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Enantioselective Mukaiyama–Michael with 2-enoyl pyridine *N*-oxides catalyzed by PYBOX-DIPH-Zn(II)-complexes at ambient temperature†‡

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A chiral PYBOX-DIPH-Zn(II) catalyzed enantioselective Mukaiyama–Michael reaction of acyclic silyl enol ethers with 2-enoylpyridine *N*-oxides has been studied in external additive free conditions at ambient temperature. The methodology offers straightforward access to a variety of functionalized chiral 1,5-dicarbonyl compounds, which could easily be elaborated into synthetically viable pyrones *via* hydrolysis followed by cyclization. A transition state model has been proposed to explain the stereochemical outcome.

Formation of functionalized 1,5-dicarbonyl compounds by reaction of silyl enol ether with α,β-unsaturated ketones and esters (also known as the Mukaiyama–Michael reaction),[1] is one of the most synthetically useful tools for C–C bond forming reactions in organic chemistry. The strategy has gained significant attention due to the milder reaction conditions and extraordinary regioselectivity (1,4-addition in comparison to 1,2-addition) obtained over a metalloenolate process.[2] Enantioenriched 1,5-dicarbonyls offer an interesting synthetic platform to access a variety of biologically and pharmaceutically useful compounds and could be accessed both *via* organocatalysis as well as metal catalysis.[3,4] Although considerable efforts have already been put forth towards asymmetric Mukaiyama–Michael reactions, but it is still a difficult and challenging task to carry out the reaction without catalyst activation or in external additive free conditions to afford the corresponding product in sufficient quantities to make the reaction synthetically useful. Moreover, most of the strategies require prolonged reaction times. To our knowledge, the metal-catalyzed asymmetric version of Mukaiyama–Michael reactions known to date, mostly need some alcohol as additive and lower temperatures to achieve good chemical yields and enantioselectivities. However, the asymmetric version of Mukaiyama–Michael reaction at ambient temperature is unexplored and therefore, there is a need for the development of a catalytic system.

Recently, Pedro[5a–c] and Reddy[5d,e] have reported the potential utility of 2-enoyl pyridine *N*-oxide (a versatile prochiral template for a chiral metal complex) in various asymmetric methodologies.[5] As a part of our ongoing program to develop novel enantioselective strategies using chiral PYBOX-DIPH-metal complexes, we previously reported the utility of 2-enoyl pyridine *N*-oxides as acceptors in enantioselective Friedel–Crafts alkylation of pyrroles,[6a] indoles[6b] and dialkyl malonates addition[6c] as well as synthesis of coumarin derivatives[6d] in high yields and excellent levels of enantioselectivities.[6] Together with its high reactivity, the pyridine *N*-oxide part of 2-enoyl pyridine *N*-oxide can also be easily cleaved to afford the corresponding acid, thus making it an attractive platform to carry out desirable synthetic transformations highlighting *N*-oxide chemistry.[7] Very recently, Faita and co-workers have reported the enantioselective addition of cyclic enol ethers to 2-enoyl pyridine *N*-oxide[8a] catalyzed by enantioenriched bisoxazoline-Cu(OTf)$_2$ complex using hexafluoro propanol-2(HFIP) as an additive in good yields and >99% enantioselectivity.[8]

Continuing our efforts in this direction, herein we wish to report an additive free, and efficient catalytic asymmetric pathway to synthesize enantioenriched functionalized 1,5-dicarbonyls utilizing 2-enoyl pyridine *N*-oxide **3** as template for the Mukaiyama–Michael reaction with acyclic silyl enol ether **2** as nucleophile at ambient temperature, catalyzed by chiral PYBOX-DIPH-Zn(OTf)$_2$ complexes.[9]

The methodology is operationally simple and affords a variety of Michael adducts in excellent yields and enantioselectivities.

Our studies began with silyl enol ether **2a** as donor and 2-enoylpyridine *N*-oxide **3a** as the Michael acceptor (Table 1) in

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†This work is dedicated to Prof. Goverdhan Mehta on the occasion of his 70th birthday.

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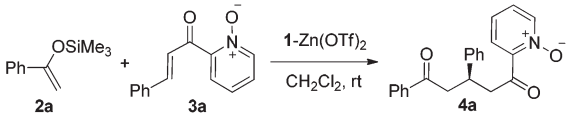
Table 1 Effect of different ligands on Mukaiyama–Michael reactions[a]



Entry[a]	Ligand	Time	Yield[b] (%)	ee[c] (%)
1	**1a**	4 h	72	81
2	**1b**	38 h	89	21
3	**1c**	13 h	88	33
4	**1d**	26 h	91	14
5	**1e**	28 h	84	52
6	**1f**	23 h	90	74
7	**1g**	24 h	70	12
8	**1h**	30 h	72	12
9	**1i**	9 h	87	30

[a] The reactions were carried out by taking 0.2 mmol **3a** and 0.6 mmol **2a** in 1.0 mL dichloromethane with 5 mol% catalyst **1a**-Zn(OTf)$_2$. [b] Isolated yield. [c] Determined by chiral HPLC (chiralcel OJ-H column).

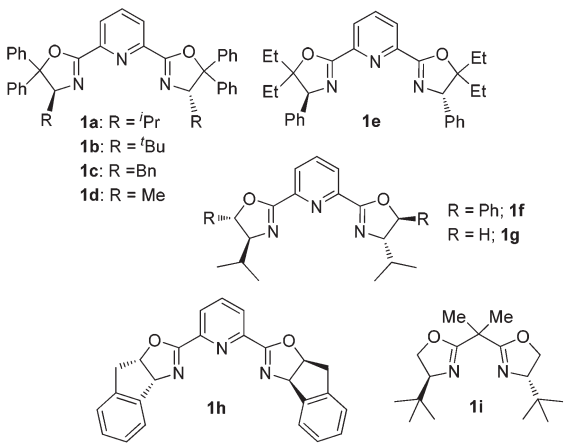
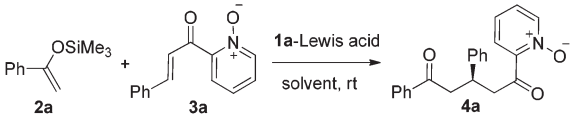


Fig. 1 Pybox and box ligands used for Mukaiyama–Michael reactions.

presence of various pyridine bis-oxazolines-Zn(OTf)$_2$ complexes as catalysts (Fig. 1). It was found that 5 mol% **1a**-Zn(OTf)$_2$ afford product **4a** in 81% ee and 72% yield (Table 1, entry 1). Under similar condition, **1f**-Zn(OTf)$_2$ afforded **4a** in 74% ee (entry 6), whereas **1b–e** and **1g–i**-Zn(OTf)$_2$ complexes were afforded products only in 12–52% ee (entries 2–5 and 7–9). In order to check the effect of solvent if any on the enantioselectivity of product, the reaction was conducted in various solvents (Table 2). We observed that, except dichloroethane (88% yield and 75% ee, entry 2) other solvents were good choices and afforded products in 89–96% ee (entries 3–9). Further screening with various Lewis acids shows that Cu(I)OTf (89–92% ee, entries 10–12) proved to be better than other metal triflates (entries 13–17).

