Synthesis of Novel Chiral Phosphoric Acid-Bearing Two Acidic Phenolic Hydroxyl Groups and its Catalytic Evaluation for Enantioselective Friedel-Crafts Alkylation of Indoles and Enones

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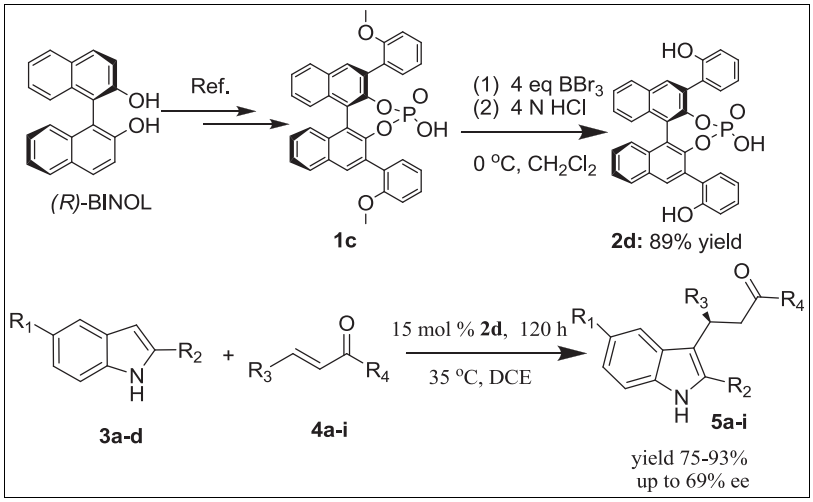

A novel chiral phosphoric acid catalyst bearing two acidic phenolic hydroxyl groups was synthesized. Its catalytic activity as a chiral Brøsted acid has been examined in the enantioselective Friedel-Crafts alkylation of indoles and enones as a model reaction. In comparison with the other chiral phosphoric acid catalysts, the reaction catalyzed by the novel chiral catalyst afforded the desired 3-substituted indoles in a higher enantioselectivity (up to 69% ee).

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INTRODUCTION

Owing to being comparably enviromentally benign and fundamentally interesting, organocatalyzed asymmetric synthesis is of great attention recently, and thus at its golden age. [1] Because an atropisomeric C_2-symmetric 1-(2-hydroxynaphthalen-1-yl)naphthalen-2-ol (BINOL)-based chiral phosphoric acid has been reported in asymmetric synthesis by Akiyama *et al.* and Terada *et al.* independently in 2004, [2] it is expected that chiral phosphoric acid catalysts would electrophilically activate carbon–oxygen or carbon–nitrogen double bonds and chiral induction would be realized. [3] The preparation of chiral phosphoric acids and their application in the asymmetric catalysis play very important roles in the catalytic asymmetric area. To date, the diverse approaches applied to chiral phosphoric acids modification may be useful and inspiring for applications in asymmetric synthesis. Many modified BINOL-based chiral phosphoric acids have also been developed by fine-tuning both the steric and electronic properties of BINOL scaffold to obtain higher efficiency and selectivity. [3]

The subtle modulation of the dihedral angle and electronic properties of BINOL-based chiral phosphoric acid maybe lead to an improvement of catalytic ability. In principal, introducing any substituent at 3,3′-positions of chiral phosphoric acid should alter the dihedral angle and electronic properties to a certain degree. At the same time, considering that the phenolic hydroxyl group has an acidic O—H proton and hydrogen bonding can play a key role in organocatalysis, we supposed introducing acidic phenolic hydroxyl group substituents at 3,3′-positions of chiral phosphoric acid would lead to an improvement of catalytic ability in some asymmetric synthesis. In addition, the indole framework has become widely identified as a "privileged" structure. [4,5] Many biologically active compounds and natural products are found to be 3-substituted indoles. [6] The Friedel-Crafts alkylation of indoles and enones is an import approach to this class of molecules.[7,8] However, indole serves as an ambient nucleophile, and selective targeting of C—H bonds in the presence of a reactive N—H functionality represents a challenging goal. [9] Furthermore, the steric similarity of the two carbonyl substituents renders the stereodifferentiation of the two enantiotopic faces of the unsaturated ketone a difficult task.[10] Recently, enantioselective versions of this fundamental transformation have been reported, including metal-

based and organocatalytic methods.[11] In this context, searching for highly efficient chiral, organocatalysts is the key objective to obtain high reactivity and enantioselectivity in some asymmetric synthesis. Herein, we describe the first synthesis of novel chiral phosphonic acid-bearing two acidic phenolic hydroxyl groups and choose the enantioselective Friedel-Crafts alkylation of indoles and enones as a model reaction to evaluate its catalytic, enantioselective ability.

RESULTS AND DISCUSSION

The catalysts (**1a–1l**) were prepared starting from (*R*)-BINOL in light of the reported methods[2,3] to search for highly efficient chiral organocatalysts in some asymmetric synthesis. We designed and synthesized the novel catalyst **2d** from **1c** followed by deprotecting the methyl group with BBr_3 and subsequent acidifing with 4*N* HCl (Scheme 1). Next, we choose the enantioselective Friedel-Crafts alkylation of indoles and enones as a model reaction to evaluate its catalytic, enantioselective ability.

