Organic & Biomolecular Chemistry

Cite this: Org. Biomol. Chem., 2012, 10, 4731

www.rsc.org/obc

PAPER

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

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Received 13th February 2012, Accepted 17th April 2012 DOI: 10.1039/c2ob25315a

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 arylidinemalonates¹⁰ have been reported as excellent reaction partners for Friedel-Crafts reactions in terms of yield and enantioselectivity. Recently, organo-catalysts¹¹ have also been shown to be efficient catalysts for enantioselective Friedel-Crafts alkylation of indoles.

While several electrophilic substrates are known to undergo $Cu(\pi)$ -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 $Cu(\pi)$ -catalyzed enantioselective Diels–Alder reactions¹² and hetero-Diels–Alder reactions.¹³ Recently, 2-enoylpyridine-*N*-oxides have successfully been utilized for enantioselective nitrone cycloaddition reactions.¹⁴ Later on, enantio-selective Friedel–Crafts reactions of indoles have been reported using $Cu(\pi)$ -PyBOX complexes.¹⁵ Subsequently, the Friedel–Crafts alkylation of pyrroles¹⁶ and Michael addition of dialkylmalonates¹⁷ 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 transformations¹⁹ (Fig. 1). Inspired by inherent catalytic features of glucoBOX, 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



Fig. 1 GlucoBOX ligands.

Natural Product Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad, Andhra Pradesh, India. E-mail: basireddy@ iict.res.in; Fax: +91-040-27160512; Tel: +91-040-27193535 †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 glucoBOX-Cu(II) complexes for enantioselective alkylation of indole with 2-enoylpyridine-N-oxide 2a



Entry	Ligand ^a	Time (h)	$\mathrm{Yield}^{b}(\%)$	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 glucoBOX (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 CH₂Cl₂ 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 glucoBOX 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 triflates (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

0-N	10 mol% 1d -Cu(OTf) ₂	
+ N H 3a	Solvent	HN 4a

Entry	Catalyst ^a	Mol%	Solvent	Temp. (°C)	Time (h)	$\mathrm{Yield}^{b}(\%)$	ee ^c (%)
1	Cu(OTf) 0.5Tol	10	CH ₂ Cl ₂	25	12	85	50
2	CuCl ₂	10	CH ₂ Cl ₂	25	12	83	17
3	CuCl	10	CH ₂ Cl ₂	25	12	70	40
4	CuBr	10	CH ₂ Cl ₂	25	24	75	60
5	CuI	10	CH ₂ Cl ₂	25	24	5	d
6	$Sc(OTf)_3$	10	CH ₂ Cl ₂	25	0.5	86	2
7	$In(OTf)_3$	10	CH ₂ Cl ₂	25	0.5	89	3
8	$Zn(OTf)_2$	10	CH ₂ Cl ₂	25	2	92	20
9	$Cu(OTf)_2^2$	10	CH ₂ Cl ₂	0	2	95	89
10	$Cu(OTf)_2^2$	10	CH ₂ Cl ₂	-30	2	94	96
11	$Cu(OTf)_2^2$	10	CH ₂ Cl ₂	-78	5	80	94
12	$Cu(OTf)_2^2$	10	CHCl ₃	-30	2	95	90
13	$Cu(OTf)_2^2$	10	THF	-30	6	88	90
14	$Cu(OTf)_2^2$	10	Et ₂ O	-30	6	76	70
15	$Cu(OTf)_2^2$	10	CH ₃ OH	-30	6	85	5
16	$Cu(OTf)_2^2$	10	Toluene	-30	4	90	96
17	$Cu(OTf)_2^2$	10	CH ₃ CN	-30	2	92	94
18	$Cu(OTf)_2^2$	10	DCE	-30	2	94	94
19	$Cu(OTf)_2$	5	CH ₂ Cl ₂	-30	3.5	94	97
20	$Cu(OTf)_2^2$	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 v	arious indoles	with 2-enoyl	pyridine-N-oxide	.s
						ry	

