JOC The Journal of Organic Chemistry

Article

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Synthesis of 3-Indolylglycine Derivatives via Dinuclear Zinc Catalytic Asymmetric Friedel–Crafts Alkylation Reaction

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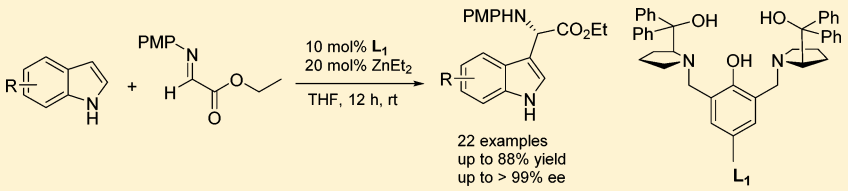
Supporting Information



ABSTRACT: A direct asymmetric Friedel–Crafts (F–C) alkylation reaction between a wide range of indoles and ethyl 2-(4-methoxyphenylimino)acetate catalyzed by Trost's dinuclear complex is reported. A series of 3-indolylglycine derivatives were synthesized in enantioselectivity of up to >99% enantiomeric excess (ee) using 10 mol% catalyst loading under mild conditions. This atom economic reaction could be run on a gram scale without impacting its enantioselectivity. The absolute stereochemistry of catalytic products was determined by correlation with a known configuration compound. A possible mechanism was proposed for the asymmetric induction.

INTRODUCTION

Optically active nonproteinogenic amino acids have captivated chemists for their biological activities and chemical transformations.[1] 3-Indolylglycine derivatives can be used as important synthetic intermediates and building blocks in natural and man-made products.[2] Several strategies have been reported for their stereoselective synthesis, including asymmetric catalysis,[3] chiral auxiliaries employed,[4] enzymatic resolution,[5] and dynamic kinetic resolution.[6] Among these methods, asymmetric catalysis is the most significant and effective approach to prepare these compounds, since limited quantity chirality controlling element is used. Wanner et al. developed chiral phosphoric acids **1** and **2** catalytic process for the synthesis of 2-nitrophenylsulfenyl-protected (*S*)-indolylglycine and triphenylmethylsulfenyl-protected (*R*)-indolylglycine (Figure 1).[3a] The enantioselective Friedel–Crafts reaction of indoles with ethyl glyoxylate imines utilizing chiral phosphoric acid **3** was described by Kang and co-workers.[3b] A water inclusion complex of *O*,*O*′-diacyl tartaric acid **4** was employed by Ube et al. to demonstrate the enantioselective Friedel–Crafts reaction of indoles with an *α*-imino ester.[3c] Although considerable efforts have been made for those Brønsted acids-catalyzed reactions, enantiometric excesses of catalytic products were relatively low (up to 88% ee).

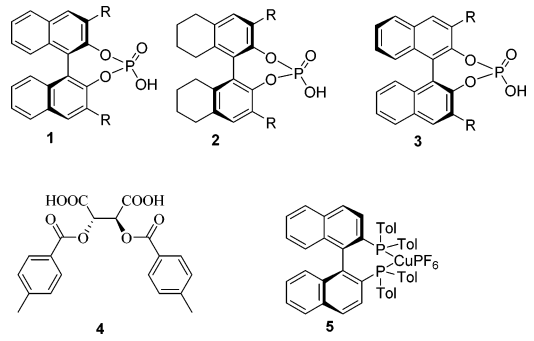


Figure 1. Catalyst structures for enantioselective synthesis of 3-indolylglycine derivatives.

Highly enantioselective synthesis of 3-indolylglycine derivatives (up to 97% ee) catalyzed by copper(I)–Tol-BINAP catalyst **5** was reported by Johannsen,[3d] which was the only one example of metal-catalyzed reaction for enantioselective synthesis of 3-indolylglycine derivatives. In his experience, limited substrates such as only 5-substituted indoles were tested. In addition, the research results showed the substituted groups of indoles had remarkable influence on reaction activity and enantioselectivity. Therefore, it is important to develop a method for metal-catalyzed highly enantioselective synthesis of various indolylglycine derivatives.

In recent years, we have explored the application of chiral small-ring heterocycle ligands containing a *β*-amino alcohol moiety in asymmetric reactions, and found the size of heterocycles play a key role in the catalytic asymmetric additions of diethylzinc to aromatic aldehydes.[7] In view of this finding, we reported Azephenol dinuclear zinc catalyst **6a**[8a] for highly enantioselective alternating copolymerization of carbon dioxide and cyclohexene oxide, based on the procedure of Trost's ProPhenol zinc catalyst **7** that has been successfully applied to the catalysis of a variety of asymmetric reactions[9] and

Received: July 27, 2016
Published: September 14, 2016

DOI: 10.1021/acs.joc.6b01805
J. Org. Chem. 2016, 81, 9227–9234

the synthesis of natural products[10] (Figure 2). Trost's ProPhenol dinuclear catalyst 7 and our Azephenol catalyst 6

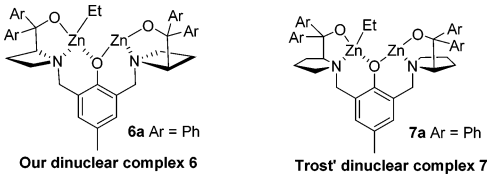


Figure 2. Dinuclear zinc catalysts.

have similar structure and function, but sometimes their catalytic performances are very different on the same reactions such as asymmetric copolymerization reaction of CO_2 and cyclohexene oxide,[8a,9d] domino Michael/hemiketalization reaction of α-hydroxyacetophenone with β,γ-unsaturated α-keto esters.[8d]

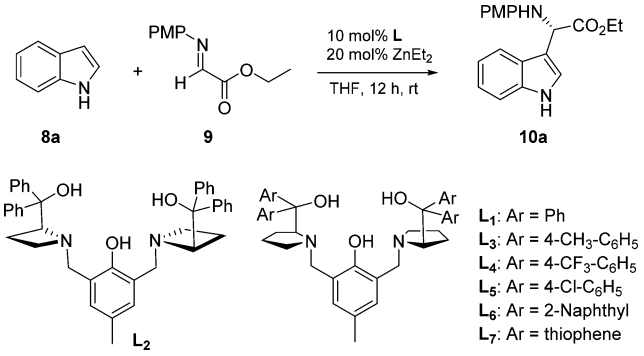
These dinuclear zinc catalysts have also shown excellent performance on asymmetric Friedel–Crafts alkylation reactions, such as pyrroles with nitroalkenes catalyzed by **7a**[9e] and pyrroles with chalcones catalyzed by **6a**.[8b] Especially in 2013, Wang et al. reported the Friedel–Crafts amidoalkylation of indoles with aryl aldimines catalyzed by **7a**, affording 3-indolyl methanamine derivatives.[11] However, only aryl aldimines were tested in their work. Herein, we report the dinuclear zinc catalyst system for asymmetric Friedel–Crafts alkylation reaction between indoles and ethyl glyoxylate imine. What's more, the products are 3-indolyl α-amino esters. In the presence of 10 mol% catalyst, a series of 3-indolylglycine derivatives were synthesized in moderate to good yields and excellent ee (up to >99%) under mild conditions.

RESULTS AND DISCUSSION

Our investigation was initiated by testing the Friedel–Crafts reaction of indole **8a** and ethyl glyoxylate imine **9** using our dinuclear zinc complex **6a**, which was easily formed from $\mathbf{L_2}$ and 2 equiv of diethylzinc in THF. In the presence of 10 mol% catalyst **6a**, the reaction of indole **8a** and ethyl glyoxylate amine **9** at room temperature (25 °C) for 12 h gave the desired product **10a** in 71% yield but only 26% ee (Table 1, entry 1). To our surprise, when Trost's ProPhenol dinuclear zinc catalyst **7a** was examined under the same condition, the enantiomeric excess of the product was up to 97% (Table 1, entry 2). Then ProPhenol ligands with various substitutions on the diaryl carbinol moiety were surveyed, and the results were summarized in Table 1 (entries 2–7). As shown in Table 1, the desired product could be obtained in moderate yield (68–78%) with varying levels of enantioselectivity excesses. Among these ligands screened for the Friedel–Crafts reaction, $\mathbf{L_1}$ afforded the best result in terms of yield and enantioselectivity (71% yield and 97% ee, Table 1, entry 2). Prolonging the reaction time resulted in increased yields but decreased ee values (Table 1, entries 8 and 9 vs 2).

