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Solvent-free enantioselective conjugate addition and bioactivities of nitromethane to Chalcone containing pyridine

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ABSTRACT

A series of chiral thioureas derived from quinine were tested as catalysts in the enantioselective Michael additions of nitromethane to α,β-unsaturated ketones containing pyridine. The best results were obtained with the bifunctional catalyst prepared from 3,5-di(trifluoromethyl)-aniline under solvent-free conditions. This thiourea promoted the reaction with high enantioselectivities and chemical yields for aryl ketones. The origins of enantioselectivity were further investigated *via* experiment and computation. Meanwhile, the products from our reaction showed potent antibacterial activities against rice bacterial leaf blight, with the *S*-enantiomer performing much better than the *R*-enantiomer. Given the promising bioactivity of this class of molecules, our work is expected to offer important applications in developing future generations for drug design.

1. Introduction

Chalcone was one of the most useful molecular frameworks in medicinal chemistry and its derivatives exhibited a broad spectrum of biological activities.[1] Especially 1,4-addition products of chalcone were reported to possess promising biological activities such as anticancer,[2] antiplant-viral,[3] antimicrobial,[4] anti-HIV,[5] and anti-urease[6] properties. The biological activity of 1,4-addition compounds depends on their absolute configuration. Therefore, the synthesis of enantiomerically pure 1,4-addition compounds has received considerable attentions.[7] At present, the enantioselective addition of different nucleophiles to chalcone were obtained successfully.[8–12] Among them, the conjugate addition of nitroalkanes to chalcone (nitro-Michael reaction) has attracted enormous attention because the nitro group can be converted to other functional groups,[13] such as pyrrolidines,[14] lactones,[15] carbocycles,[16] and amino acids.[17]

So far, there are many asymmetric approaches involving organocatalysis,[18] heterogeneous catalysis,[19] phase-transfer catalysis,[20] aqueous-phase catalysis,[21] and metal-catalysis,[22] to synthesize enantioselective compounds. However, highly selectivities are generally restricted to chalcone substrates without heterocyclic moieties that are necessary for good bioactivities.[23] In 2013, Blay and co-workers[24] first reported La^{III}-pyBOX complexes-catalyzed conjugate addition to chalcones containing pyridine to nitroalkanes, but only moderate yield and ee were obtained. In addition, there are few studies in synthesizing highly enantiomerically pure γ-nitroketones containing heterocycle that exhibit high biological activities.

It is well known that there are pronounced advantages in solvent-free synthetic approach include easy work-up procedures, short reaction time, and simple apparatus requirements, which has attracted considerable attention in recent years.[25] Herein, we report the efficient conjugate additions of nitromethane to chalcone containing pyridine *via* thiourea organic catalyst under solvent-free conditions. The origins of enantioselectivity were further investigated via experimental and computational studies. Meanwhile, the antibacterial activities against rice bacterial leaf blight of 1,4-addition chiral products were evaluated.

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2. Results and discussion

Thiourea catalysts with the cinchona motif via hydrogen-bonding interactions were successfully applied in different types of Michael reactions.[26] These findings prompted us to synthesize bifunctional thiourea derivatives of quinine **Q1**~**Q6** that are capable of dual activation through two H bonding (Fig. 1) and apply them in the conjugate addition of nitromethane (**2**) to 2-enoylpyridines (**1a**) (Table 1). These catalysts were then studied for their ability to mediate enantioselective 1,4-addition. Among them, **Q1**, **Q3**, and **Q4** turned out to be poor catalysts, and **Q2** failed to accelerate this transformation. However, catalysts **Q5** and **Q6** afforded promising results (Table 1, entries 5, 6). The change trend in the catalytic activity with the introduction of the different substituent on aromatic ring, indicating that the electron withdrawing property contributed to higher reactivity for 1,4-addition. In addition, quinine on the catalyst is crucial for the reaction enantioselectivity. Next, the influence of solvents on the enantioselective 1,4-addition was studied using the most efficient catalyst **Q5** (Table 1, entry 7–10), toluene performed better than alternative solvents (Table 1, entry 7). Most notably, when the model reaction was performed in neat nitromethane, a nearly complete conversion was achieved (Table 1, entry 11). Almost no change in enantioselectivity and reactivity was observed when the loading of **Q5** was reduced from 20 mol% to 10 mol% (Table 1, entry 12); however, a little decrease of reactivity and no significant loss of enantioselectivity were observed when a catalyst load was reduced from 10 mol% to 5 mol% (Table 1, entry 13). Under this reaction condition, the chemical yield was not improved when the reaction time was increased from 12 h to 24 h (Table 1, entry 14). It should be noted that the other enantiomer of the reaction could be obtained by using **Q6** as the catalyst (Table 1, entry 16). Based on the above results, the optimized reaction conditions (entries 12, 16) were used for the model reaction. In contrast to the conventional process (Table 1, entry 15), solvent-free synthetic approach reduced the reaction time dramatically, raised the yield and simplified the post-treatment.

