Highly efficient asymmetric organocatalytic Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes†

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The development of an improved organocatalyst, *N*-isopropylated bipyrrolidine **2a**, for the asymmetric Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes has been presented. The new organocatalyst readily facilitates the enantioselective alkylation reaction, providing 3-alkylated indoles in good to high yields (62–89%) with high levels of enantioselectivity (80–93% ee) using only 2 mol% of catalyst loading.

Introduction

During the past decade organocatalysis has witnessed an explosive growth in the field of asymmetric synthesis since it employs small organic molecules that are relatively non-toxic, inexpensive and stable to both air and moisture.[1] Organocatalysis has become the third main branch in catalytic asymmetric synthesis, together with enzymatic and organometallic catalysis, and a great number of new asymmetric transformations have been developed using small organic molecules as catalysts. However, in most organocatalytic reactions to achieve reasonable reaction rates, high catalyst loading is generally required. Therefore, the development of highly active organocatalysts aiming to lower catalyst loadings is an important challenge.

The asymmetric Friedel–Crafts reaction is one of the most powerful methods for synthesis of optically active aromatic compounds.[2] Based on the strategy of LUMO-lowering activation of α,β-unsaturated aldehydes, MacMillan and co-workers first explored organocatalytic asymmetric Friedel–Craft alkylation of pyrroles and indoles.[3] Since then, MacMillan's imidazolidinone catalysts have also been used for indole alkylation with cyclic,[4] (*E*)-dialkyl 3-oxoprop-1-enylphosphonates[5] and γ-hydroxy α,β-unsaturated aldehyde[6] as well as the intramolecular Friedel–Crafts alkylation of indoles.[7] Bonini and co-workers reported indole alkylation reactions with aziridin-2-yl methanols as catalysts, however, the enantioselectivity is not sufficiently high.[8] Most recently, Wang and Bao independently reported these transformations catalyzed by chiral diphenylprolinol trimethylsilyl ether without acid co-catalyst.[9] Lee and co-workers reported camphor sulfonyl hydrazine-catalyzed asymmetric indole alkylation reactions.[10] In spite of the further improvements in this type of organocatalytic Friedel–Crafts alkylation of indoles with α,β-unsaturated ketones have been reported,[11] higher catalyst loading (10–30 mol%) remains a main drawback for this important transformation.

Most recently, we reported new bipyrrolidine organocatalyst **1** (Fig. 1) which was successfully applied in asymmetric Diels–Alder reactions of α,β-unsaturated aldehydes.[12] It was demonstrated that the 3,3′-dibenzyloxy groups of catalyst **1** play a significant role in acceleration of the reaction rate in the Diels–Alder reaction. In our continuing effort to develop a highly active organocatalytic system, in this paper we document the efficient asymmetric organocatalytic Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes using *N*-modified bipyrrolidines **2** (Fig. 1) as catalysts. Although *N*-isopropylated bipyrrolidine has been revealed as an efficient organocatalyst for many asymmetric reactions,[13] there are no reports concerning its use as a chiral catalyst in iminium catalysis. Significantly, using only 2 mol% of our improved organocatalyst *N*-isopropylated bipyrrolidine **2a**, the Friedel–Crafts alkylation reaction afforded 3-alkylated indoles in good to high yields with high level of enantioselectivities.

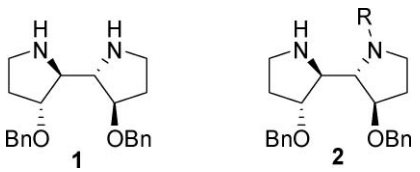
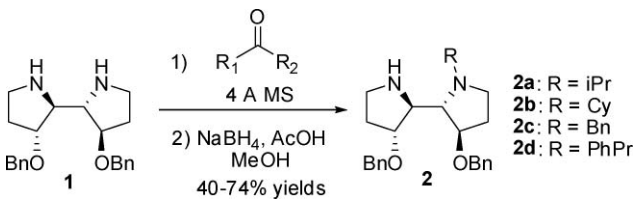


Fig. 1 Structure of bipyrrolidine catalysts **1** and **2**.

