19 (m, 3H), 7.14 (d, *J* = 8 Hz, 2H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.94 (s, 1H), 6.87−6.80 (m, 5H), 6.67 (d, *J* = 8 Hz, 1H), 5.12−5.05 (m, 2H), 3.74 (s, 6H), 3.11 (s, 3H), 1.49 (s, 3H), 1.13 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 196.2, 173.6, 168.0, 160.9, 159.9, 153.7, 144.8, 136.5, 130.4, 129.5, 127.6, 126.9, 124.1, 122.6, 117.6, 115.0, 113.9, 107.9, 79.8, 68.1, 65.6, 63.0, 55.4, 55.3, 28.1, 26.5, 15.7. HRMS (ESI-TOF): calcd for $C_{33}H_{36}N_2O_8SNa$ $[M + Na]^+$, 643.2084; found, 643.2082. HPLC (Chiralpak AD-H, *i*-propanol/*n*-hexane = 15:85, flow rate = 0.4 mL/min, λ = 254 nm): $t_{major}$ = 27.0 min, $t_{minor}$ = 34.3 min.

*(R)-4-Methoxybenzyl 2-((R)-3-((tert-Butoxycarbonyl)amino)-2-oxoindolin-3-yl)-3-((4-methoxyphenyl)thio)-2-methyl-3-oxopropanoate (**3c**).* White solid (57.8 mg, 92% yield). Mp 132−133 °C. $[\alpha]_D^{20}$ −17.1 (*c* 1.0 $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.22−7.20 (m, 3H), 7.14 (d, *J* = 8 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.97−6.95 (m, 2H), 6.85−6.80 (m, 5H), 6.63 (d, *J* = 7.6 Hz), 5.14−5.07 (m, 2H), 3.74 (s, 6H), 1.56 (s, 3H), 1.18 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 196.4, 174.8, 168.0, 161.0, 159.9, 153.9, 142.0, 136.5, 130.4, 129.4, 128.0, 126.9, 124.5, 122.5, 117.5, 115.0, 113.9, 109.9, 80.2, 68.1, 65.9, 62.9, 55.4, 55.3, 28.2, 15.6. HRMS (ESI-TOF): calcd for $C_{32}H_{34}N_2O_8SNa$ $[M + Na]^+$, 629.1928; found, 629.1930. HPLC (Chiralpak AS-H, *i*-propanol/*n*-hexane = 15:85, flow rate = 0.6 mL/min, λ = 254 nm): $t_{minor}$ = 23.2 min, $t_{major}$ = 51.2 min.

*(R)-4-Methoxybenzyl 2-((R)-1-Benzyl-3-((tert-butoxycarbonyl)-amino)-5-methyl-2-oxoindolin-3-yl)-3-((4-methoxyphenyl)thio)-2-methyl-3-oxopropanoate (**3d**).* Light yellow solid (70.3 mg, 96% yield). Mp 161−163 °C. $[\alpha]_D^{20}$ −8.2 (*c* 1.0 $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8 Hz, 2H), 7.32−7.24 (m, 7H), 7.12 (s, 1H), 6.93 (d, *J* = 8 Hz, 3H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.82 (s, 1H), 6.53 (d, *J* = 8 Hz, 1H), 5.17−5.10 (m, 2H), 4.96−4.92 (m, 1H), 4.85−4.82 (m, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 2.17 (s, 3H), 1.53 (s, 3H), 1.26 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 196.5, 173.6, 167.9, 161.0, 159.8, 153.7, 141.7, 136.5, 136.0, 132.0, 130.3, 129.6, 128.6, 127.8, 127.5, 126.9, 124.9, 117.6, 115.0, 113.9, 108.7, 79.8, 68.0, 65.8, 63.0, 55.4, 55.3, 44.5, 28.2, 21.2, 15.7. HRMS (ESI-TOF): calcd for $C_{40}H_{42}N_2O_8SNa$ $[M + Na]^+$, 733.2554; found, 733.2558. HPLC (Chiralcel OD-H, *i*-propanol/*n*-hexane = 5:95, flow rate = 0.5 mL/min, λ = 254 nm): $t_{minor}$ = 51.6 min, $t_{major}$ = 95.0 min.