R N		R1	5 mol% Cu(OTf) ₂ -1d	R1	R	0 L	o N
2	+	3 R2	CH ₂ Cl ₂ -30 °C	R ₂ N_	4	Ļ	Ú

Entry	R	R ₁	R ₂	Product ^a	Time (h)	$\text{Yield}^{b} (\%)$	ee^{c} (%)
1	4-Cl–Ph (2a)	Н	Н	4a	1.0	94	97
2	4-Cl–Ph (2a)	5-Br	Н	4b	2.0	88	90
3	4-Cl–Ph (2a)	5-C1	Н	4c	2.0	94	94
4	4-Cl–Ph (2a)	4-OMe	Н	4d	2.0	94	85
5	4-Cl–Ph (2a)	Н	Me	4 e	7.0	88	77
6	Ph (2b)	Н	Н	4 f	1.0	97	99
7	Ph (2b)	5-Br	Н	4g	2.0	91	93
8	Ph (2b)	5-C1	Н	4h	2.0	94	92
9	Ph (2b)	Н	Me	4i	2.0	84	70
10	$4-NO_2-Ph(2c)$	Н	Н	4i	1.0	98	96
11	$4-CH_3-Ph(2d)$	Н	Н	4k	4.0	87	94
12	4-F–Ph (2e)	Н	Н	41	1.0	94	95
13	4-Br–Ph (2f)	Н	Н	4m	1.0	91	92
14	2-Cl–Ph (2g)	Н	Н	4n	1.0	92	99
15	2-F–Ph (2h)	Н	Н	40	1.0	98	94
16	$2-NO_2-Ph(2i)$	Н	Н	4p	1.0	96	98
17	2-Br-Ph (2j)	Н	Н	4q	2.0	94	96
18	$3-NO_2-Ph(2k)$	Н	Н	4r	2.0	94	99
19	2-Furyl (21)	Н	Н	4s	2.0	91	94
20	1-Naphthyl (2m)	Н	Н	4t	4.0	88	90
21	^t Butyl $(2n)$	Н	Н	4u	24	65	33
22	Cyclohexyl (20)	Н	Н	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 CH₂Cl₂. ^{*b*} Yield after chromatographic purification. ^{*c*} Enantiomeric excess was determined by chiral HPLC analysis (see ESI for details[†]). ^{*d*} nd = not determined.

enoylp	yridin	e-1-oxides				
		R N	+ () + () + () + () + () + () + () + ()	DTf) ₂ -1d H ₂ Cl ₂ 30 °C	R O O-N	
Entry	R		Product ^a	Time (h)	$\mathrm{Yield}^{b}\left(\%\right)$	ee ^c (%)

Table 4 Enantioselective Friedel-Crafts reaction of pyrrole with 2-

14-Cl-Ph (2a)5a492862Ph (2b)5b48885a All the reactions were carried out in 0.5 mmol scale using 1.0 mmol of pyrrole at -30 °C in CH₂Cl₂. b Yield after chromatographic purification.c Enantiomeric excess was determined by chiral HPLC analysis. (see

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 3alkylated 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, 2furyl substituted 2-enoylpyridine-1-oxide **21** 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. 6b). 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 group¹⁸ 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*-anisalde-hyde followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were recorded on a FT-IR spectrometer. ¹H and ¹³C NMR spectra were recorded in CDCl₃ 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

ESI for details[†]).

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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. $[\alpha]_{25}^{25} = +58.5$ (c = 1.0, in CHCl₃). ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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): v_{max} 3467, 2975, 1747, 1654, 1372, 1227, 1039, 935, 877 cm⁻¹. HRMS (ESI): Exact mass calcd for C₃₁H₄₂N₂O₁₆Na 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 (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 C₁₅H₁₄NO₂ [M + H]: 240.1025 Found: 240.1028.