In further investigation, we used **7a** as catalyst for the Friedel–Crafts alkylation process, and various reaction conditions were examined (Table 2). The product **10a** was obtained in 84% yield and 92% ee when toluene was tested as solvent. CH_2Cl_2 was also effective for the reaction with 73% yield and 89% ee (Table 2, entry 3). The reaction went sluggish in CH_3CN and $CHCl_3$ affording product with decreased ee (Table 2, entries 4 and 5). We took notice that the oxygen of THF coordinating to zinc in Ding's single-crystal X-ray analysis

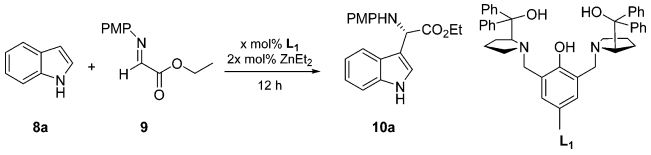
Table 1. Effect of Ligand Structure and Reaction Time on Friedel–Crafts Alkylation Reaction of Indole 8a and Imine 9



entry	time (h)	ligand	yield (%)[b]	ee (%)[c]
1	12	$\mathbf{L_2}$	71	26
2	**12**	$\mathbf{L_1}$	**71**	**97**
3	12	$\mathbf{L_3}$	69	64
4	12	$\mathbf{L_4}$	68	65
5	12	$\mathbf{L_5}$	78	68
6	12	$\mathbf{L_6}$	76	18
7	12	$\mathbf{L_7}$	73	73
8	18	$\mathbf{L_1}$	77	88
9	24	$\mathbf{L_1}$	81	81

[a]Reactions were performed with **8a** (0.60 mmol) and **9** (0.30 mmol) using 10 mol% **L** and 20 mol% $ZnEt_2$ in THF (1.5 mL) at room temperature (25 °C). [b]Isolated yields. [c]Determined by HPLC.

Table 2. Further Condition Optimization Using Complex 7a as Catalyst



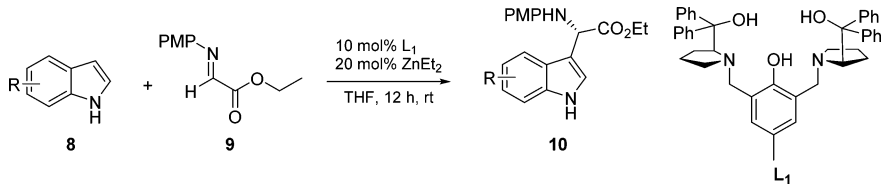
entry	solvent	temp (°C)	2a/3a	x	yield (%)[b]	ee (%)[c]
1	**THF**	**rt**	**2**	**10**	**71**	**97**
2	toluene	rt	2	10	84	92
3	CH_2Cl_2	rt	2	10	73	89
4	CH_3CN	rt	2	10	56	82
5	$CHCl_3$	rt	2	10	59	80
6	THF	0	2	10	59	88
7	THF	40	2	10	72	86
8	THF	rt	1.5	10	60	88
9	THF	rt	3	10	77	87
10[d]	THF	rt	2	10	68	82
11	THF	rt	2	5	50	83
12	THF	rt	2	15	80	89

[a]Reactions were performed with **8a** (0.60 mmol) and **9** (0.30 mmol) using 10 mol% $\mathbf{L_1}$ and 20 mol% $ZnEt_2$ unless otherwise noted. [b]Isolated yields. [c]Determined by HPLC. [d]In presence of 30 mg 4 Å MS.

for Zn-ProPhenol complex;[9d] furthermore, pyridine could be used as additive to boost enantioselectivity reported by Wang et al.[12] Those results suggested that THF acted as not only the reaction media but also weak catalytic auxiliary in this reaction. Lowering temperature to 0 °C, enantiomeric excess value decreased to 88% (Table 2, entry 6). When the temperature was raised to 40 °C, ee value dropped to 86% (Table 2, entry 7). Reducing the ratio of indole to 1.5 equiv, the product could

DOI: 10.1021/acs.joc.6b01805
J. Org. Chem. 2016, 81, 9227–9234

Table 3. Catalytic Asymmetric Friedel–Crafts of Various Indoles 8 and Imine 9



8 9 10

entry	substrate	R	product	yield (%)[b]	ee (%)[c]
1	**8a**	H	**10a**	71	97
2	**8b**	4-F	**10b**	68	66
3	**8c**	4-Cl	**10c**	59	49
4	**8d**	4-Br	**10d**	80	> 99
5	**8e**	4-OMe	**10e**	63	94
6	**8f**	4-OBoc	**10f**	64	91
7	**8g**	4-OAc	**10g**	72	91
8	**8h**	4-Ph	**10h**	48	54
9	**8i**	5-NO_2	**10i**	81	30
10	**8j**	5-F	**10j**	77	86
11	**8k**	5-Cl	**10k**	78	80
12	**8l**	5-Br	**10l**	78	70
13	**8m**	5-Me	**10m**	85	59
14	**8n**	5-OMe	**10n**	83	76
15	**8o**	6-F	**10o**	72	85
16	**8p**	6-Cl	**10p**	79	83
17	**8q**	6-Br	**10q**	68	76
18	**8r**	6-Me	**10r**	85	72
19	**8s**	6-CO_2Me	**10s**	68	66
20	**8t**	2-Me	**10t**	88	51
21	**8u**	7-Me	**10u**	36	12
22	**8v**	7-Cl	**10v**	trace	

[a]Reactions were performed with **8** (0.60 mmol) and **9** (0.30 mmol) using 10 mol% catalyst loading in THF (1.5 mL) at room temperature for 12 h. [b]Isolated yields. [c]Determined by HPLC.

be obtained in only 50% yield (Table 2, entry 8). Increasing the amount of indole to 3 equiv gave **10a** with 77% yield and 87% ee. In the presence of 30 mg 4 Å MS, **10a** was achieved with loss in both of yield and enantioselectivity (Table 2, entry 10). Using higher catalyst loading, **10a** could be given in better yield, but a drop of enantioselectivity was observed (Table 2, entries 12 vs 1). A decrease in the catalyst loading led to the lowering of both yield and enantioselectivity (Table 2, entry 11). Therefore, the optimal conditions for the enantioselective Friedel–Crafts reaction were as follows: 10 mol% ligand $\mathbf{L_1}$, 20 mol% $ZnEt_2$, 2 equiv of indole **8a** to imine **9** in THF at room temperature for 12 h.

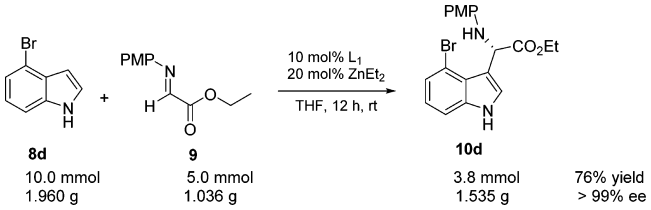
With the optimal reaction conditions in hand, we evaluated the generality of substrates. As summarized in Table 3, the substituted groups of indoles played an important role in controlling the reaction activity and enantioselectivity. Most of indoles bearing different groups furnished corresponding products in good yield and high enantioselectivity. A variety of 4-substituted indole derivatives were tested for enantioselective synthesis of 3-indoleglycine derivatives (Table 3, entries 2–8). Among these compounds, the best result was given by 4-bromoindole in good yield, and with excellent enantioselectivity (>99% ee). 4-Substituted substrates bearing electron-rich groups offered adducts in 63–72% yields with excellent enantioselectivities (91–94% ee, Table 3, entries 5–7). With electron-withdrawing groups F and Cl, the indoles reacted slowly with imine **9** and modest ee were obtained (Table 3, entries 2 and 3). For 5- and 6-substituted indoles, enantioselectivity could be improved by decreasing the bulkiness of substitutions (Table 3, entries 9–19). Indoles bearing electron-withdrawing groups F and Cl led to desired products with good ee values (80–86%). Electron-rich indoles reacted faster with imine **9**, and 3-indolylglycine derivatives were obtained in good yields (Table 3, entries 13, 14, and 18). 5-Nitro substituted indole **8i** afforded product **10i** in 81% yield (entry 9). This outcome cannot be rationalized by electron effect. The result indicated the rate-determining step of the dinuclear zinc catalytic asymmetric reaction may change when the substrate was bearing such strong electron-withdrawing group. When indole **8t** with methyl substituent close to the reaction site was tested, the reaction proceeded smoothly, affording product **10t** in good yield (88%) and moderate enantioselectivity (Table 3, entry 20). However, when indoles with substitutions next to nitrogen atom were performed, the reactions went sluggish with poor enantioselectivities (Table 3, entries 21 and 22).