*(R)-4-Methoxybenzyl 2-((R)-1-Benzyl-5-bromo-3-((tert-butoxycarbonyl)amino)-2-oxoindolin-3-yl)-3-((4-methoxyphenyl)-thio)-2-methyl-3-oxopropanoate (**3e**).* White solid (74.0 mg, 93% yield). Mp 171−172 °C. $[\alpha]_D^{20}$ −9.8 (*c* 2.0 $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.44−7.42 (m, 2H), 7.36−7.32 (m, 2H), 7.30−7.22 (m, 7H), 7.01 (s, 1H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.52 (d, *J* = 8.0 Hz, 1H), 5.11 (m, 2H), 4.97−4.83 (m, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 1.63 (s, 3H), 1.30 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 197.0, 173.2, 167.8, 161.1, 159.9, 153.7, 143.2, 136.6, 135.4, 132.1, 130.5, 130.3, 129.8, 128.7, 127.8, 127.7, 127.4, 126.6, 117.2, 115.3, 115.1, 114.0, 110.4, 80.2, 68.2, 65.2, 63.1, 55.4, 55.3, 44.6, 28.2, 15.9. HRMS (ESI-TOF): calcd for $C_{39}H_{39}BrN_2O_8S$ $[M + Na]^+$, 797.1502; found, 797.1505. HPLC (Chiralpak AD-H, *i*-propanol/*n*-hexane = 15:85, flow rate = 0.4 mL/min, λ = 254 nm): $t_{minor}$ = 34.0 min, $t_{major}$ = 35.6 min.

*(R)-4-Methoxybenzyl 2-((R)-1-Benzyl-3-((tert-butoxycarbonyl)-amino)-5-fluoro-2-oxoindolin-3-yl)-3-((4-methoxyphenyl)thio)-2-methyl-3-oxopropanoate (**3f**).* White solid (66.2 mg, 90% yield). Mp 164−165 °C. $[\alpha]_D^{20}$ +21.0 (*c* 1.0 $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.45−7.41 (m, 2H), 7.36−7.32 (m, 2H), 7.30−7.25 (m, 5H), 7.05 (s, 1H), 6.96 (d, *J* = 7.6 Hz, 2H), 6.93−6.83 (m, 4H), 6.58−6.55 (m, 1H), 5.13 (m, 2H), 4.99−4.87 (m, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 1.59 (s, 3H), 1.30 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 196.7, 173.6, 167.8, 161.0, 159.9, 153.7, 140.1, 136.5, 135.6, 130.4, 128.7, 127.8, 127.6, 126.7, 117.3, 115.6, 115.4, 115.0, 114.0, 112.8, 112.5, 109.4, 109.3, 80.1, 68.2, 65.7, 63.0, 55.4, 55.3, 44.7, 28.2, 15.8. HRMS (ESI-TOF): calcd for $C_{39}H_{39}FN_2O_8S$ $[M + Na]^+$, 737.2303; found, 737.2300. HPLC (Chiralpak AD-H, *i*-propanol/*n*-hexane = 8:92, flow rate = 0.8 mL/min, λ = 254 nm): $t_{minor}$ = 41.0 min, $t_{major}$ = 44.2 min.

*(R)-4-Methoxybenzyl 2-((R)-1-Benzyl-3-((tert-Butoxycarbonyl)-amino)-6-chloro-2-oxoindolin-3-yl)-3-((4-methoxyphenyl)thio)-2-methyl-3-oxopropanoate (**3g**).* White solid (67.0 mg, 90% yield). Mp 162−163.5 °C. $[\alpha]_D^{20}$ +19.0 (*c* 2.0 $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.45−7.43 (m, 2H), 7.37−7.28 (m, 3H), 7.25−7.21 (m, 4H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.90−6.85 (m, 3H), 6.64 (s, 1H), 5.14−5.07 (m, 2H), 4.97−4.84 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 1.61 (s, 3H), 1.29 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 196.8, 173.8, 167.9, 161.0, 159.9, 153.8, 145.4, 136.5, 135.3, 135.0, 130.3, 128.8, 127.8, 126.7, 126.1, 125.2, 122.4, 117.3, 115.0, 113.9, 109.5, 80.2, 68.1, 65.0, 63.2, 55.4, 55.3, 44.7, 28.2, 15.9. HRMS (ESI-TOF): calcd for $C_{39}H_{39}ClN_2O_8S$ $[M + Na]^+$, 753.2007; found, 753.2009. HPLC (Chiralpak AD-H, *i*-propanol/*n*-hexane = 20:80, flow rate = 0.1 mL/min, λ = 254 nm): $t_{minor}$ = 71.8 min, $t_{major}$ = 83.9 min.