Thus, extensive optimization studies revealed that benzene proves to be the best solvent and Zn(OTf)$_2$ the best Lewis acid for this reaction, to afford products comparatively faster in good yields and higher enantioselectivities, and hence chosen for further studies. Optimization towards the catalyst loading

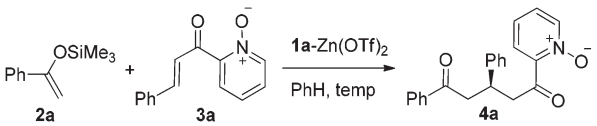
Table 2 Reaction optimization studies for the Mukaiyama–Michael reactions[a]



Entry	Solvent	Lewis acid	Time	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	Zn(OTf)$_2$	4 h	72	81
2	DCE	Zn(OTf)$_2$	7 h	88	75
3	$CHCl_3$	Zn(OTf)$_2$	6 h	92	89
4	THF	Zn(OTf)$_2$	11 h	87	90
5	1,4-Dioxane	Zn(OTf)$_2$	42 h	90	90
6	Toluene	Zn(OTf)$_2$	12 h	88	93
7	Benzene	Zn(OTf)$_2$	13 h	88	96
8	*o*-Xylene	Zn(OTf)$_2$	40 h	90	95
9	CCl_4	Zn(OTf)$_2$	40 h	75	91
10	Benzene	Cu(OTf)$_2$	4.5 h	87	89
11	Benzene	CuOTf·PhH	4 h	92	91
12	Benzene	CuOTf·PhMe	4.5 h	95	92
13	Benzene	Sc(OTf)$_3$	14 h	99	04
14	Benzene	In(OTf)$_3$	4 h	94	03
15	Benzene	Yb(OTf)$_3$	5 h	84	02
16	Benzene	Mg(OTf)$_2$	5 d	Trace	06
17	Benzene	Sn(OTf)$_2$	7 d	Trace	19

[a] The reactions were carried out by taking 0.2 mmol **3a** and 0.6 mmol **2a** in 1.0 mL solvent with 5 mol% catalyst. [b] Isolated yield. [c] Determined by chiral HPLC using Chiralcel OJ-H column.

Table 3 Effect of catalyst loading and temperature in the Mukaiyama–Michael reactions using Zn(OTf)$_2$[a]

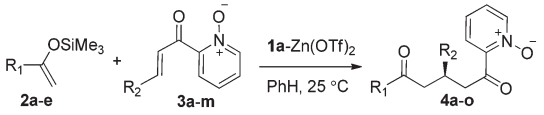


Entry	Catalyst (mol%)	Temp	Time	Yield[b] (%)	ee[c] (%)
1	5	25 °C	13 h	88	96
2	10	25 °C	7 h	92	95
3	15	25 °C	3 h	88	88
4	2	25 °C	30 h	90	90
5	1	25 °C	52 h	93	93
6	10	0 °C	12 h	92	92

[a] The reactions were carried out by taking 0.2 mmol **3a** and 0.6 mmol **2a** in 1.0 mL benzene with 5 mol% catalyst **1a**-Zn(OTf)$_2$. [b] Isolated yield. [c] Determined by chiral HPLC using Chiralcel OJ-H column.

(Table 3) showed that 10 mol% of **1a**-Zn(OTf)$_2$ complex was found to be best in terms of yield and reaction rate (Table 3, entry 2). The enantioselectivity was found to be almost the same in case of 5 mol% catalyst but it needed a longer reaction time compared to the use of 10 mol% catalyst loading (Table 3, entry 1). Further lowering the catalyst loading to 1–2 mol% of **1a**-Zn(OTf)$_2$ afforded products in 90–93% ee, but with longer reaction times (entries 4–5). No appreciable improvement could be observed in the enantioselectivity, by lowering the reaction temperature to 0 °C, even using 10 mol% of catalyst (entry 6, Table 3). Hence, we chose to carry out further studies using 10 mol% **1a**-Zn(OTf)$_2$ in benzene.

Table 4 Substrates scope under optimized conditions[a]



Entry	R_1	R_2	Product	Time	Yield[b] (%)	ee[c] (%)
1	Ph (**2a**)	Ph (**3a**)	(**4a**)	7 h	92	95
2	Ph (**2a**)	2-ClC_6H_4 (**3b**)	(**4b**)	4 h	91	83
3	Ph (**2a**)	3-ClC_6H_4 (**3c**)	(**4c**)	4 h	89	90
4	Ph (**2a**)	4-ClC_6H_4 (**3d**)	(**4d**)	4 h	88	95
5	Ph (**2a**)	2-$NO_2C_6H_4$ (**3e**)	(**4e**)	2.5 h	87	92
6	Ph (**2a**)	3-$NO_2C_6H_4$ (**3f**)	(**4f**)	2.5 h	88	95
7	Ph (**2a**)	4-$NO_2C_6H_4$ (**3g**)	(**4g**)	3 h	88	90
8	Ph (**2a**)	4-FC_6H_4 (**3h**)	(**4h**)	3.5 h	89	96
9	Ph (**2a**)	4-$OMeC_6H_4$ (**3i**)	(**4i**)	18 h	86	92
10	Ph (**2a**)	2-Furyl (**3j**)	(**4j**)	20 h	81	90
11	Ph (**2a**)	1-Naphthyl (**3k**)	(**4k**)	10 h	82	90
12	Ph (**2a**)	(*E*)-PhCH=CH (**3l**)	(**4l**)	28 h	80	83
13	Ph (**2a**)	^{t}Bu (**3m**)	—	98 h	nr[d]	nd[e]
14	4-FC_6H_4 (**2b**)	Ph (**3a**)	(**4m**)	8 h	82	91
15	2-Thienyl (**2c**)	Ph (**3a**)	(**4n**)	2 h	88	81
16	4-BrC_6H_4 (**2d**)	4-ClC_6H_4 (**3d**)	(**4o**)	10 h	83	87
17	^{t}Bu (**2e**)	4-ClC_6H_4 (**3d**)	—	96 h	nr[d]	nd[e]

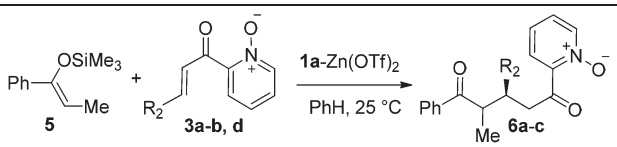
[a] The reactions were carried out by taking 0.2 mmol **3** and 0.6 mmol **2** in 1.0 mL benzene with 10 mol% catalyst **1a**-$Zn(OTf)_2$. [b] Isolated yield. [c] Determined by chiral HPLC. [d] nr = no reaction. [e] nd = not determined.

