CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200902705

Chiral Brønsted Acid Directed Iron-Catalyzed Enantioselective Friedel–Crafts Alkylation of Indoles with β-Aryl α′-Hydroxy Enones

Lei Yang, Qiming Zhu, Shengmei Guo, Bo Qian, Chungu Xia,* and Hanmin Huang*[a]

Abstract: A cooperative catalytic system established by the combination of an iron salt and a chiral Brønsted acid has proven to be effective in the asymmetric Friedel–Crafts alkylation of indoles with β-aryl α′-hydroxy enones. Good to excellent yields and enatioselectivities were observed for a variety of α′-hydroxy enones and indoles, particularly for the β-aryl α′-hydroxy enones bearing an electron-withdrawing group at the *para* position of the phenyl ring (up to 90% yield and 91% *ee*). The proton of the chiral Brønsted acid, the Lewis acid activation site, as well as the inherent basic site for the hydrogen-bonding interaction of the Brønsted acid are responsible for the high catalytic activities and enantioselectivities of the title reaction. A possible reaction mechanism was proposed. The key catalytic species in the catalytic system, the phosphate salt of Fe^{III}, which was thought to be responsible for the high activity and good enantioselectivity, was then confirmed by ESIMS studies.

Keywords: alkylation · asymmetric catalysis · Brønsted acids · iron · proton acceleration

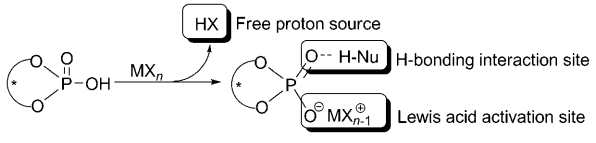
Introduction

Cooperative asymmetric catalysis through the combination of metal complexes and organocatalysts has experienced significant growth over the last several years,[1] as this strategy has the ability to realize some new asymmetric transformations by mutual activation and organization of reactants that are different to those promoted by the metal catalysts or organocatalysts alone. Both transition-metal catalysis and organocatalysis have been applied to a broad range of organic transformations in synthetic organic chemistry,[2] but asymmetric catalysis by using this strategy is still in its developmental stages by comparison.[3]

Proton transfer is among the most elementary of reaction steps in many chemical reactions that have played an important role in both chemistry and biology.[4] In Lewis acid catalyzed Michael-type Friedel–Crafts alkylation of indoles with α,β-unsaturated compounds, which is among the most important C–C bond-forming reactions in organic synthesis,[5,6] fast proton transfer from the indole moiety to newly generated enolate components is required, but this step is often slow and catalyst turnover is limited significantly. To overcome this problem, some proton sources such as alcohols and protic acids have usually been applied as additives to accelerate the proton-transfer step and thus facilitate the catalytic turnover.[7] Given that Lewis acid metal complexes can catalyze Friedel–Crafts reactions and that an appropriate proton source might facilitate the catalytic turnover, we envisioned that this kind of asymmetric reaction could be realized by using a cooperative catalytic system with a Lewis acid site for activating the electrophile, a base site for activating the nucleophile through a hydrogen-bonding interaction, and a free proton source for accelerating the proton transfer. All these can be incorporated into one chiral platform to achieve high asymmetric induction. As shown in Scheme 1, once the chiral phosphoric acid used as Brønsted acid,[8] the Lewis acid activation site, and the free proton source could be constructed through anion metathe-

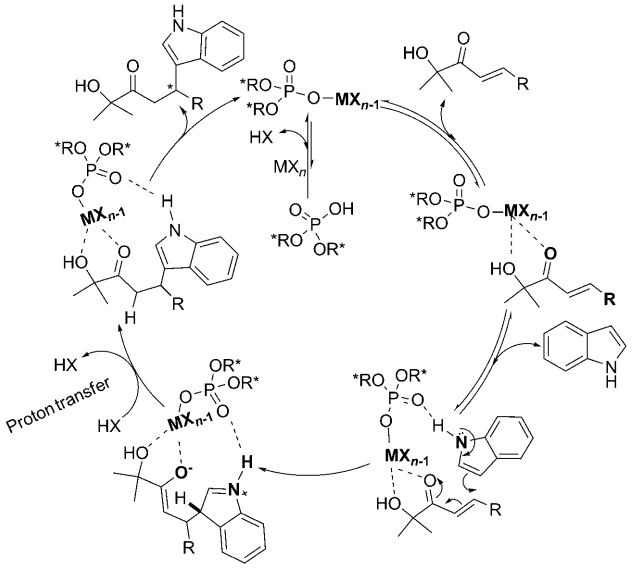
[a] Dr. L. Yang, Q. Zhu, S. Guo, B. Qian, C. Xia, Prof. H. Huang
State Key Laboratory for Oxo Synthesis and Selective Oxidation
Lanzhou Institute of Chemical Physics
Lanzhou, 730000 (P.R. China)
Fax: (+86) 931-4968129
E-mail: hmhuang@licp.cas.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200902705.



Scheme 1. Proposed cooperative catalytic system.

sis of the Brønsted acid and Lewis acid metal salt, the inherent Brønsted base site can activate the nucleophile through a hydrogen-bonding interaction. The interaction would allow the reaction to proceed under a chiral environment regulated by the chiral conjugated base. To ascertain the feasibility of this hypothesis, we aimed to develop a chiral Brønsted acid controlled, iron-catalyzed[9] enantioselective Friedel–Crafts alkylation of indoles with α′-hydroxy enones,[10] which was first developed by Palomo and coworkers, who used chiral bis(oxazoline)/$Cu(OTf)_2$ (2–30 mol%; OTf = trifluoromethanesulfonate) as a catalyst.[6h] Based on the cooperative working hypothesis proposed above, we assumed the reaction would be performed according to the catalytic cycle depicted in Scheme 2.



Scheme 2. Proposed proton-accelerated asymmetric Friedel–Crafts reaction process.

Results and Discussion

To validate our hypothesis, we attempted the reaction of 4-chlorophenyl-substituted α′-hydroxy enone (**2a**) with indole (**3a**) in the binary catalytic system to provide the Friedel–Crafts product (**4aa**). Our initial experiment was carried out using $Cu(OTf)_2$ (5 mol%) as Lewis acid and **1a** as Brønsted acid (5 mol%) to establish a binary catalyst. The reaction was carried out at room temperature in dichloromethane for 24 h, and only moderate yield (52%) and poor enantioselectivity (3% *ee*) were observed. Further screening of a number of other metal salts under the same reaction conditions showed that no transformation occurred at all when $Zn(OTf)_2$, $Mg(ClO_4)_2$, $Ni(ClO_4)_2{\cdot}6H_2O$, AgOAc, and $Pd(OAc)_2$ were used as Lewis acids (Figure 1; OAc = O_2CCH_3). The partners $InCl_3$/**1a** and $Ti(O\text{-}iPr)_4$/**1a** could give the desired product in 40% yield, but an almost racemic product was observed. To our delight, the inexpensive $FeCl_3$ was found to be the best partner of **1a** and provided 96% yield with 53% *ee* for **4aa** (Figure 1).

