Tetrahedron 65 (2009) 1603–1607

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Enantioselective synthesis of (3-indolyl)glycine derivatives via asymmetric Friedel–Crafts reaction between indoles and glyoxylate imines

Qiang Kang, Zhuo-An Zhao, Shu-Li You *

*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China*

ARTICLE INFO

*Article history:*
Received 12 October 2008
Received in revised form 17 December 2008
Accepted 19 December 2008
Available online 25 December 2008

ABSTRACT

Chiral phosphoric acid-catalyzed enantioselective Friedel–Crafts reaction of indoles with ethyl glyoxylate imines was developed. With 10 mol % of the catalyst, the Friedel–Crafts reactions between a wide range of indoles and imines have been carried out, affording optically active (3-indolyl)glycine derivatives with excellent yields and high enantioselectivities (up to 87% ee).



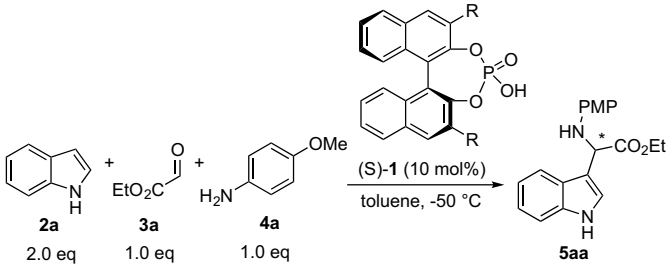
## 1. Introduction

(3-Indolyl)glycine derivatives are an important class of non-proteinogenic amino acids, which are very useful synthetic intermediates or building blocks for numerous biologically important compounds such as dragmacidins and pemedolac.[1,2] Among the current methods for the synthesis of this class of compounds,[3] Friedel–Crafts reaction[4,5] of indole with glyoxylate imine represents one of the most direct accesses.[6] Moreover, to our knowledge, the catalytic asymmetric synthesis of this class of compound is limited to the addition of *N*-tosylimino esters of ethyl glyoxylate to indoles promoted by a chiral copper complex.[7] In our group, we recently found that chiral phosphoric acid[8,9] could catalyze efficiently the asymmetric Friedel–Crafts reaction of indoles and dihydroindoles with *N*-tosylimines.[9a,c] The reactions provide facile synthesis of 3-indolyl methanamine and 2-indolyl methanamine derivatives, respectively. As part of our continuing efforts on the chiral phosphoric acid-catalyzed Friedel–Crafts reaction of indole with imines,[10] we recently realized the asymmetric Friedel–Crafts reaction of indoles with glyoxylate imines. The reaction proceeds smoothly to afford (3-indolyl)glycine derivatives in good yields with good enantiomeric excesses. Notably, during the preparation of this manuscript, Hiemstra et al. reported chiral phosphoric acid-catalyzed Friedel–Crafts reactions of tritylsulfenyl- and 2-nitrophenylsulfenyl-substituted glyoxyl imines with indole.[11] The results for other imine substrates and substituted indoles have not been disclosed in their paper. Herein, we report our results on the asymmetric Friedel–Crafts reactions between a wide range of indoles and imines.

## 2. Results and discussion

We first examined the reaction of indole **2a**, ethyl glyoxylate **3a**, and *p*-anisidine **4a** catalyzed by different chiral phosphoric acids. The results are summarized in Table 1. With 10 mol % of **1**, all reactions proceeded smoothly at −50 °C in toluene and afforded the desired product with variable enantiomeric excesses (<1–73% ee,

**Table 1**
Screening of phosphoric acids **1** in enantioselective Friedel–Crafts reaction



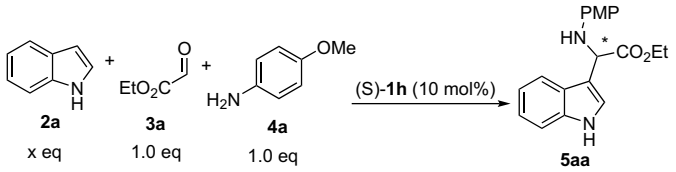

| Entry[a] | **1**, R | Time (min) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | **1a**, phenyl | 10 | 98 | 36 |
| 2 | **1b**, $SiPh_3$ | 10 | 80 | 3 |
| 3 | **1c**, 3,5-$(CF_3)_2C_6H_3$ | 10 | 92 | −7 |
| 4 | **1d**, 4-$NO_2$-$C_6H_4$ | 10 | 82 | −7 |
| 5 | **1e**, 1-naphthyl | 10 | 91 | 45 |
| 6 | **1f**, 2-naphthyl | 10 | 88 | 39 |
| 7 | **1g**, 9-anthryl | 10 | 90 | 36 |
| 8 | **1h**, 9-phenanthryl | 10 | 91 | 73 |
| 9 | **1i**, 2,4,6-(*i*-Pr)$_3C_6H_2$ | 10 | 98 | 26 |
| 10 | **1j**, 4-biphenyl | 10 | 91 | <1 |

[a] Reaction conditions: 10 mol % of **1**, 0.125 mol/L of **3a** in toluene at −50 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H).