With optimized conditions in hand, we turned our attention to the substrate scope. As shown in Table 4, a variety of acyclic silyl enol ethers **2a–e** as donors and a variety of 2-enoylpyridine *N*-oxide **3a–m** as the Michael acceptors were studied for the Mukaiyama–Michael reactions affording the required adducts in good to excellent enantioselectivities with very high yields (Table 4). Most of the 2-enoylpyridine *N*-oxides **3a–i** and **3k** reacted smoothly with silyl enol ether (**2a**) to afford products in high yields (86–92%) with excellent enantioselectivities (90–96% ee, entries 1–9 and 11). It is noteworthy that 2-enoylpyridine *N*-oxide **3j** containing furan as heteroaromatics also afforded products in 90% ee (entry 10). Silyl enol ethers **2b–d** also found to be suitable for this reaction and afforded products in 87–91% ee (entries 14 and 16). The silyl enol ether derived from tertiary-butyl methyl ketone failed to react with **3d** to produce the corresponding adduct even after 4 days (entry 17). However, in the case of 2-enoylpyridine *N*-oxide **3l**, prepared from cinnamaldehyde, we found that the reaction became sluggish and took 28 h to afford the product in 80% yield with 83% ee (entry 12). Also, the silyl enol ether **2c**, on reacting with **3a**, afforded products in 81% ee (entry 15). The sterically hindered substrate **3m** prepared from trimethyl acetaldehyde did not respond to the protocol.

With these successful results in hand using acyclic disubstituted silyl enol ethers as Michael donor, we looked forward to check the substrate scope with acyclic trisubstituted silyl enol ether (**5**) for Mukaiyama–Michael reactions. Silyl enol ether (**5**), prepared from propiophenone on treatment with **3a–b, d**, afforded corresponding Mukaiyama–Michael adducts in good diastereoselectivity and up to excellent enantioselectivity (Table 5).

Further, in order to explain the stereochemical outcome of the Michael adduct, a transition state model has been proposed (see Fig. 2). Among two possible transition states, **TS-1** if favored over **TS-2** because of steric hindrance. In case of **TS-1**, the attack of silyl enol ethers takes place from the less hindered *Re*-face of complex (**TS-1**) formed by the coordination of ligand and substrate to Zn(II)-complexes. The *Si*-face is not accessible due to the steric hindrance between the ^{i}Pr group of **1a** and the approaching silyl enol ethers **2a–d**.

Table 5 Use of acyclic trisubstituted silyl enol ether in Mukaiyama–Michael reactions[a]



Entry	R2	Product	Time	Yield[b] (%)	de[c] (%)	ee[d,e] (%)
1	Ph (**3a**)	(**6a**)	61 h	91	3 : 2	97/64
2	2-ClC_6H_4 (**3b**)	(**6b**)	50 h	90	4 : 1	65/nd[f]
3	4-ClC_6H_4 (**3d**)	(**6c**)	42 h	92	3 : 1	98/68

[a] The reactions were carried out by taking 0.2 mmol **3** and 0.8 mmol **2** in 1.0 mL benzene with 10 mol% catalyst **1a**-$Zn(OTf)_2$. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by chiral HPLC (ee reported for major diastereomer). [e] ee of minor diastereomer. [f] nd = not determined.

The single crystal X-ray analysis of compound **4n** and the comparison of optical rotation of compound **8** with literature confirm the proposed stereochemistry of the product (Fig. 3).[12]

To show the versatility of our methodology, one of the products (**4a** with 95% ee) was converted to carboxylic acid **7** under saponification conditions (Scheme 1), which was then

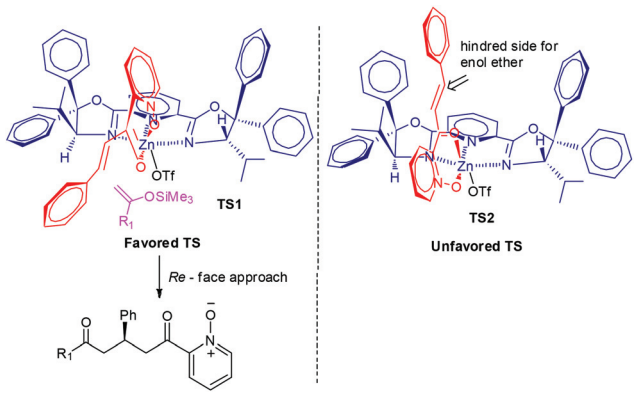


Fig. 2 Proposed transition states of Mukaiyama–Michael reactions.

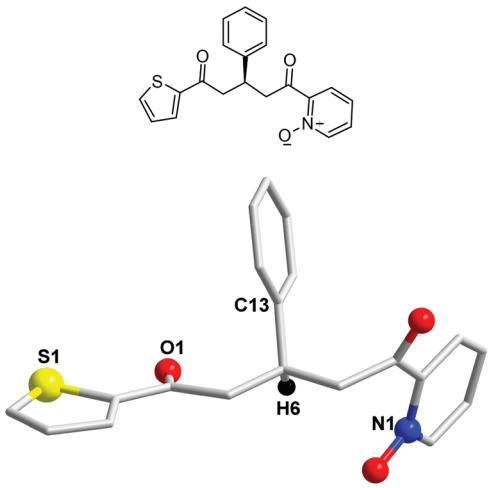
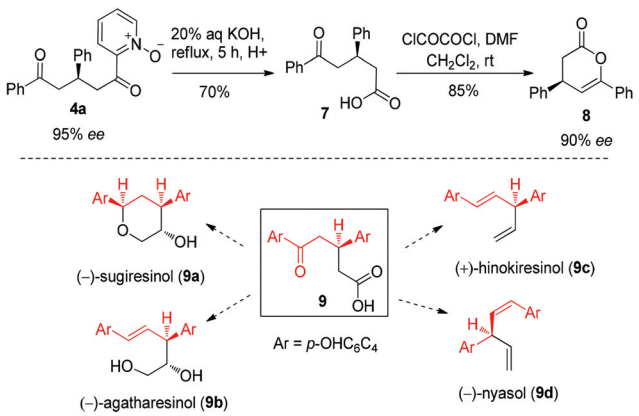


Fig. 3 X-ray structure of **4n**.



Scheme 1 Synthetic elaboration of compound **4a** and further opportunity to access various natural products.

treated with excess oxalyl chloride and catalytic amount of dimethylformamide to afford the synthetically useful 3,4-dihydro-α-pyrone **8** with slight loss in enantioselectivity (90% ee). Besides this, the enantioenriched δ-keto acid (**7**) could also serve as a template for the synthesis of various biologically important natural products (**9a–d**) on further synthetic elaboration.[10]

In conclusion, an additive-free enantioselective methodology for the Mukaiyama–Michael reaction of a variety of 2-enoylpyridine *N*-oxides **3** with acyclic silyl enol ethers **2** and **5** has been developed at room temperature using **1a**-Zn(OTf)$_2$ complex. The strategy offers an interesting platform to synthesize functionalized 1,5-dicarbonyl compounds in very good yields and excellent enantioselectivities (up to 96%). A transition state has been proposed to explain the stereochemical outcome of the Mukaiyama–Michael adduct. Further efforts towards its application in the natural product synthesis are currently under way.