Results and discussion

The new bipyrrolidine catalysts **2** were readily prepared from bipyrrolidine **1** and ketones or aldehydes *via* reductive amination process. As shown in Scheme 1, the monoalkylation of 1,2-diamines consists of the formation of intermediate aminals from aldehydes or ketones followed by their reduction with sodium borohydride.[13a] According to this general procedure several



Scheme 1 Preparation of *N*-substituted bipyrrolidines **2**

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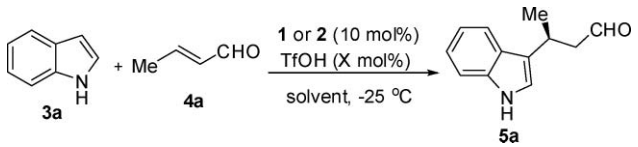
† Electronic supplementary information (ESI) available: ^{1}H NMR and ^{13}C NMR spectra of all new synthesized compounds, and HPLC traces for enantioselectivity determination. See DOI: 10.1039/c0ob00016g

Table 1 Optimization of reaction conditions[a]



Entry	Cat.	X	Solvent	*T*/h	Yield (%)[b]	ee (%)[c]
1	**1**	20	CH_2Cl_2/*i*PrOH	48	49	55
2	**2a**	20	CH_2Cl_2/*i*PrOH	2	85	76
3	**2a**	—	CH_2Cl_2/*i*PrOH	24	NR	—
4	**2a**	10	CH_2Cl_2/*i*PrOH	5	81	72
5	**2a**	30	CH_2Cl_2/*i*PrOH	2	49	73
6	**2a**	40	CH_2Cl_2/*i*PrOH	2	38	66
7	**2a**	20	CH_2Cl_2	24	11	7
8	**2a**	20	CH_3Cl	14	77	31
9	**2a**	20	*i*PrOH	2	85	76
10	**2a**	20	EtOH	2	89	74
11	**2a**	20	MeOH	2	90	76
12	**2a**	20	MeOH–H_2O	2	90	68
13	**2a**	20	THF	12	95	58
14	**2a**	20	Et_2O	5	67	52
15	**2a**	20	CH_3CN	14	16	7
16	**2a**	20	DMF	2	70	75
17	**2a**	20	NMP	24	65	74

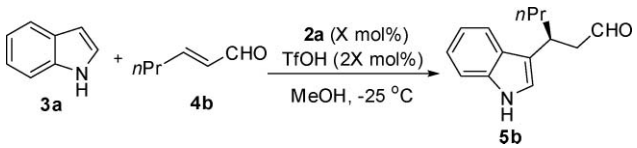
[a] The reactions were carried out with 0.5 mmol of indole, 1.5 mmol of crotonaldehyde, 0.05 mmol of bipyrrolidine, and 0.10 mmol of TfOH in solvent (2.0 mL, 0.25 M). [b] Isolated yield after purification by column chromatography on silica gel. [c] Determined by chiral HPLC. Absolute configurations determined by comparison with literature data. CH_2Cl_2/iPrOH = 85/15 (v/v); MeOH–H_2O = 19/1 (v/v); NMP = *N*-methyl-2-pyrrolidinone. NR = no reaction.

mono-*N*-alkylated bipyrrolidines **2** were synthesized starting from bipyrrolidine **1** (40–74% yields).

A model experiment was conducted with indole (**3a**) and (*E*)-crotonaldehyde (**4a**) in the presence of 10 mol% of bipyrrolidine **1** and 20 mol% of TfOH as cocatalyst in methylene chloride and isopropanol (v/v = 85/15) at −25 °C. As shown in Table 1, the reaction gave 3-alkylated indole **5a** in only 49% yield with 55% ee for 48 h (entry 1). Interestingly, when using *N*-isopropylated bipyrrolidine **2a** as catalyst, the reaction remarkably improved. The alkylation reaction with 10 mol% of **2a** as a catalyst afforded **5a** in 85% isolated yield with 76% ee within only 2 h (entry 2). The amounts of the acid co-catalyst had large effects on the reaction. The reaction without acid additive did not proceed at all (entry 3). When the reaction was performed with 10 mol% of TfOH, the enantioselectivity slightly decreased (entry 4). Upon further increasing of the dosage of acid co-catalyst, the reaction efficiencies were remarkably decreased (entries 5 and 6). The results demonstrated that the diammonium salt of bipyrrolidine **2a** is the best catalytic species for the reaction. With 10 mol% of *N*-isopropylated bipyrrolidine **2a** and 20 mol% of TfOH, different reaction solvents were screened (entries 7–17). It was found that the alkylation reaction largely depended on the solvent. The results indicated that CH_2Cl_2, CH_3Cl, Et_2O, THF and CH_3CN are unsuitable solvents for the reaction (entries 7, 8, 13–15). Protic solvents are better for the reaction (entries 9–12) and methanol is the best solvent (entry 11).