* Corresponding author. Tel.: +86 21 5492 5085; fax: +86 21 5492 5087.
*E-mail address:* slyou@mail.sioc.ac.cn (S.-L. You).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.12.061

**Table 2**
Optimization of the reaction conditions



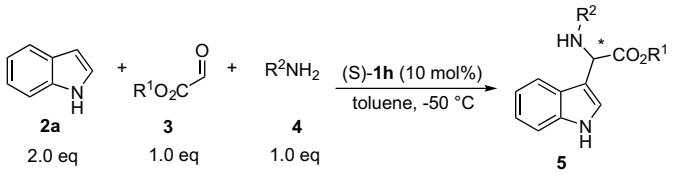

| Entry[a] | *x* (equiv) | Solvent | *T* (°C) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | 2.0 | Toluene | −40 | 99 | 70 |
| 2 | 2.0 | Toluene | −50 | 91 | 73 |
| 3 | 2.0 | Toluene | −60 | 99 | 71 |
| 4 | 2.0 | Toluene | −70 | 99 | 70 |
| 5 | 1.0 | Toluene | −50 | 90 | 40 |
| 6 | 3.0 | Toluene | −50 | 95 | 74 |
| 7 | 2.0 | $CH_2Cl_2$ | −50 | 93 | 69 |
| 8 | 2.0 | THF | −50 | 85 | 19 |
| 9 | 2.0 | $Et_2O$ | −50 | 50 | 33 |
| 10 | 2.0 | EtOAc | −50 | 66 | 32 |
| 11[d] | 2.0 | Toluene | −50 | 98 | 49 |
| 12[e] | 2.0 | Toluene | −50 | 95 | 64 |

[a] Reaction conditions: 10 mol % of (*S*)-**1h**, *x* equiv of **2a**, 0.125 mol/L of **3a** unless noted otherwise.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H).
[d] Compound **3a** (0.25 mol/L).
[e] Compound **3a** (0.025 mol/L).

Table 1). The best result was obtained with 10 mol % of **1h**, bearing two 9-phenanthryl groups at the 3,3′ positions of the binaphthyl scaffold, providing the addition product **5aa** in 91% yield with 73% ee (entry 8, Table 1).

We further optimized the reaction conditions by using the chiral phosphoric acid **1h** as the catalyst. The results are summarized in Table 2. Firstly we investigated the effect of the reaction temperature. In general, low temperature resulted in a slight decrease of the enantioselectivity but no effect on the reaction rate (73–70% ee, from −50 °C to −70 °C, entries 2–4, Table 2). The suitable amount of indole was examined by running the reaction at −50 °C. There was almost no difference on the outcome of the reaction by using either 3 or 2 equiv of indole. However, with 1 equiv of indole, the product was obtained with only 40% ee (entries 5 and 6, Table 2). Different solvents were then tested for the reaction with 10 mol % of **1h** and 2 equiv of indole **2a** at −50 °C. The reaction in $CH_2Cl_2$ afforded **5aa** in 93% yield but with a slight drop of enantioselectivity (69% ee, entry 7, Table 2). A significant drop of enantioselectivity was observed for many other solvents tested such as THF, $Et_2O$, and EtOAc (entries 8–10, Table 2). Interestingly, lower enantioselectivities were observed with either higher or lower substrate concentration (entries 11 and 12, Table 2).

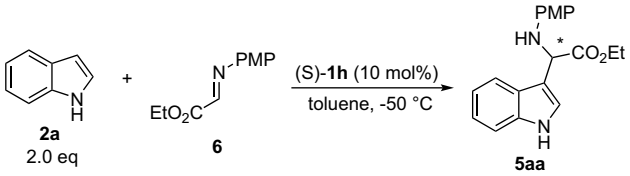
**Table 3**
Effect of the glyoxylates and aryl amines




| Entry[a] | $R^1$ | $R^2$ | **5**, yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | Et | 4-$MeOC_6H_4$, **4a** | **5aa**, 91 | 73 |
| 2 | Bn | 4-$MeOC_6H_4$, **4a** | **5ab**, 85 | 39 |
| 3 | Et | 2-Me-4-$MeOC_6H_3$, **4b** | **5ac**, 92 | 34 |
| 4 | Et | 3,4-$(MeO)_2C_6H_3$, **4c** | — | — |
| 5 | Et | 3,4,5-$(MeO)_3C_6H_2$, **4d** | — | — |
| 6 | Et | 2,5-$(MeO)_2C_6H_3$, **4e** | — | — |

[a] Reaction conditions: 10 mol % of (*S*)-**1h**, 2 equiv of **2a**, 0.125 mol/L of **3a** in toluene at −50 °C for 10 min.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H).