To measure the practicality of the reaction, we established the process on a large scale employing 5.0 mmol imine **9** and 2 equiv of indole **8d** (Scheme 1). The desired product was obtained in comparable yield (76%) and excellent enantioselectivity (>99% ee).

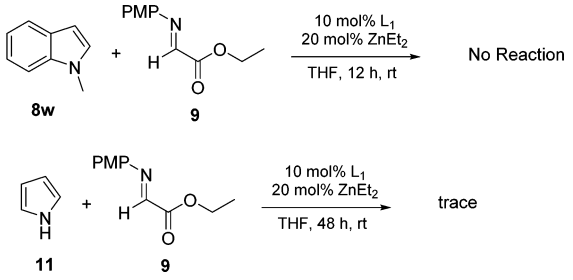
Furthermore, when *N*-methylindole **8w** was examined in the catalytic system, no reaction could be observed, which was in accordance with the report by Wang (Scheme 2).[11] This finding demonstrated the free N–H of indole was critical for the reaction. However, with unprotected pyrrole **11** tested, only trace amounts of products were observed after prolonged reaction time of 48 h.

DOI: 10.1021/acs.joc.6b01805
J. Org. Chem. 2016, 81, 9227–9234

Scheme 1. Reaction on Gram-Scale



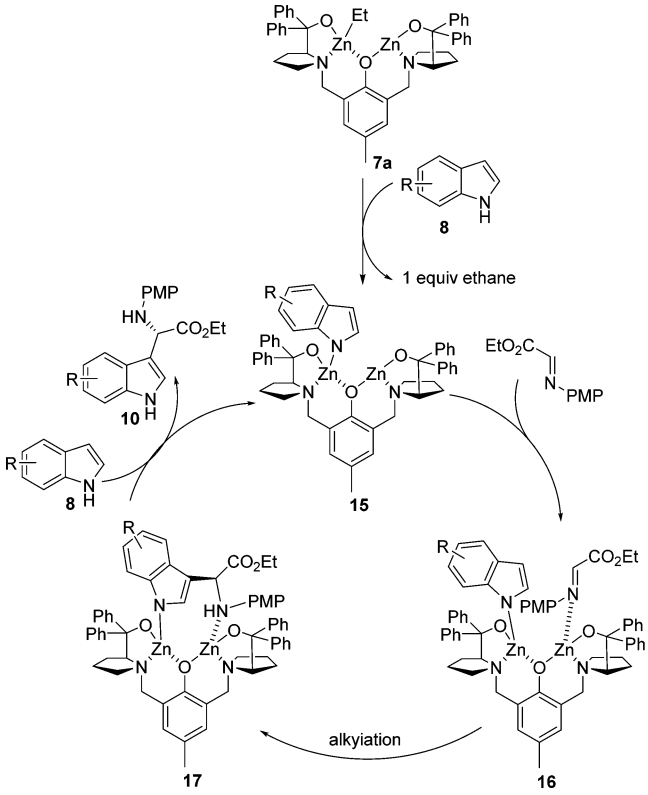
Scheme 2. Asymmetric Reaction of Imine 9 and Indole 8w, Pyrrole 11



The absolute stereochemistry of the products was determined by correlation with a known configuration compound **13** (Scheme 3).[4c,d] (*S*)-Ethyl 2-[(*S*)-*tert*-butylsulfinyl]amino-2-(1H-indol-3-yl)acetate **13** was prepared from indole **8a** and ethyl (*S*,*E*)-*N*-(*tert*-butylsulfinyl)-iminoacetate **12** according to Ji et al.[4d] Treatment of **13** with 4.0 M HCl in methanol removed sulfinyl group,[4c,d,13] and neutralizing with saturated Na_2CO_3 solution afforded (*S*)-ethyl 2-amino-2-(1H-indol-3-yl)acetate **14** in 92% yield and 94% ee. (*S*)-**10a** was obtained with little racemization (92% ee) in 28% yield by copper-promoted *N*-arylation of (*S*)-**14** with 4-methoxyphenylboronic acid.[14] By comparison of the optical rotations and HPLC retention time, the absolute stereochemistry of the dinuclear zinc catalytic product was thus determined to be of the *S*-configuration.

A plausible mechanism to illustrate the Friedel–Crafts alkylation process can be proposed on the basis of Ding's X-ray analysis of ProPhenol-zinc complex,[9d] dinuclear zinc catralyzed asymmetric Friedel–Crafts reactions, and our observed results (Scheme 4).[8b,9e,11] One equivalent of ethane is liberated by deprotonation of indole to form intermediate **15**. Ethyl glyoxylate imine **9** is activated after coordination to the other zinc, and intermediate **16** is formed. Indole attacks preferentially from *Si*-face of the C=N bond of imine, giving the corresponding intermediate **17**. A proton transfer between intermediate **17** and incoming indole **8** releases the adduct **10** and restarts catalytic cycle.

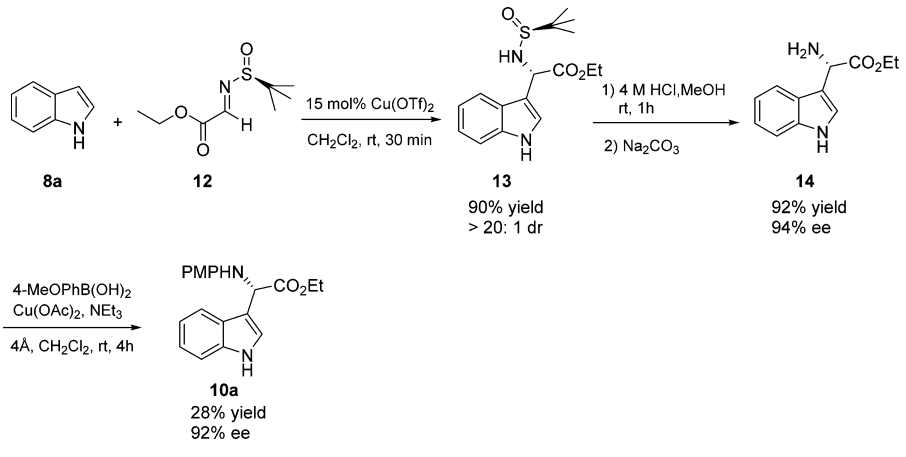
Scheme 4. Proposed Catalytic Cycle



CONCLUSION

In conclusion, we have developed a new catalytic asymmetric system for an atom economic Friedel–Crafts alkylation reaction of unprotected indoles and ethyl glyoxylate imine under mild condition using Trost's dinuclear catalyst. The protocol provides an effective and straightforward access to obtain 3-indolylglycine derivatives with high enantioselectivity (up to >99% ee) and moderate to good yield. This process can proceed on a gram scale without the loss in enantioselectivity.

Scheme 3. Determination of Absolute Configuration



DOI: 10.1021/acs.joc.6b01805
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These products are potentially available for organic synthesis and pharmaceutical chemistry. Further exploring concerning application of the catalytic products is underway in our group.

EXPERIMENTAL SECTION

General Method. NMR spectra were measured on 400 MHz NMR or 600 MHz spectrometer with $CDCl_3$ as the solvent and TMS as an internal reference (400 or 600 MHz for ^1H and 100 or 150 MHz for ^{13}C). High−resolution mass spectra were recorded under ESI QTOF conditions. The enantiomeric excesses (ee) were determined by HPLC (chiral column; mobile phase hexane/*i*-PrOH). Optical rotation values were measured with instruments operating at λ = 589 nm, corresponding to the sodium D line at 20 °C. Indoles **8a−c**, **8i−w**, and pyrrole **11** are commercially available. Indoles **8e**, **8f**, **8g**, and **8h** were prepared according to the literature procedures.[15−17] Prophenol ligands,[9a] compound**12**,[18] and compound **13**[4d] were synthesized following the literature procedures.

*4-Methoxy-1H-indole (**8e**).*[15] ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.10 (t, J = 8.0 Hz 1H), 6.98−7.03 (m, 1H), 6.95 (d, J = 8.2 Hz, 1H), 6,62−6.68 (m, 1H), 6.51(d, J = 7.8 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 137.3, 122.8 118.6, 104.6, 99.8, 98.6, 55.4.