Under these optimized reaction conditions (Table 1, entry 12), a series of enones were investigated in the asymmetric Michael addition reaction. As illustrated in Table 2, consistently excellent enantioselectivity was observed for a broad range of enones. β-Aryl substituted enones with various substituents afforded 1,4-adducts with excellent enantioselectivities (Table 2, entries 1–11). β-Heteroaromatic enones were also excellent substrates for the present transformation (Table 2, entries 12–13). β-Aryl and β-heteroaromatic enones underwent the Michael addition reaction smoothly to give the corresponding products in high yields. By comparison, enones with a *para*-substituted phenyl (Table 2, entry 9) or heteroaromatic (Table 2, entries 12–13) showed a slightly reduced reactivity.

To understand the reaction mechanism, we applied both theoretical and experimental approaches to clarify how the catalyst (Cat) activates the nucleophilic (Nu) and the electrophilic (EI) groups. *Via* the experiments, the key factors for the enantioselective

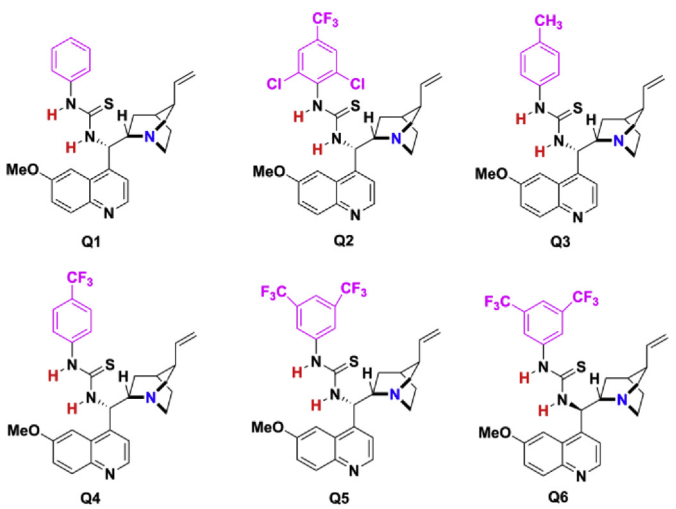
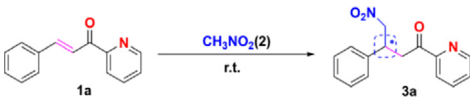


Fig. 1. Thiourea-quinine organocatalysts (**Q1**–**Q6**).

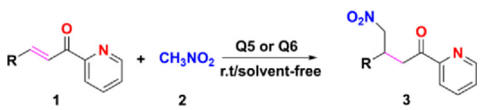
Table 1
Optimization of reaction conditions for conjugate addition of nitromethane (**2**) with trans-chalcone (**1a**).