To optimize the reaction conditions, we first investigated the effects of solvents with **1a**/$FeCl_3$ as the binary catalyst at room temperature (typically 15–20°C). The results in Table 1 demonstrated that CH_2Cl_2 was the best choice. We then concentrated on the modification of the chiral phosphoric acid for the binary catalyst. A series of chiral phosphoric acids (**1**) with different substituents at the 3,3′-positions of the binaphthyl scaffold were prepared and tested in the reaction of indole (**3a**) and 4-chlorophenyl-substituted α′-hydroxy enone (**2a**). As shown in Table 1, the reaction could be catalyzed by all the binary catalysts combined with $FeCl_3$ and the phosphoric acids that were tested here. Among the phosphoric acids examined, **1a** (bearing 2-naphthyl groups) and **1b** (bearing 9-phenanthryl groups) exhibited high enantioselectivities of 53 and 55% *ee* with high reactivities (up to 94% yield; Table 1, entries 1 and 7). The existence of the

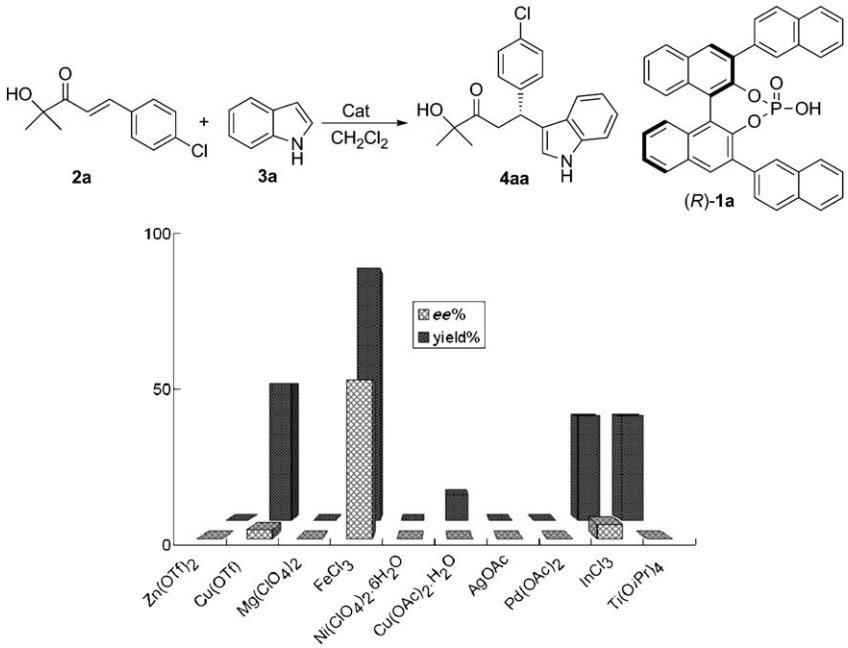
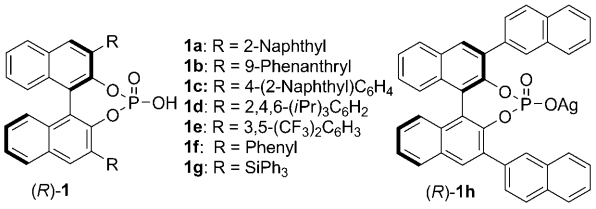


Figure 1. Screening of metal salts for the asymmetric Friedel–Crafts alkylation of indole with **1a** as Brønsted acid.

Table 1. Enantioselective Friedel–Crafts alkylation of indole with **2a** catalyzed by different phosphoric acid/$FeCl_3$ combinations.[a]



Entry	Catalyst	Solvent	t [h]	Yield [%][b]	*ee* [%][c]
1	**1a**/$FeCl_3$	CH_2Cl_2	3	94	53
2	**1a**/$FeCl_3$	CH_2ClCH_2Cl	4	90	46
3	**1a**/$FeCl_3$	toluene	6	91	30
4	**1a**/$FeCl_3$	THF	24	20	10
5	**1a**/$FeCl_3$	dioxane	24	54	−3
6	**1a**/$FeCl_3$	CH_3CN	24	35	27
7	**1b**/$FeCl_3$	CH_2Cl_2	6	91	55
8	**1c**/$FeCl_3$	CH_2Cl_2	8	75	40
9	**1d**/$FeCl_3$	CH_2Cl_2	24	66	−3
10	**1e**/$FeCl_3$	CH_2Cl_2	24	76	16
11	**1f**/$FeCl_3$	CH_2Cl_2	48	80	31
12	**1g**/$FeCl_3$	CH_2Cl_2	48	45	35
13	**1h**/$FeCl_3$	CH_2Cl_2	24	61	19
14	$FeCl_3$	CH_2Cl_2	24	85	–
15	**1a**	CH_2Cl_2	24	trace	–

[a] General conditions: **1** (5 mol%), $FeCl_3$ (5 mol%), enone (0.2 mmol), indole (0.3 mmol), CH_2Cl_2 (1 mL), RT (15–20°C). [b] Isolated yield. [c] Determined by chiral HPLC.

phosphate salt of Fe^{III} in the catalytic system of **1b**/$FeCl_3$ might be responsible for the high activity and good enantioselectivity, a postulation that was confirmed by ESIMS studies (Figure 2). To further clarify the mechanism of the reaction, control experiments were carried out. Chiral silver phosphate salt **1h** without an acidic proton was prepared and combined with $FeCl_3$ to act as the binary catalyst. This led to lower activity and *ee* values under the same reaction conditions and showed the importance of the proton for this trifunctional catalyst system. The transformation became slow (24 h, 85% yield) when only using $FeCl_3$ as the catalyst (Table 1, entry 14). Virtually no reaction occurred when phosphoric acid **1a** alone was used as the catalyst (Table 1, entry 15). These results demonstrate that both the phosphoric acid and $FeCl_3$ are essential for this cooperative catalytic process and also suggest that the Brønsted acid here not only acts as chiral counteranion but also provides a free proton source for facilitating catalytic turnover through accelerating the proton-transfer step of the Friedel–Crafts reaction, which led the $FeCl_3$-catalyzed nonenantioselective background reaction to be suppressed.

To further optimize the enantioselectivity of the reaction, a number of different iron salts were subsequently investigated with phosphoric acid **1a** as Brønsted acid under the above reaction conditions, and some selected results are summarized in Table 2. It appears that the binary catalyst with Fe^{III} induces higher enantioselectivity and activity than the catalyst with Fe^{II}. The anions of the iron salts are crucial for the performance of this binary catalytic system. For example, with covalent-type iron salts such as [Fe(acac)$_3$] (acac = acetylacetonate) as precatalyst, no reaction occurred. Among the simple iron salts tested, $FeCl_3$ was found to be optimal. To further improve the enantioselectivity, silver salts with different anions as additives were screened, and AgOTf showed positive effects (65% *ee*; Table 2 entry 12). Other silver additives such as $AgSbF_6$, $AgBF_4$, and $Ag_3PW_{12}O_{40}$ could give good yields, but negative effects on the enantioselectivity were observed. An increase in the loading of silver additive could be favorable for obtaining higher enantioselectivity (70% *ee*; Table 2, entry 16). Further screening of the reaction conditions revealed that a lower temperature could improve the enantioselectivity (Table 2, entries 17 and 18). Under the optimized conditions (at −40°C and with CH_2Cl_2 as solvent), **4aa** was obtained in 83% yield with 90% *ee* when the combination of **1b** (5 mol%)/$FeCl_3$ (5 mol%)/AgOTf (30 mol%) was used as catalyst (Table 2, entry 19).