In our initial study, for evaluating the chiral phosphoric acid (**2d**), indole (0.22 mmol), as an electron-rich heteroaromatic substrate, was chosen to react with chalcone (0.2 mmol) in dry $CHCl_3$ (2 mL) at 25°C for 96 h, a variety of other chiral Brøsted acid catalysts **1a–1l** (15 mmol%) in Figure 1 were also evaluated in the illustrated reaction, and the results are summarized in Table 1. As shown in Table 1, in the absence of catalyst, the reaction did not occur under otherwise identical experimental conditions (entry 1). The simplest catalyst **1a** could catalyze the reaction smoothly (67% yield) but afforded nearly a racemic product (entry 2). The catalysts **1b** and **1c** afforded the desired product in a modest yields and enantioselectivities (entries 3 and 4), whereas the other chiral Brøsted acid catalysts **1d–1l** resulted in poor enantioselectivities and moderate yields (entries 5–13). In comparison with the chiral Brøsted acid catalysts **1a–1l**, the catalyst **2d** afforded the desired 3-substituted indoles in a higher enantioselectivity (entry 14, 63% ee). Hence, the chiral Brøsted acid catalyst **2d** was selected for further studies.

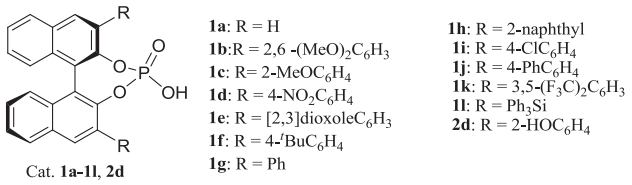


Figure 1. Chiral phosphoric acid evaluated in this study.

We then continuously explored the effect of solvent, benzene, toluene, CH_2Cl_2, and 1,2-dichloroethane (DCE) were used, the results indicated that DCE was slightly better than the other solvents (entries 14–18). We also found that addition of activated, powdered molecular sieves (M. S.) 4 Å gave relatively lower enantiomeric excess value and yield (Table 1, entry 19). A further survey of reaction temperature revealed that lowering the reaction temperature to 0°C had no any improvement in the ee value (entry 20). Interestingly, increasing the reaction temperature from 25°C to 35°C had a little positive effect on the enantioselectivity (entry 21). By decreasing the catalyst **2d** to 10 mol%, enantioselectivity was decreased to 64% (entry 23). Finally, a set of optimal reaction conditions was found to be as follows: using 15 mol%, the catalyst **2d**, indole (0.22 mmol), was reacted with chalcone (0.2 mmol) in DCE (2.0 mL) at 35°C for 120 h.

With these optimized reaction conditions in hand, we next turned our interest to the reaction generality. The scope of the enantioselective Friedel-Craft alkylation of indoles with a variety of enones under these optimized reaction conditions was explored (Table 2). Through exploring the reaction generality, we have shown the catalytic activity of the catalyst **2d** in comparison with the catalyst **1c**. The reaction catalyzed by the catalyst **2d** afforded the desired product in a higher enantioselectivity (with moderate to good enantioselectivities).

Aryl enone (**4a**) was firstly used as a standard substrate to probe the reactivity of different indoles (**3a–3d**) in this reaction. The reaction of indole (**3a**) afforded the corresponding product **5aa** in good yield and ee value (entry

Scheme 1. Synthesis of chiral phosphoric acid (**2d**) starting from (*R*)-1-(2-hydroxynaphthalen-1-yl)naphthalen-2-ol(BINOL).

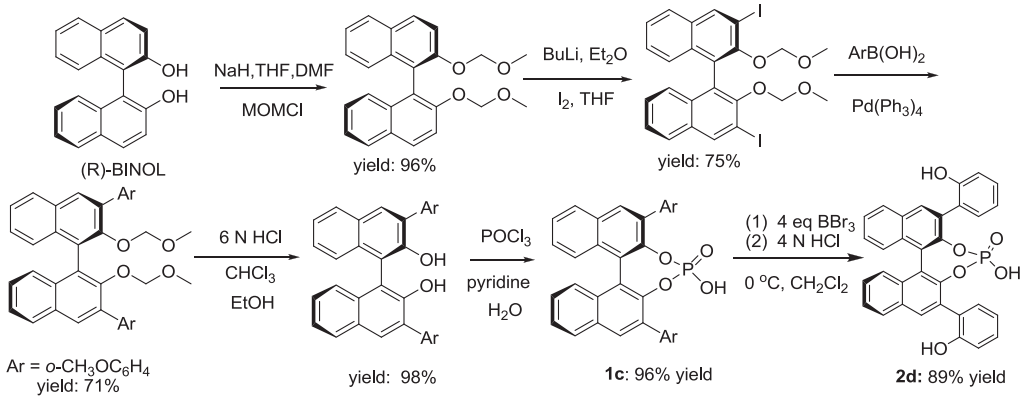
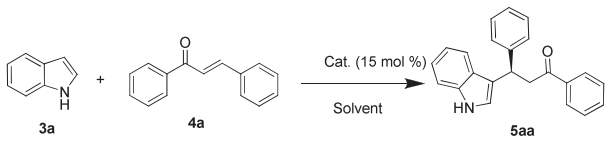


Table 1

Catalyst evaluation and optimization of reaction conditions.[a]