Experimental section

^{1}H and ^{13}C NMR spectra were recorded on Jeol (500 MHz) spectrometers in $CDCl_3$. Chemical shifts are reported in delta (δ) units, in parts per million (ppm). Coupling constants were reported in Hz. Splitting patterns are designated as s for singlet; d for doublet; t for triplet; q for quartet; m for multiplet and bs for broad singlet. IR spectra were measured with Bruker FT/IR Vector 22 spectrometer. Mass spectrometric analysis was done on waters Q Tof Premier Micromass (ESI). All the chromatographic separations were carried out by using silica gel (Acme's, 100–200 mesh). Zinc(II) triflate, Silyl enol ether **2a** and **2e** were commercially available from Sigma-Aldrich and used without further purification. Silyl enol ether **2b–2d** were prepared according to literature known procedure.[11] Silyl enol ether **5** was prepared according to literature reported procedure.[13] Ligands **1a–1g** were prepared according to our procedure.[9e–g] **1h–1i** were commercially available. 2-Enoylpyridine-*N*-oxides were prepared by earlier reported method.[6a,b]

General procedure of silyl enol ether preparation

A solution of ketone (1 eq) in anhydrous dichloromethane was stirred at room temperature under N_2 atmosphere. Triethylamine (1.8 eq) and then trimethylsilyltrifluoromethanesulfonate (1.2 eq) were added to the reaction mixture. After three hours, the reaction was diluted with dichloromethane and washed with a solution of sat. NH_4Cl. The aqueous layer was extracted thrice with ethyl acetate. The organic layers were further washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Silyl enol ethers were used without further purification.

General procedure for enantioselective Mukaiyama–Michael reaction

A solution of a ligand **1a** (14.54 mg, 0.024 mmol) and Zn(OTf)$_2$ (7.26 mg, 0.02 mmol) in dry dichloromethane (1 mL) was stirred at room temperature for 1 h under nitrogen atmosphere. *trans*-2-Enoylpyridine-*N*-oxide (0.20 mmol) was added and the whole mixture was stirred for an additional 15 min at rt. Silyl enol ether (0.6 mmol) was added and the reaction

mixture and stirred at room temperature until the completion of the reaction (monitored by TLC). The mixture was concentrated *in vacuo* and purified over silica gel by column chromatography (methanol–ethyl acetate 1 : 20) to afford the product.

(*R*)-2-(5-Oxo-3,5-diphenylpentanoyl)pyridine 1-oxide (4a). The compound **4a** was isolated as solid in 92% yield and 95% ee; $[\alpha]_D^{25}$ = +49.5 (*c* 0.3, $CHCl_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OJ-H column, *n*-hexane–2-propanol (70 : 30) as eluent, flow rate = 1.0 mL min^{-1}. t_R (major) = 28.86 min, t_R (minor) = 42.95 min. ^1H NMR (500 MHz; $CDCl_3$): δ 3.34–3.44 (m, 2H), 3.65 (dd, *J* = 6.5, 17.1 Hz, 1H), 3.73 (dd, *J* = 8.0, 17.1 Hz, 1H), 4.05–4.08 (m, 1H), 7.12–7.45 (m, 10H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.89 (dd, *J* = 7.0, 8.6 Hz, 2H), 8.23 (d, *J* = 6.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 37.0, 45.1, 48.9, 126.7, 126.9, 127.4, 127.7, 127.9, 128.1, 128.6, 135.1, 140.3, 143.6, 146.8, 195.9, 198.3. IR (thin film): ν = 3457.3, 2924.3, 2052.9, 1682.9, 1601.7, 1494.9, 1448.5, 1430.4 cm^{-1}. HRMS (ES+): Exact mass calc for $C_{22}H_{20}NO_3$ $[M + H]^+$: 346.1443. Found: 346.1445.

(*R*)-2-(3-(2-Chlorophenyl)-5-oxo-phenylpentanoyl)pyridine 1-oxide (4b). The compound **4b** was isolated as solid in 91% yield and 83% ee; $[\alpha]_D^{25}$ = +35.9 (*c* 0.5, $CHCl_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OJ-H column, *n*-hexane–2-propanol (70 : 30) as eluent, flow rate = 1.0 mL min^{-1}. t_R (major) = 19.25 min, t_R (minor) = 27.24 min. ^1H NMR (500 MHz; $CDCl_3$): δ 3.40–3.46 (m, 2H), 3.74 (dd, *J* = 6.7, 18.0 Hz, 1H), 3.80 (dd, *J* = 7.5, 17.6 Hz, 1H), 4.49–4.55 (m, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.32–7.36 (m, 2H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.52–7.69 (m, 4H), 7.92 (d, *J* = 7.1 Hz, 2H), 8.45–8.50 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 33.4, 43.6, 47.1, 126.9, 127.1, 127.8, 128.2, 128.4, 128.6, 130.0, 133.2, 133.8, 136.8, 140.8, 195.6, 198.2. IR (thin film): ν = 3447, 3048, 2923, 2852, 1683, 1650, 1579, 1475, 1447, 1354 cm^{-1}. HRMS (ES+): Exact mass calc for $C_{22}H_{19}ClNO_3$ $[M + H]^+$: 380.1053. Found: 380.1052.

(*R*)-2-(3-(3-Chlorophenyl)-5-oxo-phenylpentanoyl)pyridine 1-oxide (4c). The compound **4c** was isolated as semisolid in 89% yield and 90% ee; $[\alpha]_D^{25}$ = +3.1 (*c* 0.9, $CHCl_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OD-H column, *n*-hexane–2-propanol (90 : 10) as eluent, flow rate = 1.0 mL min^{-1}. t_R (major) = 74.27 min, t_R (minor) = 85.42 min. ^1H NMR (500 MHz; $CDCl_3$): δ 3.42–3.70 (m, 2H), 3.65 (dd, *J* = 6.4, 18.0 Hz, 1H), 3.71 (dd, *J* = 8.0, 16.8 Hz, 1H), 4.02–4.07 (m, 1H), 7.12–7.25 (m, 4H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.53–7.57 (m, 4H), 7.89 (d, *J* = 7.3 Hz, 2H), 8.45 (bs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.5, 44.8, 48.8, 114.1, 126.0, 127.0, 127.1, 127.8, 128.1, 128.7, 129.9, 133.3, 134.3, 136.7, 139.3, 145.8, 194.8, 198.0. IR (thin film): ν = 3385, 3061, 2924, 2853, 1684, 1597, 1572, 1475, 1470, 1430, 1360 cm^{-1}. HRMS (ES+): Exact mass calc for $C_{22}H_{19}ClNO_3$ $[M + H]^+$: 380.1053. Found: 380.1059.

