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PAPER

Enantioselective Friedel–Crafts alkylation of indoles with 2-enoylpyridine-*N*-oxides catalyzed by *gluco*BOX-Cu(II) complex†

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The glucosamine derived *gluco*BOX-Cu(II) complex was found to be a unique catalytic system for enantioselective Friedel–Crafts alkylation of indoles with 2-enoylpyridine-1-oxides. A large number of 3-alkylated indole derivatives were prepared using 5 mol% *gluco*BOX-Cu(II) complex in excellent yields with high enantioselectivity up to 99% ee.

Introduction

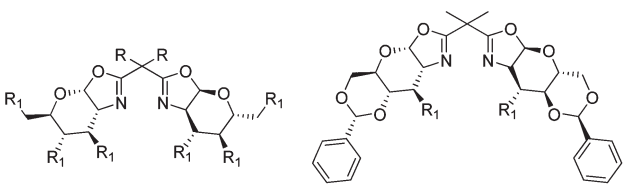
In recent years, tremendous interest has been devoted to the preparation of substituted indoles due to their varied biological activities including antioxidant, antibacterial, and insecticidal behavior.[1] Some of the indole derivatives are found to exhibit anticancer activity against various human cancers.[2] Among various derivatives of indoles, 3-substituted indoles are important as they are widely distributed in nature and show a broad range of biological activities.[3] Therefore, there is a growing interest in the development of improved methods for the synthesis of 3-substituted indoles.[4] As a result, several substrates such as nitrostyrenes,[5] α-ketoesters,[6] 2-acyl ketophosphonates,[7] α-hydroxyenones,[8] *N*-methylimidazoles,[9] and arylidinemalonates[10] have been reported as excellent reaction partners for Friedel–Crafts reactions in terms of yield and enantioselectivity. Recently, organo-catalysts[11] have also been shown to be efficient catalysts for enantioselective Friedel–Crafts alkylation of indoles.

While several electrophilic substrates are known to undergo Cu(II)-catalyzed enantioselective Friedel–Crafts reactions, (ref. 5–10) 2-enoylpyrinine-*N*-oxides are less explored. Pedro *et al.* have reported the 2-enoylpyridine-*N*-oxides as excellent substrates for Cu(II)-catalyzed enantioselective Diels–Alder reactions[12] and hetero-Diels–Alder reactions.[13] Recently, 2-enoylpyridine-*N*-oxides have successfully been utilized for enantioselective nitrone cycloaddition reactions.[14] Later on, enantioselective Friedel–Crafts reactions of indoles have been reported using Cu(II)-PyBOX complexes.[15] Subsequently, the Friedel–Crafts alkylation of pyrroles[16] and Michael addition of dialkylmalonates[17] have also been reported with chiral zinc complexes. The co-ordinating group, *i.e.* the pyridine-*N*-oxide moiety can easily be converted into the corresponding carboxylic acid.[18]

In most cases, L-amino acid derived bisoxazoline ligands are known to provide the corresponding products with the same absolute configuration (ref. 6 and 10). In the view of medicinal chemistry, the syntheses of both enantiomers are equally important. By applying an inversion protocol, some chiral compounds (for example those with a hydroxyl group) can be converted into the opposite enantiomer. However, in the case of Friedel–Crafts reactions, the inversion of a chiral center has not been successful yet. Therefore, the synthesis of both enantiomers requires the expensive D-amino acid derived bisoxazoline ligands. Therefore, D-sugar based bisoxazoline ligands have gained importance as alternatives to D-amino acid derived bisoxazolines. Consequently, Boysen *et al*. have introduced the sugar based bisoxazoline ligands for the first time for enantioselective transformations[19] (Fig. 1). Inspired by inherent catalytic features of *gluco*BOX, we attempted the Friedel–Crafts alkylation of indoles with 2-enoylpyridine-*N*-oxides using D-sugar derived bisoxazolines.

Results and discussion

Following our interest in the Cu(II)-*gluco*BOX catalyzed enantioselective nitroaldol reaction,[20] we herein report a highly efficient



1a. R = CH_3, R_1 = OAc
1b. R = C_2H_5, R_1 = OAc
1c. R = CH_3, R_1 = OPiv
1d. R_1 = OAc
1e. R_1 = OH
1f. R_1 = OPiv

Fig. 1 *Gluco*BOX ligands.

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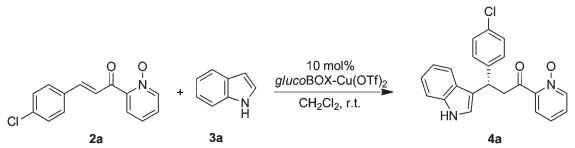
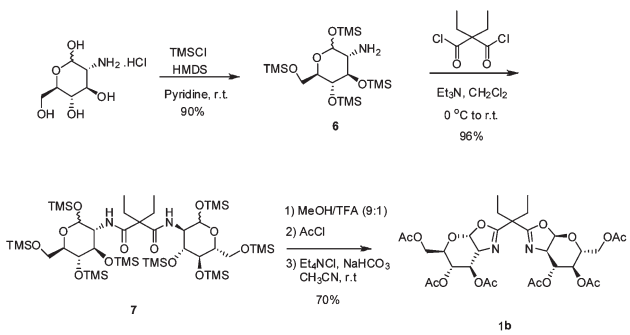
†Electronic supplementary information (ESI) available: Experimental details, characterization of all ligands, NMR spectra, and HPLC chromatogram of Friedel–Crafts products. See DOI: 10.1039/c2ob25315a

Table 1 Screening of various *gluco*BOX-Cu(II) complexes for enantioselective alkylation of indole with 2-enoylpyridine-*N*-oxide **2a**



Entry	Ligand[a]	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	1	96	77
2	**1b**	1	94	58
3	**1c**	36	35	25
4	**1d**	1.5	97	80
5	**1e**	2.5	85	05
6	**1f**	1.5	90	70

[a] All the reactions were carried out in 0.5 mmol scale using 0.75 mmol of indole in 2.0 mL of dichloromethane at room temperature. [b] Yield refers to pure products after purification. [c] Enantiomeric excess was determined by chiral HPLC analysis.



Scheme 1 Preparation of *gluco*BOX (**1b**).

catalytic enantioselective Friedel–Crafts alkylation of indoles and pyrrole with 2-enoylpyridine-*N*-oxides. Accordingly, we first attempted the Friedel–Crafts alkylation of indole with enoylpyridine-1-oxide **2a** using a 1 : 1 ratio of $Cu(OTf)_2$ and the ligand **1a**. The active catalyst *i.e. gluco*BOX-Cu(II) complex was generated *in situ* by mixing an equimolar ratio of the ligand **1a** with $Cu(OTf)_2$ in CH_2Cl_2 at room temperature (Table 1).

The use of a copper(II) complex of *gluco*BOX bearing acetate groups **1a** gave the Michael adduct **4a** in 96% yield with a moderate enantioselectivity (77% ee, Table 1, entry 1). Therefore, we next prepared ligand **1b** by simply replacing the geminal dimethyl groups of ligand **1a** with geminal diethyl groups (Scheme 1). Though the product **4a** was obtained in 94% yield using ligand **1b**-$Cu(OTf)_2$ complex, the enantioselectivity was quite low (58% ee, Table 1, entry 2). Surprisingly, a sterically crowded ligand **1c** also gave the product **3c** in low ee (Table 1, entry 3). The reason may be due to the presence of more bulkiness from the pivolyl group in ligand **1c**. Therefore, we further examined the efficiency of a modified *gluco*BOX **1d**, wherein two acetate groups in each pyranoside ring were replaced by a benzal group. By using **1d**-$Cu(OTf)_2$ complex, the 3-alkylated indole was obtained in 97% yield with 80% ee (Table 1, entry 4). Subsequently, acetate groups of ligand **1d** were deprotected to produce the ligand **1e** bearing two free hydroxyl groups. Though Friedel–Crafts alkylation proceeds well with **1e**-$Cu(OTf)_2$ complex, the enantioselectivity was negligible, 5% only (entry 5). Similarly, a pivolyl derivative of *gluco*BOX, **1f**-$Cu(OTf)_2$ complex also gave the corresponding alkylated indole in good yield with a moderate ee (70%) (Table 1, entry 6).