Encouraged by these initial results, the effect of catalyst loading on reaction efficiency was evaluated (Table 2). When the Friedel–Crafts alkylation reaction of indole (**3a**) with (*E*)-2-hexenal (**4b**)

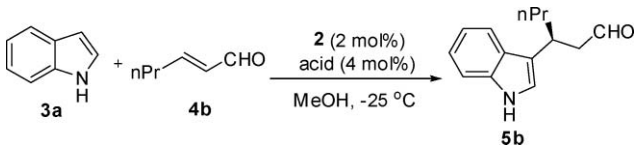
Table 2 Effect of catalyst loading on the alkylation reaction[a]



Entry	X	*T*/h	Yield (%)[b]	ee (%)[c]
1	10	2	90	88
2	5	4	87	90
3	2	4	80	90

[a] The reactions were carried out with 0.5 mmol of indole, 1.5 mmol of crotonaldehyde in methanol (2.0 mL, 0.25 M). [b] Isolated yield after purification by column chromatography on silica gel. [c] Determined by chiral HPLC. Absolute configurations determined by comparison with literature data.

Table 3 Asymmetric Friedel–Crafts alkylation of indole (**3a**) with (*E*)-2-hexenal (**4b**)



Entry	Bipyrr.	Acid	*T*/h	Yield (%)[b]	ee (%)[c]
1	**2a**	TfOH	4	80	90
2	**2a**	$HClO_4$	5	80	90
3	**2a**	TFA	20	79	86
4	**2a**	*p*-TSA	24	trace	—
5	**2a**	*p*-NO_2BzOH	24	trace	—
6	**2b**	TfOH	7	81	89
7	**2c**	TfOH	7	70	90
8	**2d**	TfOH	7	80	86
9[d]	**2a**	TfOH	36	88	92

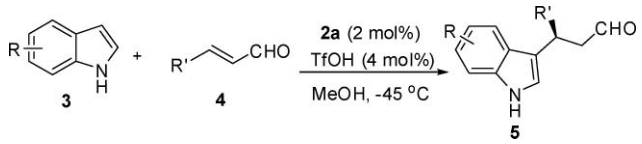
[a] The reactions were carried out with 0.5 mmol of indole, 1.5 mmol of hexenal, 0.01 mmol of bipyrrolidine, and 0.02 mmol of acid in MeOH (2.0 mL, 0.25 M). [b] Isolated yield after purification by column chromatography on silica gel. [c] Determined by chiral HPLC. Absolute configurations determined by comparison with literature data. [d] The reaction was carried out at −45 °C.

was performed in methanol at −25 °C, it was found that catalyst loadings as low as 2 mol% provide alkylated product **5b** in high isolated yield (80%) with useful levels of enantioselectivity (90% ee) within 4 h.

To further improve the reaction, the effect of acid co-catalyst on reaction efficiency was investigated (Table 3). The Brønsted acid co-catalyst had large effects on the reaction (entries 1–5). When using $HClO_4$ as cocatalyst, the reaction gave similar results as with TfOH (entry 2). When the reaction was performed with trifluoroacetic acid (TFA), a longer reaction time was needed (entry 3). However, only trace amounts of products were observed using *p*-toluenesulfonic acid (*p*-TSA) or *p*-nitrobenzoic acid as co-catalysts (entries 4 and 5). Further tuning of *N*-substituent of catalyst **2** did not improve the enantioselectivity (entries 6–8). However, when the reaction temperature was decreased to −45 °C, the reaction gave 3-substituted indole **5b** in 88% isolated yield with 92% ee (entry 9).

With optimized conditions in hand, the scope of the Friedel–Crafts alkylations of substituted indoles with various

Table 4 Organocatalytic Friedel–Crafts alkylation of indoles **3** with α,β-unsaturated aldehydes **4**[a]