Having succeeded in developing an efficient enantioselective catalyst, we then turned our attention to the substrate scope (Table 3). For the enone **2j**, which had no substituent on the phenyl ring, and enones such as **2a** and **2c**–**h**, which bore an electron-withdrawing group at the *meta* or *para* position of the phenyl ring, the reactions went smoothly and afforded the products with high

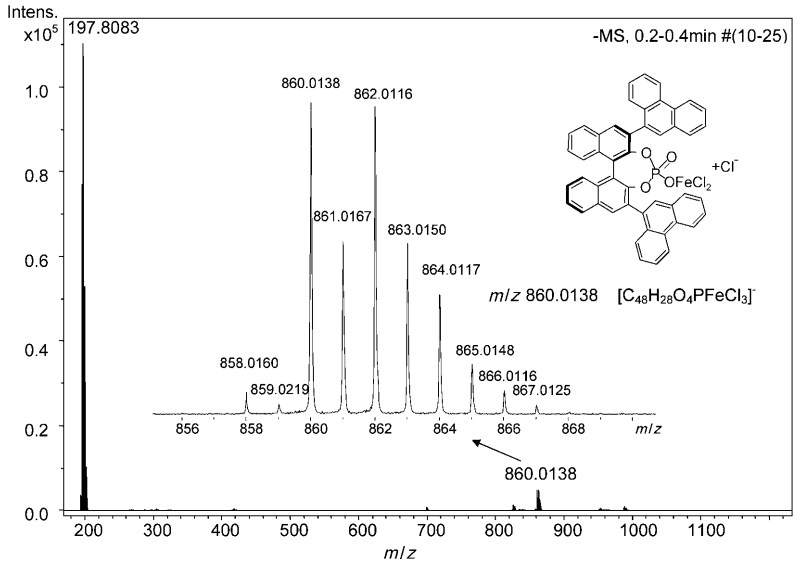


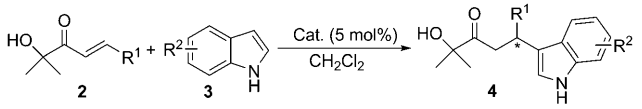
Figure 2. Confirmation of the existence of iron phosphate salt **1b**/$FeCl_3$.

Table 2. Enantioselective Friedel–Crafts alkylation of indole with **2a** catalyzed by different iron salt/phosphoric acid combinations.[a]

Entry	Catalyst	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1a**/$FeCl_3$	3	94	53
2	**1a**/$FeCl_3$·6 H_2O	3	90	51
3	**1a**/$FeCl_2$·4 H_2O	96	30	47
4	**1a**/$Fe_2(SO_4)_3$·*x* H_2O	24	45	43
5	**1a**/$Fe(NO_3)_3$·9 H_2O	18	95	52
6	**1a**/$Fe(ClO_4)_3$·*x* H_2O	24	80	47
7	**1a**/$Fe(ClO_4)_3$	24	82	43
8	**1a**/$Fe(OTf)_2$·2 CH_3CN	24	90	19
9	**1a**/$FeBr_3$	24	80	43
10	**1a**/$Fe(OTs)_3$ (Ts = tosyl)	18	88	37
11	**1a**/[$Fe(acac)_3$]	24	–	–
12	**1a**/$FeCl_3$ (5 mol%)/AgOTf (15 mol%)	22	88	65
13	**1a**/$FeCl_3$ (5 mol%)/$AgBF_4$ (15 mol%)	5	92	20
14	**1a**/$FeCl_3$ (5 mol%)/$AgSbF_6$ (15 mol%)	22	83	10
15	**1a**/$FeCl_3$ (5 mol%)/$Ag_3PW_{12}O_{40}$ (15 mol%)	24	64	42
16	**1a**/$FeCl_3$ (5 mol%)/AgOTf (30 mol%)	24	90	70
17	**1a**/$FeCl_3$ (5 mol%)/AgOTf (30 mol%)	24	87	75[d]
18[f]	**1a**/$FeCl_3$ (5 mol%)/AgOTf (30 mol%)	24	85	88[d]
19[f]	**1a**/$FeCl_3$ (5 mol%)/AgOTf (30 mol%)	24	83	90[e]

[a] General conditions: **1a** (5 mol%), iron salt (5 mol%), enone (0.2 mmol), indole (0.3 mmol), CH_2Cl_2 (1 mL), RT. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The reaction was run at −20 °C. [e] The reaction was run at −40 °C. [f] Compound **1b** was used as Brønsted acid.

Table 3. Enantioselective Friedel–Crafts alkylation of indoles **3** with various β-aryl α′-hydroxy enones **2**.[a]



2 3 4

Entry	R^1	R^2	*T* [°C]	Product (Yield [%])[b]	*ee* [%][c]
1	4-ClC_6H_4 (**2a**)	H (**3a**)	−40	**4aa** (83)	90
2	4-$MeOC_6H_4$ (**2b**)	H (**3a**)	−20	**4ba** (76)	73
3	4-$CF_3C_6H_4$ (**2c**)	H (**3a**)	−40	**4ca** (90)	91
4	4-FC_6H_4 (**2d**)	H (**3a**)	−40	**4da** (84)	85
5	4-BrC_6H_4 (**2e**)	H (**3a**)	−40	**4ea** (80)	90
6	4-$NO_2C_6H_4$ (**2f**)	H (**3a**)	−40	**4fa** (68)	84
7	3-ClC_6H_4 (**2g**)	H (**3a**)	−20	**4ga** (82)	85
8	3-FC_6H_4 (**2h**)	H (**3a**)	−40	**4ha** (82)	84
9	2-ClC_6H_4 (**2i**)	H (**3a**)	−40	**4ia** (75)	69
10	C_6H_5 (**2j**)	H (**3a**)	−40	**4ja** (70)	86
11	2-naphthyl (**2k**)	H (**3a**)	−40	**4ka** (66)	80
12[d]	2-furan (**2l**)	H (**3a**)	−20	**4la** (70)	43
13	$C_6H_5CH_2CH_2$ (**2m**)	H (**3a**)	−40	**4ma** (95)	47
14[e]	4-ClC_6H_4 (**2a**)	5-Br (**3b**)	−20	**4ab** (82)	72
15[e]	4-ClC_6H_4 (**2a**)	2-Me (**3c**)	−20	**4ac** (86)	24
16	4-ClC_6H_4 (**2a**)	*N*-Me (**3d**)	−40	**4ad** (92)	12

[a] General conditions: **1b** (5 mol%), $FeCl_3$ (5 mol%), AgOTf (30 mol%), enone (0.2 mmol), indole (0.3 mmol), CH_2Cl_2 (1 mL), 24 h. [b] Isolated yield. [c] Determined by chiral HPLC. [d] For 36 h. [e] Compound **1a** was used as Brønsted acid.

yields and good to excellent enantioselectivities (84–91% *ee*). However, by contrast, *ortho* substitutents in the β-aryl α′-hydroxy enones strongly diminished the enantioselectivity of the reaction, which may be due to steric interaction of the *o*-substituent to the indole during the reaction. For example, the reaction of 2-chloro-substituted β-aryl α′-hydroxy enone **2i** under the optimized conditions generated the Friedel–Crafts product in only 69% *ee* (Table 3, entry 9). By introducing an electron-donating group into the β-aryl α′-hydroxy enone, we observed a drop in the enantioselectivity. In the case of **2b**, which has a 4-OCH_3 group, 73% *ee* was obtained (Table 3, entry 2). Besides the substituted phenyl enones, the naphthyl enone **2k** also gave the asymmetric Friedel–Crafts product in good yield and enantioselectivity (Table 3, entry 11). Unfortunately, when β-enones derived from heteroaromatic or alkyl aldehyde compounds such as **2l** and **2m** were tested, only moderate enantioselectivity was obtained (Table 3, entries 12 and 13).[11] Finally, various substituted indoles were also investigated in the Friedel–Crafts reaction with 4-chlorophenyl-substituted α′-hydroxy enone **2a**. Similarly, the indole bearing an electron-withdrawing group gave the corresponding adduct in high yield and enantioselectivity, but upon introducing an electron-donating group into the indole, we also observed a dramatic drop in the enantioselectivity (Table 3, entry 14 vs. 15). When *N*-methylindole (**3d**) was prepared and treated with β-aryl α′-hydroxy enone (**2a**), a very low *ee* value was observed (Table 3, entry 16), thereby demonstrating that the hydrogen-bonding interaction site is important for our cooperative catalytic system. The absolute configuration of **4ea** was assigned as *R* by X-ray diffraction analysis (Figure 3).