(*R*)-2-(3-(4-Chlorophenyl)-5-oxo-phenylpentanoyl)pyridine 1-oxide (4d). The compound **4d** was isolated as semisolid in 88% yield and 95% ee; $[\alpha]_D^{25}$ = +31.2 (*c* 0.8, $CHCl_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OJ-H column, *n*-hexane–2-propanol (80 : 20) as eluent, flow rate = 1.0 mL min^{-1}. t_R (major) = 31.77 min, t_R (minor) = 43.16 min. ^1H NMR (500 MHz; $CDCl_3$): δ 3.33 (dd, *J* = 7.4, 17.1 Hz, 1H), 3.40 (dd, *J* = 6.45, 17.4 Hz, 1H), 3.64 (dd, *J* = 5.5, 17.8 Hz, 1H), 3.72 (dd, *J* = 7.9, 17.4 HZ, 1H), 4.02–4.06 (m, 1H), 7.18–7.48 (m, 9H), 7.53 (td, *J* = 1.5, 7.4 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 2H), 8.17–8.19 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.2, 44.9, 48.8, 126.2, 127.0, 128.0, 128.1, 128.7, 129.1, 132.3, 133.2, 136.8, 140.5, 146.6, 195.7, 198.0. IR (thin film): ν = 3061, 2923, 2852, 1684, 1597, 1580, 1492, 1448, 1429, 1360 cm^{-1}. HRMS (ES+): Exact mass calc for $C_{22}H_{19}ClNO_3$ $[M + H]^+$: 380.1053. Found: 380.1053.

(*R*)-2-(3-(2-Nitrophenyl)-5-oxo-5-phenylpentanoyl)pyridine 1-oxide (4e). The compound **4e** was isolated as semisolid in 87% yield and 92% ee; $[\alpha]_D^{25}$ = +24.1 (*c* 0.7, $CHCl_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OD-H column, *n*-hexane–2-propanol (70 : 30) as eluent, flow rate = 1.0 mL min^{-1}. t_R (major) = 28.01 min, t_R (minor) = 36.80 min. ^1H NMR (500 MHz; $CDCl_3$): δ 3.41–3.52 (m, 2H), 3.77 (dd, *J* = 7.2, 12.5 Hz, 1H), 3.82 (dd, *J* = 4.5, 7.0 Hz, 1H), 4.51–4.57 (m, 1H), 7.27–7.64 (m, 8H), 7.71–7.77 (m, 1H), 7.89–7.92 (m, 3H), 8.22 (d, *J* = 6.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.2, 44.1, 48.1, 114.1, 124.4, 127.1, 127.3, 128.1, 128.6, 128.8, 129.4, 132.8, 133.3, 134.6, 136.5, 139.3, 140.6, 146.2, 152.2, 197.5. IR (thin film): ν = 3432, 2922, 2852, 1683, 1599, 1579, 1523, 1423, 1353, 1297 cm^{-1}. HRMS (ES+): Exact mass calc for $C_{22}H_{19}N_2O_5$ $[M + H]^+$: 391.1294. Found: 391.1293.

(*R*)-2-(3-(3-Nitrophenyl)-5-oxo-5-phenylpentanoyl)pyridine 1-oxide (4f). The compound **4f** was isolated as semisolid in 88% yield and 95% ee; $[\alpha]_D^{25}$ = +24.5 (*c* 0.5, $CHCl_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OJ-H column, *n*-hexane–2-propanol (80 : 20) as eluent, flow rate = 1.0 mL min^{-1}. t_R (major) = 74.62 min, t_R (minor) = 99.75 min. ^1H NMR (500 MHz; $CDCl_3$): δ 3.43 (dd, *J* = 7.4, 17.4 Hz, 1H), 3.51 (dd, *J* = 6.5, 17.5 Hz, 1H), 3.62–3.71 (m, 2H), 3.99–4.05 (m, 1H), 7.18–7.22 (m, 4H), 7.239–7.44 (m, 2H), 7.51 (dd, *J* = 2.2, 7.1 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.6 Hz, 3H), 8.31 (d, *J* = 5.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.2, 44.5, 48.8, 121.9, 122.5, 127.2, 128.1, 128.2, 128.4, 128.7, 129.5, 133.5, 134.6, 136.5, 140.8, 146.0, 148.4, 194.6, 197.5. IR (thin film): ν = 3435, 3061, 2923, 2853, 1685, 1674, 1596, 1579, 1530, 1480, 1437, 1348 cm^{-1}. HRMS (ES+): Exact mass calc for $C_{22}H_{19}N_2O_5$ $[M + H]^+$: 391.1294. Found: 391.1299.

(*R*)-2-(3-(4-Nitrophenyl)-5-oxo-5-phenylpentanoyl)pyridine 1-oxide (4g). The compound **4g** was isolated as semisolid in 88% yield and 90% ee; $[\alpha]_D^{25}$ = +45.5 (*c* 1.1, $CHCl_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralpak IA-3 column, *n*-hexane–2-propanol (80 : 20) as eluent, flow rate = 1.0 mL min^{-1}. t_R (major) = 58.84 min, t_R (minor) = 70.50 min. ^1H NMR (500 MHz; $CDCl_3$): δ 3.41 (dd, *J* = 7.6, 17.4 Hz, 1H), 3.48 (dd, *J* = 6.5, 17.4 Hz, 1H), 3.72 (dd, *J* = 6.1, 18.0 Hz, 1H), 3.79 (dd, *J* = 8.0, 18.0 Hz, 1H), 4.18–4.23 (m, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.40–7.58 (m, 7H), 7.88 (d, *J* = 8.3 Hz, 2H), 8.10 (d, *J* = 8.3 Hz, 2H), 8.25 (d, *J* = 6.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.3, 44.4, 48.6, 123.8, 127.1, 127.5, 128.0, 128.4, 128.7, 133.5, 136.5, 140.7, 146.1, 146.7, 151.7,

194.8, 197.5. IR (thin film): ν = 2922, 2851, 1683, 1597, 1516, 1429, 1345 cm^{-1}. HRMS (ES+): Exact mass calc for $C_{22}H_{19}N_2O_5$ $[M + H]^+$: 391.1294. Found: 391.1290.

(*R*)-2-(3-(4-Fluorophenyl)-5-oxo-phenylpentanoyl)pyridine 1-oxide (4h). The compound **4h** was isolated as semisolid in 89% yield and 96% ee; $[\alpha]_D^{25}$ = +28.3 (*c* 1.1, $CHCl_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OJ-H column, *n*-hexane–2-propanol (90 : 10) as eluent, flow rate = 1.0 mL min^{-1}. t_R (major) = 87.65 min, t_R (minor) = 110.12 min. ^1H NMR (500 MHz; $CDCl_3$): δ 3.32 (dd, *J* = 7.6, 16.8 Hz, 1H), 3.29 (dd, *J* = 6.4, 16.8 Hz, 1H), 3.62 (dd, *J* = 6.4, 17.1 Hz, 1H), 3.70 (dd, *J* = 8.0, 17.4 Hz, 1H), 4.03–4.08 (m, 1H), 6.92 (t, *J* = 8.3 Hz, 2H), 7.21–7.27 (m, 2H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.50–7.55 (m, 4H), 7.88 (d, *J* = 7.7 Hz, 2H), 8.45 (bs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.1, 45.1, 49.0, 115.2, 115.4, 126.8, 127.0, 128.1, 128.3, 128.6, 129.1, 129.3, 133.2, 136.8, 139.4, 140.5, 146.6, 160.5, 162.5, 196.0, 198.2. IR (thin film): ν = 2923, 2833, 1684, 1593, 1509, 1462, 1376 cm^{-1}. HRMS (ES+): Exact mass calc for $C_{22}H_{19}FNO_3$ $[M + H]^+$: 364.1349. Found: 364.1349.