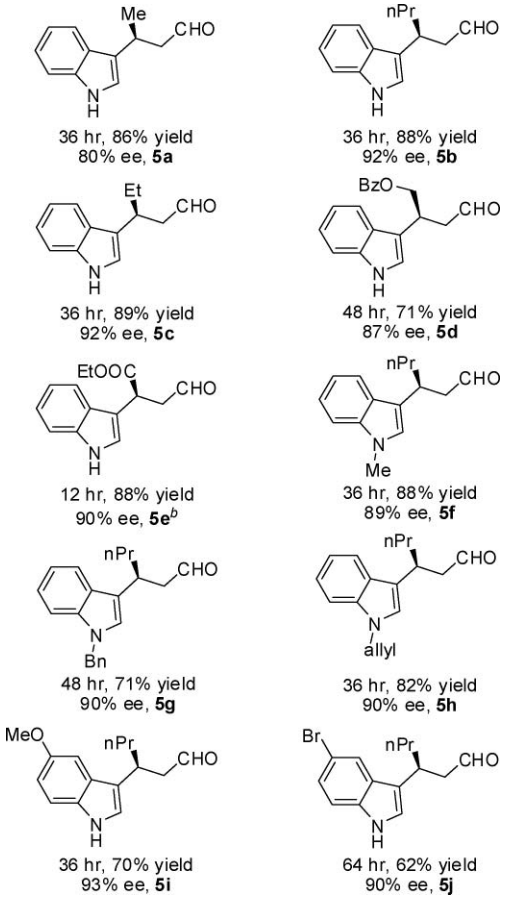
3

4

5

3a, R = H; **3b**, *R* = 1-Me; **3c**, *R* = 1-Bn; **3d**, *R* = 1-allyl; **3e**, *R* = 5-OMe; **3f**, *R* = 5-Br

4a, R′ = Me; **4b**, R′ = *n*Pr; **4c**, R′ = Et; **4d**, R′ = CH_2OBz; **4e**, R′ = COOEt



[a] Yields are of alkylated products isolated by column chromatography on silica gel. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. See the ESI† for further details. [b] The reaction was carried out at −25 °C.

α,β-unsaturated aldehydes was explored using 2 mol% of **2a** and 4 mol% of TfOH as co-catalyst (Table 4). Reactions of indole **3a** with functionalized α,β-unsaturated aldehydes afforded 3-alkylated indoles **5a–5e** in high isolated yields (71–89%) with good to excellent enantioselectivities (80–92% ee). Substituted indoles were subjected to alkylation with 2-hexenal giving products **5f–5j** in good to high yields (62–88%) with high level of enantioselectivities (89–93% ee). Notably, the yields and enantioselectivities of the alkylation reactions obtained with only 2 mol% of *N*-isopropylated bipyrrolidine **2a** are comparable to those obtained with former catalytic systems, requiring higher catalyst loading.[3–10]

To elucidate the origin of asymmetric induction, the lowest energy conformer of iminium ion **6** formed from catalyst **2a** and 2-hexenal was calculated (Fig. 2, DFT calculation at B3LYP/6-31g(d) level). Inspection of the structure of intermediate **6** reveals (i) selective formation of the (*E*)-iminium isomer to avoid nonbonding interactions between the substrate olefin and the pyrrolidine group at the other side, (ii) the *N*-isopropyl group effectively shields the *Re*-face of the iminium ion, leaving the *Si*-face exposed to indole attack, and (iii) two benzyloxy groups on the catalyst likely further restrict conformational flexibility having a positive effect on the enantioselectivity.

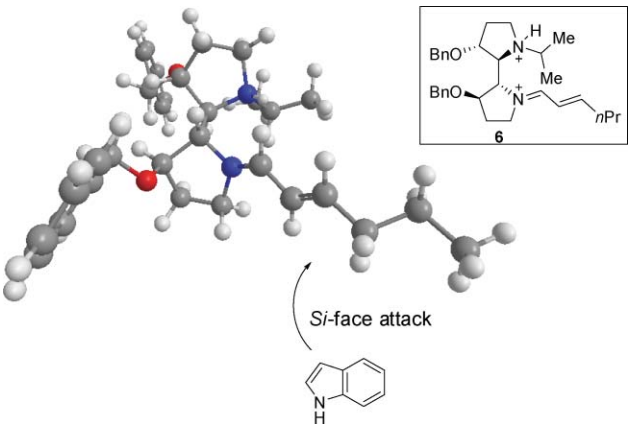


Fig. 2 Minimum energy iminium ion **6** formed from **2a** and 2-hexenal.

Conclusion

In conclusion, we have documented our development of an improved organocatalyst *N*-isopropylated bipyrrolidine **2a** for the asymmetric Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes. The new organocatalyst readily facilitates the enantioselective alkylation reaction, providing 3-alkylated indoles in good to high yields (62–89%) with high levels of enantioselectivity (80–93% ee) using only 2 mol% of catalyst loading. Further studies on development of new organocatalytic transformations aiming to lower catalyst loading will be forthcoming.