*tert-Butyl (1H-Indol-4-yl) Carbonate (**8f**).* 67% yield (782 mg); white soild; mp 128.6−129.7 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H), 7.06 (d, J = 4.5 Hz, 2H), 6.83−6.94 (m, 2H), 6.40 (t, J = 2.5 Hz, 1H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 143.8, 137.8, 124.9, 121.8, 121.0, 111.4, 109.5, 98.7, 83.5, 27.8; IR (film): 3343, 2892, 1731, 1627, 1583, 1509, 1370, 1286, 1225, 1209, 1141, 882, 753 cm^{-1}; HRMS (ESI) *m*/*z* [M+H]+ calcd for $C_{13}H_{15}NO_3$ 234.1125, found 234.1127.

*1H-Indol-4-yl Acetate (**8g**).*[16] ^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.07−7.17 (m, 2H), 6.83−6.88 (dd, J = 7.6 Hz, 1H), 6.38−6.44 (m, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 143.6, 137.7, 124.5, 122.1, 121.2, 111.8, 109.2, 99.2, 21.1.

*4-Phenyl-1H-indole (**8h**).*[17] ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.66−7.73 (m, 2H), 7.44 (t, J = 7.4 Hz, 2H), 7.15−7.28 (m, 3H), 7.05(t, J = 2.8 Hz, 1H), 6.68 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.4, 136.4, 134.6, 128.9, 128.7, 127.1, 126.2, 124.7, 122.4, 111.9, 110.5, 102.1.

General Procedure for the Asymmetric Friedel−Crafts Alkylation Reaction of Indoles and Ethyl Glyoxylate Imine. Under a nitrogen atmosphere, diethylzinc (60 μL, 1.0 M in hexane, 0.06 mmol) was added dropwise to a solution of $\mathbf{L_1}$ (19.2 mg, 0.03 mmol) in THF (0.5 mL). After stirring for 30 min at room temperature, indole **8** (0.6 mmol) and imine **9** (0.3 mmol) in THF (0.5 mL) were added respective to the generated catalyst. The mixture was stirred for 12 h at the same temperature. Then the reaction was quenched with a phosphate buffer (pH = 7) solution (2 mL) and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude adducts were purified by silica gel column chromatography (petroleum ether/ethyl acetate =5/1) to afford pure product **10**.

*(S)-Ethyl 2-(1H-Indol-3-yl)-2-(4-methoxyphenylamino)acetate (**10a**).*[4b] 71% yield (68.9 mg); 97% ee, determined by HPLC (Chiralcel OD-H, λ = 254 nm, hexane/*i*-PrOH = 80/20, flow rate 0.8 mL/min), t_R = 14.01 min (minor enantiomer) and t_R = 16.29 min (major enantiomer); $[\alpha]_D^{20}$ = +58.7 (c 1.16, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.23−7.12 (m, 3H), 6.74 (d, J = 8.9 Hz, 2H), 6.60 (d, J = 9.0 Hz, 2H), 5.31 (d, J = 6.8 Hz, 1H), 4.33−4.07 (m, 2H), 3.70 (s, 3H), 1,29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 152.6, 140.9, 136.5, 125.8, 123.2, 122.5, 120.0, 119.5, 114.93, 114.90, 112.6, 111.5, 61.6, 55.8, 55.3, 14.2.

*(S)-Ethyl 2-(4-Fluoro-1H-indol-3-yl)-2-(4-methoxyphenylamino)-acetate (**10b**).* 66% yield (68.2 mg); 66% ee, determined by (HPLC Chiralpak IC, λ = 254 nm, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min), t_R = 7.98 min (minor enantiomer) and t_R = 9.32 min (major enantiomer); $[\alpha]_D^{20}$ = +18.4 (c 0.88, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.47 (s, 1H), 7.11−7.01 (m, 3H), 6.83−6.76 (m, 1H), 6.73 (d, J = 9.0 Hz, 2H), 6.65 (d, J = 9.0 Hz, 2H), 5.51 (s, 1H), 4.27−4.06 (m, 2H), 3.70 (s, 3H), 2.42(s, 3H) 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 158.0, 155.5, 152.7, 140.7, 139.0 (J = 11.3 Hz), 123.3, 122.9(J = 7.8 Hz), 115.4, 114.8, 111.9(J = 3.8 Hz), 107.6(J = 3.6 Hz), 105.3(J = 19.6), 61.6, 55.7, 55.2, 14.1; IR (film): 3319, 3012, 1728, 1509, 1465, 1350, 1256, 1230, 1188, 1091, 935, 844, 750, 733 cm^{-1}; HRMS (ESI) *m*/*z* $[M]^+$ calcd for $C_{19}H_{19}FN_2O_3$ 342.1380, found 342.1373.

*(S)-Ethyl 2-(4-Chloro-1H-indol-3-yl)-2-(4-methoxyphenylamino)-acetate (**10c**).* 59% yield (64.3 mg); 49% ee, determined by (HPLC Chiralpak IF, λ = 254 nm, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min), t_R = 6.61 min (minor enantiomer) and t_R = 7.45 min (major enantiomer); $[\alpha]_D^{20}$ = +12.4 (c 0.73, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.24−7.19 (m, 2H), 7.13−7.06 (m, 2H), 6.75 (d, J = 9.0 Hz, 2H), 6.67 (d, J = 8.9 Hz, 2H), 5.97 (s, 1H), 4.31−4.10 (m, 2H), 3.72 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 152.6, 140.8, 137.8, 126.1, 124.2, 123.3, 123.0, 121.4, 115.1, 114.8, 113.5, 110.3, 61.5, 55.7, 54.3, 14.1; IR (film): 3359, 2921, 1724, 1509, 1456, 1337, 1239, 1182, 1131, 1033, 939, 817, 737 cm^{-1}; HRMS (ESI) *m*/*z* $[M]^+$ calcd for $C_{19}H_{19}ClN_2O_3$ 358.1084, found 358.1078.

*(S)-Ethyl 2-(4-Bromo-1H-indol-3-yl)-2-(4-methoxyphenylamino)-acetate (**10d**).* 80% yield (96.3 mg); > 99% ee, determined by (HPLC Chiralpak IB, λ = 254 nm, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min), t_R = 9.31 min (major enantiomer) and t_R = 15.51 min (minor enantiomer); $[\alpha]_D^{20}$ = +27.2 (c 0.66, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H), 7.37−7.24 (m, 3H), 7.03 (t, J = 7.8 Hz, 2H), 6.75 (d, J = 8.9 Hz, 2H), 6.67 (d, J = 8.9 Hz, 2H), 6.10 (s, 1H), 4.32−4.11 (m, 2H), 3.72 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 152.6, 140.7, 137.6, 124.9, 124.5, 123.3, 115.1, 114.8, 113.9, 113.8, 110.9, 61.5, 55.7, 53.7, 14.1; IR (film): 3383, 3279, 2975, 1728, 1512, 1340, 1232, 1181, 1036, 919, 814, 740 cm^{-1}; HRMS (ESI) *m*/*z* $[M]^+$ calcd for $C_{19}H_{19}BrN_2O_3$ 402.0579, found 402.0575.

*(S)-Ethyl 2-(4-Methoxy-1H-indol-3-yl)-2-(4-methoxyphenyl-amino)acetate (**10e**).* 63% yield (67.4 mg); 94% ee, determined by HPLC (Chiralcel OD-H, λ = 254 nm, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min), t_R = 56.78 min (major enantiomer) and t_R = 70.15 min (minor enantiomer); $[\alpha]_D^{20}$ = +46.3 (c 0.61, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.07 (d, J = 8.0 Hz, 1H), 7.01−6.81 (m, 3H), 6.74 (d, J = 9.0 Hz, 2H), 6.68 (d, J = 8.8 Hz, 2H),6.50 (d, J = 7.8 Hz, 1H), 5.64 (s, 1H), 4.22−4.05 (m, 2H), 3.88 (s, 3H), 3.71 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 154.0, 152.6, 141.3, 138.0, 123.2, 122.1, 116.2, 115.7, 114.7, 113.1, 104.8, 100.1, 61.2, 55.7, 55.2, 14.2; IR (film): 3356, 2931, 1724, 1512, 1360, 1236, 1175, 1084, 1027, 821, 730 cm^{-1}; HRMS (ESI) *m*/*z* $[M]^+$ calcd for $C_{20}H_{22}N_2O_4$ 354.1580, found 354.1573.