(*R*)-2-(3-(4-Methoxyphenyl)-5-oxo-phenylpentanoyl)pyridine 1-oxide (4i). The compound **4i** was isolated as semisolid in 86% yield and 92% ee; $[\alpha]_D^{25}$ = +40.7 (*c* 0.8, $CHCl_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OJ-H column, *n*-hexane–2-propanol (70 : 30) as eluent, flow rate = 1.0 mL min^{-1}. t_R (major) = 24.44 min, t_R (minor) = 36.68 min. ^1H NMR (500 MHz; $CDCl_3$): δ 3.31–3.40 (m, 2H), 3.58–3.70 (m, 2H), 3.73 (s, 3H), 3.96–4.01 (m, 1H), 6.76 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.40–7.54 (m, 6H), 7.89 (d, *J* = 7.7 Hz, 2H), 8.44 (bs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.3, 45.3, 49.2, 55.3, 114.0, 127.1, 128.1, 128.6, 130.3, 133.2, 135.4, 136.9, 140.4, 158.3, 195.4, 198.5. IR (thin film): ν = 3361, 3060, 2923, 2851, 1683, 1580, 1513, 1448, 1362, 1296 cm^{-1}. HRMS (ES+): Exact mass calc for $C_{23}H_{22}NO_4$ $[M + H]^+$: 376.1549. Found: 376.1543.

(*R*)-2-(3-(Furan-2-yl)-5-oxo-5-phenylpentanoyl)pyridine 1-oxide (4j). The compound **4j** was isolated as semisolid in 81% yield and 90% ee; $[\alpha]_D^{25}$ = +12.0 (*c* 0.5, $CHCl_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OD-H column, *n*-hexane–2-propanol (85 : 15) as eluent, flow rate = 1.0 mL min^{-1}. t_R (major) = 43.94 min, t_R (minor) = 51.55 min. ^1H NMR (500 MHz; $CDCl_3$): δ 3.35 (dd, *J* = 7.0, 17.4 Hz, 1H), 3.47 (dd, *J* = 6.7, 17.1 Hz, 1H), 3.60 (dd, *J* = 6.1, 17.4 Hz, 1H), 3.73 (dd, *J* = 7.7, 17.4 Hz, 1H), 4.15–4.21 (m, 1H), 6.07 (d, *J* = 2.8 Hz, 1H), 6.20–6.21 (m, 1H), 7.22–7.28 (m, 1H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.48–7.56 (m, 3H), 7.65–7.69 (m, 1H), 7.91–7.93 (m, 2H), 8.47–8.49 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.5, 42.5, 46.6, 105.6, 110.3, 114.1, 127.1, 128.1, 128.5, 133.2, 136.8, 140.4, 141.2, 146.5, 155.9, 195.2, 198.0. IR (thin film): ν = 2922, 2851, 1684, 1597, 1505, 1448, 1480, 1360 cm^{-1}. HRMS (ES+): Exact mass calc for $C_{20}H_{18}NO_4$ $[M + H]^+$: 336.1236. Found: 336.1236.

(*R*)-2-(3-(Naphthalen-1-yl)-5-oxo-5-phenylpentanoyl)pyridine 1-oxide (4k). The compound **4k** was isolated as semisolid in 82% yield and 90% ee; $[\alpha]_D^{25}$ = +43.4 (*c* 0.4, $CHCl_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralpak IA-3 column, *n*-hexane–2-propanol (80 : 20) as eluent, flow rate = 1.0 mL min^{-1}. t_R (major) = 30.02 min, t_R (minor) = 27.52 min. ^1H NMR (500 MHz; $CDCl_3$): δ 3.47–3.56 (m, 2H), 3.80 (dd, *J* = 6.2, 17.1 Hz, 1H), 3.93 (dd, *J* = 7.6, 16.8 Hz, 1H), 4.91–5.02 (m, 1H), 7.31–7.51 (m, 10H), 7.67 (d, *J* = 8.00 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.89 (m, 2H), 8.19 (d, *J* = 6.4 Hz, 1H), 8.24 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 37.3, 44.9, 48.3, 123.2, 125.4, 125.7, 126.4, 126.8, 127.3, 127.9, 128.1, 128.6, 128.9, 133.2, 134.0, 136.9, 140.0, 140.3, 146.7, 196.1, 198.5. IR (thin film): ν = 3250, 2920, 2850, 1682, 1597, 1429, 1293 cm^{-1}. HRMS (ES+): Exact mass calc for $C_{26}H_{22}NO_3$ $[M + H]^+$: 396.1600. Found: 396.1600.

(*R*,*E*)-2-(3-(2-Oxo-2-phenylethyl)-5-phenylpent-4-enoyl)pyridine 1-oxide (4l). The compound **4l** was isolated as semisolid in 80% yield and 83% ee; $[\alpha]_D^{25}$ = +20.3 (*c* 0.5, $CHCl_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OD-H column, *n*-hexane–2-propanol (90 : 10) as eluent, flow rate = 1.0 mL min^{-1}. t_R (major) = 69.62 min, t_R (minor) = 86.40 min. ^1H NMR (500 MHz; $CDCl_3$): δ 3.19–3.28 (m, 2H), 3.49 (dd, *J* = 6.1, 17.1 Hz, 1H), 3.55 (dd, *J* = 7.0, 16.8 Hz, 1H), 3.59, 3.64 (m, 1H), 6.21 (dd, *J* = 8.3, 15.9 Hz, 1H), 6.43 (d, *J* = 16.2 Hz, 1H), 7.16–7.19 (m, 1H), 7.23–7.29 (m, 4H), 7.343–7.56 (m, 5H), 7.70 (dd, *J* = 1.9, 7.7 Hz, 1H), 7.94 (m, 2H), 8.48 (d, *J* = 6.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.7, 43.5, 47.5, 126.3, 127.0, 127.2, 127.3, 128.0, 128.5, 128.7, 130.8, 131.7, 133.2, 137.0, 139.3, 140.5, 146.5, 146.8, 196.1, 198.6. IR (thin film): ν = 2921, 2851, 1683, 1597, 1492, 1448, 1429, 1361, 1293 cm^{-1}. HRMS (ES+): Exact mass calc for $C_{24}H_{22}NO_3$ $[M + H]^+$: 372.1600. Found: 372.1593