**Table 4**
Effects of syringe pump addition and molecular sieves



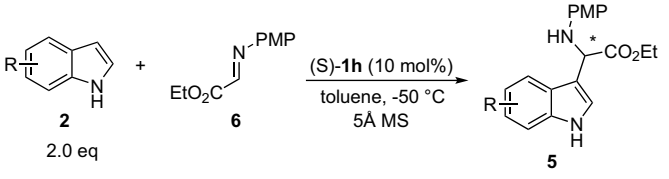

| Entry[a] | Additive | Time (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | — | 1.5 | 89 | 79 |
| 2 | 3 Å MS | 1.5 | 86 | 85 |
| 3 | 4 Å MS | 1.5 | 88 | 82 |
| 4 | 5 Å MS | 1.5 | 90 | 87 |

[a] Reaction conditions: 10 mol % of (*S*)-**1h**, 2 equiv of **2a**, addition of **6** was performed through a syringe pump over 1.5 h.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H).

In the presence of 10 mol % of **1h** and 2 equiv of **2a**, a variety of glyoxylates **3** and electron-rich aryl amines **4** have been investigated under the reaction conditions. The results are summarized in Table 3. The effect of different esters was first examined. When a bulky ester group was introduced to the reaction, such as Bn, the product was obtained with only 39% ee (entry 2, Table 3). When amine **4b** was examined, a significant drop of ee was observed (34% ee, entry 3, Table 3). This is likely due to the *ortho*-substituted effect. Unfortunately, a complicated mixture was obtained when several other electron-rich aryl amines such as **4c–e** were used (entries 4–6, Table 3).

It should be noted that the reaction was complete in 10 min even without the catalyst. We hypothesized that the moderate enantioselectivity of the reaction might be partially resulted from this strong background reaction. In order to overcome this, addition of ethyl glyoxylate imine **6** to the reaction mixture through a syringe pump (1.5 h) was carried out to keep the high catalyst/imine ratio during the reaction. To our delight, the reaction afforded the product with 79% ee (entry 1, Table 4) by applying this

**Table 5**
Enantioselective Friedel–Crafts reaction of indoles with glyoxylate imines.




| Entry[a] | R | Product (**5**) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | H, **2a** | **5aa** | 90 | 87 |
| 2 | 2-Me, **2b** | **5ba** | 91 | 51 |
| 3 | 5-Me, **2c** | **5ca** | 91 | 85 |
| 4 | 5-OMe, **2d** | **5da** | 93 | 79 |
| 5 | 6-OBn, **2e** | **5ea** | 90 | 87 |
| 6 | 5-Br, **2f** | **5fa** | 91 | 73 |
| 7 | 5-F, **2g** | **5ga** | 91 | 74 |
| 8 | 6-Br, **2h** | **5ha** | 85 | 57 |

[a] Reaction conditions: 10 mol % of (*S*)-**1h**, 2 equiv of **2**, addition of **6** was performed through a syringe pump over 1.5 h.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis.

methodology. In addition, we found that higher ees were obtained by using molecular sieves (MS) as additives (entries 2–4, Table 4). Particularly, with 5 Å MS, the reaction afforded the desired product in 90% yield with 87% ee (entry 4, Table 4).

Under the above optimized reaction conditions (entry 4, Table 4), various substituted indoles were examined to test the generality of the reaction, as summarized in Table 5. The phosphoric acid-catalyzed Friedel–Crafts reaction of indoles **2** with ethyl glyoxylate imine **6** was found to be general with indoles bearing different substituents. For the substrates with electron-donating group such as **2c**–**e**, the reaction went smoothly, affording the products with high yields and good enantioselectivities (entries 3–5, Table 5). Unfortunately, only moderate ee was obtained when 2-Me substituted indole was tested (51% ee, entry 2, Table 5). By introducing an electron-withdrawing group into the indole, we observed a drop of the enantioselectivity. In the case of **2f** and **2g** having the 5-Br and 5-F group, 73% and 74% ee were given, respectively (entries 6 and 7, Table 5). 6-Br substituted indole **2h** led to the addition product **5ha** with 57% ee (entry 8, Table 5).