Entry	1	solvent	Temp. (°C)	Time (h)	Yield[b]/%	ee[c]/%
1	–	$CHCl_3$	25	96	0	–
2	**1a**	$CHCl_3$	25	96	67	<5
3	**1b**	$CHCl_3$	25	96	67	54
4	**1c**	$CHCl_3$	25	96	60	52
5	**1d**	$CHCl_3$	25	96	59	40
6	**1e**	$CHCl_3$	25	96	72	27
7	**1f**	$CHCl_3$	25	96	54	28
8	**1g**	$CHCl_3$	25	96	67	32
9	**1h**	$CHCl_3$	25	96	54	21
10	**1i**	$CHCl_3$	25	96	62	43
11	**1j**	$CHCl_3$	25	96	59	26
12	**1k**	$CHCl_3$	25	96	67	39
13	**1l**	$CHCl_3$	25	96	54	27
14	**2d**	$CHCl_3$	25	96	68	63
15	**2d**	CH_2Cl_2	25	96	67	60
16	**2d**	toluene	25	96	71	62
17	**2d**	benzene	25	96	71	59
18	**2d**	DCE	25	96	68	65
19[d]	**2d**	DCE	25	96	63	62
20	**2d**	DCE	0	120	62	61
21	**2d**	DCE	35	120	91	67
22	**2d**	DCE	50	120	92	59
23[e]	**2d**	DCE	35	120	85	64

DCE, 1,2-dichloroethane.
[a]Unless noted, reactions were carried out with 0.22 mmol of indole and 0.2 mmol of chalcone and catalyst (15 mol%) in 2.0 mL of solvent.
[b]Isolated yield after flash chromatography.
[c]Determined by HPLC analysis on Chiralpak AD-H columns.
[d]Adding 30 mg of powered molecular sieves 4 Å.
[e]This reaction was carried out with 0.22 mmol of indole, 0.2 mmol of chalcone, and catalyst **2d** (10 mol%) in 2.0 mL of DCE.

1, Table 2), and the Friedel-Craft alkylation of electron-rich 5-methoxyindole (**3b**) and 2-methylindole (**3c**) proceeded also at a reasonable reaction rate, furnishing the corresponding derivatives **5ba** and **5ca** in good yields but relatively lower ee value (entries 2 and 3, Table 2). However, an electron-withdrawing group such as bromine in the 5-position of indole ring in **3d** caused a slight decrease in the yield of **5da**, without loss in reaction enantiocontrol (entry 4, Table 2). We then tested alkyl enone (**4b**) and a variety of indoles **3a–3d** bearing different groups in the reaction, and the reactions all proceeded smoothly in good yields and moderate enantioselectivities (entries 5–8, Table 2). In the case of **3c** with Me- in the 2-position of indole ring, The reaction still proceeded cleanly, but the ee was distinctly decreased (entries 3 and 7, Table 2).

In addition, we continuously explored the Friedel-Craft alkylation of 2-methylindole (**3c**) and **4c** with β-aryl R^4 alkyl group, it also provided satisfactory yield but low enantioselectivity (entry 9, Table 2).

The generality of the reaction was further demonstrated by variation of the enones partner (entries 10–15, Table 2). The highest selectivity (69% ee) was displayed by containing electron-withdrawing substituent of para-chloride in **4d**, albeit with the high yield. However, a slight decrease in enantioselectivity and yield were observed with **4e** bearing an electron-donating substituent (entries 10 and 11, Table 2). The use of **4f** with β-2-naphthyl group (entry 12, Table 2) in the reaction gave the alkylated product in satisfactory enantioselectivity. Furthermore, the present catalytic system allowed for heteroaromatic-substituted enones and also afforded the Friedel-Craft product in satisfactory yield, although with a slight reduction in reaction enantioselectivity (entries 13–15, Table 2). The configuration of **5aa** was assigned as *R* by comparing the optical rotation of the synthesized compound with the literature data.[11] The configurations of all other products were assigned by analogy with this product.

To search for the more effective catalyst than the catalyst **2d**, we were also interested to synthesize chiral phosphoric acid catalyst (**2n**) bearing four acidic phenolic hydroxyl groups. Unfortunately, the instability of **2n** has made it difficult to obtain the pure compound, and we always gained intractable product mixtures (Scheme 2). The HRMS spectra of the intractable product mixtures revealed the presence of the desired catalyst **2n** [HRMS (ESI) exact mass Calcd for $(C_{32}H_{20}O_8P_1 + Na_2)^+$ requires *m/z* 609.0686, found *m/z* 609.0627]. Further studies on the reason of instability of **2n** are now in progress in our laboratory.

CONCLUSIONS

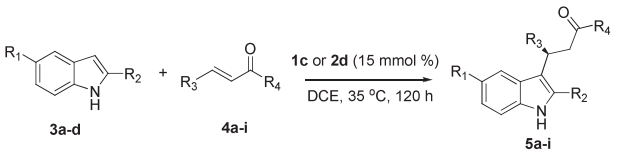
In summary, we designed and synthesized the first novel chiral phosphonic acid catalyst (**2d**) bearing two acidic phenolic hydroxyl groups. Its catalytic activity as a chiral Brøsted acid has been examined in the enantioselective Friedel-Crafts alkylation of indoles and enones as a model reaction. We found that two acidic phenolic hydroxyl groups on the phosphoric acid based on the BINOL scaffold play an important role in controlling of stereochemistry. The dependence of catalytic performance of the catalyst **2d** could be due to variation of bite angle and hydrogen bonding of acidic phenolic hydroxyl groups. Therefore, our preliminary results have demonstrated that the new catalyst **2d** was useful in asymmetric catalysis. Further studies on the mechanism of the present reaction catalyzed by the catalyst **2d** and its application to other asymmetric reactions are now in progress in our laboratory.