Entry[a]	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[b]	Ee (%)[c]
1	**Q1** (20)	xylene	48	13	90
2	**Q2** (20)	xylene	48	0	0
3	**Q3** (20)	xylene	48	5	81
4	**Q4** (20)	xylene	48	37	95
5	**Q5** (20)	xylene	48	74	96
6	**Q6** (20)	xylene	48	73	−95
7	**Q5** (20)	toluene	48	79	95
8	**Q5** (20)	THF	48	69	93
9	**Q5** (20)	CH_2Cl_2	48	72	92
10	**Q5** (20)	neat	48	95	98
11	**Q5** (20)	neat	12	94	98
12	**Q5** (10)	neat	12	94	97
13	**Q5** (5)	neat	12	80	95
14	**Q5** (5)	neat	24	81	95
15	**Q5** (10)	toluene	12	32	94
16	**Q6** (10)	neat	12	93	−96

[a] Reactions were carried out with **1a** (0.2 mmol), 10 equiv of **2** (2 mmol) in capped vials at R.T.
[b] Isolated yields.
[c] The ee was determined by chiral HPLC analysis.

Table 2
Enantioselective conjugate addition of nitromethane to a series of β-substituted 2-enoylpyridines (**3a**~**3m**).



Entry	R	Product	Yield (%)[a]	Ee (%)[b]
1	Ph	**3a** (*R*)/(*S*)	93/94	96/97
2	2-FC_6H_4	**3b** (*R*)/(*S*)	95/97	96/98
3	2-$CF_3C_6H_4$	**3c** (*R*)/(*S*)	96/97	94/95
4	2-BrC_6H_4	**3d** (*R*)/(*S*)	96/98	96/97
5	2-$CH_3C_6H_4$	**3e** (*R*)/(*S*)	91/93	95/96
6	3-$CH_3OC_6H_4$	**3f** (*R*)/(*S*)	92/94	95/97
7	3-BrC_6H_4	**3g** (*R*)/(*S*)	93/92	97/98
8	4-ClC_6H_4	**3h** (*R*)/(*S*)	94/93	96/97
9	4-BrC_6H_4	**3i** (*R*)/(*S*)	93/92	96/97
10	4-$CH_3C_6H_4$	**3j** (*R*)/(*S*)	92/91	98/99
11	4-$CH_3OC_6H_4$	**3k** (*R*)/(*S*)	83/85	95/96
12	2-furan	**3l** (*R*)/(*S*)	76/79	98/99
13	2-thienyl	**3m** (*R*)/(*S*)	81/82	96/97

[a] Isolated yield after silica gel chromatography.
[b] The ee was determined by chiral HPLC analysis; and absolute configuration of the product 3a obtained using **Q5** catalyst was determined by X-ray analysis of *S* (CCDC:1457122) and the absolute configuration of all other product 3 were assigned by analogy.

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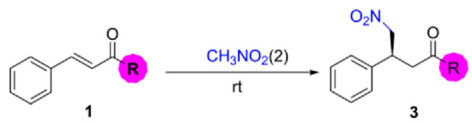
1,4-addition reaction were observed from the results summarized in Table 3. The reaction using KOH as base to afford the racemic product containing phenyl moiety in high yield (Table 3, entry 1), however, in the same reaction condition, the reaction didn't afford the racemic product containing pyridine (Table 3, entry 2). The reaction afforded the product **3a** in good yield (Table 3, entry 3) only with strong base (NaH). The result implies that the substrate with pyridine hinders Michael addition in alkaline condition. The best enantioselectivity was obtained using thiourea-quinine (**Q5**) catalyst (Table 3, entry 4 and entry 5); however, the reactivity of the substrate with pyridine is higher than those with phenyl moiety. The result shows that the nitrogen on pyridine is beneficial for the reactivity via thiourea-quinine catalyst.

In short, the oxygen and nitrogen on chalone are key factors for achieving the high enantioselectivity and reactivity; however, it is not very important that nitromethane was activated by the nitrogen on quinine. *Via* the DFT calculations, the most stable Cat−Ei complex (Fig. 2) are well consistent with our above experimental results (Table 3). In addition, the most stable Cat−Nu complex showed that hydrogen bonding was formed between the oxygen on Nu and the N−H on thiourea together with the protonated quinine amine. Based on the above results and the latest mechanism reported by Wang and coworkers[27] in 2012, a plausible mechanism was proposed in Fig. 3. The oxygen and nitrogen on chalcone (**1a**) activated by the NH on thiourea and nitromethane activated by both the NH of thiourea and the nitrogen on quinine to form the transition state, which undergoes the Michael reaction to afford the product **3a**.