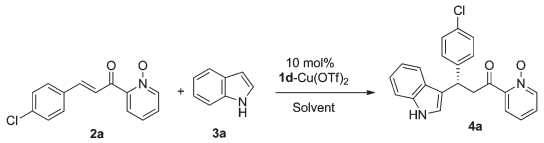
Further studies were focused on different Lewis acid catalysts to improve the enantioselectivity. The efficiencies of various copper salts and metal triflate catalysts were tested in the Friedel–Crafts alkylation of indole with enone **2a** (Table 2). The reaction was extremely sluggish with copper halides (Table 2, entries 2–5) compared to trifates (Table 2, entries 6–9). Of various Lewis acids, metal triflates were found to be the most effective catalysts. Of various copper salts, $Cu(OTf)_2$ afforded high enantioselectivity. Thus, the combination of $Cu(OTf)_2$ and ligand **1d** was found to give the best yield and enantioselectivity (Table 2).

After optimizing the ligand and catalyst, we next studied the effect of temperature on enantioselectivity. By decreasing the reaction temperature from 25 to −30 °C, the enantioselectivity was considerably increased from 80 to 96%. At −30 °C, **4a** was obtained in 94% yield and with excellent enantiomeric excess (96% ee) (Table 2, entry 10) whereas at −78 °C, the yield of **4a** was declined to 80% but the ee was decreased to 94% (Table 2, entry 11). In order to optimize the solvent, we performed the reaction of enone **2a** with indole **3a** in various solvents at −30 °C. The desired product **4a** was obtained with 90% ee either in chloroform or THF (Table 2, entries 12 and 13). However, the above reaction in diethyl ether gave the product **4a** with moderate enantiomeric excess (70% ee) (Table 2, entry 14). Surprisingly, methanol gave very poor enantiomeric excess (5% ee, Table 2, entry 15). However, toluene was equally as good as dichloromethane for the enantioselective Friedel–Crafts reaction (96% ee, Table 2, entry 16). Furthermore, acetonitrile and dichoroethane were also found to be equally effective for this reaction (94% ee) (Table 2, entries 17 and 18). The maximum of 97% ee was obtained with 5 mol% catalyst in dichloromethane (Table 2, entry 19). No improvements in yield and enantioselectivity were observed by further decreasing the amount of the catalyst (Table 2, entry 20).

The scope and limitations of the enantioselective Friedel–Crafts reaction were studied using $Cu(OTf)_2$-**1d** complex (Table 3).

The alkylation proceeds smoothly with various indoles to produce the corresponding 3-alkylated indoles in high yields with excellent enantioselectivity (Table 3, entries 2–5 and 7–9). For instance, 5-bromoindole gave the 3-substituted indole **4b** in 88% yield with 90% ee (Table 3, entry 2). Similarly, 5-chloroindole gave the Michael adduct **4c** in 94% yield with 94% ee (Table 3, entry 3). Like halogenated indoles, 4-methoxyindole also afforded **4d** in 94% yield with 85% ee (Table 3, entry 4). In contrast, the alkylation of **2a** with *N*-methylindole afforded **4e** in 88% yield with fairly low ee (77%, Table 3, entry 5). On the other hand, **2b** reacts with indole efficiently to furnish the corresponding 3-alkylated product **4f** in 97% yield with 99% ee (Table 3, entry 6). Similarly, 5-bromo- and 5-chloroindoles reacts well with **2b** to produce the corresponding products **4g** and **4h** with high enantiomeric excess (Table 3, entries 7 and 8). Furthermore, *N*-methyl indole also reacts well with **2b** to afford the product **4i** in 84% yield with 70% ee (Table 3, entry 9).

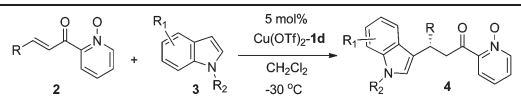
Table 2 Screening of various parameters for enantioselective Friedel–Crafts reaction of indole with 2-enoylpyridine-*N*-oxide **2a**



Entry	Catalyst[a]	Mol%	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	Cu(OTf) 0.5Tol	10	CH_2Cl_2	25	12	85	50
2	$CuCl_2$	10	CH_2Cl_2	25	12	83	17
3	CuCl	10	CH_2Cl_2	25	12	70	40
4	CuBr	10	CH_2Cl_2	25	24	75	60
5	CuI	10	CH_2Cl_2	25	24	5	[d]
6	$Sc(OTf)_3$	10	CH_2Cl_2	25	0.5	86	2
7	$In(OTf)_3$	10	CH_2Cl_2	25	0.5	89	3
8	$Zn(OTf)_2$	10	CH_2Cl_2	25	2	92	20
9	$Cu(OTf)_2$	10	CH_2Cl_2	0	2	95	89
10	$Cu(OTf)_2$	10	CH_2Cl_2	−30	2	94	96
11	$Cu(OTf)_2$	10	CH_2Cl_2	−78	5	80	94
12	$Cu(OTf)_2$	10	$CHCl_3$	−30	2	95	90
13	$Cu(OTf)_2$	10	THF	−30	6	88	90
14	$Cu(OTf)_2$	10	Et_2O	−30	6	76	70
15	$Cu(OTf)_2$	10	CH_3OH	−30	6	85	5
16	$Cu(OTf)_2$	10	Toluene	−30	4	90	96
17	$Cu(OTf)_2$	10	CH_3CN	−30	2	92	94
18	$Cu(OTf)_2$	10	DCE	−30	2	94	94
19	$Cu(OTf)_2$	5	CH_2Cl_2	−30	3.5	94	97
20	$Cu(OTf)_2$	2	CH_2Cl_2	−30	10	76	93

[a] All the reactions were performed with indole **3a** (0.75 mmol) and pyridin-1-oxide **2a** (0.5 mmol) with 10 mol% catalyst ($Cu(OTf)_2$: **1d**, 1 : 1) in 2 mL solvent under nitrogen. [b] Yield after chromatography. [c] Enantiomeric excess was determined by HPLC with AD-H column. [d] Not determined.

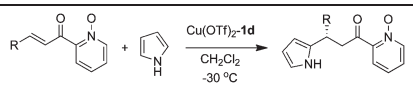
Table 3 Enantioselective Friedel–Crafts reaction of various indoles with 2-enoylpyridine-*N*-oxides



Entry	R	R_1	R_2	Product[a]	Time (h)	Yield[b] (%)	ee[c] (%)
1	4-Cl–Ph (**2a**)	H	H	**4a**	1.0	94	97
2	4-Cl–Ph (**2a**)	5-Br	H	**4b**	2.0	88	90
3	4-Cl–Ph (**2a**)	5-Cl	H	**4c**	2.0	94	94
4	4-Cl–Ph (**2a**)	4-OMe	H	**4d**	2.0	94	85
5	4-Cl–Ph (**2a**)	H	Me	**4e**	7.0	88	77
6	Ph (**2b**)	H	H	**4f**	1.0	97	99
7	Ph (**2b**)	5-Br	H	**4g**	2.0	91	93
8	Ph (**2b**)	5-Cl	H	**4h**	2.0	94	92
9	Ph (**2b**)	H	Me	**4i**	2.0	84	70
10	4-NO_2–Ph (**2c**)	H	H	**4j**	1.0	98	96
11	4-CH_3–Ph (**2d**)	H	H	**4k**	4.0	87	94
12	4-F–Ph (**2e**)	H	H	**4l**	1.0	94	95
13	4-Br–Ph (**2f**)	H	H	**4m**	1.0	91	92
14	2-Cl–Ph (**2g**)	H	H	**4n**	1.0	92	99
15	2-F–Ph (**2h**)	H	H	**4o**	1.0	98	94
16	2-NO_2–Ph (**2i**)	H	H	**4p**	1.0	96	98
17	2-Br–Ph (**2j**)	H	H	**4q**	2.0	94	96
18	3-NO_2–Ph (**2k**)	H	H	**4r**	2.0	94	99
19	2-Furyl (**2l**)	H	H	**4s**	2.0	91	94
20	1-Naphthyl (**2m**)	H	H	**4t**	4.0	88	90
21	^{t}Butyl (**2n**)	H	H	**4u**	24	65	33
22	Cyclohexyl (**2o**)	H	H	**4v**	200	trace	nd[d]

[a] All the reactions were carried out in 0.5 mmol scale using 0.75 mmol of indole derivatives at −30 °C in CH_2Cl_2. [b] Yield after chromatographic purification. [c] Enantiomeric excess was determined by chiral HPLC analysis (see ESI for details†). [d] nd = not determined.

Table 4 Enantioselective Friedel–Crafts reaction of pyrrole with 2-enoylpyridine-1-oxides



Entry	R	Product[a]	Time (h)	Yield[b] (%)	ee[c] (%)
1	4-Cl–Ph (**2a**)	**5a**	4	92	86
2	Ph (**2b**)	**5b**	4	88	85

[a] All the reactions were carried out in 0.5 mmol scale using 1.0 mmol of pyrrole at −30 °C in CH_2Cl_2. [b] Yield after chromatographic purification. [c] Enantiomeric excess was determined by chiral HPLC analysis. (see ESI for details†).