(*R*)-2-(5-(4-Fluorophenyl)-5-oxo-phenylpentanoyl)pyridine 1-oxide (4m). The compound **4m** was isolated as semisolid in 82% yield and 91% ee; $[\alpha]_D^{25}$ = +40.0 (*c* 0.6, $CHCl_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OJ-H column, *n*-hexane–2-propanol (80 : 20) as eluent, flow rate = 1.0 mL min^{-1}. t_R (major) = 57.67 min, t_R (minor) = 78.60 min. ^1H NMR (500 MHz; $CDCl_3$): 3.33 (dd, *J* = 7.4, 17.1 Hz, 1H), 3.39 (dd, *J* = 6.7, 16.8 Hz, 1H), 3.63–3.73 (m, 2H), 4.00–4.06 (m, 1H), 7.08 (t, *J* = 8.6 Hz, 2H), 7.14 (t, *J* = 6.7 Hz, 1H), 7.21–7.26 (m, 4H), 7.32–7.42 (m, 3H), 7.90–7.93 (m, 2H), 8.26 (d, *J* = 6.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 37.0, 45.1, 48.9, 115.6, 115.8, 126.8, 126.9, 127.6, 128.0, 128.7, 130.7, 130.8, 133.3, 140.4, 143.5, 146.7, 164.7, 166.8, 195.9, 196.8. IR (thin film): ν = 3419, 3063, 2919, 2851, 1884, 1597, 1506, 1453, 1430, 1410, 1365 cm^{-1}. HRMS (ES+): Exact mass calc for $C_{22}H_{19}FNO_3$ $[M + H]^+$: 364.1349. Found: 364.1345.

(*S*)-2-(5-Oxo-3-phenyl-5-(thiophen-2-yl)pentanoyl)pyridine 1-oxide (4n). The compound **4n** was isolated as solid in 88% yield and 81% ee; $[\alpha]_D^{25}$ = −41.3 (*c* 0.4, $CHCl_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OJ-H column, *n*-hexane–2-propanol (70 : 30) as eluent, flow rate = 1.0 mL min^{-1}. t_R (major) = 39.37 min, t_R (minor) = 59.52 min. ^1H NMR (500 MHz; $CDCl_3$): δ 3.31 (d, *J* = 7.1 Hz, 2H), 3.64 (dd, *J* = 6.1, 17.1 Hz, 1H), 3.74 (dd, *J* = 8.3, 17.4 Hz, 1H), 3.99–4.05 (m, 1H), 7.09 (t, *J* = 4.6 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.22–7.28 (m, 3H), 7.47–7.58 (m, 4H), 7.60 (d, *J* = 5.2 Hz, 1H), 7.68 (d, *J* = 3.4 Hz, 1H), 8.54 (d, *J* = 5.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 37.4, 45.8, 48.7, 114.1, 127.0, 127.2, 127.6, 128.2, 128.7, 132.2, 134.0, 140.3, 143.1, 191.3, 194.8. IR (thin film): ν = 2921, 2856, 1656, 1415, 1254 cm^{-1}. HRMS (ES+): Exact mass calc for $C_{20}H_{18}NO_3S$ $[M + H]^+$: 352.1007. Found: 352.1004.

(*R*)-2-(5-(4-Bromophenyl)-3-(4-chlorophenyl)-5-oxopentanoyl)pyridine 1-oxide (4o). The compound **4o** was isolated as semisolid in 83% yield and 87% ee; $[\alpha]_D^{25}$ = +38.2 (*c* 0.3, $CHCl_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OD-H column, *n*-hexane–2-propanol (70 : 30) as eluent, flow rate = 1.0 mL min^{-1}. t_R (major) = 35.86 min, t_R (minor) = 23.92 min. ^{1}H NMR (500 MHz; $CDCl_3$): δ 3.29 (dd, *J* = 7.7, 17.1 Hz, 1H), 3.37 (dd, *J* = 6.4, 17.1 Hz, 1H), 3.62–3.71 (m, 2H), 4.00–4.05 (m, 1H), 7.18–7.22 (m, 4H), 7.39–7.52 (m, 3H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 2H), 8.31 (d, *J* = 5.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ IR (thin film): ν = 3083, 2923, 2852, 1684, 1584, 1491, 1429, 1397, 1360 cm^{-1}. HRMS (ES+): Exact mass calc for $C_{22}H_{18}BrClNO_3$ $[M + H]^+$: 458.0159. Found: 458.0159.

2-((3*S*)-4-Methyl-5-oxo-3,5-diphenylpentanoyl)pyridine 1-oxide (6a). The compound **6a** was isolated as semisolid in 91% overall yield, 97% ee (for major diastereomer) and 64% ee (for minor diastereomer). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OD-H column, *n*-hexane–2-propanol (90 : 10) as eluent, flow rate = 1.0 mL min^{-1}. For major diastereomer, t_R (major) = 42.41 min, t_R (minor) = 40.41 min. and for minor diastereomer, t_R (major) = 77.61 min, t_R (minor) = 52.37 min. ^{1}H NMR (500 MHz; $CDCl_3$): δ 0.96 (d, *J* = 9.0 Hz, 1.8H), 1.26 (d, *J* = 3.1 Hz, 1.2 H), 3.37–3.42 (m, 0.6H), 3.67–3.87 (m, 3.4H), 7.00–7.55 (m, 11H), 7.75 (dd, *J* = 1.0, 7.9 Hz, 1H), 7.97–7.99 (m, 1H), 8.12 (d, *J* = 6.4 Hz, 0.6H), 8.18 (d, *J* = 6.4 Hz, 0.4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.3, 16.7, 43.6, 44.2, 45.0, 45.9, 46.3, 47.4, 126.6, 126.7, 126.8, 126.9, 127.0, 127.7, 127.8, 128.1, 128.2, 128.3, 128.4, 128.5, 128.8, 132.9, 133.2, 136.8, 140.1, 141.6, 142.6, 146.8, 147.0, 196.2, 196.9, 203.3, 203.5. IR (thin film): ν = 3060, 2927, 1679, 1597, 1495, 1448, 1429, 1373, 1294 cm^{-1}. HRMS (ES+): Exact mass calc for $C_{23}H_{22}NO_3$ $[M + H]^+$: 360.1600. Found: 360.1602.