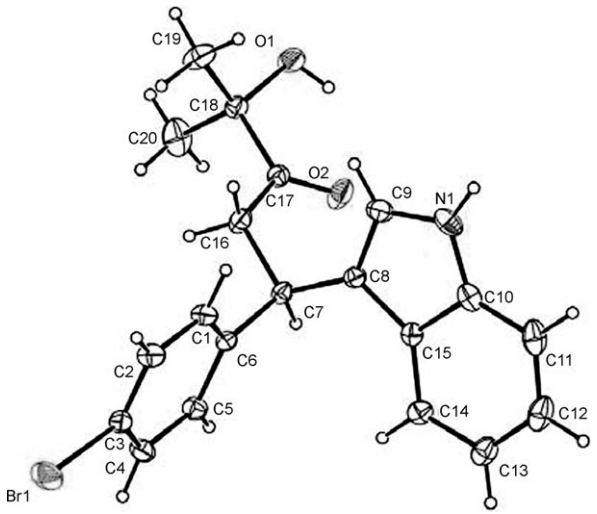


Figure 3. X-ray structure of **4ea**.

Conclusion

In summary, a cooperative catalytic system has been successfully established by the combination of an iron salt and a chiral phosphoric acid through taking advantage of the fact that the free proton source could promote the catalytic turnover for the Friedel–Crafts reaction. This newly prepared catalytic system has proven to be effective in the enantioselective Friedel–Crafts alkylation of indoles with β-aryl α′-hydroxy enones. Further studies of the reaction mechanism and the applicability of this concept involving other asymmetric transformations are currently being investigated in our laboratory and will be reported in due course.

Experimental Section

General: All reactions were performed in sealed oven-dried glass tubes under an atmosphere of argon unless otherwise noted. All common reagents were obtained from commercial suppliers and used without further purification. All solvents before use were dried and degassed by standard methods and stored under nitrogen. α′-Hydroxy enones were prepared following literature procedures.[12] Chiral 1,1′-bi-2-naphthol (BINOL)-derived phosphoric acids and the silver phosphate salt were prepared according to or analogously to the reported procedures.[13] Thin-layer chromatography (TLC) was performed on silica gel GF254 with a mixture of petroleum and ethyl acetate as the eluent unless otherwise noted. Column chromatography was carried out using silica gel (200–300 mesh) and petroleum/ethyl acetate as the eluent. NMR spectra were obtained using a Bruker DRX spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C in $CDCl_3$ unless otherwise noted. Coupling constants (J) are reported in Hz and refer to apparent peak multiplications. High-resolution mass spectra (HRMS) were obtained using a Bruker Apex II instrument (ESI). The ESIMS was performed using Micro-QOF-II instrument. Enantiomeric excess (*ee*) values were determined by HPLC analysis using an Agilent HP-1200. Optical rotations were measured on a Perkin–Elmer polarimeter (model 341LC).

General procedure for the enantioselective Friedel–Crafts alkylation of indoles with β-aryl α′-hydroxy enones: An oven-dried Schlenk tube was charged with AgOTf (30 mol%) and $FeCl_3$ (5 mol%). The tube was evacuated and refilled with Ar, and this process was repeated three times. Then CH_2Cl_2 (1 mL) was injected. The reaction mixture was heated at 50 °C and stirred vigorously for 2 h. After cooling to RT, **2a** (0.2 mmol) was added and the mixture was stirred for 20 min at RT, and then chiral phosphoric acid **1b** (5 mol%) was added into the reaction mixture. After 10 min of being stirred at the same temperature, the reactor was cooled to −40 °C. Compound **3a** (0.3 mmol) was added directly into the reaction mixture at −40 °C. After 24 h, the mixture was then diluted with NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The organic layers were combined, dried over anhydrous $NaSO_4$, and concentrated. Subsequent purification by flash chromatography using silica gel (ethyl acetate/petroleum, ca. 1:10 to 1:3) to afford the chiral product **4aa**.

Compound 4aa: The title compound was prepared according to the general procedure and purified by chromatography to give a white solid, which was a known compound. Chiral HPLC was performed using an HP series 1200 (Chiralpak AD-H column; hexane/2-propanol 85:15; 1.0 mL min^{-1}, 254 nm): t_R(major) = 13.48 min, t_R(minor) = 18.55 min, 90% *ee*; $[\alpha]_D^{20} = -18.7$ ($c = 0.32$ in CH_2Cl_2). The absolute configuration was assigned as *R* by comparison of the optical rotation with the reported value (ref. [6h]: $[\alpha]_D^{25} = -12.3$ ($c = 1.0$ in CH_2Cl_2), 83% *ee* for *R* isomer). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.95$ (br, 1H), 7.35 (d, $J = 8.0$ Hz, 1H), 7.23–7.26 (m, 2H), 7.17–7.20 (m, 2H), 7.06–7.12 (m, 2H), 6.93–6.98 (m, 1H), 6.89 (s, 1H), 4.88 (t, $J = 7.2$ Hz, 1H), 3.59 (s, 1H), 3.27 (d, $J = 7.6$ Hz, 2H), 1.18 (s, 3H), 1.06 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.6$, 143.6, 136.6, 128.5, 127.8, 126.6, 126.4, 122.3, 121.2, 119.6, 119.5, 118.9, 111.2, 76.4, 42.4, 37.9, 26.1, 26.0 ppm.

Compound 4ba: The title compound was prepared according to the general procedure and purified by chromatography to give a white solid, which was an unknown compound. Chiral HPLC was performed using an HP series 1200 (Chiralpak AD-H column; hexane/2-propanol 90:10; 1.0 mL min^{-1}, 254 nm): t_R(major): 44.61 min, t_R(minor) = 50.13 min, 73% *ee*; $[\alpha]_D^{20} = -16.7$ ($c = 0.12$ in CH_2Cl_2). The absolute configuration was assigned as *R* by analogy. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.92$ (br, 1H), 7.35 (d, $J = 7.6$ Hz, 1H), 7.26 (d, $J = 8.0$ Hz, 1H), 7.13–7.19 (m, 2H), 7.07–7.11 (m, 1H), 6.94–6.98 (m, 1H), 6.90 (s, 1H), 6.71–6.75 (m, 1H), 4.83 (t, $J = 7.2$ Hz, 1H), 3.69 (s, 3H), 3.58 (s, 1H), 3.25 (dd, $^1J = 8.0$ Hz, $^2J = 5.2$ Hz, 2H), 1.19 (s, 3H), 1.06 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.7$, 158.1, 136.6, 135.7, 128.8, 126.4, 122.3, 121.0, 119.5, 119.3, 113.8, 111.2, 76.4, 55.2, 42.5, 37.1, 26.1, 25.9 ppm; HRMS (ESI): m/z: calcd for $C_{21}H_{23}NO_3$ $[M+H]^+$: 338.1751; found: 338.1757.