EXPERIMENTAL

All other commercially obtained reagents were used as received. The silica gel used for the column chromatography was purchased from Qingdao Haiyang Chemistry Plant. Thin-Layer

Table 2

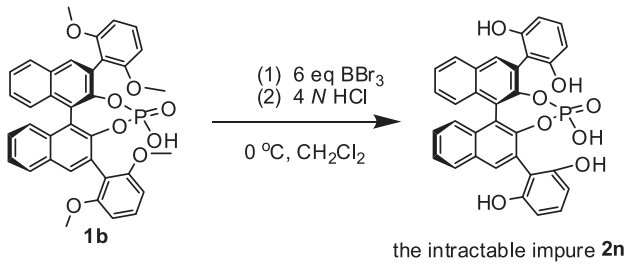
Direct organocatalytic asymmetric Friedel-Crafts type alkylation of indoles and enones.[a]



Entry	Indole R_1, R_2	Ketone R_3, R_4	Product **5**	Cat. **1c** Yield/% (ee/%)	Cat. **2d** Yield/% (ee/%)
1	**3a**, H, H	**4a**, Ph, Ph	**5aa**	91 (55)	91 (67)
2	**3b**, OCH_3, H	**4a**, Ph, Ph	**5ba**	90 (54)	91 (65)
3	**3c**, H, CH_3	**4a**, Ph, Ph	**5ca**	92 (45)	93 (58)
4	**3d**, Br, H	**4a**, Ph, Ph	**5da**	75[d] (51)	77[d] (68)
5[e]	**3a**, H, H	**4b**, *n*-Pr, CH_3	**5ab**	91 (56)	93 (55)
6[e]	**3b**, OCH_3, H	**4b**, *n*-Pr, CH_3	**5bb**	90 (50)	91 (48)
7[e]	**3c**, H, CH_3	**4b**, *n*-Pr, CH_3	**5cb**	93 (39)	92 (42)
8[e]	**3d**, Br, H	**4b**, *n*-Pr, CH_3	**5db**	86 (56)	85 (54)
9	**3c**, H, CH_3	**4c**, Ph, CH_3	**5cc**	78 (42)	77 (46)
10	**3a**, H, H	**4d**, Ph, *p*-ClC_6H_4	**5ad**	91 (51)	91 (69)
11	**3a**, H, H	**4e**, Ph, *p*-$CH_3OC_6H_4$	**5ae**	76[d] (43)	78[d] (63)
12	**3a**, H, H	**4f**, 2-Naphthyl, Ph	**5af**	89 (53)	86 (68)
13	**3a**, H, H	**4g**, 2-Thienyl, Ph	**5ag**	77[d] (41)	76[d] (59)
14	**3a**, H, H	**4h**, Ph, 2-Thienyl	**5ah**	71[d] (48)	75[d] (63)
15	**3a**, H, H	**4i**, 2-Furyl, Ph	**5ai**	70[d] (43)	75[d] (58)

DCE, 1,2-dichloroethane.
[a]Unless noted, reactions were carried out with 0.2 mmol of enones, 0.22 mmol of indoles in 2.0 mL anhydrous DCE with 15 mol% Cat. **2d** at 35°C for 120 h.
[b]Isolated yield after flash chromatography.
[c]Determined by chiral stationary phase HPLC.
[d]The reaction was carried out for 150 h.
[e]Employed 0.22 mmol of indoles and 1.5 equiv of **4b**.

Scheme 2. Synthesis of chiral phosphoric acid catalyst (**2n**) bearing four phenolic hydroxyl groups.



chromatography (TLC): silica gel 60 GF_{254} plate. All reactions were conducted in a closed system with an atomsphere of air and were monitored by TLC unless otherwise stated. ^{1}H NMR and ^{13}C NMR spectra were performed on a Bruker DRX-300 Avance spectrometer for products dissolved by $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. Data for ^{1}H are reported as follows: chemical shift (in ppm) and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Splitting patterns that could not be clearly distinguished are designated as multiplets (m). Data for ^{13}C NMR are reported in ppm. HPLC analysis was performed on BECKMAN (110B Solvent Delivery Module and 168 Detector). Optical rotations were measured on a PerPerkin-Elmer 241 Polarimeter. Melting points were recorded on a Buchi Melting Point B-545 unit. Electrospray ionization high resolution mass spectra (ESI-HRMS) were recorded on a Bruker P-SIMS-Gly FT-ICR mass spectrometer. Binaphthol derivatives were prepared by modified literature procedure.[2,3]

Preparation of the phosphoric acid catalysts (1a–1l). The binaphthol derivative (0.5 mmol) was dissolved into 1 mL of pyridine under N_2 atmosphere. To the resulting solution was added phosphorous oxychloride (2.0 equiv) at RT, and the reaction mixture was stirred for 5 h at 70°C. One milliliter of water was added, and the resulting suspension was stirred for 2 h at 70°C. Dichloromethane was added, and all pyridine was removed by reverse extraction with 4*N* HCl. Organic phase was dried over Na_2SO_4 and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$) to afford the catalyst.

(R)-2,6-Bis-(2-methoxy-phenyl)-4-oxo-3,5-dioxa-4l5-phospha-cyclohepta[2,1-a;3,4-a′]dinaphthalen-4-ol (1c). White solid; ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 3.55 (s, 6H), 6.70–6.80 (m, 4H), 7.07 (d, J = 6.9 Hz, 2H), 7.22–7.31 (m, 2H), 7.46 (d, J = 7.2 Hz, 4H), 7.70 (s, 2H), 7.90 (d, J = 8.3 Hz, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 55.4, 110.7, 120.0, 121.5, 125.2, 125.7, 125.8, 126.8, 127.9, 128.9, 130.9, 131.0, 131.4, 131.7, 144.76, 144.9, 156.7.