Compound **2h**. Yield 75%. m.p. 108–110 °C. ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 C₁₄H₁₁N₂O₂F [M + H]: 244.0774 Found: 244.0768.

Compound **2j**. Yield 55%. m.p. 114–116 °C. ¹H NMR (CDCl₃, 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). ¹³C NMR (CDCl₃, 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 C₁₄H₁₁N₂O₂Br [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; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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 C₂₂H₁₇ClN₂O₂Na 399.0876. Found: 399.0870.

(S)-2-(3-(5-Bromo-1H-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; $t_{\rm R}$ = 14.24 min (S) and 22.10 min (*R*); ¹H NMR (500 MHz; CDCl₃ + DMSO-d₆) 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). ¹³C NMR (75 MHz; CDCl₃ + DMSO-d₆) *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): v 3414, 3113, 3074, 2922, 1715, 1674, 1601, 1562, 1487, 1458, 1425, 1319, 1287 cm⁻¹. HRMS (ESI): Exact mass calcd for C₂₂H₁₆BrClN₂O₂Na 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; CDCl₃ + DMSO-d₆) 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). ¹³C NMR (75 MHz; CDCl₃ + DMSO-d₆) 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): v 3223, 2917, 1682, 1647, 1599, 1569, 1488, 1460, 1426, 1361, 1297, 1249, 1249 cm⁻¹; HRMS (ESI): Exact mass calcd for C₂₂H₁₆Cl₂N₂O₂Na 433.0487. Found: 433.0476.

(S)-2-(3-(4-Chlorophenyl)-3-(4-methoxy-1H-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; $t_{\rm R}$ = 61.1 min (R) and 63.79 min (S); ¹H NMR (500 MHz; CDCl₃ + DMSO-d₆) 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). ¹³C NMR (75 MHz; CDCl₃) 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): v 3396, 3113, 2928, 1699, 1589, 1499, 1428, 1361, 1428, 1361, 1254, 1167 cm^{-1} ; HRMS (ESI): Exact mass calcd for C₂₃H₁₉ClN₂O₃Na 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*); ¹H NMR (300 MHz; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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 C₂₃H₁₉ClN₂O₂Na 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); ¹H NMR (500 MHz; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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 C₂₂H₁₈N₂O₂Na 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; $t_{\rm R}$ = 16.92 min (*R*) and 19.68 min (*S*); ¹H NMR (500 MHz; CDCl₃ + DMSO-d₆) 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). ¹³C NMR (75 MHz; CDCl₃ + DMSO-d₆) 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 C₂₂H₁₇BrN₂O₂ 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*); ¹H NMR (500 MHz; CDCl₃ + DMSO-d₆) 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). ¹³C NMR (75 MHz; CDCl₃ + DMSO-d₆) 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 C₂₂H₁₇ClN₂O₂ 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). ¹H NMR (500 MHz; CDCl₃) 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). ¹³C 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 C₂₃H₂₀N₂O₂Na 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*); ¹H NMR (500 MHz; CDCl₃ + DMSO-d₆) 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). ¹³C NMR (75 MHz; CDCl₃) 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 C₂₂H₁₇N₃O₄Na 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); ¹H NMR (500 MHz; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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): v 3211, 3050, 2919, 2869, 1680, 1599, 1509, 1456, 1429, 1341, 1292, 1250, 1220, 1179, 1117 cm⁻¹. HRMS (ESI): Exact mass calcd for C₂₃H₂₀N₂O₂Na 379.1423 Found: 379.1416.

(S)-2-(3-(4-Fluorophenyl)-3-(1*H*-indol-3-yl)propanoyl)pyridine-1-oxide.¹⁵ (41) (entry 12, Table 3). Yield 94% and 95% ee. $[\alpha]_D^{25}$

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= -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; $t_{\rm R}$ = 13.82 min (R) and 17.47 min (S); ¹H NMR (500 MHz; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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 C₂₂H₁₇FN₂O₂Na 383.1172. Found: 383.1168.