Compound 4ca: The title compound was prepared according to the general procedure and purified by chromatography to give a white solid, which was an unknown compound. Chiral HPLC was performed using an HP series 1200 (Chiralpak AD-H column; hexane/2-propanol 85:15; 1.0 mL min^{-1}, 254 nm): t_R(major) = 9.49 min, t_R(minor) = 12.08 min, 91% *ee*; $[\alpha]_D^{20} = -23.3$ ($c = 0.24$ in CH_2Cl_2). The absolute configuration was assigned as *R* by analogy. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.97$ (br, 1H), 7.30 (d, $J = 8.0$ Hz, 1H), 7.26 (d, $J = 8.0$ Hz, 1H), 7.17–7.22 (m, 2H), 7.07–7.12 (m, 1H), 6.94–6.98 (m, 1H), 6.84–6.90 (m, 3H), 4.86 (t, $J = 7.2$ Hz, 1H), 3.55 (s, 1H), 3.25 (d, $J = 7.6$ Hz, 2H), 1.19 (s, 3H), 1.06 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.4$, 162.7, 160.3, 139.4 (d, $J = 31$ Hz), 136.6, 129.3 (d, $J = 80$ Hz), 126.3, 122.4, 121.1, 119.6, 119.4, 118.8, 115.3 (d, $J = 212$ Hz), 111.3, 76.4, 42.5, 37.1, 26.1, 25.9 ppm; HRMS (ESI): m/z: calcd for $C_{21}H_{20}NO_2F_3$ $[M+H]^+$: 376.1519; found: 376.1513.

Compound 4da: The title compound was prepared according to the general procedure and purified by chromatography to give a white solid, which was an unknown compound. Chiral HPLC was performed using an HP series 1200 (Chiralpak IA column; hexane/2-propanol 85:15; 1.0 mL min^{-1}, 254 nm): t_R(major) = 10.76 min, t_R(minor) = 15.17 min, 85% *ee*; $[\alpha]_D^{20} = -35.7$ ($c = 0.14$ in CH_2Cl_2). The absolute configuration was assigned as *R* by analogy. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.99$ (br, 1H), 7.45 (d, $J = 8.4$ Hz, 1H), 7.37 (d, $J = 8.0$ Hz, 1H), 7.27–7.33 (m, 4H), 7.09–7.13 (m, 1H), 6.94–7.00 (m, 1H), 6.93 (s, 1H), 4.94 (t, 1H, $J = 7.2$ Hz), 3.46 (s, 1H), 3.25–3.37 (m, 2H), 1.21 (s, 3H), 1.11 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.1$, 147.8, 136.6, 128.2, 126.2, 125.5, 125.4, 122.6, 121.2, 119.8, 119.2, 118.1, 111.3, 76.4, 42.1, 37.5, 26.2, 26.1 ppm; HRMS (ESI): m/z: calcd for $C_{20}H_{20}NO_2F$ $[M+H]^+$: 326.1551; found: 326.1544.

Compound 4ea: The title compound was prepared according to the general procedure and purified by chromatography to give a white solid, which was an unknown compound. Chiral HPLC was performed using an HP series 1200 (Chiralpak AD-H column; hexane/2-propanol 85:15; 1.0 mL min^{-1}, 254 nm): t_R(major) = 13.91 min, t_R(minor) = 19.33 min, 90% *ee*; $[\alpha]_D^{20} = -14.2$ ($c = 0.12$ in CH_2Cl_2). The absolute configuration was assigned as *R* by using X-ray crystallography. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.98$ (br, 1H), 7.25–7.31 (m, 4H), 7.08–7.18 (m, 3H), 6.90–6.99 (m, 1H), 6.89 (s, 1H), 4.84 (t, $J = 7.2$ Hz, 1H), 3.51 (s, 1H), 3.20–3.29 (m, 2H), 1.19 (s, 3H), 1.09 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.3$, 142.7, 136.6, 131.6, 129.6, 126.2, 122.5, 121.2, 120.3, 119.7, 119.3, 118.4, 111.3, 76.4, 42.2, 37.2, 26.1, 26.0 ppm; HRMS (ESI): m/z: calcd for $C_{20}H_{20}NO_2Br$ $[M+H]^+$: 386.0750; found: 386.0747.

Crystal data for ***4ea***: $M_r = 386.28$; crystal size 0.38×0.35×0.31 mm; orthorhombic; space group $P2_12_12_1$; $a = 9.6040(6)$, $b = 11.5562(7)$, $c = 15.9003(10)$ Å; $\alpha = 90$, $\beta = 90$, $\gamma = 90°$; $V = 1764.71(19)$ Å^3; $Z = 4$; $\lambda = 0.71073$ Å; $\mu = 2.341$ mm^{-1}; $\rho_{calcd} = 1.454$ mg m^{-3}; $T = 296(2)$ K; $F(000) = 792$; 3463 independent reflections ($R_{int} = 0.0282$); 9923 collected reflections; refinement method: full-matrix least-squares on F^2; goodness-of-fit on F^2: 1.037; final R indices ($I > 2\sigma(I)$) $R1 = 0.0327$, $wR2 = 0.0687$; R indices (all data): $R1 = R1 = 0.0495$ and $wR2 = 0.0741$; absolute structure parameter was 0.000(9); largest difference peak and hole: 0.290 and −0.419 e Å^{-3}, respectively. CCDC-749512 (**4ea**) 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.

Compound 4fa: The title compound was prepared according to the general procedure and purified by chromatography to give a white solid, which was an unknown compound. Chiral HPLC was performed using an HP series 1200 (Chiralpak IA column; hexane/2-propanol 85:15; 1.0 mL min^{-1}, 254 nm): t_R(major) = 19.50 min, t_R(minor) = 26.51 min, 84% *ee*; $[\alpha]_D^{20} = -2.6$ ($c = 0.15$ in CH_2Cl_2). The absolute configuration was assigned as *R* by analogy. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.08$ (br, 1H), 8.03–8.05 (m, 2H), 7.41 (d, $J = 8.8$ Hz, 2H), 7.28 (t, $J = 7.2$ Hz, 2H), 7.09–7.13 (m, 1H), 6.95–6.99 (m, 2H), 4.97 (m, 1H), 3.27–3.41 (m, 3H), 1.19 (s, 3H), 1.14 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 211.9$, 151.6, 146.6, 136.6, 128.8, 126.0, 123.8, 122.7, 121.3, 119.9, 119.0, 117.4, 111.5, 76.4, 41.9, 37.6, 26.2 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{20}H_{20}N_2O_4$ $[M+H]^+$: 353.1496; found: 353.1501.

Compound 4ga: The title compound was prepared according to the general procedure and purified by chromatography to give a white solid, which was an unknown compound. Chiral HPLC was performed using an HP series 1200 (Chiralpak AD-H column; hexane/2-propanol 80:20; 1.0 mL min^{-1}, 254 nm): t_R(major) = 20.86 min, t_R(minor) = 10.25 min, 85% *ee*; $[\alpha]_D^{20} = -23.1$ ($c = 0.13$ in CH_2Cl_2). The absolute configuration was assigned as *R* by analogy. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.99$ (br, 1H), 7.34 (d, $J = 7.6$ Hz, 1H), 7.26 (d, $J = 8.0$ Hz, 1H), 7.21 (s, 1H), 7.06–7.16 (m, 4H), 6.91–6.99 (m, 1H), 6.90 (s, 1H), 4.85 (t, $^1J = 7.2$ Hz, $^2J = 7.2$ Hz, 1H), 3.53 (s, 1H), 3.20–3.31 (m, 2H), 1.19 (s, 3H), 1.09 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.2$, 145.8, 136.6, 134.3, 129.8, 127.9, 126.8, 126.2, 126.1, 122.5, 121.2, 119.7, 119.3, 118.2, 111.3, 76.4, 42.2, 37.5, 26.1, 26.0 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{20}H_{20}NO_2Cl$ $[M+H]^+$: 342.1255; found: 342.1251.