## 3. Conclusion

In summary, we have developed the enantioselective Friedel–Crafts reaction of indoles with ethyl glyoxylate imine by utilizing chiral phosphoric acid as the catalyst. Although a strong background reaction was observed, excellent yields and high enantioselectivities (up to 87%) were obtained for a wide range of substrates by combining the slow addition of the imine substrates and the use of molecular sieve additive. The reaction features including metal-free approach, mild reaction conditions, and suitability of three-component operation make the current methodology a potentially useful synthesis of optically active (3-indolyl)glycine derivatives.

## 4. Experimental section

### 4.1. General methods

Unless stated otherwise, all reactions were carried out in flame-dried glassware under a dry argon atmosphere. All solvents were purified and dried according to standard methods prior to use. $^1$H and $^{13}$C NMR spectra were recorded on a Varian instrument (300 MHz and 75 MHz, respectively) and internally referenced to tetramethylsilane signal or residual protio solvent signals. Data for $^1$H NMR are recorded as follows: chemical shift ($\delta$, ppm), multiplicity (s=singlet, d=doublet, t=triplet, m=multiplet or unresolved, br=broad singlet, coupling constant(s) in hertz, integration). Data for $^{13}$C NMR are reported in terms of chemical shift ($\delta$, ppm).

### 4.2. General procedure for the catalytic asymmetric Friedel–Crafts reaction (Table 5)

In a dry Schlenk tube, indole **2** (0.50 mmol) and chiral phosphoric acid **1h** (17.6 mg, 0.025 mmol) were dissolved in toluene (1 mL) under argon. The solution was stirred for 10 min at room temperature and then for another 5 min at −50 °C. Subsequently, at this temperature, ethyl glyoxylate imine **6** (0.25 mmol) in toluene (2 mL) was added through a syringe pump during 1.5 h. After the reaction was complete (monitored by TLC), saturated $NaHCO_3$ (3 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (10 mL). The organic layer was washed with brine (5 mL), separated, and dried over anhydrous $Na_2SO_4$. The solvents were removed under reduced pressure and the residue was purified by column chromatography (ethyl acetate/petroleum ether 1/5 to 1/3) to afford product **5**.

#### 4.2.1. Ethyl 2-(1H-indol-3-yl)-2-(4-methoxyphenylamino)-acetate (*5aa*)

Colorless oil, 90% yield, 87% ee; $[\alpha]_D^{20}$ −54.1 (*c* 1.0, acetone). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.22 (t, *J*=7.2 Hz, 3H), 3.72 (s, 3H), 4.09–4.28 (m, 2H), 5.33 (s, 1H), 6.62 (d, *J*=9.0 Hz, 2H), 6.75 (d, *J*=9.0 Hz, 2H), 7.12–7.23 (m, 3H), 7.32 (d, *J*=8.1 Hz, 1H), 7.82 (d, *J*=7.2 Hz, 1H), 8.55 (br, 1H). The enantiomeric ratio was determined by Daicel Chiralcel OD-H (25 cm), Hexanes/IPA=70/30, 0.7 mL/min, $\lambda$=254 nm, $t_R$ (major)=12.32 min, $t_R$ (minor)=14.95 min.

#### 4.2.2. Benzyl 2-(1H-indol-3-yl)-2-(4-methoxyphenylamino)-acetate (*5ab*)

Colorless oil, 85% yield, 39% ee; $[\alpha]_D^{20}$ −16.4 (*c* 1.0, acetone). $^1$H NMR (300 MHz, $CDCl_3$) 3.72 (s, 3H), 4.48 (br, 1H), 5.23 (AB, $J_{AB}$=12.3 Hz, 1H), 5.23 (BA, $J_{BA}$=12.0 Hz, 1H), 5.39 (s, 1H), 6.59 (d, *J*=9 Hz, 2H), 6.72 (d, *J*=9 Hz, 2H), 7.11–7.29 (m, 8H), 7.34 (d, *J*=8.1 Hz, 1H), 7.78 (d, *J*=8.1 Hz, 1H), 8.17 (br, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 55.2, 55.6, 67.0, 111.4, 114.7, 114.8, 114.9, 116.4, 119.4, 119.9, 122.5, 123.1, 125.7, 128.1, 128.2, 128.4, 135.4, 136.3, 140.6, 152.5, 172.7. IR (film) 3405, 3302, 2957, 1743, 1515, 1457, 1232, 1173, 1141, 1030, 819, 743 cm$^{-1}$. LRMS (EI): *m*/*z* (% relative intensity) 386 ($M^+$, 14), 251 (100). HRMS (EI) exact mass calculated for ($C_{24}H_{22}N_2O_3$) requires *m*/*z* 386.1633, found *m*/*z* 386.1630. The enantiomeric ratio was determined by Daicel Chiralcel OD-H (25 cm), Hexanes/IPA=75/25, 1.0 mL/min, $\lambda$=254 nm, $t_R$ (major)=14.54 min, $t_R$ (minor)=17.53 min.