Next we studied the reactivity of *p*-substituted arylidinenoyl pyridine-1-oxides for the Friedel–Craft reaction of indoles (Table 3, entries 10–13). Both electron-rich and electron-deficient enoylpyridine-1-oxides gave the corresponding products in high yields and enantioselectivities. The *p*-nitro-substituted pyridine-1-oxide **2c** afforded **4j** in 98% yield with 96% ee (Table 3, entry 10). Similarly, arylidinenoyl pyridine-1-oxide **2d** also gave **4k** in excellent yield with 94% ee (Table 3, entry 11). The halogen substituted pyridine-1-oxides **2e** and **2f** gave the expected products **4l** and **4m** in 95% and 92% ee respectively (Table 3, entries 12 and 13).

Furthermore, we examined the efficiency of *o*-substituted arylidinenoyl pyridine-1-oxides **2g**, **2h**, **2i** and **2j**. For example, treatment of indole with **2g** and **2h** gave the 3-alkylated indoles **4n** and **4o** in 99% ee and 94% eerespectively (Table 3, entries 14 and 15). Other enoylpyridine-1-oxides **2i** and **2j** gave the 3-alkylated indoles **4p** and **4q** with 98% ee and 96% ee respectively (Table 3, entries 16 and 17). Furthermore, 3-nitrobenzylidin-2-enoylpyridine-1-oxide **2k** also afforded the 3-alkylated indole **4r** in 94% yield and 99% ee (Table 3, entry 18).

Next, we extended our investigation to arylidinenoyl pyridine-1-oxides derived from heteroaromatic aldehydes. For instance, 2-furyl substituted 2-enoylpyridine-1-oxide **2l** gave the corresponding Michael adduct **4s** in 91% yield with 94% ee (Table 3, entry 19). Notably, a sterically hindered 1-naphthyl-2-enoylpyridine-1-oxide **2m** furnished the corresponding Michael adduct **4t** in 88% yield with 90% ee (Table 3, entry 20).

However, alkyl substituted 2-enoylpyridine-1-oxide **2n** gave the respective Michael adducts in low yield and enantioselectivity compared to its aromatic analogues (Table 3, entries 20 and 21). In addition, the reaction was too sluggish with alkylidinenoyl pyridine-1-oxides. For instance, *tert*-butyl 2-enoylpyridine-1-oxide **2n** gave the corresponding 1,4-adduct **4u** in moderate yield (65%) with low ee (33%, Table 3, entry 21).

Inspired by the results obtained with indoles, we attempted the Friedel–Crafts alkylation of pyrrole with 2-enoylpyridine-1-oxide (Table 4).

Interestingly, high enantioselectivity was achieved with pyrrole as well under the optimized reaction conditions. The enoyl pyridine-1-oxide **2a** gave the 2-alkylated pyrrole **5a** in 92% yield with 86% ee (Table 4, entry 1). The substrate **2b** also reacts effectively with pyrrole to afford **5b** in 88% yield with 85% ee (Table 4, entry 2).

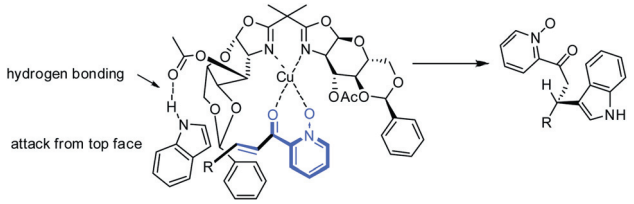


Fig. 2 A plausible transition state model for the enantioselective Friedel–Crafts reaction of indole.

Finally, we correlated all our observations to devise a plausible mechanism which reasonably explains the reactivity and stereochemical outcome of the reaction. Mechanistically, we assume that the reaction proceeds through a transition state which is almost similar to Jørgensen's transition state for Friedel–Crafts reaction of indoles with α-ketoesters (see ref. 6*b*). A plausible transition state model for the enantioselective Friedel–Crafts reaction is presented in Fig. 2.The low enantioselectivity of *N*-methylindole may be due to the unavailability of the N–H group for hydrogen bonding with the acetate moiety in the transition state. The low enantioselectivity of pyrrole in Friedel–Crafts alkylation also supports the above transition state. Though the hydrogen bond exists between pyrrole and catalyst, the π-orbital of pyrrole, which is involved in Friedel–Crafts alkylation, is different from that of indoles.

Conclusions

In summary, we have demonstrated a highly efficient Friedel–Crafts alkylation of indoles with 2-enoylpyridine-1-oxides to afford the 3-substituted indole derivatives with excellent enantioselectivities. This is the first report on the use of sugar based chiral ligands for the enantioselective Friedel–Crafts reaction of indoles. The end products could easily be converted into the corresponding carboxylic acid derivatives through the cleavage of the pyridine-*N*-oxide moiety. The notable features are the high enantioselectivity, excellent yields, ease of installation/removal of co-ordinating group[18] and short reaction times. Further application of *gluco*BOX ligands for other enantioselective transformations are in progress in our laboratory.

Experimental

General

The solvent dichloromethane was dried according to a standard literature procedure. The reactions were performed in oven-dried two necked round bottom flasks under an argon atmosphere. Glass syringes were used to transfer the solvent. The products were purified by column chromatography on silica gel of 60–120 or 100–200 mesh. Thin layer chromatography plates were visualized by ultraviolet light and/or by exposure to iodine vapours and/or by exposure to methanolic acidic solution of *p*-anisaldehyde followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on rotary evaporator at 35–40 °C. IR spectra were recorded on a FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using 300, 400, 500 or 600 MHz NMR spectrometers. The chemical shifts (δ) were reported in parts per million (ppm) with respect to TMS as

an internal standard. The coupling constants (J) are quoted in Hertz (Hz). Mass spectra were recorded on a mass spectrometer by electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI).

Preparation of ligands

Ligands **1a**, **1c**, **1d**, **1e** and **1f** were prepared according to the procedure reported previously in the literature.[19b] The ligand **1b** was also prepared by following a known procedure as reported for ligand **1a**.[19a]

Spectral data for ligand 1b. $[\alpha]_D^{25}$ = +58.5 (c = 1.0, in $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.84 (s, 6H), 1.92–2.20 (m, 4H), 2.04 (s, 12H), 2.12 (s, 6 H), 3.96 (ddd, J = 3.1, 9.8, 6.8 Hz, 2H), 4.12 (dd, J = 3.8, 12.8 Hz, 2H), 4.18–4.32 (m, 2 H), 4.24 (dd, J = 3.1, 12.8 Hz, 2H), 4.98 (d, J = 9.8 Hz, 2H), 5.38 (t, J = 2.3Hz, 2H), 5.98 (d, J = 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 8.2, 20.6, 20.7, 20.8, 26.5, 47.1, 62.5, 64.3, 67.5, 68.2, 70.0, 99.4, 168.9, 169.1, 169.4, 170.6. IR (KBr): ν_{max} 3467, 2975, 1747, 1654, 1372, 1227, 1039, 935, 877 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{31}H_{42}N_2O_{16}Na$ 721.2432. Found: 721.2438.

Preparation of 2-enoylpyridine-*N*-oxides.[2] All the starting materials were prepared according to the reported procedure.[12,15,16]

Compound **2d**. Yield 60%. m.p. 130–133 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.36 (s, 3H), 7.16 (d, J = 8.3 Hz, 2H), 7.34–7.42 (m, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.62–7.74 (m, 2H), 7.76 (d, J = 15.9 Hz, 1H), 8.22 (d, J = 5.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.5, 123.2, 125.7, 127.1, 127.5, 128.8, 129.5, 131.7, 140.3, 141.4, 144.5, 147.2, 186.3. HRMS (APCI): Exact mass calcd for $C_{15}H_{14}NO_2$ [M + H]: 240.1025 Found: 240.1028.

Compound **2h**. Yield 75%. m.p. 108–110 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.04–7.20 (m, 2H), 7.32–7.46 (m, 2H), 7.64 (dd, J = 2.4, 7.3 Hz, 2H), 7.74 (d, J = 16.0 Hz, 1H), 7.94 (d, J = 16.0 Hz, 1H), 8.24 (d, J = 5.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 116.0, 116.3, 124.4, 125.9, 126.3 (d, J = 6.5 Hz), 127.3, 127.8, 129.1, 132.3 (d, J = 8.7 Hz), 136.2, 140.4, 147.0, 163.4 (d, J = 254.6 Hz), 186.3 HRMS (APCI): Exact mass calcd for $C_{14}H_{11}N_2O_2F$ [M + H]: 244.0774 Found: 244.0768.