Compound 4ha: The title compound was prepared according to the general procedure and purified by chromatography to give a white solid, which was an unknown compound. Chiral HPLC was performed using an HP series 1200 (Chiralpak AD-H column; hexane/2-propanol 85:15; 1.0 mL min^{-1}, 254 nm): t_R(major) = 12.07 min, t_R(minor) = 15.19 min, 84% *ee*; $[\alpha]_D^{20} = -28.3$ ($c = 0.18$ in CH_2Cl_2). The absolute configuration was assigned as *R* by analogy. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.13$ (br, 1H), 7.33 (d, $J = 7.6$ Hz, 1H), 7.26 (d, $J = 8.0$ Hz, 1H), 7.03–7.18 (m, 3H), 6.81–6.99 (m, 3H), 6.76–6.79 (m, 1H), 4.87 (t, $J = 7.6$ Hz, 1H), 3.30 (s, 1H), 3.25–3.27 (m, 2H), 1.19 (s, 3H), 1.09 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.3$, 164.1, 161.7, 146.4 (d, $J = 66$ Hz), 136.6, 129.9 (d, $J = 82$ Hz), 126.3, 123.6 (d, $J = 27$ Hz), 122.4, 121.2, 119.4 (d, $J = 335$ Hz), 118.2, 114.7 (d, $J = 221$ Hz), 113.4 (d, $J = 210$ Hz), 111.3, 76.4, 42.3, 37.5, 26.1, 26.0 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{20}H_{20}NO_2F$ $[M+H]^+$: 326.1551; found: 326.1545.

Compound 4ia: The title compound was prepared according to the general procedure and purified by chromatography to give a white solid, which was an unknown compound. Chiral HPLC was performed using an HP series 1200 (Chiralpak AD-H column; hexane/2-propanol 90:10; 1.0 mL min^{-1}, 254 nm): t_R(major) = 22.17 min, t_R(minor) = 34.15 min, 69% *ee*; $[\alpha]_D^{20} = -35.8$ ($c = 0.12$ in CH_2Cl_2). The absolute configuration was assigned as *R* by analogy. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.97$ (br, 1H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.30–7.32 (m, 1H), 7.24 (d, $J = 8.0$ Hz, 1H), 7.16–7.18 (m, 1H), 7.03–7.11 (m, 3H), 6.87–7.00 (m, 1H), 6.88 (s, 1H), 5.35 (t, $J = 7.2$ Hz, 1H), 3.57 (s, 1H), 3.37 (dd, $^1J = 7.8$ Hz, $^2J = 17.6$ Hz, 1H), 3.22 (dd, $^1J = 6.8$ Hz, $^2J = 17.6$ Hz, 1H), 1.24 (s, 3H), 1.23 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 211.9$, 141.0, 136.5, 133.7, 129.9, 128.8, 127.8, 126.9, 126.5, 122.4, 121.7, 119.7, 119.4, 117.5, 111.2, 76.3, 41.3, 34.2, 26.5, 26.4 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{20}H_{20}NO_2Cl$ $[M+H]^+$: 342.1255; found: 342.1261.

Compound 4ja: The title compound was prepared according to the general procedure and purified by chromatography to give a white solid, which was an unknown compound. Chiral HPLC was performed using an HP series 1200 (Chiralpak IA column; hexane/2-propanol 85:15; 1.0 mL min^{-1}, 254 nm): t_R(major) = 10.56 min, t_R(minor) = 13.47 min, 86% *ee*; $[\alpha]_D^{20} = -28.3$ ($c = 0.12$ in CH_2Cl_2). The absolute configuration was assigned as *R* by analogy. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.04$ (br, 1H), 7.46 (d, $J = 2.0$ Hz, 1H), 7.10–7.22 (m, 8H), 6.92 (d, $J = 2.4$ Hz, 1H), 4.81 (t, $J = 7.2$ Hz, 1H), 3.53 (s, 1H), 3.21–3.29 (m, 2H), 1.19 (s, 3H), 1.08 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.3$, 141.1, 135.2, 128.6, 128.2, 127.7, 126.8, 125.2, 122.3, 121.9, 118.6, 112.8, 112.7, 76.4, 42.4, 37.6, 26.1, 25.9 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{20}H_{21}NO_2$ $[M+H]^+$: 308.1645; found: 308.1639.

Compound 4ka: The title compound was prepared according to the general procedure and purified by chromatography to give a white solid, which was an unknown compound. Chiral HPLC was performed using an HP series 1200 (Chiralpak OD-H column; hexane/2-propanol 80:20; 1.0 mL min^{-1}, 254 nm): t_R(minor) = 13.45 min, t_R(major) = 22.49 min, 80% *ee*; $[\alpha]_D^{20} = -12.8$ ($c = 0.18$ in CH_2Cl_2). The absolute configuration was assigned as *R* by analogy. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.95$ (br, 1H), 7.66–7.71 (m, 4H), 7.33–7.39 (m, 4H), 7.27 (d, $J = 8.0$ Hz, 1H), 7.06–7.10 (m, 1H), 6.92–6.96 (m, 2H), 5.06 (t, $J = 7.2$ Hz, 1H), 3.54 (s, 1H), 3.33–3.43 (m, 2H), 1.19 (s, 3H), 1.07 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.5$, 142.0, 136.6, 133.4, 132.3, 128.2, 127.8, 127.6, 126.5, 126.4, 126.0, 125.9, 125.5, 122.3, 121.3, 119.6, 119.4, 118.8, 111.2, 76.4, 42.2, 37.9, 26.1, 26.0 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{24}H_{23}NO_2$ $[M+H]^+$: 358.1802; found: 358.1800.

Compound 4la: The title compound was prepared according to the general procedure and purified by chromatography to give a white solid, which was an unknown compound. Chiral HPLC was performed using an HP series 1200 (Chiralpak OD-H column; hexane/2-propanol 90:10; 1.0 mL min^{-1}, 254 nm): t_R(minor) = 24.03 min, t_R(major) = 34.05 min, 43% *ee*; $[\alpha]_D^{20} = +12.0$ ($c = 0.10$ in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.00$ (br, 1H), 7.48 (d, $J = 8.0$ Hz, 1H), 7.23–7.27 (m, 2H), 7.08–7.13 (m, 1H), 6.96–6.99 (m, 2H), 6.18–6.20 (m, 1H), 5.98 (d, $J = 3.2$ Hz, 1H), 4.94 (t, $J = 7.2$ Hz, 1H), 3.64 (s, 1H), 3.33 (dd, $^1J = 8.0$ Hz, $^2J = 17.2$ Hz, 1H), 3.14 (dd, $^1J = 6.8$ Hz, $^2J = 16.8$ Hz, 1H), 1.20 (s, 3H), 1.08 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.4$, 156.2, 141.2, 136.4, 125.9, 122.3, 122.1, 119.6, 119.2, 116.1, 111.4, 110.3, 105.9, 76.5, 40.6, 32.1, 26.1, 25.8 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{18}H_{19}NO_3$ $[M+H]^+$: 298.1438; found: 298.1435.