*(S)-Ethyl 2-(4-(tert-Butoxycarbonyloxy)-1H-indol-3-yl)-2-((4-methoxyphenyl)amino)acetate (**10f**).* 64% yield (84.3 mg); 91% ee, determined by HPLC (Chiralpak IB, λ = 254 nm, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min), t_R = 19.97 min (minor enantiomer) and t_R = 21.29 min (major enantiomer); $[\alpha]_D^{20}$ = +44.1 (c 0.90, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 7.13−7.09(m, 2H), 7.03 (d, J = 2.4 Hz, 1H), 6.99 (dd, J = 6.6 Hz, 1H), 6.75 (d, J = 9.0 Hz, 2H), 6.68 (d, J = 9.0 Hz, 2H), 5.59 (s, 1H), 4.23−4.06 (m, 2H), 3.72 (s, 3H), 1.41 (s, 9H),1.15 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 152.6, 152.3, 144.1, 141.1, 138.5, 123.6, 122.6, 118.9, 115.4, 114.8, 113.2, 111.6, 109.3, 83.4, 61.3, 55.8, 54.7, 27.5, 14.1; IR (film): 3373, 2927, 1751, 1731, 1509, 1367, 1273, 1219, 1145, 1080, 1030, 888, 821, 740 cm^{-1}; HRMS (ESI) *m*/*z* $[M]^+$ calcd for $C_{24}H_{28}N_2O_6$ 440.1947, found 440.1945.

*(S)-Ethyl 2-(4-Acetoxy-1H-indol-3-yl)-2-((4-methoxyphenyl)-amino)acetate (**10g**).* 72% yield (82.7 mg); 91% ee, determined by HPLC (Chiralpak IC, λ = 254 nm, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min), t_R = 12.04 min (major enantiomer) and t_R = 13.39 min (minor enantiomer); $[\alpha]_D^{20}$ = +19.8 (c 0.98, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.16−7.08(m, 2H), 7.00 (d, J = 2.2 Hz, 1H), 6.88−6.82 (m, 2H), 6.75 (d, J = 8.9 Hz, 2H), 6.58 (d, J = 8.9 Hz, 2H), 5.43 (s, 1H), 4.28−4.06 (m, 2H), 3.71 (s, 3H), 2.12 (s, 3H),1.19

DOI: 10.1021/acs.joc.6b01805
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(t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 170.2, 169.0, 152.5, 143.6, 140.9, 138.7, 123.8, 122.6, 118.8, 114.9, 113.5, 111.2, 109.5, 61.5, 55.7, 54.9, 21.2, 14.2; IR (film): 3370, 2921, 1731, 1509, 1445, 1370, 1293, 1232, 1198, 1134, 1037, 898, 821, 743 cm^{-1}; HRMS (ESI) *m/z* $[M]^+$ calcd for $C_{21}H_{22}N_2O_5$ 382.1529, found 382.1527.

*(S)-Ethyl 2-(4-Methoxyphenylamino)-2-(4-phenyl-1H-indol-3-yl)-acetate (**10h**).* 48% yield (58.6 mg); 53% ee, determined by HPLC (Chiralpak IF, λ = 254 nm, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min), t_R = 7.41 min (minor enantiomer) and t_R = 10.25 min (major enantiomer); $[\alpha]_D^{20}$ = +14.6 (c 0.60, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.44 (s, 1H), 7.51 (d, J = 7.1 Hz, 2H), 7.43−7.11 (m, 6H), 7.01 (dd, J = 7.1 Hz, 1H), 6.65 (d, J = 8.9 Hz, 2H),6.21 (d, J = 8.8 Hz, 2H), 4.81 (s, 1H), 4.12−3.99 (m, 2H), 3.72 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.8, 152.4, 141.0, 140.8, 136.6, 135.6, 129.4, 128.0, 127.0, 123.7, 123.6, 122.4, 122.2, 114.8, 114.5, 113.7, 110.6, 61.1, 55.7, 53.7, 14.1; IR (film): 3363, 2931, 1724, 1512, 1441, 1410, 1363, 1296, 1231, 1192, 1131, 11094, 929, 821, 753 cm^{-1}; HRMS (ESI) *m/z* $[M]^+$ calcd for $C_{25}H_{24}N_2O_3$ 400.1787, found 400.1785.

*(S)-Ethyl 2-(4-Methoxyphenylamino)-2-(5-nitro-1H-indol-3-yl)-acetate (**10i**).*[4b] 81% yield (90.3 mg); 30% ee, determined by HPLC (Chiralcel OD-H, λ = 254 nm, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min), t_R = 13.14 min (minor enantiomer) and t_R = 17.52 min (major enantiomer); $[\alpha]_D^{20}$ = +12.8 (c 1.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.84 (d, J = 2.2 Hz, 1H), 7.13 (dd, J = 9.0 Hz, 1H), 7.47−7.36(m, 2H), 6.75 (d, J = 8.9 Hz, 2H),6.61 (d, J = 8.9 Hz, 2H), 5.36 (d, J = 5.0 Hz, 1H), 4.33−4.09 (m, 2H), 3.72 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 152.7, 142.0, 140.2, 139.6, 123.6, 125.3, 118.1, 117.3, 115.6, 115.0, 114.9, 115.3, 62.1, 55.7, 55.0, 14.1.

*(S)-Ethyl 2-(5-Fluoro-1H-indol-3-yl)-2-(4-methoxyphenylamino)-acetate (**10j**).*[3b] 77% yield (78.7 mg); 86% ee, determined by HPLC (Chiralcel OD-H, λ = 254 nm, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min), t_R = 28.01 min (minor enantiomer) and t_R = 32.30 min (major enantiomer); $[\alpha]_D^{20}$ = +38.1 (c 1.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.48 (dd, J = 9.7 Hz, 2H), 7.28−7.24 (m, 2H), 6.99−6.94 (dm, 1H), 6.74 (d, J = 8.9 Hz, 2H),6.61 (d, J = 8.8 Hz, 2H), 5,52 (s, 1H), 4.28−4.22 (m, 1H), 4.18−4.11 (m, 1H), 3.72 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 158.7, 157.2, 152.6, 140.6, 133.0, 126.4(J = 10.0 Hz), 124.7, 114.9(J = 9.1 Hz), 113.1, 112.0(J = 9.6 Hz), 104.7(J = 24.1),61.7, 55.7, 55.2, 14.1.

*(S)-Ethyl 2-(5-Chloro-1H-indol-3-yl)-2-(4-methoxyphenylamino)-acetate (**10k**).* 78% yield (83.4 mg); 80% ee, determined by HPLC (Chiralcel OD-H, λ = 254 nm, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min), t_R = 12.35 min (minor enantiomer) and t_R = 14.75 min (major enantiomer); $[\alpha]_D^{20}$ = +25.7 (c 0.76, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.81 (d, J = 1.9 Hz, 2H), 7.28−7.12 (m, 3H), 6.74 (d, J = 8.9 Hz, 2H),6.60 (d, J = 8.9 Hz, 2H), 5.26 (s, 1H), 4.30−4.08 (m, 2H), 3.72 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 152.7, 140.6, 134.9, 126.9, 125.8, 124.4, 122.9, 119.2, 115.0, 114.9, 112.7, 112.4, 61.7, 55.7, 55.1, 14.1; IR (film): 3400, 2972, 1731, 1458, 1367, 1293, 1235, 1188, 1134, 1101, 1037, 892, 817, 791 cm^{-1}; HRMS (ESI) *m/z* $[M]^+$ calcd for $C_{19}H_{19}ClN_2O_3$ 358.1084, found 358.1079.

*(S)-Ethyl 2-(5-Bromo-1H-indol-3-yl)-2-(4-methoxyphenylamino)-acetate (**10l**).*[4b] 71% yield (68.9 mg); 70% ee, determined by HPLC (Chiralcel OD-H, λ = 254 nm, hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min), t_R = 8.63 min (minor enantiomer) and t_R = 10.92 min (major enantiomer); $[\alpha]_D^{20}$ = +18.4 (c 0.61, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): 8.29 (s, 1H), 7.97 (d, J = 1.8 Hz, 1H), 7.30 (dd, J = 8.0 Hz, 1H), 7.24−7.19(m, 2H), 6.74 (d, J = 8.9 Hz, 2H),6.60 (d, J = 8.9 Hz, 2H), 5.26 (s, 1H), 4.28−4.12 (m, 2H), 3.72 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.5, 152.6, 140.5, 135.2, 127.6, 125.4, 124.2, 122.3, 114.94, 114.87, 113.3, 112.8, 112.7, 61.7, 55.7, 55.1, 14.1.