Compound **2j**. Yield 55%. m.p. 114–116 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.20 (ddd, J = 1.51, 2.2, 6.8 Hz, 1H), 7.28 (dd, J = 6.8, 7.6 Hz, 1H), 7.38–7.46 (m, 2H), 7.58 (dd, J = 6.8, 1.5 Hz, 1H), 7.70 (dd ~ q, J = 3.0, 3.8 Hz, 2H), 7.76 (dd, J = 1.5, 6.8 Hz, 1H), 8.14 (d, J = 15.9 Hz, 1H), 8.24 (dd, J = 2.2, 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 126.1, 126.5, 127.4, 127.6, 127.9, 128.2, 131.5, 132.5, 133.3, 134.4, 140.4, 142.0, 146.8, 185.8. HRMS (APCI): Exact mass calcd for $C_{14}H_{11}N_2O_2Br$ [M + H]: 303.9973 Found: 303.9980.

General procedure for the enantioselective Friedel–Crafts reaction

A solution of a ligand **1d** (17.0 mg, 0.025 mmol) and $Cu(OTf)_2$ (9.0 mg, 0.025 mmol) in dry dichloromethane (2.0 mL) was stirred at room temperature for 1 h under a nitrogen atmosphere. To this solution, 2-enoylpyridine-1-oxide (0.5 mmol) was added. The resulting mixture was stirred at room temperature for 10 min and then cooled to −30 °C. To this mixture, a solution of indole (0.75 mmol) in 0.5 mL dichloromethane was added and then allowed to stir at −30 °C until completion of the reaction (as judged by TLC analysis). The solvent was removed and the resulting mixture was purified by column chromatography on silica gel using 5% methanol in ethyl acetate to afford the pure product (Note: All the products are moisture sensitive and become brownish in colour. Therefore optical rotations were measured after drying the products twice azeotropically with THF to remove the brown colour). The absolute configuration of the products was determined by comparing the optical rotation with known values reported in literature.[15,16] The absolute configuration of new compounds were determined by analogy.

(*S*)-2-(3-(4-Chlorophenyl)-3-(1*H*-indol-3-yl)propanoyl)pyridine-1-oxide.[15] (4a) (entry 1, Table 3). Yield 95% with 97% ee. $[\alpha]_D^{25}$ = −21 (c = 0.5, in THF). HPLC on Chiralpak AD-H column (15 cm × 0.46 cm), hexane/i-PrOH = 80 : 20, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 14.55 min (R) and 18.96 min (S); ^1H NMR (500 MHz; $CDCl_3$) δ: 3.92 (dd, J = 7.9, 8.8 Hz, 1H), 4.20 (dd, J = 6.9, 8.8 Hz, 1H), 4.88 (t, J = 6.9 Hz, 1H), 6.96 (t, J = 6.9 Hz), 7.08–7.20 (m, 4H), 7.20–7.30 (m, 4H), 7.32–7.38 (m, 2H), 7.44–7.50 (m, 1H), 8.10 (brs, 1H), 8.14 (d, J = 6.0 Hz, 1H). ^{13}C NMR (75 MHz; $CDCl_3$) δ: 37.6, 48.8, 111.0, 118.0, 119.2, 119.3, 121.5, 122.1, 125.8, 126.3,126.6 127.7, 128.2, 129.2, 131.8, 136.4, 140.1, 142.4, 146.7, 196.4. HRMS (ESI): Exact mass calcd for $C_{22}H_{17}ClN_2O_2Na$ 399.0876. Found: 399.0870.

(*S*)-2-(3-(5-Bromo-1*H*-indol-3-yl)-3-(4-chlorophenyl)propanoyl)pyridine-1-oxide (4b) (entry 2, Table 3). Yield 88% and ee 90%. m.p. 181–184 °C. $[\alpha]_D^{25}$ = −71.7 (c = 0.5, in THF). HPLC on Chiralpak AD-H column (25 cm × 0.46 cm), hexane/i-PrOH = 80 : 20, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 14.24 min (S) and 22.10 min (R); ^1H NMR (500 MHz; $CDCl_3$ + DMSO-d_6) δ: 3.76 (dd, J = 7.0, 8.0 Hz, 1H), 3.92 (dd, J = 7.0. 8.0 Hz, 1H), 4.76 (t, J = 8.0 Hz, 1H), 7.06 (dd, J = 7.0, 2.0 Hz, 1H), 7.14 (d, J = 2.0 Hz, 1H), 7.18–7.30 (m, 7H), 7.36 (s, 1H), 7.40 (m, 1H), 8.18 (d, J = 6.0 Hz, 1H), 10.78 (brs, 1H). ^{13}C NMR (75 MHz; $CDCl_3$ + DMSO-d_6) δ: 36.2, 48.1, 118.6, 112.1, 115.5, 119.9, 122.5, 122.9, 124.7, 125.2, 127.0, 127.2, 128.1, 130.5, 141.6, 143.9, 145.3, 195.1. IR (KBr): ν 3414, 3113, 3074, 2922, 1715, 1674, 1601, 1562, 1487, 1458, 1425, 1319, 1287 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{22}H_{16}BrClN_2O_2Na$ 476.9981. Found: 476.9986.

(*S*)-2-(3-(5-Chloro-1*H*-indol-3-yl)-3-(4-chlorophenyl)propanoyl)-pyridine-1-oxide (4c) (entry 3, Table 3). Yield 94% with 94% ee. m.p. 209–212 °C $[\alpha]_D^{25}$ = −36.6 (c = 0.5, in THF). HPLC on Chiralpak AD-H column (25 cm × 0.46 cm), hexane/i-PrOH = 80 : 20, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 19.94 min (R) and 21.48 min (S); ^1H NMR (500 MHz; $CDCl_3$ + DMSO-d_6) δ: 3.76 (dd, J = 6.9, 9.8 Hz, 1H), 3.92 (dd, J = 7.9, 8.0 Hz, 1H), 4.76 (t, J = 7.9 Hz, 1H), 6.92 (d, J = 7.9 Hz, 1H), 7.13–7.28 (m, 8H), 7.36 (t, J = 6.9 Hz, 2H), 8.16 (d, J = 6.9 Hz, 1H), 10.70 (bs, 1H). ^{13}C NMR (75 MHz; $CDCl_3$ + DMSO-d_6) δ: 35.3, 46.7, 111.2, 114.7, 116.1, 119.6, 121.9, 122.2, 124.1, 124.5, 125.6, 126.5, 127.7, 129.5, 133.4, 138.5, 141.2, 144.6, 152.7, 194.6. IR (KBr): ν 3223, 2917, 1682, 1647, 1599, 1569, 1488, 1460, 1426, 1361, 1297, 1249, 1249 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{22}H_{16}Cl_2N_2O_2Na$ 433.0487. Found: 433.0476.

(*S*)-2-(3-(4-Chlorophenyl)-3-(4-methoxy-1*H*-indol-3-yl)propanoyl)pyridine-1-oxide (4d). (entry 4, Table 3). Yield 94% and ee 85%. m.p. 85–87 °C. $[\alpha]_D^{25}$ = +62.0 (*c* = 0.5, in THF). HPLC on Daicel Chiralpak AD-H column (25 cm × 0.46 cm), hexane/i-PrOH = 80 : 20, flow rate 0.6 mL min^{-1}, 254 nm; t_R = 61.1 min (*R*) and 63.79 min (*S*); ^{1}H NMR (500 MHz; $CDCl_3$ + DMSO-d_6) *δ*: 3.70 (s, 3H), 3.84 (d, *J* = 8.0 Hz, 1H), 5.18 (dd, *J* = 8.0, 7.0 Hz, 1H), 6.28 (d, *J* = 8.0 Hz, 1H), 6.88–7.00 (m, 3H), 7.08 (ddd, *J* = 8.0, 11.1, 7.0 Hz, 3H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 6.0 Hz, 1H), 8.14 (d, *J* = 6.0 Hz, 1H), 10.22 (s, 1H). ^{13}C NMR (75 MHz; $CDCl_3$) *δ*: 36.6, 47.7, 53.2, 97.5, 103.4, 114.9, 116.3,119.2, 120.8, 124.1, 124.6, 126.4, 126.5, 128.1, 129.3, 136.7, 138.6, 142.8, 145.3, 195.4. IR (KBr): *ν* 3396, 3113, 2928, 1699, 1589, 1499, 1428, 1361, 1428, 1361, 1254, 1167 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{23}H_{19}ClN_2O_3Na$ 429.0982. Found: 429.0979.