#### 4.2.3. Ethyl 2-(1H-indol-3-yl)-2-(4-methoxy-2-methylphenylamino)acetate (*5ac*)

Colorless oil, 92% yield, 34% ee; $[\alpha]_D^{20}$ −12.7 (*c* 1.0, acetone). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.20 (t, *J*=7.2 Hz, 3H), 2.20 (s, 3H), 3.71 (s, 3H), 4.08–4.30 (m, 2H), 4.38 (br, 1H), 5.36 (s, 1H), 6.50 (d, *J*=8.7 Hz, 1H), 6.59–6.63 (m, 1H), 6.70–6.71 (m, 1H), 7.12–7.23 (m, 3H), 7.32 (d, *J*=7.8 Hz, 1H), 7.84 (d, *J*=7.8 Hz, 1H), 8.24 (br, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.0, 17.7, 55.0, 55.5, 61.5, 111.4, 111.4, 111.8, 112.4, 116.9, 119.4, 119.8, 122.3, 123.1, 124.5, 125.7, 136.4, 138.8, 151.9, 173.0. IR (film) 3409, 2982, 2907, 1732, 1512, 1458, 1293, 1220, 1196, 1050, 803, 745 cm$^{-1}$. LRMS (EI): *m*/*z* (% relative intensity) 338 ($M^+$, 32), 265 (100). HRMS (EI) exact mass calculated for ($C_{20}H_{22}N_2O_3$) requires *m*/*z* 338.1623, found *m*/*z* 338.1630. The enantiomeric ratio was determined by Daicel Chiralcel AD-H (25 cm), Hexanes/IPA=80/20, 1.0 mL/min, $\lambda$=254 nm, $t_R$ (major)=12.59 min, $t_R$ (minor)=14.51 min.

#### 4.2.4. Ethyl 2-(4-methoxyphenylamino)-2-(2-methyl-1H-indol-3-yl)acetate (*5ba*)

Colorless oil, 91% yield, 51% ee; $[\alpha]_D^{20}$ −51.2 (*c* 1.0, acetone). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.15 (t, *J*=7.5 Hz, 3H), 2.40 (s, 3H), 3.69 (s, 3H), 4.01–4.25 (m, 2H), 4.50 (br, 1H), 5.21 (s, 1H), 6.57 (d, *J*=8.7 Hz, 2H), 6.72 (d, *J*=8.7 Hz, 2H), 7.07–7.23 (m, 3H), 7.75–7.79 (m, 1H), 8.01 (br, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 12.0, 14.1, 54.8, 55.6, 61.3, 107.5, 110.4, 114.5, 114.7, 118.7, 119.7, 121.3, 126.7, 133.3, 135.0, 140.9, 152.3, 172.6. The enantiomeric ratio was determined by Daicel Chiralcel OD-H (25 cm), Hexanes/IPA=80/20, 1.0 mL/min, $\lambda$=254 nm, $t_R$ (major)=10.33 min, $t_R$ (minor)=12.73 min.

#### 4.2.5. Ethyl 2-(4-methoxyphenylamino)-2-(5-methyl-1H-indol-3-yl)acetate (*5ca*)

White solid, 91% yield, 85% ee; $[\alpha]_D^{20}$ −55.2 (*c* 1.0, acetone). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.19 (t, *J*=6.9 Hz, 3H), 2.45 (s, 3H), 3.71 (s, 3H), 4.07–4.26 (m, 2H), 4.44 (br, 1H), 5.28 (s, 1H), 6.61 (d, *J*=9.3 Hz, 2H), 6.75 (d, *J*=9.0 Hz, 2H), 7.00–7.05 (m, 2H), 7.14–7.21 (m, 1H), 7.59 (s, 1H), 8.01 (br, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.0,

21.5, 55.1, 55.6, 61.4, 111.1, 111.7, 114.7, 118.9, 123.2, 124.0, 125.9, 129.1, 134.6, 140.7, 152.4, 173.0. IR (film) 3324, 3126, 2885, 1729, 1510, 1463, 1174, 1036, 839, 797, 746 $cm^{-1}$. LRMS (EI): *m*/*z* (%relative intensity) 338 ($M^+$, 36), 123 (100). HRMS (EI) exact mass calculated for ($C_{20}H_{22}N_2O_3$) requires *m*/*z* 338.1630, found *m*/*z* 338.1638. The enantiomeric ratio was determined by Daicel Chiralcel OD-H (25 cm), Hexanes/IPA=70/30, 1.0 mL/min, $\lambda$=254 nm, $t_R$ (major)=9.69 min, $t_R$ (minor)=12.00 min; mp: 125–126 °C.