*(R)-4-Methoxybenzyl 2-((R)-1-Benzyl-6-bromo-3-((tert-butoxycarbonyl)amino)-2-oxoindolin-3-yl)-3-((4-methoxyphenyl)-thio)-2-methyl-3-oxopropanoate (**3h**).* Light yellow solid (76.5 mg, 96% yield). Mp 148−150 °C. $[\alpha]_D^{20}$ −2.5 (*c* 1.0 $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 7.2 Hz, 2H), 7.27−7.24 (m, 2H), 7.21−7.18 (m, 1H), 7.15−7.11 (m, 4H), 6.94−6.92 (m, 2H), 6.85 (d, *J* = 8.4 Hz, 3H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.70 (s, 1H), 5.04−4.96 (m, 2H), 4.87−4.83 (m, 1H), 4.73−4.69 (m, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 1.53 (s, 3H), 1.19 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 196.7, 173.7, 167.9, 161.1, 159.9, 153.8, 145.5, 136.5, 135.3, 130.3, 128.8, 127.8, 126.7, 125.6, 125.4, 123.0, 117.3, 115.1, 113.9, 112.3, 80.2, 68.2, 65.1, 63.1, 55.4, 55.3, 44.7, 28.2, 15.9. HRMS (ESI-TOF): calcd for $C_{39}H_{39}N_2O_8SBrNa$ $[M + Na]^+$, 797.1502; found, 797.1502. HPLC (Chiralcel OD-H, *i*-propanol/*n*-hexane = 5:95, flow rate = 0.5 mL/min, λ = 254 nm): $t_{major}$ = 40.7 min, $t_{minor}$ = 62.4 min.

*(R)-4-Methoxybenzyl 2-((R)-1-Benzyl-3-((tert-butoxycarbonyl)-amino)-7-chloro-2-oxoindolin-3-yl)-3-((4-methoxyphenyl)thio)-2-methyl-3-oxopropanoate (**3i**).* Light yellow solid (70.0 mg, 93% yield). Mp 168−169.5 °C. $[\alpha]_D^{20}$ −9.3 (*c* 1.0 $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.2 Hz, 2H), 7.23−7.12 (m, 7H), 7.08−7.05 (m, 2H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.74 (t, *J* = 8 Hz, 1H), 5.34−5.30 (m, 1H), 5.18−5.14 (m, 1H), 5.09−5.03 (m, 2H), 3.75 (s, 3H), 3.73 (s, 3H), 1.47 (s, 3H), 1.20 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 196.2, 174.6, 167.8, 161.0, 159.9, 153.7, 140.3, 137.6, 136.5, 132.0, 130.7, 130.4, 128.3, 127.3, 127.0, 126.8, 123.3, 122.6, 117.4, 115.2, 115.0, 114.0, 80.2, 68.2, 65.0, 63.0, 55.4, 55.3, 45.7, 28.2, 15.7. HRMS (ESI-TOF): calcd for $C_{39}H_{39}N_2O_8SClNa$ $[M + Na]^+$, 753.2007; found, 753.2003. HPLC (Chiralcel OD-H, *i*-propanol/*n*-hexane = 5:95, flow rate = 0.4 mL/min, λ = 254 nm): $t_{major}$ = 47.9 min.

*(R)-4-Methoxybenzyl 2-((R)-1-Benzyl-3-((tert-butoxycarbonyl)-amino)-7-fluoro-2-oxoindolin-3-yl)-3-((4-methoxyphenyl)thio)-2-methyl-3-oxopropanoate (**3j**).* Light yellow solid (66.3 mg, 90% yield). Mp 144−146 °C. $[\alpha]_D^{20}$ −3.9 (*c* 1.0 $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 7.2 Hz, 2H), 7.32−7.29 (m, 2H), 7.26−7.21 (m, 5H), 7.08 (s, 1H), 6.95−6.91 (m, 3H), 6.87−6.79 (m, 4H), 5.08−4.99 (m, 4H), 3.83 (s, 3H), 3.81 (s, 3H), 1.48 (s, 3H), 1.25 (s, 9 H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 196.4, 173.5, 167.8, 161.0, 159.9, 153.7, 148.4, 146.0, 137.0, 136.5, 130.7, 130.3, 128.4, 128.2, 127.5, 126.7, 123.1, 123.0, 120.0, 117.8, 117.6, 117.4, 115.0, 113.9, 80.1, 68.1, 65.5, 63.0, 55.4, 55.3, 46.1, 28.1, 15.6. HRMS (ESI-TOF): calcd for $C_{39}H_{39}N_2O_8FSNa$ $[M + Na]^+$, 737.2303; found, 737.2303. HPLC (Chiralcel OD-H, *i*-propanol/*n*-hexane = 5:95, flow rate = 0.4 mL/min, λ = 254 nm): $t_{minor}$ = 33.4 min, $t_{major}$ = 38.6 min.