(*S*)-2-(3-(4-Chlorophenyl)-3-(1-methyl-1*H*-indol-3-yl)propanoyl)-pyridine-1-oxide (4e) (entry 5, Table 3). Yield 88% and 77% ee. Viscous liquid. $[\alpha]_D^{25}$ = +4.2 (*c* = 0.4, in THF). HPLC on Chiralpak OD-H column (25 cm × 0.46 cm), hexane/i-PrOH = 80 : 20, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 19.7 min (*S*) and 24.57 min (*R*); ^{1}H NMR (300 MHz; $CDCl_3$) *δ*: 3.64 (s, 3H) 3.80–4.06 (m, 2H), 3.80–3.94 (m, 1H), 6.84–7.00 (m, 2H), 7.0–7.36 (m, 14H), 8.1 (bs, 1H). ^{13}C NMR (75 MHz; $CDCl_3$) *δ*: 32.7, 37.7, 48.9, 109.1, 116.7, 118.9, 119.3, 121.7, 125.9, 126.2, 126.7, 127.4, 128.2, 128.3, 129.2, 131.8, 137.1, 140.3, 142.5, 145.3, 196.3. IR (KBr): 3448, 3054, 2925, 1687, 1603, 1545, 1486, 1427, 1372, 1294, 1252, 1176, 1089 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{23}H_{19}ClN_2O_2Na$ 413.1032. Found: 413.1028.

(*S*)-2-(3-(1*H*-Indol-3-yl)-3-phenylpropanoyl)pyridine-1-oxide.[15] (4f) (entry 6, Table 3). Yield 97% and 99% ee. $[\alpha]_D^{25}$ = −17.1 (*c* = 0.5, in THF). HPLC on Chiralpak AD-H column (25 cm × 0.46 cm), hexane/i-PrOH = 80 : 20, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 19.60 min (*R*) and 23.79 min (*S*); ^{1}H NMR (500 MHz; $CDCl_3$) *δ*: 3.80 (m, 1H), 3.92 (m, 1H), 4.78 (m, 1H), 6.80 (t, *J* = 6.9 Hz, 2H), 6.98 (t, *J* = 7.9 Hz, 2H), 7.02 (t, *J* = 6.9 Hz, 2H), 7.10–7.20 (m, 4H), 7.20–7.28 (m, 2H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.90 (bs, 1H), 8.40 (s, 1H). ^{13}C NMR (75 MHz; $CDCl_3$) *δ*: 38.5, 48.9, 11.0, 118.4, 119.2, 119.3, 121.6, 121.9, 126.2, 126.6, 126.8, 127.4, 127.8, 128.2, 136.5, 140.2, 143.8, 147.3, 196.9. HRMS (ESI): Exact mass calcd for $C_{22}H_{18}N_2O_2Na$ 365.1266. Found: 365.1262.

(*S*)-2-(3-(5-Bromo-1*H*-indol-3-yl)-3-phenylpropanoyl)pyridine-1-oxide.[15] (4g) (entry 7, Table 3). Yield 91% and 93% ee. $[\alpha]_D^{25}$ = −51.2 (c = 0.4, in THF). HPLC on Chiralpak AD-H column (25 cm × 0.46 cm), hexane/i-PrOH = 80 : 20, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 16.92 min (*R*) and 19.68 min (*S*); ^{1}H NMR (500 MHz; $CDCl_3$ + DMSO-d_6) *δ*: 3.72 (dd, *J* = 7.8, 8.8 Hz, 1H), 3.94 (dd, *J* = 7.8, 8.8 Hz, 1H), 4.74 (t, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 1H), 7.08–7.16 (m, 4H), 7.16 (m, 3H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.34 (m, 2H) 8.14 (d, *J* = 5.8 Hz, 1H), 10.7 (brs, 1H). ^{13}C NMR (75 MHz; $CDCl_3$ + DMSO-d_6) *δ*: 36.2, 46.9, 109.7, 111.7, 115.4, 119.3, 122.0, 122.1, 124.1, 124.4, 124.6, 125.9, 126.4, 126.5, 126.7, 133.6, 138.4, 142.4, 144.8, 194.9. HRMS (ESI): Exact mass calcd for $C_{22}H_{17}BrN_2O_2$ 443.0371. Found: 443.0366.

(*S*)-2-(3-(5-Chloro-1*H*-indol-3-yl)-3-phenylpropanoyl)pyridine-1-oxide.[15] (4h) (entry 8, Table 3). Yield 94% and 92% ee. $[\alpha]_D^{25}$ = −45.3 (*c* = 0.7, in THF). HPLC on Chiralpak AD-H column (25 cm × 0.46 cm), hexane/i-PrOH = 80 : 20, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 16.85 min (*R*) and 19.20 min (*S*); ^{1}H NMR (500 MHz; $CDCl_3$ + DMSO-d_6) *δ*: 3.74 (dd, *J* = 6.9, 7.9 Hz, 1H), 3.94 (dd, *J* = 7.9, 7.9 Hz, 1H), 4.74 (t, *J* = 6.9 Hz, 1H), 6.92 (d, *J* = 8.9 Hz, 1H), 7.08–7.30 (m, 10H), 7.32 (m, 1H), 8.14 (d, *J* = 5.9 Hz, 1H), 10.60 (brs, 1H). ^{13}C NMR (75 MHz; $CDCl_3$ + DMSO-d_6) *δ*: 36.9, 47.5, 11.5, 116.0, 116.8, 120.1, 122.4, 125.0, 125.1, 126.4, 126.5, 126.8, 127.1, 133.9, 138.9, 142.7, 145.0, 195.5. HRMS (ESI): Exact mass calcd for $C_{22}H_{17}ClN_2O_2$ 399.0876. Found: 399.0880.

(*S*)-2-(3-(1-Methyl-1*H*-indol-3-yl)-3-phenylpropanoyl)pyridine-1-oxide.[15] (4i) (entry 9, Table 3). Yield 84% and 70% ee. $[\alpha]_D^{25}$ = +1.8 (*c* = 0.5, in THF). HPLC on Chiralpak OD-H column (25 cm × 0.46 cm), hexane/i-PrOH = 80 : 20, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 19.7 min (*S*) and 26.3 min (*R*). ^{1}H NMR (500 MHz; $CDCl_3$) *δ*: 3.68 (s, 3H), 3.86 (dd, *J* = 8.0, 9.0 Hz, 1H), 3.96 (dd, *J* = 8.0, 9.0 Hz, 1H), 4.84 (t, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 2.0 Hz, 1H), 6.98 (t, *J* = 7.0 Hz, 1H), 7.04–7.12 (m, 3H), 7.12–7.22 (m, 3H), 7.26 (d, *J* = 7.0 Hz, 2H), 8.06 (d, *J* = 6.0 Hz, 1H). ^{13}C NMR (75 MHz; CDCl3) *δ*: 32.5, 38.4, 48.9, 108.9, 117.1, 118.7, 119.3, 121.5, 126.2, 126.4, 126.9, 127.4, 127.7, 128.2, 137.0, 139.9, 143.8, 146.8, 196.9. HRMS (ESI): Exact mass calcd for $C_{23}H_{20}N_2O_2Na$ 379.1422. Found: 379.1418.

(*S*)-2-(3-(1*H*-Indol-3-yl)-3-(*p*-nitrophenyl)propanoyl)pyridine-1-oxide.[15] (4j) (entry 10, Table 3). Yield 98% and 96% ee. $[\alpha]_D^{25}$ = −21.4 (*c* = 0.5, in THF). HPLC on Chiralpak AD-H column (15 cm × 0.46 cm), hexane/i-PrOH = 70 : 30, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 22.70 min (*R*) and 25.25 min (*S*); ^{1}H NMR (500 MHz; $CDCl_3$ + DMSO-d_6) *δ*: 3.90–4.08 (m, 2H), 4.94 (t, *J* = 7.3 Hz, 1H), 6.94 (t, *J* = 7.1 Hz, 1H), 7.20–7.36 (m, 5H), 7.38 (m, 1H), 7.50 (d, *J* = 8.1 Hz, 2H), 8.02 (d, *J* = 8.3 Hz, 2H), 8.14 (d, *J* = 6.2 Hz, 1H), 10.58 (brs, 1H). ^{13}C NMR (75 MHz; $CDCl_3$) *δ*: 36.7, 47.2, 110.4, 114.8, 117.3, 117.7, 120.4, 121.1, 122.2, 124.6, 125.0, 125.3, 127.1, 127.7, 135.6, 139.1, 145.0, 147.3, 151.3, 194.6. HRMS (ESI): Exact mass calcd for $C_{22}H_{17}N_3O_4Na$ 410. 1117. Found: 410.1124.