The antibacterial activities of chiral products from our reactions against rice bacterial leaf blight were evaluated via the turbid meter test. Bismerthiazol was used as the positive controls.[28] The bioassay results in *vitro* were shown in Table 4.

The result showed that (*S*)-compounds generally exhibited higher antibacterial activity than the corresponding (*R*)-enantiomer. Among them, some compounds exhibited higher antibacterial activities than controls. Especially, compounds (*S*)-**3b** and (*S*)-**3h** possessed excellent activity at 100 μg/mL (inhibition, 100%), and Subsequently, compound (*R*)-**3b** and (*R*)-**3h** had slightly lower activity (inhibition, 65% and 57% respectively) at 100 μg/mL, which is higher than that of Bismerthiazol (inhibition, 55%). Compounds (*S*)-**3c**, (*S*)-**3d**, (*S*)-**3k** and (*S*)-**3m** showed good antibacterial activity, which is higher than that of the control at 100 μg/mL. Subsequently, their enantiomers displayed lower activity than the control. Furthermore, two enantiomers of compounds **3a**, **3e**, **3f**, **3i**, **3j** and **3l** showed poor antibacterial activity. In short, the above results indicated that the phenyl substitution pattern markedly affected the antibacterial activity of title compounds. Among them, compounds with hydrogen bonding moieties (2-F, 2-CF_3, 2-Br, 4-Cl, 4-Br, 4-CH_3O) at the 2 or 4 position of phenyl ring exhibited good antibacterial activities. In contrast, compounds without hydrogen bonding moieties (2-CH_3 and 4-CH_3) showed very low antibacterial activities. In addition, compounds with the moieties (3-CH_3O and 3-Br) at the 3 position of phenyl ring also show very low antibacterial activities. However, introduction of the thiophene

Table 3
The key factors for the enantioselective addition of nitromethane to chalcone.



Entry	R	Cat. (equ)	Yield (%)[c]	Ee (%)[d]
1[a]	phenyl	KOH (1.0)	92	0
2[a]	2-pyridine	KOH (1.0)	0	0
3[a]	2-pyridine	NaH (1.0)	72	0
4[b]	phenyl	Q5 (0.1)	40	93
5[b]	2-pyridine	Q5 (0.1)	94	97

[a] Reactions were carried out with **2a** (0.2 mmol), 10 equiv of **1** (2 mmol) in THF solvent at R.T.
[b] Under solvent-free condition.
[c] Isolated yield after silica gel chromatography.
[d] Determined by HPLC using a Chiralpak IA column.

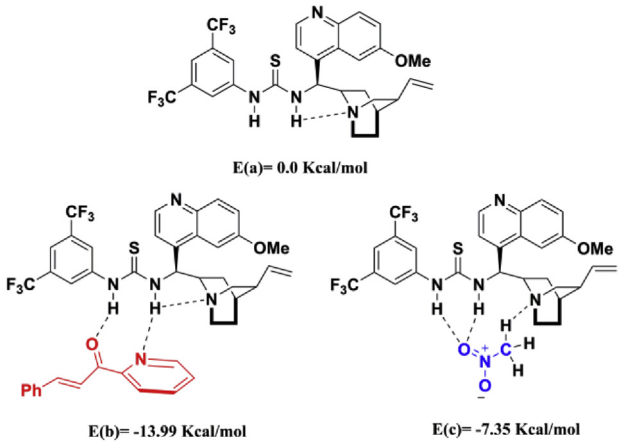


Fig. 2. The most stable structures of Cat (a), Cat−EI binary complex (b) and Cat−Nu binary complex (c).

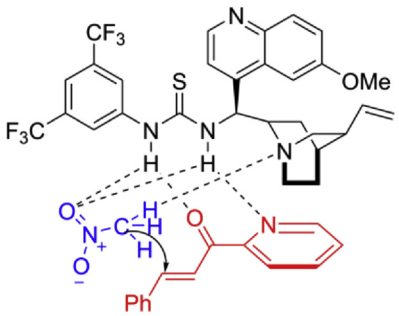


Fig. 3. A plausible mechanism.