(R)-2,6-Bis-(2,6-dimethoxy-phenyl)-4-oxo-3,5-dioxa-415-phospha-cyclohepta[2,1-a;3,4-a′]dinaphthalen-4-ol (1b). $[\alpha]_{RT}^{D} = -72.9$ ($c = 0.438$, $CHCl_3$); white solid; mp > 300°C; ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 3.52 (s, 6H), 3.64 (s, 6H), 6.51 (d, $J = 8.2$ Hz, 2H), 6.44 (d, $J = 8.2$ Hz, 2H), 7.12–7.18 (t, $J = 8.2$ Hz, 2H), 7.25 (m, 2H), 7.40–7.46 (m, 4H), 7.88 (d, $J = 6.9$ Hz, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 55.4, 55.8, 103.3, 104.3, 114.1, 121.2, 124.8, 125.4, 126.5, 127.1, 127.9, 129.0, 131.0, 131.6, 132.5, 145.3, 145.4, 157.7, 157.8; HRMS (ESI) exact mass Calcd for $(C_{36}H_{28}O_8P_1 + Na_2)^+$ requires *m/z* 665.1395, found *m/z* 665.1306.

Preparation of the phosphoric acid catalysts (2d). The phosphoric acid catalysts (**1c**) (1 mmol) was dissolved in dry CH_2Cl_2 (30 mL) and cooled to 0°C, BBr_3 (4 mmol) was added, and the reaction mixture was stirred for 18 h at 0°C. The solution was then quenched with the addition of water (2 mL). The 4*N* HCl (40 mL) and dichloromethane (60 mL × 5) were added. Organic phase was dried over Na_2SO_4 and purified by column chromatography on silica gel ($MeOH/CH_2Cl_2$) to afford the desired catalyst. Yield: 89%.

(R)-2,6-Bis-(2-hydroxy-phenyl)-4-oxo-3,5-dioxa-415-phospha-cyclohepta[2,1-a;3,4-a′]dinaphthalen-4-ol (2d). $[\alpha]_{RT}^{D} = -184.5$ ($c = 0.358$, $CHCl_3$); white solid; mp > 300°C; ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 5.93 (s, 2H), 6.37–6.72 (m, 6H), 6.98–7.67 (m, 8H), 7.88 (s, 2H), 7.91 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 116.8, 120.3, 122.0, 124.1, 125.7, 126.4, 126.6, 128.0, 129.1, 129.6, 131.0, 131.2, 131.7, 132.0, 144.6, 152.5; HRMS (ESI) exact mass Calcd for $(C_{32}H_{20}O_6P_1 + Na_2)^+$ requires *m/z* 577.0871, found *m/z* 577.0769.

General procedure for the organocatalytic asymmetric Friedel-Crafts alkylation of indoles with enones. Under an argon atmosphere, in an ordinary test tube equipped with a magnetic stirring bar, enone (0.2 mmol) and indole (0.22 mmol) were dissolved in 2.0 mL of freshly distilled DCE (CaH_2), and catalyst **2d** (15 mg, 0.03 mmol) was added. Then, the tube was closed with a rubber stopper, and the reaction mixture was stirred for 120 h at 35°C. Then, the solvent was removed *in vacuo*, and the residue was purified by flash chromatography to yield the desired product.

(R)-3-(1H-Indol-3-yl)-1,3-diphenylpropan-1-one (5aa) *(Table 2, entry 1).* The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; $\tau_{minor} = 16.9$ min; $\tau_{major} = 18.9$ min). $[\alpha]_{RT}^{D} = -23.2$ ($c = 0.67$, $CHCl_3$, 67% ee). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 3.67–3.76 (m, 1H), 3.81 (dd, $J = 6.7$, 16.6 Hz, 1H), 5.06 (t, $J = 7.1$ Hz, 1H), 6.98–7.53 (m, 13H), 7.91–7.93 (d, $J = 7.5$ Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 37.8, 44.8, 110.7, 118.9, 119.1, 121.0, 121.7, 125.8, 126.2, 127.4, 127.6, 128.0, 128.1, 132.5, 136.2, 136.7, 143.8, 198.2.

(R)-3-(5-Methoxy-1H-indol-3-yl)-1,3-diphenylpropan-1-one (5ba) *(Table 2, entry 2).* The ee was determined by HPLC analysis using an OD-H column (15/85 *i*-PrOH/hexane; flow rate 1.0 mL/min; λ = 254 nm; $\tau_{minor} = 17.83$ min; $\tau_{major} = 19.32$ min). $[\alpha]_{D}^{RT} = -11.4$ ($c = 0.54$, $CHCl_3$, 65% ee). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 3.71 (s, 3H), 3.73–3.77 (m, 2H), 5.01 (t, $J = 7.0$ Hz, 1H), 6.80 (t, $J = 8.3$ Hz, 2H), 6.92 (s, 1H), 7.14–7.52 (m, 9H), 7.92 (t, $J = 7.6$ Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 38.2, 45.2, 55.8, 101.6, 111.8, 112.2, 119.0, 122.2, 126.3, 127.1, 127.9, 128.1, 128.5, 128.6, 131.8, 133.1, 137.2, 144.2, 153.8, 198.7; HRMS (ESI) exact mass Calcd for ($C_{24}H_{21}NO_2$ + Na) requires *m/z* 378.1572, found *m/z* 378.1459.