(*S*)-2-(3-(1*H*-Indol-3-yl)-3-*p*-tolylpropanoyl)pyridine-1-oxide (4k) (entry 11, Table 3). Yield 87% and 94% ee. m.p. 190–192 °C. $[\alpha]_D^{25}$ = −4.2 (*c* = 0.5, in THF). HPLC on Chiralpak AD-H column (15 cm × 0.46 cm), hexane/i-PrOH = 80 : 20, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 13.10 min (minor) and 16.56 min (major); ^{1}H NMR (500 MHz; $CDCl_3$) *δ*: 2.22 (s, 3H), 3.80 (m, 1H), 3.94 (m, 1H), 4.78 (s, 1H), 6.82 (t, *J* = 6.9 Hz, 1H), 6.90–6.98 (m, 5H), 6.98 (m, 1H), 7.08 (d, *J* = 6.9 Hz, 4H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 8.0 (s, 1H), 8.36 (brs, 1H). ^{13}C NMR (75 MHz; $CDCl_3$) *δ*: 20.9, 38.1, 48.9, 110.9, 118.7, 119.2, 119.3, 121.4, 121.9, 125.8, 126.3, 126.5, 127.3, 127.6, 128.9, 135.6, 136.4, 139.9, 140.6, 146.9, 197.1. IR (KBr): *ν* 3211, 3050, 2919, 2869, 1680, 1599, 1509, 1456, 1429, 1341, 1292, 1250, 1220, 1179, 1117 cm^{-1}. HRMS (ESI): Exact mass calcd for $C_{23}H_{20}N_2O_2Na$ 379.1423 Found: 379.1416.

(*S*)-2-(3-(4-Fluorophenyl)-3-(1*H*-indol-3-yl)propanoyl)pyridine-1-oxide.[15] (4l) (entry 12, Table 3). Yield 94% and 95% ee. $[\alpha]_D^{25}$

= −9.1 (*c* = 1, in THF). HPLC on Chiralpak AD-H column (15 cm × 0.46 cm), hexane/i-PrOH = 80 : 20, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 13.82 min (*R*) and 17.47 min (*S*); ^{1}H NMR (500 MHz; $CDCl_3$) *δ*: 3.84 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.94 (dd, *J* = 7.0, 10.0 Hz, 1H), (4.80 (m, 1H), 6.82–6.88 (m, 3H), 7.02–7.10 (m, 3H), 7.16–7.28 (m, 5H), 8.04–8.22 (m, 2H). ^{13}C NMR (75 MHz; $CDCl_3$) *δ*: 37.6, 49.0, 111.0, 114.8, 115.1, 118.4, 119.2, 119.3, 121.4, 122.0, 125.7, 126.4, 126.5, 127.6, 129.1, 136.4, 140.1, 146.8, 162.9, 196.6. HRMS (ESI): Exact mass calcd for $C_{22}H_{17}FN_2O_2Na$ 383.1172. Found: 383.1168.

(*S*)-2-(3-(4-Bromophenyl)-3-(1*H*-indol-3-yl)propanoyl)pyridine-1-oxide (4m) (entry 13, Table 3). Yield 91% and 92% ee. m.p. 201–203 °C. $[\alpha]_D^{25}$ = −16.9 (*c* = 0.5, in THF). HPLC on Chiralpak AD-H column (15 cm × 0.46 cm), hexane/i-PrOH = 80 : 20, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 15.60 min (*R*) and 20.19 min (*S*); ^{1}H NMR (500 MHz; $CDCl_3$) *δ*: 3.88 (dd, *J* = 7.9, 8.8 Hz, 1H), 3.96 (dd, *J* = 7.9, 8.8 Hz, 1H), 4.84 (t, *J* = 7.9 Hz, 1H), 6.90 (t, *J* = 6.9 Hz, 1H), 7.04–7.12 (m, 2H), 7.15 (d, *J* = 8.8 Hz, 2H), 7.20–7.28 (m, 3H), 7.28 (d, *J* = 8.8 Hz, 3H), 7.48 (s, 1H), 8.02 (bs, 1H), 8.08 (d, *J* = 5.9 Hz, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) *δ*: 38.2, 49.2, 115.5, 118.4, 119.6, 120.4, 122.0, 122.5, 126.1, 126.8, 127.0, 128.1, 130.0, 131.7, 136.9, 140.5, 143.4, 147.1, 196.7. IR (KBr): *ν* 3417, 3209, 2920, 2873, 1682, 1599, 1484, 1430, 1343, 1294, 1251, 1221, 1181, 1122 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{22}H_{17}BrN_2O_2Na$ 443.0371. Found: 443.0366.

(*R*)-2-(3-(2-Chlorophenyl)-3-(1*H*-indol-3-yl)propanoyl)pyridine-1-oxide.[15] (4n) (entry 14, Table 3). Yield 92% and 99% ee. $[\alpha]_D^{25}$ = +71.4 (*c* = 0.6, in THF). HPLC on Chiralpak AD-H column (25 cm × 0.46 cm), hexane/i-PrOH = 80 : 20, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 24.20 min (*R*) and 31.44 min (*S*); ^{1}H NMR (500 MHz; $CDCl_3$) *δ*: 3.68 (dd, *J* = 7.0, 10.0 Hz, 1H), 4.16 (dd, *J* = 8.0, 9.0 Hz, 1H), 5.38 (t, *J* = 7.0 Hz, 1H), 6.94 (t, *J* = 7.0 Hz, 1H), 7.02–7.12 (m, 4H), 7.18–7.38 (m, 6H), 7.42 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 6.0 Hz, 1H), 8.16 (brs, 1H). ^{13}C NMR (75 MHz; $CDCl_3$) *δ*: 34.4, 47.6, 111.0, 117.3, 119.2, 122.0, 122.1, 125.7, 126.0, 126.4, 126.8, 127.5, 128.1, 129.1, 129.4, 133.4, 136.4, 140.0, 140.9, 146.7, 196.1. HRMS (ESI): Exact mass calcd for $C_{22}H_{17}ClN_2O_2Na$ 399.0786. Found: 399.0779.

(*R*)-2-(3-(2-Fluorophenyl)-3-(1*H*-indol-3-yl)propanoyl)pyridine-1-oxide (4o) (entry 15, Table 3). Yield 98% and 94% ee. Viscous, $[\alpha]_D^{25}$ = +15.6 (*c* = 0.4, in THF). HPLC on Chiralpak AD-H column (25 cm × 0.46 cm), hexane/i-PrOH = 80 : 20, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 20.90 min (*S*) and 28.41 min (*R*); ^{1}H NMR (300 MHz; $CDCl_3$) *δ*: 4.044.14 (m, 2H), 5.12 (m, 1H), 6.84–7.38 (m, 12H), 7.38 (d, *J* = 7.5 Hz, 1H), 8.40 (bs, 1H). ^{13}C NMR (75 MHz; $CDCl_3$) *δ*: 31.0, 47.5, 111.1, 115.1, 115.4, 117.2, 119.0, 119.2, 121.8, 121.9, 124.0, 126.3, 126.4, 127.5, 127.7, 127.9, 129.3, 129.4, 130.5, 130.6, 136.3, 158.7, 161.9, 196.2. IR (KBr): *ν* 3404, 3109, 3054, 2922, 2854, 1692, 1602, 1487, 1455, 1428, 1338, 1293, 1224, 1172 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{22}H_{17}FN_2O_2Na$ 383.1172. Found: 383.1166.

(*R*)-2-(3-(1*H*-Indol-3-yl)-3-(2-nitrophenyl)propanoyl) pyridine-1-oxide.[15] (4p) (entry 16, Table 3). Yield 96% and 98% ee. $[\alpha]_D^{25}$ = +68.0 (*c* = 0.75, in THF). HPLC on Chiralpak AD-H column (25 cm × 0.46 cm), hexane/i-PrOH = 70 : 30, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 16.82 min (*S*) and 25.70 min (*R*); ^{1}H NMR (500 MHz; $CDCl_3$) *δ*: 3.80 (dd, *J* = 6.7, 10.5 Hz, 1H), 4.22 (dd, *J* = 7.5, 9.8 Hz, 1H), 5.54 (t, *J* = 6.7 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 6.7 Hz, 1H), 7.18–7.64 (m, 10H), 7.74 (d, *J* = 7.5 Hz, 1H), 8.14 (bs, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) *δ*: 32.4, 48.5, 111.0, 116.9, 119.2, 119.5, 122.1, 122.4, 124.1, 125.9, 126.3, 126.8, 127.0, 127.8, 130.1, 132.6, 136.4, 138.4, 140.3, 146.2, 149.5, 195.0. HRMS (ESI): Exact mass calcd for $C_{22}H_{17}N_3O_4Na$ 410. 1117, Found: 410.1121.