Compound 4ma: The title compound was prepared according to the general procedure and purified by chromatography to give a white solid, which was a known compound. Chiral HPLC was performed using an HP series 1200 (Chiralpak OD-H column; hexane/2-propanol 80:20; 1.0 mL min^{-1}, 254 nm): t_R(major) = 13.32 min, t_R(minor) = 10.15 min, 47% *ee*; $[\alpha]_D^{20} = +10.5$ ($c = 0.19$ in CH_2Cl_2). The absolute configuration was assigned as *S* by comparison of the optical rotation with the reported value (ref. [6h]: $[\alpha]_D^{25} = +27.2$ ($c = 1.0$ in CH_2Cl_2), 98% *ee* for *S* isomer). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.07$ (s, 1H), 7.64 (d, $J = 8.0$ Hz, 1H), 7.34 (d, $J = 8.0$ Hz, 1H), 7.08–7.25 (m, 7H), 7.06 (d, $J = 2.4$ Hz, 1H), 3.70 (s, 1H), 3.58–3.65 (m, 1H), 3.07 (dd, $J = 6.8$ Hz, 1H), 2.88 (dd, $J = 6.8$ Hz, 1H), 2.50–2.57 (m, 2H), 2.02–2.19 (m, 2H), 1.29 (s, 3H), 1.04 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 213.5$, 142.2, 136.6, 128.4, 128.3, 126.3, 125.7, 122.0, 121.6,119.4, 119.3, 118.2, 111.4, 76.3, 42.6, 36.9, 34.1, 32.5, 26.2, 25.8 ppm.

Compound 4ab: The title compound was prepared according to the general procedure and purified by chromatography to give a white solid, which was an unknown compound. Chiral HPLC was performed using an HP series 1200 (Chiralpak AD-H column; hexane/2-propanol 90:10; 1.0 mL min^{-1}, 254 nm): t_R(major) = 20.62 min, t_R(minor) = 23.26 min, 72% *ee*; $[\alpha]_D^{20} = +23.1$ ($c = 0.13$ in CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3COCD_3): $\delta = 10.37$ (br, 1H), 7.61 (s, 1H), 7.42–7.46 (m, 3H), 7.37 (d, $J = 8.8$ Hz, 1H), 7.30–7.33 (m, 2H), 7.19–7.22 (m, 1H), 4.86 (t, $J = 7.2$ Hz, 1H), 4.38 (s, 1H), 3.51–3.63 (m, 2H), 1.23 (s, 3H), 1.22 ppm (s, 3H); ^{13}C NMR (100 MHz, CD_3COCD_3): $\delta = 213.3$, 144.9, 136.5, 132.1, 130.6, 129.5, 125.0, 124.3, 122.2, 118.9, 114.1, 112.5, 77.2, 43.2, 37.5, 26.7, 26.6 ppm; HRMS (ESI): *m*/*z*: calcd for $C_{20}H_{19}NO_2BrCl$ $[M+H]^+$: 420.0360; found: 420.0357.

Compound 4ac: The title compound was prepared according to the general procedure and purified by chromatography to give a white solid, which was an unknown compound. Chiral HPLC was performed using an HP series 1200 (Chiralpak AD-H column; hexane/2-propanol 90:10; 1.0 mL min^{-1}, 254 nm): t_R(minor) = 18.31 min, t_R(major) = 24.42 min, 24% *ee*; $[\alpha]_D^{20} = +8.85$ ($c = 0.26$ in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.74$ (br, 1H), 7.27 (d, $J = 7.6$ Hz, 1H), 7.13–7.19 (m, 5H), 6.94–7.02 (m, 1H), 6.89–6.94 (m, 1H), 4.84 (m, 1H), 3.50–3.58 (m, 2H), 3.21 (dd,

$^1J=6.0$ Hz, $^2J=16.8$ Hz, 1H), 2.36 (s, 3H), 1.19 (s, 3H), 0.79 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=213.0$, 142.1, 135.4, 132.0, 131.8, 128.8, 128.4, 126.9, 121.1, 119.4, 118.9, 112.4, 110.6, 76.5, 40.5, 36.2, 26.1, 25.6, 12.1 ppm; HRMS (ESI): m/z: calcd for $C_{21}H_{22}NO_2Cl$ $[M+H]^+$: 356.1412; found: 356.1409.

Compound 4ad: The title compound was prepared according to the general procedure and purified by chromatography to give a white solid, which was an unknown compound. Chiral HPLC was performed using an HP series 1200 (Chiralpak OD-H column; hexane/2-propanol 80:20; 1.0 mL min^{-1}, 254 nm): t_R(minor) = 11.40 min, t_R(major) = 16.62 min, 12% *ee*; $[\alpha]_D^{20}=-4.1$ ($c=0.22$ in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.30$ (d, $J=8.0$ Hz, 1H), 7.11–7.21 (m, 6H), 7.94–7.98 (m, 1H), 6.74 (s, 1H), 4.84 (t, $J=7.2$ Hz, 1H), 3.67 (s, 3H), 3.51 (s, 1H), 3.25 (d, $J=7.2$ Hz, 2H), 1.20 (s, 3H), 1.09 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=212.3$, 142.3, 137.3, 132.1, 129.2, 128.6, 126.6, 125.9, 121.9, 119.4, 119.1, 116.9, 109.4, 76.3, 42.3, 37.2, 32.8, 26.1, 26.0 ppm; HRMS (ESI): m/z: calcd for $C_{21}H_{22}NO_2Cl$ $[M+H]^+$: 356.1412; found: 356.1410.

Acknowledgements

This work was supported by the Chinese Academy of Sciences, National Natural Science Foundation of China (nos. 20802085, 20625308). We thank Dr. Chensong Pan in the Beijing office of Bruker Daltonics, Inc. for ESIMS analysis. H.H. gratefully acknowledges Professor Huilin Chen at DICP for his encouragement and important suggestions.

[1] For reviews, see: Y. J. Park, J. W. Park, C. H. Jun, *Acc. Chem. Res.* **2008**, *41*, 222. For selected examples, see: a) M. Nakoji, T. Kanayama, T. Okino, Y. Takemoto, *Org. Lett.* **2001**, *3*, 3329; b) V. Komanduri, M. J. Krische, *J. Am. Chem. Soc.* **2006**, *128*, 16448; c) V. Komanduri, M. J. Krische, *J. Am. Chem. Soc.* **2006**, *128*, 16448; d) M. Rueping, A. P. Antonchick, C. Brinkmann, *Angew. Chem.* **2007**, *119*, 7027; *Angew. Chem. Int. Ed.* **2007**, *46*, 6903; e) A. Yamaguchi, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2008**, *10*, 2319; f) S. B. J. Kan, R. Matsubara, F. Berthiol, S. Kobayashi, *Chem. Commun.* **2008**, 6354; g) W. H. Hu, X. F. Xu, J. Zhou, W. J. Liu, H. X. Huang, J. Hu, L. P. Yang, L. Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 7782; h) X. F. Xu, J. Zhou, L. P. Yang, W. H. Hu, *Chem. Commun.* **2008**, 6564.

[2] a) E. N. Jacobsen, A. Pfaltz, H. Yamamoto, *Comprehensive Asymmetric Catalysis*, Springer, Heidelberg, **1999**; b) M. Beller, C. Bolm, *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals, Vols. 1 and 2*, 2nd ed., Wiley-VCH, Weinheim **2004**; c) A. Berkessel, H. Groger, *Asymmetric Organocatalysis-From Biomimetic Concepts to Powerful Methods for Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2005**.

[3] a) Z.-Y. Han, H. Xiao, X.-H. Chen, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 9182; b) T. Yang, A. Ferrali, F. Sladojevich, L. Campbell, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 9140; c) M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 10796; d) Y. Lu, T. C. Johnstone, B. A. Arndtsen, *J. Am. Chem. Soc.* **2009**, *131*, 11284.

[4] *Electron and Proton Transfer in Chemistry and Biology* (Ed.: A. Muller), Elsevier, Amsterdam, **1992**.