*(R)-4-Methoxybenzyl 2-((R)-1-Benzyl-7-bromo-3-((tert-butoxycarbonyl)amino)-2-oxoindolin-3-yl)-3-((4-methoxyphenyl)-thio)-2-methyl-3-oxopropanoate (**3k**).* White solid (72.4 mg, 91% yield). Mp 160−162 °C. $[\alpha]_D^{20}$ +31.0 (*c* 1.0 $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.2 Hz, 2H), 7.37−7.33 (m, 1H), 7.31−7.26 (m, 5H), 7.24−7.21 (m, 2H), 7.16 (s, 1H), 7.03−7.01 (m, 1H),



DOI: 10.1021/acs.joc.5b00302
J. Org. Chem. 2015, 80, 4950−4956

6.95−6.89 (m, 4H), 6.78 (t, $J$ = 8.0 Hz, 1H), 5.48−5.44 (m, 1H), 5.32−5.28 (m, 1H), 5.17 (m, 2H), 3.85 (s, 3H), 3.84(s, 3H), 1.59 (s, 3H), 1.30 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 196.2, 174.8, 167.8, 161.0, 159.9, 153.7, 141.7, 137.5, 136.5, 135.4, 131.0, 130.4, 128.3, 127.1, 126.9, 126.8, 123.7, 123.2, 117.3, 115.0, 114.0, 102.3, 80.2, 68.2, 64.9, 63.0, 55.4, 55.3, 45.4, 28.2, 15.7. HRMS (ESI-TOF): calcd for $C_{39}H_{39}BrN_2O_8S$ [M + Na]$^+$, 797.1502; found, 797.1499. HPLC (Chiralpak AD-H, $i$-propanol/$n$-hexane = 20:80, flow rate = 0.2 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 39.6 min, $t_{major}$ = 58.5 min.

*(R)-4-Methoxybenzyl 2-((R)-1-Benzyl-3-((tert-butoxycarbonyl)-amino)-2-oxo-7-(trifluoromethyl)indolin-3-yl)-3-((4-methoxyphenyl)thio)-2-methyl-3-oxopropanoate (**3l**).* White solid (71.5 mg, 91% yield). Mp 155−157 °C. $[\alpha]_D^{20}$ +19.0 ($c$ 1.0 $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.57 (d, $J$ = 8.0 Hz, 1H), 7.40−7.38 (m, 2H), 7.33−7.27 (m, 5H), 7.23−7.21 (m, 1H), 7.16 (m, 3H), 7.03 (t, $J$ = 8.0 Hz, 1H), 6.92 (t, $J$ = 8.0 Hz, 4H), 5.26−5.16 (m, 3H), 5.10−5.06 (m, 1H), 3.84 (s, 6H), 1.65 (s, 3H), 1.31 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 196.1, 175.6, 167.9, 161.1, 159.9, 153.8, 142.6, 136.4, 130.6, 130.4, 128.1, 127.7, 127.6, 127.5, 126.7, 126.6, 126.4, 124.7, 121.9, 117.1, 115.0, 114.0, 112.6, 80.4, 68.3, 63.7, 63.1, 55.4, 55.3, 47.1, 28.1, 15.8. HRMS (ESI-TOF): calcd for $C_{40}H_{39}F_3N_2O_8S$ [M + Na]$^+$, 787.2271; found, 787.2274. HPLC (Chiralpak AD-H, $i$-propanol/$n$-hexane = 20:80, flow rate = 0.2 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 36.2 min, $t_{major}$ = 50.0 min.

*(R)-4-Methoxybenzyl 2-((R)-3-((Ethoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)-3-((4-methoxyphenyl)thio)-2-methyl-3-oxopropanoate (**3m**).* White solid (55.5 mg, 91% yield). Mp 142−144 °C. $[\alpha]_D^{20}$ +7.8 ($c$ $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.29−7.23 (m, 6H), 7.06 (d, $J$ = 7.2 Hz, 1H), 6.95−6.87 (m, 5H), 6.77 (d, $J$ = 8.0 Hz, 1H), 5.22−5.14 (m, 2H), 3.88 (q, $J$ = 6.4 Hz, 2H), 3.82 (s, 6H), 3.21 (s, 3H), 1.54 (s, 3H), 1.10 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 196.2, 173.4, 168.0, 161.0, 159.9, 154.6, 145.0, 136.5, 130.4, 129.7, 127.1, 126.8, 124.2, 122.8, 117.5, 115.0, 114.0, 108.1, 68.1, 65.8, 62.7, 61.0, 55.4, 55.3, 26.6, 15.5, 14.3. HRMS (ESI-TOF): calcd for $C_{31}H_{32}N_2O_8S$ [M + Na]$^+$, 615.1771; found, 615.1771. HPLC (Chiralpak AD-H, $i$-propanol/$n$-hexane = 15:85, flow rate = 0.5 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 22.7 min, $t_{major}$ = 39.7 min.