(*R*)-2-(3-(2-Bromophenyl)-3-(1*H*-indol-3-yl)propanoyl)pyridine-1-oxide (4q) (entry 17, Table 3). Yield 94% and 96% ee. m. p. 97–99 °C. $[\alpha]_D^{25}$ = +56.1 (*c* = 0.5, in THF). HPLC on Chiralpak AD-H column (25 cm × 0.46 cm), hexane/i-PrOH = 80 : 20, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 20.52 min (*S*) and 25.25 min (R); ^{1}H NMR (500 MHz; $CDCl_3$) *δ*: 3.60 (dd, *J* = 6.0, 11.0 Hz, 1H), 4.18 (dd, *J* = 9.0, 8.0 Hz, 1H), 5.34 (t, *J* = 7.0 Hz, 1H), 6.92 (t, *J* = 7.0Hz, 1H), 7.00 (m, 4H), 7.14–7.28 (m, 4H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 8.26 (bs, 1H). ^{13}C NMR (75 MHz; $CDCl_3$) *δ*: 37.2, 47.7, 111.0, 117.3, 119.2, 119.3, 121.9, 122.2, 124.2, 126.0, 126.4, 127.4, 127.5, 127.8, 129.2, 132.7, 136.4, 140.0, 142.5, 146.6, 196.1. IR (KBr): *ν* 3405, 3054, 2922, 2854, 1692, 1600, 1462, 1428, 1340, 1294, 1229, 1103 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{22}H_{17}BrN_2O_2Na$ 443.0371. Found: 443.0365.

(*S*)-2-(3-(1*H*-Indol-3-yl)-3-(3-nitrophenyl)propanoyl)pyridine-1-oxide.[15] (4r) (entry 18, Table 3). Yield 94% and 99% ee. $[\alpha]_D^{25}$ = +3.3 (*c* = 1.0, in THF). HPLC on Chiralpak AD-H column (15 cm × 0.46 cm), hexane/i-PrOH = 80 : 20, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 40.28 min (*R*) and 42.20 min (*S*); ^{1}H NMR (500 MHz; $CDCl_3$) *δ*: 4.02 (dd, *J* = 8.0, 9.0 Hz, 1H), 4.12 (dd, *J* = 7.0, 10.0 Hz, 1H), 5.08 (t, *J* = 7.0 Hz, 1H), 6.96 (t, *J* = 7.0 Hz, 1H), 7.12–7.22 (m, 3H), 7.28–7.42 (m, 5H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 8.16–8.20 (m, 2H), 8.28 (bs, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) *δ*: 37.7, 48.7, 111.2, 117.1, 118.8, 119.4, 121.4, 121.7, 122.2, 122.7, 125.8, 126.1, 126.7, 127.9, 128.1, 129.1, 134.3, 140.3, 146.3, 148.2, 195.5. HRMS (ESI): Exact mass calcd for $C_{22}H_{17}N_3O_4Na$ 410. 1117 Found: 410.1114.

(*R*)-2-(3-(Furan-2-yl)-3-(1*H*-indol-3-yl)propanoyl)pyridine-1-oxide.[15] (4s) (entry 19, Table 3). Yield 91% and 94% ee. $[\alpha]_D^{25}$ = +5.2 (*c* = 0.5, in THF). HPLC on Chiralpak OJ-H column (25 cm × 0.46 cm), hexane/i-PrOH = 70 : 30, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 42.22 min (*R*) and 76.45 min (*S*); ^{1}H NMR (500 MHz; $CDCl_3$) *δ*: 3.88 (m, 2H), 4.94 (t, *J* = 8.0, 10.0 Hz, 1H), 5.96 (d, *J* = 2.0 Hz, 1H), 6.14 (s, 1H), 6.94–7.02 (m, 2H), 7.02 (q, *J* = 8.0 Hz, 2H), 7.14–7.26 (m, 4H), 7.48 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 6.0 Hz, 1H), 8.12 (bs, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) *δ*: 32.2, 46.9, 105.5, 110.0, 111.1, 115.6, 119.0, 119.2, 121.8, 122.1, 125.8, 126.1, 126.2, 127.5, 136.2, 139.8, 141.0, 146.5, 156.5, 196.4. HRMS (ESI): Exact mass calcd for $C_{20}H_{16}N_2O_3Na$ 355.1058. Found: 355.1050.

(*S*)-2-(3-(1*H*-Indol-3-yl)-3-(naphthalen-1-yl)propanoyl)pyridine-1-oxide.[15] (4t) (entry 20, Table 3). Yield 88% and 90% ee. $[\alpha]_D^{25}$ = +30.2 (*c* = 1, in THF). HPLC on Chiralpak AD-H column

(15 cm × 0.46 cm), hexane/i-PrOH = 80 : 20, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 13.31 min (*S*) and 17.75 min (*R*); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.98 (dd, J = 7.7, 10.0 Hz, 1H), 4. 24 (dd, J = 7.8, 8.9 Hz, 1H), 5.82 (t, J = 7.7 Hz, 1H), 6.94–7.06 (m, 3H), 7.10–7.20 (m, 3H), 7.26 (q, J = 7.7, 8.8 Hz, 2H), 7.38–7.52 (m, 4H), 7.66 (d, J = 8.9 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 8.12 (d, J = 6.6 Hz, 1H), 8.14 (bs, 1H), 8.32 (d, J = 8.9 Hz, 1H). ^{13}C NMR (75 MHz; $CDCl_3$) δ: 33.5, 48.6, 111.0, 118.5, 119.2, 121.9, 122.4, 123.3, 124.7, 125.3, 125.4, 125.5, 126.0, 126.3, 126.6, 127.0, 127.3, 128.1, 128.7, 131.4, 133.9, 136.4, 139.4, 139.8, 146.9, 197.2. HRMS (ESI): Exact mass calcd for $C_{26}H_{20}N_2O_2Na$ 415.1423. Found: 415.1418.

(*S*)-2-(3-(1*H*-Indol-3-yl)-4,4-dimethylpentanoyl)pyridine-1-oxide (4u) (entry 21, Table 3). Yield 65% yield with 33% ee. Paste. $[\alpha]_D^{25}$ = +17.4 (c = 0.5, in THF). HPLC on Chiralpak AD-H column (15 cm × 0.46 cm), hexane/i-PrOH = 90 : 20, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 19.34 min (*R*) and 27.64 min (*S*); ^{1}H NMR (500 MHz; $CDCl_3$) δ: 0.83 (s, 6H), 3.34 (dd, J = 3.0, 10.9 Hz, 1H), 3.60 (dd, J = 3.9, 10.9 Hz, 1H), 4.14 (dd, J = 7.9, 6.9 Hz, 1H), 6.36 (d, J = 7.9 Hz, 1H), 6.74 (dd, J = 6.9, 7.9 Hz, 1H), 6.90–7.00 (m, 2H), 7.04–7.14 (m, 2H), 7.22 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 7.9 Hz, 1H), 8.06 (s, 1H), 8.10 (d, J = 6.9 Hz, 1H). ^{13}C NMR (75 MHz; CDCl3) δ: 39.2, 48.4, 105.9, 108.0, 117.2, 126.2, 126.7, 127.9, 128.5, 129.1, 129.6, 132.3, 132.9, 140.2, 141.5, 195.9. IR (KBr): ν 3407, 3111, 3056, 2959, 2868, 1693, 1602, 1458, 1428, 1364, 1298, 1218; HRMS (ESI): Exact mass calcd for $C_{20}H_{22}N_2O_2Na$ 345.1579. Found: 345.1572.

(*S*)-2-(3-(4-Chlorophenyl)-3-(1*H*-pyrrol-2-yl)propanoyl)pyridine-1-oxide.[16] (5a) (entry 1, Table 4). Yield 92% with 86% ee. $[\alpha]_D^{25}$ = +2.4 (c = 0.5, in THF). HPLC on Chiralpak OJ-H column (25 cm × 0.46 cm), hexane/i-PrOH = 90 : 20, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 16.9 min (*R*) and 26.0 min (*S*); ^{1}H NMR (500 MHz; $CDCl_3$) δ: 3.62 (dd, J = 5.9, 10.9 Hz, 1H), 4.40 (dd, J = 8.0, 9.0 Hz, 1H), 4.68 (t, J = 8.0 Hz, 1H), 6.04 (s, 1H), 6.62 (s, 1H), 7.06 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.22 (t, J = 8.0 Hz, 1H), 7.30 (t, J = 7.0 Hz, 1H), 7.38 (dd, J = 2.0, 5.9 Hz, 1H), 8.14 (d, J = 7.0 Hz, 1H), 8.14 (d, J = 6.0 Hz, 1H). ^{13}C NMR (75 MHz; $CDCl_3$) δ: 39.3, 48.4, 105.9, 108.1, 117.3, 126.3, 126.8, 127.9, 128.6, 129.2, 132.4, 140.3, 141.5, 196.0; HRMS (ESI): Exact mass calcd for $C_{18}H_{15}ClN_2O_2Na$ 349.0720. Found: 349.0718.