(R)-3-(2-Methyl-1H-indol-3-yl)-1,3-diphenylpropan-1-one (5ca) *(Table 2, entry 3).* The ee was determined by HPLC analysis using a Chiralpak AD-H column (15/85 *i*-PrOH/hexane; flow rate 1.0 mL/min; λ = 254 nm; $\tau_{minor} = 11.59$ min; $\tau_{major} = 12.36$ min). $[\alpha]_{D}^{RT} = +9.3$ ($c = 0.85$, $CHCl_3$, 58% ee). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 2.36 (s, 3H), 3.87 (dd, $J = 6.1$, 16.4 Hz, 1H), 3.95 (dd, $J = 6.8$, 16.3 Hz, 1H), 5.08 (t, $J = 6.9$ Hz, 1H), 6.98–7.47 (m, 12H), 7.73 (br, 1H), 7.86 (d, $J = 0.53$, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 11.6, 36.3, 43.1, 110.0, 113.1, 118.7, 118.8, 120.3, 125.4, 127.0, 127.1, 127.6, 127.8, 128.0, 131.3, 132.4, 135.0, 136.7, 143.7, 198.6.

(R)-3-(5-Bromo-1H-indol-3-yl)-1,3-diphenylpropan-1-one (5da) *(Table 2, entry 4).* The ee was determined by HPLC analysis using a Chiralpak AD-H column (15/85 *i*-PrOH/hexane; flow rate 1.0 mL/min; λ = 254 nm; $\tau_{minor} = 13.33$ min; $\tau_{major} = 14.42$ min). $[\alpha]_{D}^{RT} = -7.9$ ($c = 0.68$, $CHCl_3$, 68% ee). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 3.68 (dd, $J = 7.2$, 16.9 Hz, 1H), 3.76 (dd, $J = 7.2$, 16.9 Hz, 1H), 4.99 (t, $J = 7.0$ Hz, 1H), 6.97 (s, 1H), 7.12–7.56 (m,11H), 7.91 (d, $J = 7.4$ Hz, 2H), 8.02 (bs, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 37.5, 44.7, 112.1, 112.2, 118.4, 121.5, 122.1, 124. 6, 126.0, 127.2, 127.6, 127.9, 128.1, 128.2, 132.7, 134.7, 136.5, 143.3, 197.9.

(S)-4-(1H-Indol-3-yl)heptan-2-one (5ab) (Table 2, entry 5). The ee was determined by HPLC analysis using a Chiralpak AD-H column (5/95 *i*-PrOH/hexane; flow rate 1.0 mL/min; λ = 254 nm; $\tau_{minor} = 15.94$ min; $\tau_{major} = 17.48$ min). $[\alpha]_{D}^{RT} = +11.8$ ($c = 0.61$, $CHCl_3$, 55% ee). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 0.84 (t, $J = 7.2$ Hz, 3H), 1.18–1.28 (m, 2H), 1.62–1.74 (m, 2H), 2.00 (s, 3H), 2.78 (dd, $J = 6.8$, 15.7 Hz, 1H), 2.85 (dd, $J = 7.9$, 15.6 Hz,1H), 3.47 (t, $J = 6.8$ Hz, 1H), 6.90 (d, $J = 1.5$ Hz, 1H), 7.06–7.22 (m, 2H), 7.30 (d, $J = 7.9$ Hz, 1H), 7.64 (d, $J = 7.6$ Hz, 1H), 8.08 (br s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 14.1, 20.8, 30.4, 32.7, 38.2, 50.3, 111.4, 118.9, 119.2, 119.3, 121.3, 121.9, 126.6, 136.6, 209.2.

(S)-4-(5-Methoxy-1H-indol-3-yl)heptan-2-one (5bb) *(Table 2, entry 6).* The ee was determined by HPLC analysis using a Chiralpak AD-H column (5/95 *i*-PrOH/hexane; flow rate 1.0 mL/min; λ = 254 nm; $\tau_{minor} = 21.07$ min; $\tau_{major} = 23.39$ min). $[\alpha]_{D}^{RT} = +8.6$ ($c = 0.76$, $CHCl_3$, 48% ee). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 0.84–0.88 (m, 3H), 1.23–1.29 (m, 2H), 1.66–1.74 (m, 2H), 2.02 (d, $J = 2.1$ Hz, 3H), 2.75–2.90 (m, 2H), 3.44 (s, 1H), 3.86 (d, $J = 2.2$ Hz, 3H), 6.84 (d, $J = 8.6$ Hz, 1H), 6.90 (s, 1H), 7.08 (s, 1H), 7.21 (t, $J = 8.1$ Hz, 1H), 8.08 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 14.1, 20.7, 30.5, 32.5, 38.1, 50.2, 56.0, 101.6, 111.7, 111.9, 118.7, 122.1, 127.1, 131.8, 153.7, 209.1.