*(S)-Ethyl 2-(4-Methoxyphenylamino)-2-(5-methyl-1H-indol-3-yl)-acetate (**10m**).*[3b] 85% yield (86.5 mg); 59% ee, determined by HPLC (Chiralcel OD-H, λ = 254 nm, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min), t_R = 21.47 min (minor enantiomer) and t_R = 23.75 min (major enantiomer); $[\alpha]_D^{20}$ = +25.4 (c 1.50, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.26−7.24 (m, 1H),7.18 (d, J = 2.9 Hz, 1H), 7.05 (dd, J = 8.3 Hz, 1H), 6.75 (d, J = 8.9 Hz, 2H),6.62 (d, J = 8.9 Hz, 2H), 5.29 (s, 1H), 4.28−4.10 (m, 2H), 3.72 (s, 3H), 2.46(s, 3H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.9, 152.5, 140.9, 134.8, 129.4, 126.1, 124.2, 123.1, 119.2, 114.9, 114.8, 112.3, 111.0, 61.5, 55.7, 55.2, 21.6, 14.2.

*(S)-Ethyl 2-(5-Methoxy-1H-indol-3-yl)-2-(4-methoxyphenylamino)acetate (**10n**).*[4b] 83% yield (86.9 mg); 76% ee, determined by (HPLC Chiralcel IC, λ = 254 nm, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min), t_R = 12.82 min (minor enantiomer) and t_R = 19.02 min (major enantiomer); $[\alpha]_D^{20}$ = +46.3 (c 0.61, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.27−7.18 (m, 2H), 7.15 (d, J = 2.4 Hz, 1H), 6.87 (dd, J = 8.8 Hz, 1H), 6.75 (d, J = 8.9 Hz, 2H),6.61 (d, J = 8.9 Hz, 2H), 5.27 (d, J = 6.1 Hz, 1H), 4.30−4.10 (m, 2H), 3.85 (s, 3H), 3.72 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$): δ172.9, 154.3, 152.6, 140.9, 131.6, 126.3, 123.7, 114.9, 112.9, 112.4, 112.2, 101.1, 61.5, 55.9, 55.7, 55.3, 14.2.

*(S)-Ethyl 2-(6-Fluoro-1H-indol-3-yl)-2-(4-methoxyphenylamino)-acetate (**10o**).* 72% yield (74.2 mg); 85% ee, determined by HPLC Chiralcel OD-H, λ = 254 nm, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, t_R = 26.75 min (minor enantiomer) and t_R = 31.55 min (major enantiomer); $[\alpha]_D^{20}$ = +29.4 (c 0.61, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.72 (dd, J = 8.8 Hz, 1H), 7.13 (dd, J = 2.1 Hz, 1H), 7.01−6.87 (m, 2H), 6.75 (d, J = 8.9 Hz, 2H),6.61 (d, J = 8.9 Hz, 2H), 5.28 (s, 1H), 4.28−4.08 (m, 2H), 3.71 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 161.3, 158.9, 152.7, 140.7, 136.5(J = 12.4 Hz), 123.4(J = 3.3 Hz), 122.4, 120.4(J = 10.0 Hz), 114.9(J = 8.1 Hz), 112.8, 108.8(J = 24.5 Hz), 97.7(J = 25.8 Hz), 61.6, 55.7, 55.3, 14.1. IR (film): 3407, 2975, 1731, 1600, 1509, 1458, 1428, 1320, 1249, 1219, 1178, 1137, 1097, 1023, 935, 841, 733 cm^{-1}; HRMS (ESI) *m/z* $[M]^+$ calcd for $C_{19}H_{19}FN_2O_3$ 342.1380, found 342.1375.

*(S)-Ethyl 2-(6-Chloro-1H-indol-3-yl)-2-(4-methoxyphenylamino)-acetate (**10p**).*[19] 79% yield (84.9 mg); 83% ee, determined by HPLC Chiralcel OD-H, λ = 254 nm, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, t_R = 10.93 min (minor enantiomer) and t_R = 13.17 min (major enantiomer); $[\alpha]_D^{20}$ = +33.9 (c 1.18, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.32 (d, J = 1.7 Hz, 1H), 7.18 (d, J = 2.3 Hz, 1H), 7.13 (dd, J = 8.5 Hz, 1H) 6.74 (d, J = 8.9 Hz, 2H), 6.60 (d, J = 8.9 Hz, 2H), 5.28 (s, 1H), 4.28−4.08 (m, 2H), 3.72 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 152.7, 140.6, 136.9, 128.5, 124.4, 123.7, 120.8, 120.5, 114.9445, 114.8806, 113.1, 111.3, 61.7, 55.7, 55.1, 14.2.

*(S)-Ethyl 2-(6-Bromo-1H-indol-3-yl)-2-(4-methoxyphenylamino)-acetate (**10q**).*[4b] 68% yield (82.3 mg); 76% ee, determined by HPLC (Chiralcel OD-H, λ = 254 nm, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min), t_R = 11.00 min (minor enantiomer) and t_R = 13.16 min (major enantiomer); $[\alpha]_D^{20}$ = +31.4 (c 1.08, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.29 (s, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 3.1 Hz, 1H), 7.27−7.24 (m, 1H), 7.17 (d, J = 2.4 Hz, 1H) 6.74 (d, J = 8.9 Hz, 2H), 6.60 (d, J = 8.9 Hz, 2H), 5.28 (s, 1H), 4.27−4.10 (m, 2H), 3.72 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.5, 152.7, 140.6, 137.3, 124.8, 123.4, 120.9, 116.1, 115.0, 114.9, 114.3, 113.2, 61.7, 55.7, 55.1, 14.1.

*(S)-Ethyl 2-(4-Methoxyphenylamino)-2-(6-methyl-1H-indol-3-yl)-acetate (**10r**).* 85% yield (65.8 mg); 76% ee, determined by HPLC (Chiralcel OD-H, λ = 254 nm, hexane/*i*-PrOH = 80/20, flow rate 0.5 mL/min), t_R = 28.25 min (minor enantiomer) and t_R = 35.25 min (major enantiomer); $[\alpha]_D^{20}$ = +44.1 (c 1.25, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.17−7.12 (m, 2H), 7.00 (dd, J = 8.2 Hz, 1H), 6.74 (d, J = 8.9 Hz, 2H), 6.61 (d, J = 8.9 Hz, 2H), 5.29 (s, 1H), 4.28−4.09 (m, 2H), 3.72 (s, 3H), 2.46 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 172.8, 152.5, 140.9, 136.9, 132.4, 123.7, 122.4, 121.8, 119.2, 114.84, 114.83, 112.7, 111.3, 61.5, 55.7, 55.3, 21.7, 14.2; IR (film): 3407, 2972, 1731, 1509, 1456, 1303, 1236, 1185, 1097, 1037, 821, 801, 737 cm^{-1}; HRMS (ESI) *m/z* $[M]^+$ calcd for $C_{20}H_{22}N_2O_3$ 338.1630, found 338.1621.

DOI: 10.1021/acs.joc.6b01805
J. Org. Chem. 2016, 81, 9227−9234

*(S)-Ethyl 2-(6-Methoxycarbonyl-1H-indol-3-yl)-2-(4-methoxyphenylamino)acetate (**10s**).*[4b] 68% yield (78.3 mg); 66% ee, determined by (HPLC Chiralcel IB, λ = 254 nm, hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min), t_R = 8.24 min (minor enantiomer) and t_R = 9.50 min (major enantiomer); $[\alpha]_D^{20}$ = +8.7 (c 0.60, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 8.11(s,1H), 7.84(s, 2H), 7.36 (d, J = 2.4 Hz, 1H) 6.74 (d, J = 8.9 Hz, 2H), 6.61 (d, J = 8.9 Hz, 2H), 5.33 (s, 1H), 4.30−4.08 (m, 2H), 3.71 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 168.1, 152.7, 140.5, 135.9, 129.4, 126.4, 124.2, 121.0, 119.2, 115.0, 114.9, 113.8, 113.4, 61.7, 55.7, 55.1, 52.1, 14.1.