*(R)-4-Methoxybenzyl 2-((R)-3-(((Benzyloxy)carbonyl)amino)-1-methyl-2-oxoindolin-3-yl)-3-((4-methoxyphenyl)thio)-2-methyl-3-oxopropanoate (**3n**).* White solid (60.8 mg, 90% yield). Mp 150−152 °C. $[\alpha]_D^{20}$ +12.0 ($c$ $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.43 (s, 1H), 7.33−7.22 (m, 10H), 7.08 (d, $J$ = 7.2 Hz, 1H), 6.98−6.93 (m, 3H), 6.87 (d, $J$ = 8.8 Hz, 2H), 6.77 (br, 1H), 5.20 (q, $J$ = 12.0 Hz, 2H), 4.92 (q, $J$ = 12.4 Hz, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.21 (br, 3H), 1.56 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 196.1, 173.3, 168.0, 161.0, 159.9, 154.3, 144.9, 136.5, 130.4, 129.8, 128.3, 128.0, 127.9, 126.7, 124.2, 122.8, 117.5, 115.0, 114.0, 108.1, 68.2, 66.9, 65.9, 62.7, 55.4, 55.3, 26.5, 15.5. HRMS (ESI-TOF): calcd for $C_{36}H_{34}N_2O_8S$ [M + Na]$^+$, 677.1928; found, 677.1933. HPLC (Chiralcel OD-H, $i$-propanol/$n$-hexane = 20:80, flow rate = 0.6 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 36.2 min, $t_{major}$ = 46.5 min.

*(R)-4-Methoxybenzyl 2-((R)-1-Benzyl-3-((tert-butoxycarbonyl)-amino)-2-oxoindolin-3-yl)-3-((4-chlorophenyl)thio)-2-methyl-3-oxopropanoate (**3o**).* Yellow solid (65.0 mg, 90% yield). Mp 157−159 °C. $[\alpha]_D^{20}$ +42.0 ($c$ 2.0 $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.46 (d, $J$ = 7.2 Hz, 2H), 7.39−7.28 (m, 6H), 7.27−7.17 (m, 4H), 7.12 (d, $J$ = 7.6 Hz, 1H), 7.06 (s, 1H), 6.94−6.89 (m, 3H), 6.70 (d, $J$ = 8.0 Hz, 1H), 5.18 (m, 2H), 5.03−4.84 (m, 2H), 3.84 (s, 3H), 1.56 (s, 3H), 1.28 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 194.7, 173.8, 168.0, 159.9, 153.7, 144.2, 136.2, 135.8, 130.3, 129.5, 129.4, 128.7, 127.8, 127.6, 127.3, 126.8, 125.5, 124.2, 122.7, 114.0, 109.0, 80.0, 68.2, 65.7, 63.3, 55.3, 44.6, 28.2, 15.7. HRMS (ESI-TOF): calcd for $C_{38}H_{37}ClN_2O_7S$ [M + Na]$^+$, 723.1902; found, 723.1903. HPLC (Chiralcel OD-H, $i$-propanol/$n$-hexane = 8:92, flow rate = 0.5 mL/min, $\lambda$ = 254 nm): $t_{minor}$ =30.8 min, $t_{major}$ = 27.1 min.

*(R)-4-Methoxybenzyl 2-((R)-1-Benzyl-6-bromo-3-((tert-butoxycarbonyl)amino)-2-oxoindolin-3-yl)-2-(((4-methoxyphenyl)-thio)carbonyl)butanoate (**3p**).* Light yellow solid (68.9 mg, 85% yield). Mp 165−167 °C. $[\alpha]_D^{20}$ −12.3 ($c$ 1.0 $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.32 (d, $J$ = 7.2 Hz, 2H), 7.26−7.22 (m, 3H), 7.20−7.19 (m, 1H), 7.01−7.00 (m, 6H), 6.85 (d, $J$ = 8.8 Hz, 2H), 6.78−6.76 (m, 3H), 6.60 (s, 1H), 4.91−4.88 (m, 1H), 4.76−4.73 (m, 1H), 4.65 (m, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 2.65−2.56 (m, 1H), 2.46−2.37 (m, 1H), 1.18 (s, 9H), 0.94 (t, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 197.2, 172.5, 166.7, 160.1, 158.8, 152.8, 144.3, 135.3, 134.4, 129.8, 129.4, 127.7, 126.8, 126.6, 125.3, 124.5, 124.1, 122.0, 116.6, 114, 0, 112.8, 111.3, 79.3, 67.9, 66.9, 63.4, 54.4, 54.2, 43.7, 27.1, 22.5, 9.3. HRMS (ESI-TOF): calcd for $C_{40}H_{41}N_2O_8SBrNa$ [M + Na]$^+$, 811.1659; found, 811.1661. HPLC (Chiralpak AD-H, $i$-propanol/$n$-hexane = 10:90, flow rate = 0.5 mL/min, $\lambda$ = 254 nm): $t_{major}$ = 35.7 min, $t_{minor}$ = 45.2 min.