(S)-4-(2-Methyl-1H-indol-3-yl)heptan-2-one (5cb) *(Table 2, entry 7).* The ee was determined by HPLC analysis using a Chiralpak AD-H column (5/95 *i*-PrOH/hexane; flow rate 1.0 mL/min; λ = 254 nm; $\tau_{minor} = 10.91$ min; $\tau_{major} = 13.76$ min). $[\alpha]_{D}^{RT} = +8.1$ ($c = 0.80$, $CHCl_3$, 42% ee). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 0.81 (t, $J = 7.2$ Hz, 3H), 1.15 (t, $J = 6.4$ Hz, 2H), 1.64 (d, $J = 6.6$ Hz, 1H), 1.82–1.87 (m,1H), 1.92 (s, 3H), 2.33 (s, 3H), 2.79 (dd, $J = 5.8$, 15.8 Hz, 1H), 3.04 (dd, $J = 8.3$, 15.8 Hz, 1H), 3.34–3.38 (m, 1H), 7.00–7.09 (m, 2H), 7.21 (d, $J = 7.1$ Hz, 1H), 7.58 (d, $J = 7.2$ Hz, 1H), 7.82 (br s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 12.0, 14.0, 21.1, 30.8, 32.5, 37.4, 49.3, 110.5, 113.2, 118.8, 119.0, 120.6, 127.1, 131.5, 135.6, 209.2.

(S)-4-(5-Bromo-1H-indol-3-yl)heptan-2-one (5db) *(Table 2, entry 8).* The ee was determined by HPLC analysis using an OD-H column (5/95 *i*-PrOH/hexane; flow rate 1.0 mL/min; λ = 254 nm; $\tau_{minor} = 21.07$ min; $\tau_{major} = 23.39$ min). $[\alpha]_{D}^{RT} = +9.7$ ($c = 0.76$, $CHCl_3$, 54% ee). ^{1}H-NMR (300 MHz, $CDCl_3$, δ,

ppm): 0.84 (t, $J = 7.1$ Hz, 3H), 1.16–1.25 (m, 2H), 1.59–1.78 (m, 2H), 2.02 (s, 3H), 2.74–2.84 (m, 2H), 3.36–3.43 (m,1H), 6.92 (s, 1H), 7.20 (dd, $J = 8.4$, 18.1 Hz, 2H), 7.75 (s, 1H), 8.25 (br s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 14.0, 20.7, 30.5, 32.5, 38.1, 50.0, 112.5, 112.8, 118.6, 121.8, 122.6, 124.7, 128.3, 135.2, 208.9.

(R)-4-(2-Methyl-1H-indol-3-yl)-4-phenylbutan-2-one (5cc) *(Table 2, entry 9).* The ee was determined by HPLC analysis using a Chiralpak AD-H column (15/85 *i*-PrOH/hexane; flow rate 1.0 mL/min; $\lambda = 254$ nm; $\tau_{minor} = 7.66$ min; $\tau_{major} = 8.39$ min). $[\alpha]_D^{RT} = +4.5$ ($c = 0.48$, $CHCl_3$, 46% ee). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 1.98 (s, 3H), 2.33 (s, 3H), 3.29 (dd, $J = 6.2$, 16.2 Hz, 1H), 3.42 (dd, $J = 8.5$, 16.0 Hz, 1H), 4.84 (t, $J = 6.9$ Hz, 1H), 6.98–7.29 (m, 8H), 7.44 (d, $J = 7.5$ Hz, 1H), 7.77 (br, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 11.6, 30.3, 36.4, 47.8, 110.0, 112.7, 118.6, 118.7, 120.3, 125.5, 126.9, 127.8, 131.3, 135.0, 143.6, 207.5.

(R)-1-(4-Chlorophenyl)-3-(1H-indol-3-yl)-3-phenylpropan-1-one (5ad) *(Table 2, entry 10).* The ee was determined by HPLC analysis using a Chiralpak AD-H column (15/85 *i*-PrOH/hexane; flow rate 1.0 mL/min; $\lambda = 254$ nm; $\tau_{minor} = 21.83$ min; $\tau_{major} = 24.65$ min). $[\alpha]_D^{RT} = -28.2$ ($c = 0.58$, $CHCl_3$, 69% ee). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 3.66 (dd, $J = 7.4$, 16.6 Hz, 1H), 3.72–3.79 (m, 1H), 5.02 (t, $J = 6.5$ Hz, 1H), 6.60–7.43 (m, 12H), 7.80–7.89 (m, 2H), 7.94 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 38.4, 45.2, 111.0, 111.2, 119.1, 119.2, 119.5, 121.4, 121.9, 122.2, 123.4, 126.4, 126.6, 127.8, 128.2, 128.5, 128.9, 129.5, 135.5, 136.7, 139.5, 144.0, 197.5. HRMS (ESI) exact mass Calcd for $(C_{23}H_{18}ClNO + Na)^+$ requires *m/z* 382.1077, found *m/z* 382.0965.

(R)-3-(1H-Indol-3-yl)-1-(3-methoxyphenyl)-3-phenylpropan-1-one (5ae) *(Table 2, entry 11).* The ee was determined by HPLC analysis using an OD-H column (30/70 *i*-PrOH/hexane; flow rate 1.0 mL/min; $\lambda = 254$ nm; $\tau_{minor} = 10.7$ min; $\tau_{major} = 17.78$ min). $[\alpha]_D^{RT} = -24.0$ ($c = 0.65$, $CHCl_3$, 63% ee). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 3.67–3.74 (m, 2H), 3.83 (s, 3H), 5.05 (s, 1H), 6.87–7.43 (m, 12H), 7.91 (d, $J = 7.2$ Hz, 2H), 7.96 (bs, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 38.0, 44.4, 54.9, 110.6, 113.2, 118.9, 119.1, 121.0, 121.6, 125.7, 126.2, 127.4, 127.9, 129.9, 136.2, 143.9, 162.9, 196.6.