(S)-2-(3-(4-Bromophenyl)-3-(1H-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 \times 0.46 cm), hexane/i-PrOH = 80:20, flow rate 1.0 mL min⁻¹, 254 nm; $t_{\rm R} = 15.60$ min (R) and 20.19 min (S); ¹H NMR (500 MHz; CDCl₃) 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); ¹³C NMR (75 MHz; CDCl₃) 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): v 3417, 3209, 2920, 2873, 1682, 1599, 1484, 1430, 1343, 1294, 1251, 1221, 1181, cm^{-1} ; HRMS (ESI): 1122 Exact mass calcd for C₂₂H₁₇BrN₂O₂Na 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*); ¹H NMR (500 MHz; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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 C₂₂H₁₇ClN₂O₂Na 399.0786. Found: 399.0779.

(*R*)-2-(3-(2-Fluorophenyl)-3-(1*H*-indol-3-yl)propanoyl)pyridine-1-oxide (40) (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*); ¹H NMR (300 MHz; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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): v 3404, 3109, 3054, 2922, 2854, 1692, 1602, 1487, 1455, 1428, 1338, 1293, 1224, 1172 cm⁻¹; HRMS (ESI): Exact mass calcd for C₂₂H₁₇FN₂O₂Na 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; $t_{\rm R}$ = 16.82 min (*S*) and 25.70 min (*R*); ¹H NMR (500 MHz; CDCl₃) 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); ¹³C NMR (75 MHz; CDCl₃) 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 C₂₂H₁₇N₃O₄Na 410. 1117, Found: 410.1121.

(R)-2-(3-(2-Bromophenyl)-3-(1H-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 \times 0.46 cm), hexane/i-PrOH = 80 : 20, flow rate 1.0 mL min⁻¹, 254 nm; $t_{\rm R} = 20.52$ min (S) and 25.25 min (R); ¹H NMR (500 MHz; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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): v 3405, 3054, 2922, 2854, 1692, 1600, 1462, 1428, 1340, 1294, 1229, 1103 cm⁻¹; HRMS (ESI): Exact mass calcd for C₂₂H₁₇BrN₂O₂Na 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*); ¹H NMR (500 MHz; CDCl₃) 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); ¹³C NMR (75 MHz; CDCl₃) 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 C₂₂H₁₇N₃O₄Na 410. 1117 Found: 410.1114.

(*R*)-2-(3-(Furan-2-yl)-3-(1*H*-indol-3-yl)propanoyl)pyridine-1oxide.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*); ¹H NMR (500 MHz; CDCl₃) 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); ¹³C NMR (75 MHz; CDCl₃) 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 C₂₀H₁₆N₂O₃Na 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; $t_{\rm R}$ = 13.31 min (S) and 17.75 min (R); ¹H NMR (500 MHz, CDCl₃) & 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). ¹³C NMR (75 MHz; CDCl₃) & 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 C₂₆H₂₀N₂O₂Na 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); ¹H NMR (500 MHz; CDCl₃) 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). ¹³C 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): v 3407, 3111, 3056, 2959, 2868, 1693, 1602, 1458, 1428, 1364, 1298, 1218; HRMS (ESI): Exact mass calcd for C₂₀H₂₂N₂O₂Na 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*); ¹H NMR (500 MHz; CDCl₃) 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). ¹³C NMR (75 MHz; CDCl₃) 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 C₁₈H₁₅ClN₂O₂Na 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*); ¹H NMR (500 MHz; CDCl₃) 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); ¹³C NMR (75 MHz; CDCl₃) 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 C₁₈H₁₆N₂O₂Na 315.1110. Found: 315.1104.

Acknowledgements

J.G. thanks CSIR, New Delhi for the award of a Senior Research Fellowship.

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