#### 4.2.6. Ethyl 2-(5-methoxy-1H-indol-3-yl)-2-(4-methoxyphenylamino)acetate (**5da**)

White solid, 93% yield, 79% ee; $[\alpha]_D^{20}$ −41.6 (*c* 1.0, acetone). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.20 (t, *J*=6.9 Hz, 3H), 3.71 (s, 3H), 3.84 (s, 3H), 4.08–4.27 (m, 2H), 4.46 (br, 1H), 5.27 (s, 1H), 6.61 (d, *J*=9.0 Hz, 2H), 6.75 (d, *J*=9.0 Hz, 2H), 6.83–6.87 (m, 1H), 7.09–7.24 (m, 3H), 8.01 (br, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.1, 55.1, 55.6, 55.7, 61.5, 100.8, 112.0, 112.2, 112.7, 114.7, 114.8, 123.7, 126.1, 131.4, 140.7, 152.4, 154.1, 172.9. The enantiomeric ratio was determined by Daicel Chiralcel OD-H (25 cm), Hexanes/IPA=70/30, 1.0 mL/min, $\lambda$=254 nm, $t_R$ (major)=12.93 min, $t_R$ (minor)=14.81 min.

#### 4.2.7. Ethyl 2-(6-(benzyloxy)-1H-indol-3-yl)-2-(4-methoxyphenylamino)acetate (**5ea**)

Colorless oil, 90% yield, 87% ee; $[\alpha]_D^{20}$ −47.0 (*c* 1.0, acetone). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.18 (t, *J*=7.5 Hz, 3H), 3.69 (s, 3H), 4.06–4.25 (m, 2H), 4.44 (br, 1H), 5.01 (s, 2H), 5.26 (s, 1H), 6.60 (d, *J*=8.7 Hz, 2H), 6.73 (d, *J*=8.7 Hz, 2H), 6.77–6.78 (m, 1H), 6.88–6.97 (m, 2H), 7.30–7.43 (m, 5H), 7.68 (d, *J*=8.7 Hz, 1H), 8.16 (br, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.1, 55.2, 55.6, 61.5, 70.4, 95.9, 110.7, 112.3, 114.7, 114.8, 120.1, 120.2, 121.9, 127.4, 127.8, 128.5, 137.0, 137.2, 140.7, 152.4, 155.7, 172.8. IR (film) 3116, 1737, 1625, 1511, 1276, 1237, 1174, 1032, 1012, 696 $cm^{-1}$. LRMS (EI): *m*/*z* (%relative intensity) 430 ($M^+$, 17), 123 (100). HRMS (EI) exact mass calculated for ($C_{26}H_{26}N_2O_4$) requires *m*/*z* 430.1893, found *m*/*z* 430.1891. The enantiomeric ratio was determined by Daicel Chiralcel AD-H (25 cm), Hexanes/IPA=70/30, 1.0 mL/min, $\lambda$=254 nm, $t_R$ (major)=53.63 min, $t_R$ (minor)=68.02 min.

#### 4.2.8. Ethyl 2-(5-bromo-1H-indol-3-yl)-2-(4-methoxyphenylamino)acetate (**5fa**)

Colorless oil, 91% yield, 73% ee; $[\alpha]_D^{20}$ −39.9 (*c* 1.0, acetone). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.21 (t, *J*=7.5 Hz, 3H), 3.71 (s, 3H), 4.09–4.27 (m, 3H), 5.25 (s, 1H), 6.59 (d, *J*=8.7 Hz, 2H), 6.74 (d, *J*=8.7 Hz, 2H), 7.10–7.14 (m, 2H), 7.24–7.27 (m, 1H), 7.69 (s, 1H), 8.48 (br, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.0, 54.9, 55.6, 61.7, 112.1, 112.9, 113.1, 114.7, 114.8, 122.0, 124.3, 125.2, 127.3, 135.0, 140.4, 152.5, 172.6. The enantiomeric ratio was determined by Daicel Chiralcel OD-H (25 cm), Hexanes/IPA=70/30, 1.0 mL/min, $\lambda$=254 nm, $t_R$ (major)=8.00 min, $t_R$ (minor)=10.03 min.