*(S)-Ethyl 2-(4-Methoxyphenylamino)-2-(2-methyl-1H-indol-3-yl)-acetate (**10t**).*[4b] 88% yield (89.8 mg); 51% ee, determined by HPLC (Chiralcel OD-H, λ = 254 nm, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min), t_R = 11.41 min (minor enantiomer) and t_R = 13.74 min (major enantiomer); $[\alpha]_D^{20}$ = +25.7 (c 1.61, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.81−7.73 (m, 1H), 7.25−7.11 (m, 1H), 7.05−7.04 (m, 1H), 6.72 (d, J = 8.8 Hz, 2H), 6.57 (d, J = 8.9 Hz, 2H), 5.22 (s, 1H), 4.26−4.17 (m, 2H), 3.70 (s, 3H), 2.42 (s, 3H) 1.16 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 152.4, 141.0, 135.2, 133.3, 126.9, 121.4, 119.9, 118.9, 114.9, 114.7, 110.5, 107.8, 61.4, 55.8, 55.0, 14.2, 12.1.

*(S)-Ethyl 2-(4-Methoxyphenylamino)-2-(7-methyl-1H-indol-3-yl)-acetate (**10u**).*[3b] 36% yield (36.2 mg); 12% ee, determined by (HPLC Chiralcel IF, λ = 254 nm, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min), t_R = 9.05 min (minor enantiomer) and t_R = 10.62 min (major enantiomer); $[\alpha]_D^{20}$ = +5.1 (c 0.76, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 7.07(t, J = 5.5 Hz, 1H), 7.00 (d, J = 7.1 Hz, 1H), 6.72 (d, J = 8.9 Hz, 2H), 6.69 (d, J = 8.9 Hz, 2H), 5.31 (s, 1H), 4.28−4.05 (m, 2H), 3.69 (s, 3H), 2.42 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 152.5, 140.9, 136.1, 125.4, 123.0, 122.9, 120.3, 117.3, 114.89, 114.88, 113.2, 61.5, 55.8, 55.3, 16.6, 14.2.

*(S,E)-Ethyl 2-[(tert-Butylsulfinyl)imino]acetate (**12**).*[18] $[\alpha]_D^{20}$ = +297.3 (c 0.95, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 1H), 4.34−4.43 (m, 2H), 1.39 (t, J = 7.2 Hz, 1H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 155.6, 62.4, 58.9, 22.7, 14.0.

*(S)-Ethyl 2-[(S)-tert-Butylsulfinyl]amino-2-(1H-indol-3-yl)acetate (**13**).*[4d] 90% yield; > 20:1 dr, determined by 1H NMR; $[\alpha]_D^{20}$ = +115.8 (c 0.65, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$): δ 8.83 (s, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.16−7.22 (m, 2H), 7.07−7.13 (t, J = 7.1 Hz, 1H), 5.32 (d, J = 4.7 Hz, 1H), 4.53 (d, J = 4.7 Hz, 1H), 4.09−4.28 (m, 2H), 1,13−1.23 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 136.7, 125.6, 124.3, 119.9, 111.6, 111.3, 62.0, 55.8, 54.4, 22.7, 14.0.

*(S)-Ethyl 2-Amino-2-(1H-indol-3-yl)acetate (**14**).*[5] To a solution of *N*-sulfinyl indolylglycine derivative **13** (615 mg, 2.0 mmol) in MeOH (10 mL) was added 4 M HCl solution (2.5 mL, 10 mmol). The solution was stirred at room temperature for 1 h, and then MeOH was evaporated under reduced pressure. The residue was diluted with water (5 mL) and washed with ether (10 mL × 3). The aqueous layer was neutralized with saturated Na_2CO_3 aqueous solution and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure vacuum, affording (*S*)-**14** as white solid. 92% yield (403 mg); 94% ee, determined by HPLC (Chiralpak IC, λ = 254 nm, hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min), t_R = 7.60 min (minor enantiomer) and t_R = 8.45 min (major enantiomer); $[\alpha]_D^{20}$ = +109.4 (c 0.65, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.74 (s, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.03−7.20 (m, 3H), 4.89 (s, 1H), 4.05−4.24 (m, 2H), 2.79 (s, 2H) 1,17 (t, J = 7.1 Hz 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 136.5, 125.4, 122.6, 122.3, 119.8, 119.1, 114.7, 115.3, 61.4, 51.7, 14.1.

Procedure for Synthesis of (*S*)-10 by *N*-Arylation of (*S*)-14. To a 10 mL vial equipped with a $CaCl_2$ drying tube was added in sequence 4 Å MS(100 mg), 4-methoxyphenylboronic (76 mg, 0.5 mmol), dry CH_2Cl_2 (3 mL), triethylamine (138 μL, 1.0 mmol), (*S*)-**14** (109 mg, 0.5 mmol), and cupric acetate (100 mg, 0.55 mmol). The mixture was allowed to stir under air at room temperature and was monitored by TLC. After completion of the reaction (4 h), the mixture was filtered over Celite and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (PE/EtOAc = 5/1) to afford (*S*)-**10a** as colorless oil. 28% yield (49 mg); 92% ee, determined by HPLC (Chiralcel OD-H, λ = 254 nm, hexane/*i*-PrOH = 80/20, flow rate 0.8 mL/min), t_R = 14.72 min (minor enantiomer) and t_R = 17.16 min (major enantiomer); $[\alpha]_D^{20}$ = +49.6 (c 0.66, $CHCl_3$). NMR dates were in accordance with **10a** prepared using dinuclear zinc catalytic system.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01805.

Detail ^1H and ^{13}C NMR data for compounds **8e**−**8h**, **10**, **12**, **13**, and **14** and chiral HPLC chromatograms data for compounds **10** and **14** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Sciences Foundation of China (NNSFC: 21272216, 20972140), and the Department of Science and Technology of Henan Province for financial supports.

■ REFERENCES

(1) (a) *Amino Acids, Peptides, and Proteins in Organic Chemistry*; Hughes, A. B., Ed.;Wiley-VCH, 2009; Vol. *1* and *2*. (b) Singh, J.; Conzentino, P.; Cundy, K.; Gainor, J. A.; Gilliam, C. L.; Gordon, T. D.; Johnson, J. A.; Morgan, B. A.; Schneider, E. D.; Wahl, R. C.; Whipple, D. A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 337. (c) Kawasaki, T.; Enoki, H.; Matsumura, K.; Ohyama, M.; Inagawa, M.; Sakamoto, M. *Org. Lett.* **2000**, *2*, 3027. (d) Rutjes, F. P. J. T.; Wolf, L. B.; Schoemaker, H. E. *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 4197. (e) Hughes, R. A.; Moody, C. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7930. (f) Hupp, C. D.; Tepe, J. J. *J. Org. Chem.* **2009**, *74*, 3406. (g) Abid, M.; Teixeira, L.; Török, B. *Org. Lett.* **2008**, *10*, 933. (h) Husmann, R.; Sugiono, E.; Mersmann, S.; Raabe, G.; Rueping, M.; Bolm, C. *Org. Lett.* **2011**, *13*, 1044. (i) Han, X.; Wu, H.; Wang, W.; Dong, C.; Tien, P.; Wu, S.; Zhou, H.-B. *Org. Biomol. Chem.* **2014**, *12*, 8308.

(2) Selected publications for applications of 3-indolylglycine derivatives in organic synthesis, see: (a) Katz, A. H.; Demerson, C. A.; Shaw, C. C.; Asselin, A. A.; Humber, L. G.; Conway, K. M.; Gavin, G.; Guinosso, C.; Jensen, N. P.; Mobilio, D.; Noureldin, R.; Schmid, J.; Shah, U.; Van Engen, D.; Chau, T. T.; Weichman, B. M. *J. Med. Chem.* **1988**, *31*, 1244. (b) Jiang, B.; Gu, X.-H. *Heterocycles* **2000**, *53*, 1559. (c) Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179. (d) Kawasaki, T.; Ohno, K.; Enoki, H.; Umemoto, Y.; Sakamoto, M. *Tetrahedron Lett.* **2002**, *43*, 4245. (e) Yang, C.-G.; Wang, J.; Tang, X.-X.; Jiang, B. *Tetrahedron: Asymmetry* **2002**, *13*, 383. (f) Kouko, T.; Matsumura, K.; Kawasaki, T. *Tetrahedron* **2005**, *61*, 2309. (g) Higuchi, K.; Takei, R.; Kouko, T.; Kawasaki, T. *Synthesis* **2007**, *2007*, 669. (h) Yan, F.; Cao, X.-X.; Jiang, H.-X.; Zhao, X.-L.; Wang, J.-Y.; Lin, Y.-H.; Liu, Q.-L.; Zhang, C.; Jiang, B.; Guo, F. *J. Med. Chem.* **2010**, *53*, 5502.