*(R)-4-Methoxybenzyl 2-((R)-1-Benzyl-3-((tert-butoxycarbonyl)-amino)-2-oxoindolin-3-yl)-2-(((4-methoxyphenyl)thio)carbonyl)-pent-4-enoate (**3q**).* Light yellow solid (59.6 mg, 80% yield). Mp 152−154 °C. $[\alpha]_D^{20}$ −64 ($c$ 1.0 $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.34 (m, 2H), 7.22−7.18 (m, 6H), 7.06−7.00 (m, 4H), 6.91−6.83 (m, 4H), 6.75−6.74 (m, 2H), 6.52−6.51 (m, 1H), 5.65−5.63 (m, 1H), 5.02 (m, 1), 4.96−4.93 (m, 1H), 4.85−4.82 (m, 1H), 4.73−4.70 (m, 2H), 3.75 (d, $J$ = 4 Hz, 3H), 3.73 (d, $J$ = 4.4 Hz, 3H), 3.29 (m, 1H), 3.12 (m, 1H), 1.16 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 197.9, 173.4, 167.4, 161.0, 159.7, 153.9, 143.9, 136.3, 136.0, 132.4, 130.8, 130.4, 129.3, 128.6, 128.0, 127.7, 127.5, 126.5, 124.5, 122.4, 119.6, 117.9, 115.0, 113.7, 108.9, 80.1, 68.3, 67.7, 64.6, 55.3, 55.2, 44.6, 35.0, 28.1. HRMS (ESI-TOF): calcd for $C_{41}H_{42}N_2O_8SNa$ [M + Na]$^+$, 745.2554; found, 745.2558. HPLC (Chiralpak AD-H, $i$-propanol/$n$-hexane = 15:85, flow rate = 0.6 mL/min, $\lambda$ = 254 nm): $t_{minor}$ = 35.0 min, $t_{major}$ = 50.1 min.

## ■ ASSOCIATED CONTENT

### Supporting Information

$^1$H and $^{13}$C NMR spectra of compounds **3a−q** and CIF file of **3h**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00302.

## ■ AUTHOR INFORMATION


### Corresponding Authors

*E-mail: pengfangzhi@ynu.edu.cn

*E-mail: zhihui_shao@hotmail.com. Fax: (+86)871-65035538. Phone: (+86)871-65031119

### Author Contributions

§T.L. and W.L. contributed equally.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We acknowledge financial support from the NSFC (21162034, 21372193, 21362040), the Program for Changjiang Scholars and Innovative Research Team in University (IRT13095), the Doctoral Fund of the Ministry of Education of China (20135301110002), the Government of the Yunnan Province (2012FB114, 2013FA026), and the Program for Excellent Young Talents, Yunnan University.

## ■ REFERENCES

(1) For reviews, see: (a) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11943. (b) Christoffers, J.; Baro, A. *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2005. (c) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (d) Marek, I.; Minko, Y.; Pasco, M.; Mejuch, T.; Gilboa, N.; Chechik, H.; Das, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 2682.

(2) For selected examples, see: (a) Mitsunuma, H.; Shibasaki, M.; Kanai, M.; Matsunaga, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 5217. (b) Shimizu, Y.; Shi, S.-L.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1103. (c) Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702. (d) Lemieux, R. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1998**, *120*, 5453.



DOI: 10.1021/acs.joc.5b00302
*J. Org. Chem.* 2015, 80, 4950−4956

(3) (a) Trost, B. M.; Cramer, N.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12396. (b) Payette, J. N.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 9536. (c) DeAngelis, A.; Dmitrenko, O.; Yap, G. P. A.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 7230. (d) Gao, L.; Hwang, G.-S.; Ryu, D. H. *J. Am. Chem. Soc.* **2011**, *133*, 20708. (e) Cao, Z.-Y.; Wang, X.-M.; Tan, C.; Zhao, X.-L.; Zhou, J.; Ding, K.-L. *J. Am. Chem. Soc.* **2013**, *135*, 8197. (f) Liu, Y.; Wang, X.; Zhao, Y.; Zhu, F.; Zeng, X.; Chen, L.; Wang, C.; Zhao, L.; Zhou, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 13735. (g) Ohmatsu, K.; Imagawa, N.; Ooi, T. *Nat. Chem.* **2014**, *6*, 47. (h) Jolit, A.; Walleser, P. M.; Yap, G. P. A.; Tius, M. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 6180. (i) Zhang, H.; Gao, Z.; Ye, S. *Org. Lett.* **2014**, *16*, 3079. (j) Khan, A.; Yang, L.; Xu, J.; Jin, L.; Zhang, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 11257.

(4) (a) Du, C.; Li, L.; Li, Y.; Xie, Z. X. *Angew. Chem., Int. Ed.* **2009**, *48*, 7853. (b) Trost, B. M.; Malhotra, S.; Chan, W. H. *J. Am. Chem. Soc.* **2011**, *133*, 7328. (c) Huang, X.; Peng, J.; Dong, L.; Chen, Y. *Chem. Commun.* **2012**, *48*, 2439. (d) Trost, B. M.; Osipov, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 9176. (e) Zhang, H.; Hong, L.; Kang, H.; Wang, R. *J. Am. Chem. Soc.* **2013**, *135*, 14098. (f) Ohmatsu, K.; Ando, Y.; Ooi, T. *J. Am. Chem. Soc.* **2013**, *135*, 18706.