#### 4.2.9. Ethyl 2-(5-fluoro-1H-indol-3-yl)-2-(4-methoxyphenylamino)acetate (**5ga**)

Colorless oil, 91% yield, 74% ee; $[\alpha]_D^{20}$ −37.6 (*c* 1.0, acetone). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.20 (t, *J*=7.2 Hz, 3H), 3.70 (s, 3H), 4.08–4.27 (m, 2H), 4.48 (br, 1H), 5.24 (s, 1H), 6.58 (d, *J*=9.0 Hz, 2H), 6.74 (d, *J*=9.0 Hz, 2H), 6.89–6.96 (m, 1H), 7.14–7.20 (m, 2H), 7.44–7.48 (m, 1H), 8.41 (br, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.0, 55.1, 55.6, 61.6, 104.4 (d, *J*=23.9 Hz), 110.8 (d, *J*=26.3 Hz), 112.1 (d, *J*=9.7 Hz), 112.6 (d, *J*=4.6 Hz), 114.8 (d, *J*=6.3 Hz), 124.8, 126.0 (d, *J*=10.3 Hz), 132.9, 140.5, 152.5, 156.2, 159.4, 172.6. IR (film) 3409, 2984, 2734, 1512, 1239, 1179, 936, 823, 799, 737, 622 $cm^{-1}$. LRMS (EI): *m*/*z* (%relative intensity) 342 ($M^+$, 27), 269 (100). HRMS (EI) exact mass calculated for ($C_{19}H_{19}N_2O_3F$) requires *m*/*z* 342.1380, found *m*/*z* 342.1387. The enantiomeric ratio was determined by Daicel Chiralcel OD-H (25 cm), Hexanes/IPA=80/20, 1.0 mL/min, $\lambda$=254 nm, $t_R$ (major)=11.12 min, $t_R$ (minor)=12.76 min.

#### 4.2.10. Ethyl 2-(6-bromo-1H-indol-3-yl)-2-(4-methoxyphenylamino)acetate (**5ha**)

Colorless oil, 85% yield, 57% ee; $[\alpha]_D^{20}$ −36.3 (*c* 1.0, acetone). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.19 (t, *J*=7.5 Hz, 3H), 3.71 (s, 3H), 4.08–4.26 (m, 2H), 4.49 (br, 1H), 5.27 (s, 1H), 6.59 (d, *J*=8.7 Hz, 2H), 6.74 (d, *J*=8.7 Hz, 2H), 7.07 (d, *J*=2.4 Hz, 2H), 7.21–7.25 (m, 1H), 7.38 (s, 1H), 7.66 (d, *J*=8.7 Hz, 1H), 8.47 (br, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.0, 55.0, 55.6, 61.6, 112.6, 114.3, 114.8, 114.9, 115.9, 120.7, 123.1, 123.7, 124.5, 137.1, 140.4, 152.5, 172.6. The enantiomeric ratio was determined by Daicel Chiralcel OD-H (25 cm), Hexanes/IPA=80/20, 1.0 mL/min$^{-1}$, $\lambda$=254 nm, $t_R$ (major)=10.59 min, $t_R$ (minor)=12.67 min.

## Acknowledgements

We thank the National Natural Science Foundation of China, National Basic Research Program of China (973 Program 2009CB825300), the Knowledge Innovation Program of the Chinese Academy of Sciences, and the Science and Technology Commission of Shanghai Municipality (07pj14106, 07JC14063) for generous financial support.

## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.12.061.