(*S*)-2-(3-Phenyl-3-(1*H*-pyrrol-2-yl)propanoyl)pyridine-1-oxide.[16] (5b) (entry 2, Table 4). Yield 88% with 85% ee. $[\alpha]_D^{25}$ = +4.4 (c = 0.5, in THF). HPLC on Chiralpak OD-H column (25 cm × 0.46 cm), hexane/i-PrOH = 90 : 10, flow rate 1.0 mL min^{-1}, 254 nm; t_R = 34.4 (*R*) and 39.3 min (*S*); ^{1}H NMR (500 MHz; $CDCl_3$) δ: 3.66 (dd, J = 5.9, 11.0 Hz, 1H), 4.10 (dd, J = 9.0, 7.9 Hz, 1H), 4.70 (dd, J = 7.0, 7.9 Hz, 1H), 5.90 (s, 1H), 6.06 (q, J = 3.0 Hz, 1H), 6.62 (d, J = 2.0 Hz, 1H), 7.18–7.28 (m, 8 H), 7.28–7.42 (m, 2H), 8.18 (d, J = 6.0 Hz, 1H), 8.46 (brs, 1H); ^{13}C NMR (75 MHz; $CDCl_3$) δ: 39.9, 48.4, 105.5, 107.7, 117.0, 126.4, 126.8, 127.1, 127.3, 127.6, 128.4, 140.1, 142.3, 146.6, 196.3. HRMS (ESI): Exact mass calcd for $C_{18}H_{16}N_2O_2Na$ 315.1110. Found: 315.1104.

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Notes and references

1 (*a*) R. J. Sundberg, *Indoles*, Academic Press, San Diego, 1996; (*b*) D. J. Faulkner, *Nat. Prod. Rep.*, 2001, **18**, 1; (*c*) I. J. Ninomiya, *J. Nat. Prod.*, 1992, **55**, 541; (*d*) A. Casapullo, G. Bifulco, I. Bruno and R. Riccio, *J. Nat. Prod.*, 2000, **63**, 447; (*e*) J. Ford and R. J. Capon, *J. Nat. Prod.*, 2000, **63**, 1527; (*f*) A. Cutignano, G. Bifulco, I. Bruno, A. Casapullo, L. Gomez-Paloma and R. Riccio, *Tetrahedron*, 2000, **56**, 3743.
2 (*a*) H. C. Zhang, L. V. R. Bonaga, H. Ye, C. K. Derian, B. P. Damiano and B. E. Maryanoff, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 2863; (*b*) V. K. Rao, B. S. Chhikara, A. N. Shirazi, R. Tiwari, K. Parang and A. Kumar, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 3511; (*c*) A. Ahmad, W. A. Sakar and K. M. Rahman, *Curr. Drug Targets*, 2010, **11**, 652.
3 (*a*) B. Jiang and C.-G. J. YangWang, *J. Org. Chem.*, 2001, **66**, 4865; (*b*) H. Zhang and R. C. Larock, *Org. Lett.*, 2001, **3**, 3083; (*c*) M. Sakagami, H. Muratake and M. Natsume, *Chem. Pharm. Bull.*, 1994, **42**, 1393; (*d*) T. Fukuyama and X. Chen, *J. Am. Chem. Soc.*, 1994, **116**, 3125; (*e*) D. J. Faulkner, *Nat. Prod. Rep.*, 1999, **16**, 155.
4 (*a*) M. Bandini, A. Melloni and A. Umani-Ronchi, *Angew. Chem., Int. Ed.*, 2004, **43**, 550; (*b*) J. F. Austin and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2002, **124**, 1172; (*c*) K. B. Jensen, J. Thorhange, R. G. Hazel and K. A. Jorgensen, *Angew. Chem., Int. Ed.*, 2001, **40**, 160; (*d*) G. Bartoli, M. Bartolacci, M. Bosco, G. Foglia, A. Giuliani, E. Marcantoni, L. Sambri and E. Torregiani, *J. Org. Chem.*, 2003, **68**, 4594.
5 (*a*) B. M. Trost and C. Muller, *J. Am. Chem. Soc.*, 2008, **130**, 2438; (*b*) T. Arai and N. Yokoyama, *Angew. Chem., Int. Ed.*, 2008, **47**, 4989; (*c*) S.-F. Lu, D.-M. Du and J. Xu, *Org. Lett.*, 2006, **8**, 2115; (*d*) Y.-X. Jia, S.-F. Zhu, Y. Yang, Y. Zhou and Q.-L. Zhou, *J. Org. Chem.*, 2006, **71**, 75.
6 (*a*) G. Desimoni, G. Faita, M. Toscanini and M. Boiocchi, *Chem.–Eur. J.*, 2008, **14**, 3630; (*b*) K. B. Jensen, J. Thorhauge, R. G. Hazell and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2001, **40**, 160.
7 D. A. Evans, K. R. Fandrick, H.-J. Song, K. A. Scheidt and R. Xu, *J. Am. Chem. Soc.*, 2007, **129**, 10029.
8 C. Palomo, M. Oiarbide, B. G. Kardak, J. M. Garcıa and A. Linden, *J. Am. Chem. Soc.*, 2005, **127**, 4154.
9 D. A. Evans, K. R. Fandrick and H.-J. Song, *J. Am. Chem. Soc.*, 2005, **127**, 8942.
10 (*a*) W. Zhuang, T. Hansen and K. A. Jørgensen, *Chem. Commun.*, 2001, 347; (*b*) R. Rasappan, M. Hager, A. Gissibl and O. Reiser, *Org. Lett.*, 2006, **8**, 6099; (*c*) A. Schätz, R. Rasappan, M. Hager, A. Gissibl and O. Reiser, *Chem.–Eur. J.*, 2008, **14**, 7259; (*d*) J. Zhou, M.-C. Ye, Z.-Z. Huang and Y. Tang, *J. Org. Chem.*, 2004, **69**, 1309; (*e*) J. Zhou and Y. Tang, *Chem. Commun.*, 2004, 432.
11 (*a*) N. A. Paras and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2001, **123**, 4370; (*b*) J. F. Austin and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2002, **124**, 1172; (*c*) T. Y. Liu, H. L. Cui, Q. Chai, J. Long, B. J. Li, Y. Wu, L. S. Ding and Y. C. Chen, *Chem. Commun.*, 2007, 2228; (*d*) R. P. Herrera, V. Sgarzani, L. Bernardi and A. Ricci, *Angew. Chem., Int. Ed.*, 2005, **44**, 6576; (*e*) Y.-X. Jia, J. Zhong, S. F. Zhu, C. M. Zhang and Q. L. Zhou, *Angew. Chem., Int. Ed.*, 2007, **46**, 5565; (*f*) M. Terada and K. Sorimachi, *J. Am. Chem. Soc.*, 2007, **129**, 292; (*g*) J. Itoh, K. Fuchibe and T. Akiyama, *Angew. Chem., Int. Ed.*, 2008, **47**, 4016.
12 S. Barroso, G. Blay and J. R. Pedro, *Org. Lett.*, 2007, **9**, 1983.
13 S. Barroso, G. Blay, M. C. Muñoz and J. R. Pedro, *Adv. Synth. Catal.*, 2009, **351**, 107.
14 (*a*) S. Barroso, G. Blay, M. C. Muñoz and J. R. Pedro, *Org. Lett.*, 2011, **13**, 402; (*b*) A. Livieri, M. Boiocchi, G. Desimoni and G. Faita, *Chem.–Eur. J.*, 2011, **17**, 516.
15 P. K. Singh and V. K. Singh, *Org. Lett.*, 2008, **10**, 4121.
16 P. K. Singh and V. K. Singh, *Org. Lett.*, 2010, **12**, 80.
17 S. K. Ray, P. K. Singh and V. K. Singh, *Org. Lett.*, 2011, **13**, 5812.
18 A. R. Katritzky, *Chemistry of the Heterocyclic N-Oxides*, Academic Press, London, 1971.
19 (*a*) M. Irmak, A. Groschner and M. M. K. Boysen, *Chem. Commun.*, 2007, 177; (*b*) T. Minuth, M. Irmak, A. Groschner, T. Lehnert and M. M. K. Boysen, *Eur. J. Org. Chem.*, 2009, 997.
20 B. V. S. Reddy and J. George, *Tetrahedron: Asymmetry*, 2011, **22**, 1169.