(5) (a) Ogawa, S.; Shibata, N.; Inagaki, J.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8666. (b) Yoshino, T.; Morimoto, H.; Lu, G.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 17082. (c) Lu, G.; Yoshino, T.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4382. (d) Chen, W.-B.; Wu, Z.-J.; Hu, J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2011**, *13*, 2472. (e) Yan, W.; Wang, D.; Feng, J.; Li, P.; Zhao, D.; Wang, R. *Org. Lett.* **2012**, *14*, 2512. (f) Tang, Z.; Shi, Y.; Mao, H.; Zhu, X.; Li, W.; Cheng, Y.; Zheng, W.; Zhu, C. *Org. Biomol. Chem.* **2014**, *12*, 6085.

(6) Trost, B. M. *Science* **1991**, *254*, 1471.

(7) (a) Clerici, P.; Wennemers, H. *Org. Biomol. Chem.* **2012**, *10*, 110. (b) Arakawa, Y.; Fritz, S. P.; Wennemers, H. *J. Org. Chem.* **2014**, *79*, 3937. (c) Kolarovic, A.; Käslin, A.; Wennemers, H. *Org. Lett.* **2014**, *16*, 4236. (d) Engl, O. D.; Fritz, S. P.; Käslin, A.; Wennemers, H. *Org. Lett.* **2014**, *16*, 5454.

(8) Bahlinger, A.; Fritz, S. P.; Wennemers, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 8779.

(9) For reviews of catalytic asymmetric Mannich reactions, see: (a) Vesely, J.; Rios, R. *Chem. Soc. Rev.* **2014**, *43*, 611. (b) Karimi, B.; Enders, D.; Jafari, E. *Synthesis* **2013**, *45*, 2769. (c) Verkade, J. M. M.; Hemert, L. J. C. v.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29. (d) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797. (e) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102. (f) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

(10) For selected examples, see: (a) Ochi, M.; Kawasaki, K.; Kataoka, H.; Uchio, Y. *Biochem. Biophys. Res. Commun.* **2001**, *283*, 1118. (b) Bernard, K.; Bogliolo, S.; Ehrenfeld, J. *Br. J. Pharmacol.* **2005**, *144*, 1037. (c) Kumar, R. R.; Perumal, S.; Senthilkumar, P.; Yogeeswari, P.; Sriram, D. *J. Med. Chem.* **2008**, *51*, 5731. (d) Rottmann, M.; McNamara, C.; Yeung, B. S. K.; Lee, M. C. S.; Zou, B.; Russell, B.; Seitz, P.; Plouffe, D. M.; Dharia, N. V.; Tan, J.; Cohen, S. B.; Spencer, K. R.; Gonzalez-Paez, G.; Lakshiminarayana, L.; Goh, A.; Suwanarusk, R.; Jegla, T.; Schmitt, E. K.; Beck, H.-P.; Brun, R.; Nosten, F.; Renia, L.; Dartois, V.; Keller, T. H.; Fidock, D. A.; Winzeler, E. A.; Diagana, T. T. *Science* **2010**, *329*, 1175. (e) Crosignani, S.; Jorand-Lebrun, C.; Page, P.; Campbell, G.; Colovray, V.; Missotten, M.; Humbert, Y.; Cleva, C.; Arrighi, J.-F.; Gaudet, M.; Johnson, Z.; Ferro, P.; Chollet, A. *ACS Med. Chem. Lett.* **2011**, *2*, 644.

(11) For reviews on the catalytic asymmetric synthesis of 3-aminooxindoles, see: (a) Chauhan, P.; Chimni, S. S. *Tetrahedron: Asymmetry* **2013**, *24*, 343. (b) Shen, K.; Liu, X.; Lin, L.; Feng, X. *Chem. Sci.* **2012**, *3*, 327. (c) Zhou, F.; Liu, Y.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381.