(3) (a) Wanner, M. J.; Hauwert, P.; Schoemaker, H. E.; de Gelder, R. D.; Van Maarseveen, J. H.; Hiemstra, H. *Eur. J. Org. Chem.* **2008**, *2008*, 180. (b) Kang, Q.; Zhao, Z.-A.; You, S.-L. *Tetrahedron* **2009**, *65*, 1603. (c) Ube, H.; Fukuchi, S.; Terada, M. *Tetrahedron: Asymmetry* **2010**, *21*, 1203. (d) Johannsen, M. *Chem. Commun.* **1999**, 2233.

DOI: 10.1021/acs.joc.6b01805
J. Org. Chem. 2016, 81, 9227−9234

(4) (a) Lei, F.; Chen, Y.-J.; Sui, Y.; Liu, L.; Wang, D. *Synlett* **2003**, 1160. (b) Jiang, B.; Huang, Z.-G. *Synthesis* **2005**, 2198. (c) Andreassen, T.; Hansen, L. K.; Gautun, O. R. *Eur. J. Org. Chem.* **2008**, *2008*, 4871. (d) Ji, D.-U.; Xu, M.-H. *Chem. Commun.* **2010**, *46*, 1550. (e) Lin, D.; Wang, J.; Zhang, X.; Zhou, S.; Lian, J.; Jiang, H.; Liu, H. *Chem. Commun.* **2013**, *49*, 2575. (f) Iwanejko, j.; Wojaczyńska, E.; Wojaczyński, j.; Bąkowicz, j. *Tetrahedron Lett.* **2014**, *55*, 6619.

(5) Janczuk, A.; Zhang, W.; Xie, W.; Lou, S.; Cheng, J.-P.; Wang, P. G. *Tetrahedron Lett.* **2002**, *43*, 4271.

(6) Hang, J.; Li, H.; Deng, L. *Org. Lett.* **2002**, *4*, 3321.

(7) (a) Wang, M.-C.; Zhang, Q.-J.; Zhao, W.-X.; Wang, X.-D.; Ding, X.; Jing, T.-T.; Song, M.-P. *J. Org. Chem.* **2008**, *73*, 168. (b) Niu, J.-L.; Wang, M.-C.; Lu, L.-J.; Ding, G.-L.; Lu, H.-J.; Chen, Q.-T.; Song, M.-P. *Tetrahedron: Asymmetry* **2009**, *20*, 2616. (c) Niu, J.-L.; Wang, M.-C.; Kong, P.-P.; Chen, Q.-T.; Zhu, Y.; Song, M.-P. *Tetrahedron* **2009**, *65*, 8869. (d) Song, X.; Liu, A.-X.; Liu, S.-S.; Gao, W.-C.; Wang, M.-C.; Chang, J.-B. *Tetrahedron* **2014**, *70*, 1464. (e) Wang, M.-C.; Liu, Z.-K.; Li, S.; Ding, X.; Li, Y.; Tang, M.-S. *Tetrahedron: Asymmetry* **2010**, *21*, 486. (f) Song, X.; Hua, Y.-Z.; Shi, J.-G.; Sun, P.-P.; Wang, M.-C.; Chang, J.-B. *J. Org. Chem.* **2014**, *79*, 6087.

(8) (a) Hua, Y.-Z.; Lu, L.-J.; Huang, P.-J.; Wei, D.-H.; Tang, M.-S.; Wang, M.-C.; Chang, J.-B. *Chem. - Eur. J.* **2014**, *20*, 12394. (b) Hua, Y.-Z.; Han, X.-W.; Yang, X.-C.; Song, X.; Wang, M.-C.; Chang, J.-B. *J. Org. Chem.* **2014**, *79*, 11690. (c) Hua, Y.-Z.; Yang, X.-C.; Liu, M.-M.; Song, X.; Wang, M.-C.; Chang, J.-B. *Macromolecules* **2015**, *48*, 1651. (d) Hua, Y.-Z.; Liu, M.-M.; Huang, H.-P.; Song, X.; Wang, M.-C.; Chang, J.-B. *Chem. - Eur. J.* **2015**, *21*, 11994.

(9) For a review see: (a) Trost, B. M.; Bartlett, M. J. *Acc. Chem. Res.* **2015**, *48*, 688. For selected publications, see: (b) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (c) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. (d) Xiao, Y.; Wang, Z.; Ding, K. *Chem. - Eur. J.* **2005**, *11*, 3668. (e) Trost, B. M.; Müller, C. *J. Am. Chem. Soc.* **2008**, *130*, 2438. (f) Zhao, D.; Wang, L.; Yang, D.; Zhang, Y.; Wang, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7523. (g) Trost, B. M.; Miege, F. *J. Am. Chem. Soc.* **2014**, *136*, 3016. (h) Trost, B. M.; Saget, T.; Hung, C. *J. Am. Chem. Soc.* **2016**, *138*, 3659.

(10) Selected examples: (a) Trost, B. M.; Yeh, V. S. C.; Ito, H.; Bremeyer, N. *Org. Lett.* **2002**, *4*, 2621. (b) Trost, B. M.; Yeh, V. S. C. *Org. Lett.* **2002**, *4*, 3513. (c) Trost, B. M.; Frederiksen, M. U.; Papillon, J. P. N.; Harrington, P. E.; Shin, S.; Shireman, B. T. *J. Am. Chem. Soc.* **2005**, *127*, 3666. (d) Trost, B. M.; Weiss, A. H. *Org. Lett.* **2006**, *8*, 4461. (e) Trost, B. M.; Weiss, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7664. (f) Trost, B. M.; Michaelis, D. J.; Malhotra, S. *Org. Lett.* **2013**, *15*, 5274. (g) Trost, B. M.; Quintard, A. *Org. Lett.* **2012**, *14*, 4698. (h) Trost, B. M.; Biannic, B.; Brindle, C. S.; O'Keefe, B. M.; Hunter, T. J.; Ngai, M. Y. *J. Am. Chem. Soc.* **2015**, *137*, 11594.

(11) Wang, B.-L.; Li, N.-N.; Zhang, J.-X.; Liu, G.-G.; Liu, T.; Shen, Q.; Wang, X.-W. *Org. Biomol. Chem.* **2011**, *9*, 2614.

(12) Zhao, D.; Mao, L.; Wang, Y.; Yang, D.; Zhang, Q.; Wang, R. *Org. Lett.* **2010**, *12*, 1880.

(13) Beenen, M. A.; Weix, D. J.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 6304.

(14) (a) Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933. (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941. (c) Lam, P. Y. S.; Bonne, D.; Vincent, G.; Clark, C. G.; Combs, A. P. *Tetrahedron Lett.* **2003**, *44*, 1691. (d) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett.* **2003**, *44*, 4927.

(15) Kerschgens, I. P.; Claveau, E.; Wanner, M. J.; Ingemann, S.; van Maarseveen, J. H.; Hiemstra, H. *Chem. Commun.* **2012**, *48*, 12243.

(16) Singh, J.; Zeller, W.; Zhou, N.; Hategan, G.; Mishra, R. K.; Polozov, A.; Yu, P.; Onua, E.; Zhang, J.; Ramírez, J. L.; Sigthorsson, G.; Thorsteinnsdottir, M.; Kiselyov, A. S.; Zembower, D. E.; Andresson, T.; Gurney, M. E. *J. Med. Chem.* **2010**, *53*, 18.

(17) Boruah, P. R.; Ali, A. A.; Saikia, B.; Sarma, D. *Green Chem.* **2015**, *17*, 1442.

(18) (a) Davis, F. A.; McCoull, W. *J. Org. Chem.* **1999**, *64*, 3396. (b) Huang, W.; Ye, J.-h.; Zheng, W.; Dong, H.-Q.; Wei, B.-G. *J. Org. Chem.* **2013**, *78*, 11229.

(19) Gao, X.-W.; Meng, Q.-Y; Li, J.-X.; Zhong, J.-J.; Lei, T.; Li, X.-B.; Tung, C.-H.; Wu, L.-Z. *ACS Catal.* **2015**, *5*, 2391.

DOI: 10.1021/acs.joc.6b01805
J. Org. Chem. 2016, 81, 9227−9234