(R)-3-(1H-Indol-3-yl)-3-(naphthalen-2-yl)-1-phenylpropan-1-one (5af) *(Table 2, entry 12).* The ee was determined by HPLC analysis using an OD-H column (15/85 *i*-PrOH/hexane; flow rate 1.0 mL/min; $\lambda = 254$ nm; $\tau_{minor} = 22.10$ min; $\tau_{major} = 25.37$ min). $[\alpha]_D^{RT} = -5.7$ ($c = 0.56$, $CHCl_3$, 68% ee). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 3.79–3.90 (m, 2H), 5.23 (t, $J = 6.9$ Hz, 1H), 6.62 (s, 2H), 6.94–7.51 (9H), 7.70–7.78 (m, 4H), 7.92 (d, $J = 7.7$ Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 38.4, 45.1, 111.1, 111.2, 119.2, 119.5, 119.6, 121.6, 122.2, 125.4, 125.9, 126.0, 126.7, 127.6, 127.8, 128.1, 128.6, 132.3, 133.0, 133.5, 136.7, 137.2, 141.7, 198.5. HRMS (ESI) exact mass Calcd for $(C_{27}H_{21}NO + Na)^+$ requires *m/z* 398.1623, found *m/z* 398.1519.

(S)-3-(1H-Indol-3-yl)-1-phenyl-3-(thiophen-2-yl)propan-1-one (5ag) *(Table 2, entry 13).* The ee was determined by HPLC analysis using an AD-H column (15/85 *i*-PrOH/hexane; flow rate 1.0 mL/min; $\lambda = 254$ nm; $\tau_{minor} = 18.49$ min; $\tau_{major} = 20.97$ min). $[\alpha]_D^{RT} = -6.5$ ($c = 0.74$, $CHCl_3$, 59% ee). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 3.80 (d, $J = 6.7$ Hz, 2H), 5.35 (t, $J = 6.6$ Hz, 1H), 6.84–7.54 (m, 11H), 7.90 (d, $J = 7.3$ Hz, 2H), 7.99 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 33.1, 45.7, 110.8, 118.5, 119.0, 119.1, 121.2, 121.7, 123.0, 123. 8, 125.8, 126.1, 127.7, 128.1, 132.6, 136.1, 136.6, 148.3, 197.7. HRMS (ESI) exact mass Calcd for $(C_{21}H_{17}NOS + Na)^+$ requires *m/z* 354.1031, found *m/z* 354.0922.

(R)-3-(1H-Indol-3-yl)-3-phenyl-1-(thiophen-2-yl)propan-1-one (5ah) *(Table 2, entry 14).* The ee was determined by HPLC analysis using an AD-H column (15/85 *i*-PrOH/hexane; flow rate 1.0 mL/min; $\lambda = 254$ nm; $\tau_{minor} = 19.74$ min; $\tau_{major} = 21.52$ min). $[\alpha]_D^{RT} = -20.7$ ($c = 0.52$, $CHCl_3$, 63% ee). ^{1}H-NMR (300 MHz, DMSO-d_6, δ, ppm): 3.70 (dd, $J = 7.0$, 15.9 Hz, 1H), 3.86 (dd, $J = 6.9$, 15.9 Hz, 1H), 4.88 (d, $J = 6.5$ Hz, 1H), 6.89–7.41 (m,11H), 7.94 (s, 1H), 8.11 (s, 1H), 10.86 (s, 1H); ^{13}C-NMR (75 MHz, DMSO-d_6, δ, ppm): 38.0, 44.6, 111.3, 117.7, 118.3, 118.7, 121.0, 121.9, 125.9, 126.3, 127.7, 128.1, 128.6, 133.4, 134.8, 136.3, 144.3, 144.9, 191.4. HRMS (ESI) exact mass Calcd for $(C_{21}H_{17}NOS + Na)^+$ requires *m/z* 354.1031, found *m/z* 354.0919.

(S)-3-(Furan-2-yl)-3-(1H-indol-3-yl)-1-phenylpropan-1-one (5ai) *(Table 2, entry 15).* The ee was determined by HPLC analysis using an OD-H column (15/85 *i*-PrOH/hexane; flow rate 1.0 mL/min; $\lambda = 254$ nm; $\tau_{minor} = 13.37$ min; $\tau_{major} = 15.96$ min). $[\alpha]_D^{RT} = +8.3$ ($c = 0.52$, $CHCl_3$, 58% ee). ^{1}H-NMR (300 MHz, $CDCl_3$, δ, ppm): 3.66 (dd, $J = 6.6$, 16.7 Hz, 1H), 3.86 (dd, $J = 7.2$, 16.6 Hz, 1H), 5.13 (t, $J = 6.6$ Hz, 1H), 6.05 (s, 1H), 6.15 (s, 1H), 7.00–7.58 (m, 9H), 7.91 (d, $J = 7.3$ Hz, 2H), 8.01 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$, δ, ppm): 31.8, 42.7, 105.2, 109.7, 110.8, 116.2, 118.9, 119.1, 121.6, 125.8, 127.6, 128.1, 132.5, 136.1, 136.6, 140.7, 156.5, 197.8. HRMS (ESI) exact mass Calcd for $(C_{21}H_{17}NO_2 + Na)^+$ requires *m/z* 338.1259, found *m/z* 338.1153.

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