(12) (a) Liu, Y.-L.; Zhou, F.; Cao, J.-J.; Ji, C.-B.; Ding, M.; Zhou, J. *Org. Biomol. Chem.* **2010**, *8*, 3847. (b) Feng, J.; Yan, W.; Wang, D.; Li, P.; Sun, Q.; Wang, R. *Chem. Commun.* **2012**, *48*, 8003. (c) Hara, N.; Nakamura, S.; Sano, M.; Tamura, R.; Funahashi, Y.; Shibata, N. *Chem.—Eur. J.* **2012**, *18*, 9276. (d) Wang, D.; Liang, J.; Feng, J.; Wang, K.; Sun, Q.; Zhao, L.; Li, D.; Yan, W.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 548. (e) Liu, Y.-L.; Zhou, J. *Chem. Commun.* **2013**, *49*, 4421. (f) Nakamura, S.; Hyodo, K.; Nakamura, M.; Nakane, D.; Masuda, H. *Chem.—Eur. J.* **2013**, *19*, 7304. (g) Takizawa, S.; Rémond, E.; Arteaga, F. A.; Yoshida, Y.; Sridharan, V.; Bayardon, J.; Juge, S.; Sasai, H. *Chem. Commun.* **2013**, *49*, 8392. (h) Chen, X.; Chen, H.; Ji, X.; Jiang, H.; Yao, J.; Liu, H. *Org. Lett.* **2013**, *15*, 1846. (i) Hu, F.-L.; Wei, Y.; Shi, M.; Pindi, S.; Li, G. *Org. Biomol. Chem.* **2013**, *11*, 1921. (j) Hirata, S.; Tanaka, K.; Matsui, K.; Arteaga, F. A.; Yoshida, Y.; Takizawa, S.; Sasai, H. *Tetrahedron: Asymmetry* **2013**, *24*, 1189. (k) Li, T.-Z.; Wang, X.-B.; Sha, F.; Wu, X.-Y. *Tetrahedron* **2013**, *69*, 7314. (l) Arai, T.; Matsumura, E.; Masu, H. *Org. Lett.* **2014**, *16*, 2768. (m) Xu, J.; Mou, C.; Zhu, T.; Song, B.; Chi, Y. R. *Org. Lett.* **2014**, *16*, 3272. (n) Chen, D.; Xu, M.-H. *J. Org. Chem.* **2014**, *79*, 7746. (o) George, J.; Sridhar, B.; Reddy, B. V. S. *Org. Biomol. Chem.* **2014**, *12*, 1595. (p) Wang, X.-B.; Li, T.-Z.; Sha, F.; Wu, X.-Y. *Eur. J. Org. Chem.* **2014**, 739. (q) Zhao, X.; Li, T.-Z.; Qian, J.-Y.; Sha, F.; Wu, X.-Y. *Org. Biomol. Chem.* **2014**, *12*, 8072. (r) Li, T.; Jiang, Y.; Guan, Y.; Sha, F.; Wu, X. *Chem. Commun.* **2014**, *50*, 10790. (s) Yin, X.; Zeng, X.; Liu, Y.; Liao, F.; Yu, J.; Zhou, F.; Zhou, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 13740.

(13) (a) Lv, H.; Tiwari, B.; Mo, J.; Xing, C.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 5412. (b) Guo, Q.-X.; Liu, Y.-W.; Li, X.-C.; Zhong, L.-Z.; Peng, Y.-G. *J. Org. Chem.* **2012**, *77*, 3589. (c) Zhang, B.; Feng, P.; Sun, L.-H.; Cui, Y.; Ye, S.; Jiao, N. *Chem.—Eur. J.* **2012**, *18*, 9198. (d) Liu, Z.; Feng, X.; Du, H. *Org. Lett.* **2012**, *14*, 3154. (e) Li, T.-Z.; Wang, X.-B.; Sha, F.; Wu, X.-Y. *J. Org. Chem.* **2014**, *79*, 4332. (f) Holmquist, M.; Blay, G.; Pedro, J. R. *Chem. Commun.* **2014**, *50*, 9309. (g) Arai, T.; Matsumura, E.; Masu, H. *Org. Lett.* **2014**, *16*, 2768. (h) Wang, Y.; Zao, Z.; Niu, Y.; Zhao, X.; Zhou, J. *Acta Chim. Sinica. (Chin. Ed.)* **2014**, *72*, 867. (i) Guo, Y.; Zhang, Y.; Qi, L.; Fang Tian, F.; Wang, L. *RSC Adv.* **2014**, *4*, 27286.

(14) Zhao, J.; Fang, B.; Luo, W.; Hao, X.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 241.

(15) For selected reviews on bifunctional tertiary amine−thiourea catalysis, see: (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (b) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (d) Connon, S. J. *Chem. Commun.* **2008**, 2499. (e) Yu, X.; Wang, W. *Chem.—Asian J.* **2008**, *3*, 516. (f) Siau, W.-Y.; Wang, J. *Catal. Sci. Technol.* **2011**, *1*, 1298. For seminal reports, see: (g) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (h) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.- S.; Wu, Y. *Synlett* **2005**, 603. (i) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (j) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481. (k) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (l) Wang, C.-J.; Zhang, Z.-H.; Dong, X.-Q.; Wu, X.-J. *Chem. Commun.* **2008**, 1431.

(16) The Mannich reaction with PMP as the imine protecting group did not occur.

(17) CCDC 1047708 (**3e**) 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.

(18) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217.



DOI: 10.1021/acs.joc.5b00302
*J. Org. Chem.* 2015, 80, 4950−4956