Table 4
Activities of chiral compounds against rice bacterial leaf blight.

Compd.	Inhibition (%)[a]		Compd.	Inhibition (%)[a]	
	200 μg/mL	100 μg/mL		200 μg/mL	100 μg/mL
(*R*)-**3a**	12 ± 1.1	0	(*S*)-**3a**	23 ± 2.1	0
(*R*)-**3b**	87 ± 2.6	65 ± 3.2	(*S*)-**3b**	100 ± 2.4	100 ± 1.8
(*R*)-**3c**	72 ± 3.3	38 ± 2.8	(*S*)-**3c**	82 ± 2.2	58 ± 1.9
(*R*)-**3d**	59 ± 1.6	43 ± 1.8	(*S*)-**3d**	79 ± 2.9	59 ± 3.8
(*R*)-**3e**	32 ± 2.4	0	(*S*)-**3e**	52 ± 1.7	23 ± 2.5
(*R*)-**3f**	12 ± 1.5	0	(*S*)-**3f**	42 ± 2.3	16 ± 1.9
(*R*)-**3g**	45 ± 2.4	26 ± 2.8	(*S*)-**3g**	60 ± 2.1	46 ± 2.6
(*R*)-**3h**	81 ± 1.7	57 ± 2.6	(*S*)-**3h**	100 ± 1.4	100 ± 1.9
(*R*)-**3i**	46 ± 2.4	22 ± 2.1	(*S*)-**3i**	76 ± 2.1	51 ± 1.6
(*R*)-**3j**	0	0	(*S*)-**3j**	25 ± 1.4	0
(*R*)-**3k**	63 ± 1.5	33 ± 2.4	(*S*)-**3k**	81 ± 1.6	68 ± 2.3
(*R*)-**3l**	0	0	(*S*)-**3l**	17 ± 2.5	0
(*R*)-**3m**	68 ± 2.1	35 ± 2.7	(*S*)-**3m**	98 ± 1.8	75 ± 2.1
Control[b]	74 ± 1.7	55 ± 2.3			

[a] Average of three replicates.
[b] Bismerthiazol was used as the control.

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heterocycle at the position of phenyl ring, compound (*S*)-**3m** also possessed good activity. In short, the *S*-configuration of title compounds is the preferred antibacterial configuration. Among them, compound (*S*)-**3b** and (*S*)-**3h** could offer considerable potential for further development as chiral antibacterial agents. Meanwhile, the 1,4-addition chiral products would result in the synthesis of novel Michael addition compounds and act as new lead compounds in modern drug discovery.

3. Conclusion

In summary, we have developed a highly efficient and selective catalytic method for the synthesis of the 1,4-addition products of nitromethane to chalcones bearing pyridine by using thiourea based quinine catalysts. The Michael products were obtained in excellent enantioselectivities (up to 100% ee) and high yields. *Via* experiments and DFT calculation, we know that the oxygen and nitrogen on chalcone with pyridine was activated by the NH on thiourea; and nitromethane was activated by both the NH of thiourea and the nitrogen on quinine to form TS. This activation model may provide further insight into the bifunctional thiourea organocatalysts and their analogues. Meanwhile, the products from our reaction showed potent antibacterial activities against rice bacterial leaf blight, with the *S*-enantiomers showing superior performance than the *R*-enantiomers accordingly. Given the promising bioactivity of this class of molecules, our method is expected to offer important applications in developing future generations for drug design.

4. Experimental section

All reactions were carried out in oven dried glassware with magnetic stirring. Unless otherwise stated, all reagents were purchased from Aladdin Chemicals Co. (Aladdin, Shanghai, China) and used without further purification. All solvents used in the reactions were distilled from appropriate drying agents prior to use. Silica gel GF254-coated glass plates (Branch Qingdao Haiyang Chemical Co., Qingdao, China) were used for thin layer chromatography under detection at 254 nm. Silica gel 200–300 mesh (Branch Qingdao Haiyang Chemical Co., Qingdao, China) was applied to column chromatography. NMR spectra were recorded on a JEOL ECX-500 spectrometer (JEOL, Tokyo, Japan). Infrared (IR) spectra were recorded on Bruker VECTOR 22 spectrometer (Bruker, Karlsruhe, Germany) with KBr disks. HRMS data were measured on Thermo Scientific Q Exactive (Thermo, Missouri, USA). HPLC analysis was conducted by an Agilent Technologies 1200 Series system (Agilent, California, USA) with a 250 mm × 4.6 mm i.d., 5 μm, Chiralpak IA (Daicel) column. Optical rotation values were measured by a Wzz-2s polarimeter (Shanghai Yue Feng Instrument and Meter Co., Shanghai, China).