Experimental

All reactions were run under an atmosphere of nitrogen, unless otherwise indicated. Dry solvents were purified according to the standard method. Indoles were recrystallized before use. α,β-Unsaturated aldehydes were distilled and stored under nitrogen atmosphere at −20 °C. ^{1}H NMR spectra were measured on a MERCURY plus400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane as an internal standard. Data are reported as follows: chemical shift, integration, multiplicity, coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded on a MERCURY plus400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from the residual solvent as an internal standard. Optical rotations were taken on a SGW®-1 automatic polarimeter. High performance liquid chromatography (HPLC) was performed on Class-Vp6x, Single ee using a Daicel Chiralcel

AD-H, OD-H, or AS-H. Mass spectra were recorded by EI and ESI, and HRMS were measured on a HP-5989 instrument. For thin layer chromatography (TLC) analysis throughout this work, TLC plates were used. TLC spots were visualized under ultraviolet light or developed by heating after treatment with potassium permanganate. The products were purified by flash column chromatography on silica gel (100–200 mesh).

General procedure for the synthesis of catalyst 2

To a solution of bipyrrolidine **1** (250 mg, 0.71 mmol) in solvent (10 mL) was added activated 4 Å molecular sieves, and ketone or aldehyde (0.71 mmol). The reaction mixture was stirred overnight at ambient temperature, and then K_2CO_3 was added and stirred for 1 h. The precipitate was filtered and the filtrate was concentrated to give the crude aminal which was used without further purification. To a solution of the aminal in MeOH (10 mL) was added $NaBH_4$ (40 mg, 1.07 mmol) at 0 °C. After stirring for 10 min, acetic acid (0.12 mL, 2.13 mmol) was added and the mixture was stirred for 4 h. The reaction was quenched by 5 mL of 30% NaOH aqueous solution and extracted with ethyl acetate (20 mL × 3). The organic layer was washed with brine, dried over K_2CO_3, filtered, and the solvent was removed *in vacuo*. The obtained residue was purified by column chromatography on silica gel (ethyl acetate : petroleum ether = 1 : 4, 5% Et_3N) to afford *N*-alkylated bipyrrolidine **2**.

(2*S*,2′*S*,3*R*,3′*R*)-3,3′-bis(benzyloxy)-1-isopropyl-2,2′-bipyrrolidine (2a)

In accordance with the general procedure, the reaction was carried out in acetone (10 mL) as solvent to afford title compound **2a** as a yellowish oil (207 mg, 74% yield). $[\alpha]_D^{25}$ = +19.0 (*c* = 0.20, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.21 (m, 10H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.43 (s, 2H), 4.35 (d, *J* = 12.0 Hz, 1H), 3.83–3.80 (m, 1H), 3.74–3.69 (m, 1H), 3.03–2.76 (m, 7H), 1.92–1.72 (m, 4H), 1.65 (s, 1H), 1.08 (d, *J* = 6.0 Hz, 3H), 0.97 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.6, 128.1, 127.8, 127.7, 127.6, 82.4, 81.7, 71.3, 70.2, 68.8, 68.0, 51.2, 45.2, 44.0, 33.0, 30.8, 23.0, 15.1; HRMS (EI-TOF) calcd for $C_{25}H_{34}N_2O_2$ 394.2620, Found: 394.2629.

(2*S*,2′*S*,3*R*,3′*R*)-3,3′-bis(benzyloxy)-1-cyclohexyl-2,2′-bipyrrolidine (2b)

In accordance with the general procedure, the reaction was carried out in the presence of cyclohexenone (73.5 μL, 0.71 mmol) in THF (10 mL) as solvent to afford title compound **2b** as a yellowish oil (139 mg, 45% yield). $[\alpha]_D^{25}$ = +4.4 (*c* = 1.2, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.23 (m, 10H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.42 (d, *J* = 2.8 Hz, 2H), 4.35 (d, *J* = 11.6 Hz, 1H), 3.85–3.81 (m, 1H), 3.73–3.68 (m, 1H), 3.09 (d, *J* = 6.0 Hz, 1H), 3.01–2.84 (m, 5H), 2.63–2.52 (m, 1H), 1.82–1.69 (m, 6H), 1.61 (m, *J* = 11.6 Hz, 1H), 1.36–0.97 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 138.6, 128.6, 128.6, 128.0, 127.8, 127.7, 82.0, 81.8, 71.3, 70.3, 68.2, 68.1, 61.0, 45.7, 45.2, 33.6, 33.0, 30.9, 26.6, 26.5, 26.0, 25.9; HRMS (ESI-TOF) Calcd. For $C_{28}H_{38}N_2O_2$ [M+H] 435.3012, Found: 435.3021.