2-((3*S*)-3-(2-Chlorophenyl)-4-methyl-5-oxo-5-phenylpentanoyl)pyridine 1-oxide (6b). The compound **6b** was isolated as semisolid in 90% overall yield and 65% ee (for major diastereomer); The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralpak IC-3 column, *n*-hexane–2-propanol (70 : 30) as eluent, flow rate = 1.0 mL min^{-1}. t_R (major) = 97.28 min, t_R (minor) = 116.20 min. ^{1}H NMR (500 MHz; $CDCl_3$): δ 1.01 (d, *J* = 7.1 Hz, 2.4H), 1.22 (d, *J* = 3.0 Hz, 0.6 Hz), 3.46–4.00 (m, 3.2H), 4.36 (m, 0.8 H), 7.07–7.55 (m, 10H), 7.90 (d, *J* = 7.4 Hz, 0.4H), 7.94 (d, *J* = 7.4 Hz, 1.6H), 8.20 (d, *J* = 6.4 Hz, 0.8H), 8.25 (d, *J* = 6.4 Hz, 0.2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.6, 16.7, 43.3, 43.4, 43.6, 43.7, 46.3, 126.8, 127.1, 127.2, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 128.6, 128.8, 129.8, 129.9, 133.1, 133.3, 136.6, 136.7, 139.4, 140.3, 146.5, 195.6, 203.1, 203.2. IR (thin film): ν = 3061, 2925, 2853, 1676, 1596, 1475, 1429, 1374, 1293, 1259 cm^{-1}. HRMS (ES+): Exact mass calc for $C_{23}H_{21}ClNO_3$ $[M + H]^+$: 394.1210. Found: 394.1219.

2-((3*S*)-3-(4-Chlorophenyl)-4-methyl-5-oxo-5-phenylpentanoyl)pyridine 1-oxide (6c). The compound **6c** was isolated as semisolid in 92% overall yield, 98% ee (for major diastereomer) and 68% ee (for minor diastereomer). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralpak IC-3 column, *n*-hexane–2-propanol (70 : 30) as eluent, flow rate = 1.0 mL min^{-1}. t_R (major) = 48.69 min, t_R (minor) = 86.89 min. and for minor isomer t_R (major) = 58.80 min, t_R (minor) = 53.95 min. ^{1}H NMR (500 MHz; $CDCl_3$): δ 0.95 (d, *J* = 5.8 Hz, 2.25H), 1.29 (d, *J* = 6.4 Hz, 0.75 Hz), 3.00–3.42 (m, 1H), 3.66–3.83 (m, 3H), 7.05–7.62 (m, 10H), 7.76 (d, *J* = 7.3 Hz, 0.5H), 7.98 (d, *J* = 7.3 Hz, 1H), 7.23–7.29 (m, 4H), 7.343–7.56 (m, 5H), 7.70 (dd, *J* = 1.9, 7.7 Hz, 1H), 7.94 (m, 2H), 8.48 (d, *J* = 6.1 Hz, 1.5H), 8.16 (d, *J* = 6.1 Hz, 0.75H), 8.21 (d, *J* = 6.1 Hz, 0.25H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.6, 16.2, 42.8, 43.3, 45.2, 45.6, 46.1, 47.4, 126.8, 127.1, 127.3, 128.0, 128.1, 128.1, 128.4, 128.6, 128.7, 128.9, 129.6, 130.0, 132.3, 132.5, 133.1, 133.4, 136.5, 140.2, 140.3, 141.3, 146.5, 146.7, 195.6, 196.3, 202.9, 203.2. IR (thin film): ν = 3062, 2925, 2853, 1680, 1597, 1491, 1447, 1429, 1374, 1293 cm^{-1}. HRMS (ES+): Exact mass calc for $C_{23}H_{21}ClNO_3$ $[M + H]^+$: 394.1210. Found: 394.1214.

Cleavage of pyridine *N*-oxide ring (Scheme 1)

The compound **4a** (172.69 mg, 0.5 mmol) was suspended in 3 mL 20% aqueous KOH and the reaction mixture was heated to reflux for 5 h. The reaction mixture was cooled to room temperature and washed with ethyl acetate. The aqueous layer was cooled to 0 °C and acidified with conc. HCl and extracted with ethyl acetate thrice. The combine organic layer was washed with saturated brine solution and the mixture was concentrated *in vacuo* and purified over silica gel by column chromatography to afford the product **7**.

The compound **7** was obtained in 70% yield. $[\alpha]_D^{25}$ = −16.8 (*c* 1.1, $CHCl_3$). ^{1}H NMR (500 MHz; $CDCl_3$): 2.71 (dd, *J* = 7.7, 16.0 Hz, 1H), 2.86 (dd, *J* = 6.9, 16.0 Hz, 1H), 3.30–3.40 (m, 2H), 3.83–3.88 (m, 1H), 7.18–7.29 (m, 5H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.89 (d, *J* = 7.5 HZ, 2H). IR (thin film): ν = 3441, 2924, 2853, 1706, 1675, 1596, 1496, 1450, 1418, 1357 cm^{-1}. HRMS (ES+): Exact mass calc for $C_{17}H_{16}NaO_3$ $[M + Na]^+$: 291.0997. Found: 291.0998.

The synthesis of compound 8

The compound **7** (0.2 mmol) was suspended in 2 mL dichloromethane and allowed to stirred at room temperate. 0.3 mmol of oxalyl chloride was added to the reaction mixture slowly. Then 1–2 drops of DMF was added to the reaction mixture. After two hours, the reaction was diluted with dichloromethane. The organic layer was further washed with brine and dried over anhydrous sodium sulfate. The mixture was concentrated *in vacuo* and purified over silica gel by column chromatography to afford the product **8**.

The compound **8** was obtained in 85% yield. The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OJ-H column, *n*-hexane–2-propanol (95 : 5) as eluent, flow rate = 1.0 mL min^{-1}. t_R (major) = 32.62 min, t_R (minor) =

25.80 min. $[\alpha]_D^{25} = -36.7$ (*c* 0.5, $CHCl_3$) for 90% ee (*S*) isomer [lit[12] $[\alpha]_D^{20} = +6.0$ (*c* 0.28, $CHCl_3$) for 70% ee (*R*) isomer].

^{1}H NMR (500 MHz; $CDCl_3$): 2.77 (dd, *J* = 8.6, 15.8 Hz, 1H), 3.01 (dd, *J* = 6.6, 15.8 Hz, 1H), 3.93–3.97 (m, 1H), 5.94 (d, *J* = 5.1 Hz, 1H), 7.23–7.38 (m, 8H), 7.64–7.65 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.9, 37.1, 104.3, 124.7, 127.0, 127.6, 128.6, 129.1, 129.3, 132.2, 141.5, 150.9, 171.2. HRMS (ES+): Exact mass calc for $C_{17}H_{14}NaO_2$ $[M + Na]^+$: 273.0891 Found: 273.0891.

X-ray crystallographic study

The crystal data for the compound **4n** was collected on a Bruker SMART APEX CCD Diffractometer. We used SMART software package (version 5.628) for collecting data frames, SAINT software package (version 6.45) for integration of the intensity and scaling and SADABS for absorption correction. The structure was determined and refined by full-matrix least-squares on F^2 using SHELXTL software package.[14] Non-hydrogen atoms were refined with anisotropic displacement parameters. Fig. 3 and their bonding parameters were obtained from the DIAMOND 3.1f software package.[15] The program package ORTEP was utilized for molecular graphics generation in Fig. 3. The absolute configuration of compound **4n** is (*S*).

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