[5] For recent reviews of Friedel–Crafts alkylation reactions, see: a) G. A. Olah, R. Krishnamurti, G. K. S. Prakash, *Comprehensive Organic Synthesis, Vol. 3*, 1st ed. (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, p. 293; b) R. M. A. Roberts, A. Khalaf, *Friedel–Crafts Alkylation Chemistry: A Century of Discovery*, Marcel Dekker, New York, **1984**; c) K. A. Jørgensen, *Synthesis* **2003**, 1117; d) M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem.* **2004**, *116*, 560; *Angew. Chem. Int. Ed.* **2004**, *43*, 550; e) M. Bandini, A. Melloni, S. Tommasi, A. Umani-Ronchi, *Synlett* **2005**, 1199; f) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873; g) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701; h) T. B. Poulsen, K. A. Jørgensen, *Chem. Rev.* **2008**, *108*, 2903.

[6] For selected examples of Friedel–Crafts alkylation of indoles with α,β-unsaturated compounds, see: a) W. Zhuang, T. Hansen, K. A. Jørgensen, *Chem. Commun.* **2001**, 347; b) K. B. Jensen, J. Thorhauge, R. G. Hazell, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 164; *Angew. Chem. Int. Ed.* **2001**, *40*, 160; c) J. F. Austin, D. W. C. MacMillam, *J. Am. Chem. Soc.* **2002**, *124*, 1172; d) J. Zhou, Y. Tang, *J. Am. Chem. Soc.* **2002**, *124*, 9030; e) D. A. Evans, K. A. Scheidt, K. R. Fandrick, H. W. Lam, J. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 10780; f) D. A. Evans, K. R. Fandrick, H.-J. Song, *J. Am. Chem. Soc.* **2005**, *127*, 8942; g) R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem.* **2005**, *117*, 6734; *Angew. Chem. Int. Ed.* **2005**, *44*, 6576; h) C. Palomo, M. Oiarbide, B. G. Kardak, J. M. García, A. Linden, *J. Am. Chem. Soc.* **2005**, *127*, 4154; i) D. A. Evans, K. R. Fandrick, H.-J. Song, *J. Org. Chem.* **2006**, *71*, 75; j) S. Yamazaki, Y. Iwata, *J. Org. Chem.* **2006**, *71*, 739; k) R. Rasappan, M. Hager, A. Gissibl, O. Reiser, *Org. Lett.* **2006**, *8*, 6099; l) Y. X. Jia, S. F. Zhu, Y. Yang, Q. L. Zhou, *J. Org. Chem.* **2006**, *71*, 75; m) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2008**, *120*, 4080; *Angew. Chem. Int. Ed.* **2008**, *47*, 4016; n) H. Yang, Y. T. Hong, S. Kim, *Org. Lett.* **2007**, *9*, 2281; o) M. Rueping, B. J. Nachtsheim, S. A. Moreth, M. Bolte, *Angew. Chem.* **2008**, *120*, 603; *Angew. Chem. Int. Ed.* **2008**, *47*, 593; p) H.-Y. Tang, A.-D. Lu, Z.-H. Zhou, G.-F. Zhao, L.-N. He, C.-C. Tang, *Eur. J. Org. Chem.* **2008**, 1406.

[7] a) J. Zhou, M.-C. Ye, Z. Z. Huang, Y. Tang, *J. Org. Chem.* **2004**, *69*, 1309; b) J. Zhou, Y. Tang, *Chem. Commun.* **2004**, 432; c) T. Arai, N. Yokoyama, *Angew. Chem.* **2008**, *120*, 5067; *Angew. Chem. Int. Ed.* **2008**, *47*, 4989.

[8] For reviews, see: a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289; b) P. M. Pihko, *Angew. Chem.* **2004**, *116*, 2110; *Angew. Chem. Int. Ed.* **2004**, *43*, 2062; c) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719; d) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; e) S. J. Connon, *Angew. Chem.* **2006**, *118*, 4013; *Angew. Chem. Int. Ed.* **2006**, *45*, 3909; f) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999; g) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744; h) A. D. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; i) M. Terada, *Chem. Commun.* **2008**, 4097.

[9] For selected reviews of iron-catalyzed organic reactions, see: a) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217; b) A. Correa, O. García Mancheño, C. Bolm, *Chem. Soc. Rev.* **2008**, *37*, 1108; c) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500; d) S. Gaillard, J. L. Renaud, *ChemSusChem* **2008**, *1*, 505; e) A. Fürstner, *Angew. Chem.* **2009**, *121*, 1390; *Angew. Chem. Int. Ed.* **2009**, *48*, 1364.

[10] For selected examples of using α′-hydroxy enones as substrate, see: a) C. Palomo, M. Oiarbide, J. M. García, A. González, E. Arceo, *J. Am. Chem. Soc.* **2003**, *125*, 13942; b) C. Palomo, M. Oiarbide, E. Arceo, J. M. García, R. López, A. González, A. Linden, *Angew. Chem.* **2005**, *117*, 6343; *Angew. Chem. Int. Ed.* **2005**, *44*, 6187; c) C. Palomo, M. Oiarbide, R. Halder, M. Kelso, E. Gómez-Bengoa, J. M. García, *J. Am. Chem. Soc.* **2004**, *126*, 9188; d) C. Palomo, R. Pazos, M. Oiarbide, J. M. García, *Adv Synth. Catal.* **2006**, *348*, 1161; e) S. Lee, C. Lim, S. Kim, R. Subramaniam, J. Zimmerman, M. P. Sibi, *Org. Lett.* **2006**, *8*, 4311; f) D. Monge, E. M. -Zamora, J. Vázquez, Ma. Alcarazo, E. Álvarez, R. Fernández, J. M. Lassaletta, *Org. Lett.* **2007**, *9*, 2867; g) J. M. García, A. González, B. G. Kardak, J. M. Odriozola, M. Oiarbide, J. Razkin, C. Palomo, *Chem. Eur. J.* **2008**, *14*, 8768.

[11] It should be noted that the OH group of the α′-hydroxy enones is also important for obtaining high enantioselectivity of the Friedel–Crafts alkylation products. When the OH was replaced with OCH_3, only low *ee* values were obtained (−20 °C, 48 h, 80% yield, 18% *ee*).

[12] a) C. Palomo, M. Oiarbide, H. Raijkumar, M. Kelso, E. Gómez-Bengoa, J. M. García, *J. Am. Chem. Soc.* **2004**, *126*, 9188; b) C. Palomo, M. Oiarbide, B. G. Kardak, J. M. García, A. Linden, *J. Am. Chem. Soc.* **2005**, *127*, 4154; c) P. Chiang, M. Rommel, J. W. Bode, *J. Am. Chem. Soc.* **2009**, *131*, 8714.

[13] a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566; b) D. Uraguchi, M.

Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356; c) T. Akiyama, H. Morita, J. Itoh, K. Fuchibe, *Org. Lett.* **2005**, *7*, 2583; d) D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2005**, *127*, 9360; e) D. Uraguchi, K. Sorimachi, M. Terada, *Angew. Chem.* **2006**, *118*, 2312; *Angew. Chem. Int. Ed.* **2006**, *45*, 2254; f) J. Jiang, J. Yu, X.-X. Sun, Q.-Q. Rao, L.-Z. Gong, *Angew. Chem.* **2008**, *120*, 2492; *Angew. Chem. Int. Ed.* **2008**, *47*, 2458. also see: g) M. Terada, D. Uraguchi, K. Sorimachi, H. Shimizu, PCT Int. Appl. WO 2005070875, **2005**; h) T. Akiyama, PCT Int. Appl. WO 200409675, **2004**; i) G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496.

Received: October 1, 2009
Published online: December 23, 2009