(2S,2′*S*,3*R*,3′*R*)-1-benzyl-3,3′-bis(benzyloxy)-2,2′-bipyrrolidine (2c)

In accordance with the general procedure, the reaction was carried out in the presence of benzaldehyde (73.0 μL, 0.71 mmol) in diethyl ether (10 mL) as solvent to afford title compound **2c** as a yellowish oil (126 mg, 40% yield). $[\alpha]_D^{25}$ = −38.6 (*c* = 0.60, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.20 (m, 15H), 4.50 (dd, *J* = 2.4, 12.0 Hz, 2H), 4.38 (dd, *J* = 12.0, 14.0 Hz, 2H), 4.07 (d, *J* = 13.6 Hz, 1H), 3.90–3.87 (m, 1H), 3.80–3.75 (m, 1H), 3.54 (d, *J* = 12.8 Hz, 2H), 3.09 (dd, *J* = 4.4, 5.2 Hz, 1H), 3.03–2.87 (m, 4H), 2.62–2.54 (m, 1H), 2.02–1.58 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 138.6, 138.4, 128.9, 128.8, 128.7, 128.6, 128.5, 128.0, 127.9, 127.9, 127.3, 83.0, 81.6, 71.4, 71.2, 70.7, 67.3, 61.7, 53.1, 44.9, 32.5, 30.8; HRMS (ESI-TOF) Calcd. For $C_{29}H_{34}N_2O_2$ [M+H] 443.2699, Found: 443.2690;

(2*S*,2′*S*,3*R*,3′*R*)-3,3′-bis(benzyloxy)-1-(3-phenylpropyl)-2,2′-bipyrrolidine (2d)

In accordance with the general procedure, the reaction was carried out in the presence of 3-phenylpropanal (94.3 μL, 0.71 mmol) in diethyl ether (10 mL) as solvent to afford title compound **2d** as a yellowish oil (184 mg, 55% yield), $[\alpha]_D^{25}$ = −14.8 (*c* = 0.24, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.23 (m, 12H), 7.20–7.14 (m, 3H), 4.51–4.36 (m, 3H), 4.28 (d, *J* = 11.6 Hz, 1H), 3.85 (d, *J* = 5.2 Hz, 1H), 3.70–3.64 (m, 1H), 3.16–3.08 (m, 1H), 2.97–2.89 (m, 3H), 2.84–2.74 (m, 2H), 2.70–2.60 (m, 1H), 2.59–2.45 (m, 3H), 1.97–1.66 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 138.8, 138.7, 128.6, 128.6, 128.5, 128.0, 127.8, 127.8, 127.7, 82.8, 81.7, 72.2, 71.4, 70.4, 68.4, 57.3, 52.6, 45.2, 33.7, 32.9, 30.9, 30.7; HRMS (ESI-TOF) Calcd. for $C_{31}H_{38}N_2O_2$ [M+H] 470.2933, Found: 470.2938.

General procedure for the asymmetric Friedel–Crafts alkylation reaction

To a stirred solution of catalysts **2a** (0.01 mmol, 3.9 mg) and TfOH (0.02 mmol, 1.8 μL) in MeOH (2 mL) was added α,β-unsaturated aldehyde (1.5 mmol) at −45 °C. The solution was stirred for 10 min before indole (0.5 mmol) was added. The reaction mixture was stirred at −45 °C for 36–64 h and warmed to ambient temperature. The reaction was quenched by saturated $NaHCO_3$, extracted with CH_2Cl_2 (5 mL × 3) and washed with brine. The organic layer was dried by anhydrous Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate : petroleum ether = 1 : 6) to afford the corresponding 3-alkylated indole. To determine enantiomeric excess, the product was converted to the corresponding alcohol with $NaBH_4$ in MeOH and enantiomeric excess was determined by HPLC using a Chiracel AD-H, OD-H, or AS-H. See the ESI† for further details.

Acknowledgements

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Notes and references

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