## References and notes

1. (a) Kawasaki, T.; Ohno, K.; Enoki, H.; Umemoto, Y.; Sakamoto, M. *Tetrahedron Lett.* **2002**, *43*, 4245; (b) Kawasaki, T.; Enoki, H.; Matsumura, K.; Ohyama, M.; Inagawa, M.; Sakamoto, M. *Org. Lett.* **2000**, *2*, 3027; (c) Yang, C. G.; Wang, J.; Tang, X. X.; Jiang, B. *Tetrahedron: Asymmetry* **2002**, *13*, 383.
2. 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.
3. Jiang, B.; Huang, Z.-G. *Synthesis* **2005**, 2198 and references cited therein.
4. For reviews of Friedel–Crafts reaction: (a) Olah, G. A. *Friedel–Crafts and Related Reactions*; Wiley: New York, NY, 1963; (b) Olah, G. A. *Friedel–Crafts Chemistry*; Wiley: New York, NY, 1973; (c) Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, p 293; (d) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550; (e) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903; (f) Sheng, Y.-F.; Zhang, A.-J.; Zheng, X.-J.; You, S.-L. *Chin. J. Org. Chem.* **2008**, *28*, 605.
5. For selected examples: (a) Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030; (b) Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154; (c) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942; (d) Jia, Y.-X.; Xie, J.-H.; Duan, H.-F.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 1621; (e) Lu, S.-F.; Du, D.-M.; Xu, J. *Org. Lett.* **2006**, *8*, 2115; (f) Li, H.; Wang, Y.-Q.; Deng, L. *Org. Lett.* **2006**, *8*, 4063; (g) Zhao, J.-L.; Liu, L.; Sui, Y.; Liu, Y.-L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2006**, *8*, 6127; (h) Li, C.-F.; Liu, H.; Liao, J.; Cao, Y.-J.; Liu, X.-P.; Xiao, W.-J. *Org. Lett.* **2007**, *9*, 1847; (i) Yang, H.; Hong, Y.-T.; Kim, S. *Org. Lett.* **2007**, *9*, 2281; (j) Blay, G.; Fernández, I.; Pedro, J. R.; Vila, C. *Org. Lett.* **2007**, *9*, 2601; (k) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404; (l) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029; (m) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485; (n) Chen, W.; Du, W.; Yue, L.; Li, R.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Org. Biomol. Chem.* **2007**, *5*, 816; (o) Liu, T.-Y.; Cui, H.-L.; Chai, Q.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Chem. Commun.* **2007**, 2228; (p) Liu, W.-B.; He, H.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2008**, *10*, 1815; (q) Trost, B. M.; Müller, C. *J. Am. Chem. Soc.* **2008**, *130*, 2438.
6. (a) Hao, J.; Taktak, S.; Aikawa, K.; Yusa, Y.; Hatano, M.; Mikami, K. *Synlett* **2001**, 1443; (b) Jiang, B.; Yang, C.-G.; Gu, X.-H. *Tetrahedron Lett.* **2001**, *42*, 2545; (c) Janczuk, A.; Zhang, W.; Xie, W.; Lou, S.; Cheng, J.; Wang, P. G. *Tetrahedron Lett.* **2002**, *43*, 4271; (d) Lei, F.; Chen, Y.-J.; Sui, Y.; Liu, L.; Wang, D. *Synlett* **2003**, 1160; (e) Shirakawa, S.; Berger, R.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 2858; (f) Zhao, J.-L.; Liu, L.; Zhang, H.-B.; Wu, Y.-C.; Wang, D.; Chen, Y.-J. *Synlett* **2006**, 96; (g) Soueidan, M.; Collin, J.; Gil, R. *Tetrahedron Lett.* **2006**, *47*, 5467.
7. Johannsen, M. *Chem. Commun.* **1999**, 2233.

8. For reviews: (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520; (b) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999; (c) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909; (d) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.
9. (a) Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484; (b) Kang, Q.; Zhao, Z.-A.; You, S.-L. *Adv. Synth. Catal.* **2007**, *349*, 1657; (c) Kang, Q.; Zhen, X.-J.; You, S.-L. *Chem.—Eur. J.* **2008**, *14*, 3539; (d) Kang, Q.; Zhao, Z.-A.; You, S.-L. *Org. Lett.* **2008**, *10*, 2031; (e) Mi, Z.; Kang, Q.; He, Q.-L.; You, S.-L. *Adv. Synth. Catal.* **2008**, *350*, 2169.
10. For enantioselective Friedel–Crafts reaction catalyzed by the chiral phosphoric acids, see: (a) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804; (b) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292; (c) Terada, M.; Yokoyama, S.; Sorimachi, K.; Uraguchi, D. *Adv. Synth. Catal.* **2007**, *349*, 1863; (d) Jia, Y.; Zhong, J.; Zhu, S.; Zhang, C.; Zhou, Q. *Angew. Chem., Int. Ed.* **2007**, *46*, 5565; (e) Rowland, G. B.; Rowland, E. B.; Liang, Y.; Perman, J. A.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 2609; (f) Li, G.; Rowland, G. B.; Rowland, E. B.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 4065; (g) Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 593; (h) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 4016; (i) Tang, H.-Y.; Lu, A.-D.; Zhou, Z.-H.; Zhao, G.-F.; He, L.-N.; Tang, C.-C. *Eur. J. Org. Chem.* **2008**, 1406.
11. Wanner, M. J.; Hauwert, P.; Schoemaker, H. E.; Gelder, R.; Maarseveen, J. H.; Hiemstra, H. *Eur. J. Org. Chem.* **2008**, 180.