4.1. Procedure for synthesis

4.1.1. Procedure for synthesis of thiourea-quinine catalyst

According to the literature[18c], to a solution of 9-aminoquinine (2 mmol) in CH_2Cl_2 (10 mL) was slowly added to a solution of isothiocyanate (2 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at ambient temperature until reaction completion. The pure product was obtained after purification by column chromatography on silica gel with EtOAc/CH_3OH/Et_3N (10:1:0.1) as eluant, affording the catalyst (**Q1~Q6**).

Catalyst **Q1**: White solid, m.p. 132–133 °C, yield 81%, $[\alpha]_D^{20} = -179.6°$ (*c* 0.54, $CHCl_3$); ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.65 (d, *J* = 4.7 Hz, 1H), 8.05 (s, 1H), 7.92 (d, *J* = 9.2 Hz, 1H), 7.52 (d, *J* = 4.7 Hz, 1H), 7.43 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.34–7.26 (m, 4H), 7.13 (t, *J* = 6.4 Hz, 1H), 6.29 (d, *J* = 8.6 Hz, 1H), 5.89–5.71 (m, 1H), 4.97 (dd, *J* = 27.3, 13.7 Hz, 2H), 3.99 (s, 3H), 3.57 (s, 1H), 3.40–3.31 (m, 1H), 3.24 (dd, *J* = 13.5, 10.1 Hz, 1H), 2.81 (t, *J* = 15.1 Hz, 1H), 2.73 (dd, *J* = 13.7, 2.9 Hz, 1H), 2.34 (s, 1H), 1.65 (d, *J* = 30.6 Hz, 3H), 1.40 (t, *J* = 11.2 Hz, 1H), 0.88 (dd, *J* = 13.3, 6.0 Hz, 1H); ^{13}C NMR (126 MHz, Methanol-d_4) δ 180.85 (s), 158.24 (s), 146.92 (s), 143.78 (s), 141.14 (s), 138.57 (s), 129.82 (s), 128.80 (s), 128.68 (s), 125.10 (s), 123.81 (s), 122.40 (s), 120.00 (s), 113.70 (s), 102.89 (s), 60.08 (s), 55.20 (s), 55.13 (s), 41.34 (s), 39.38 (s), 27.50 (s), 27.26 (s), 25.53 (s).

Catalyst **Q2**: White solid, m.p. 148–150 °C, yield 81%, $[\alpha]_D^{20} = -116.4°$ (*c* 0.39, $CHCl_3$); ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.62 (d, *J* = 4.6 Hz, 1H), 7.99 (s, 1H), 7.90 (d, *J* = 9.2 Hz, 1H), 7.67 (s, 2H), 7.59 (d, *J* = 4.7 Hz, 1H), 7.39 (dd, *J* = 9.2, 2.5 Hz, 1H), 6.18 (s, 1H), 5.80–5.73 (m, 1H), 5.03–4.94 (m, 2H), 3.95 (s, 3H), 3.56 (d, *J* = 34.5 Hz, 2H), 3.33 (t, *J* = 12 Hz 1H), 2.88 (s, 2H), 2.40 (s, 1H), 1.75–1.65 (m, 3H), 1.44 (t, *J* = 11.3 Hz, 1H), 0.97 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (126 MHz, Methanol-d_4) δ 182.3 (s), 158.24 (s), 146.87 (s), 143.75 (s), 140.44 (s), 136.19 (s), 129.88 (s), 128.76 (s), 125.17 (s), 123.86 (s), 122.41 (s), 114.19 (s), 102.81 (s), 60.24 (s), 55.17 (s), 54.95 (s), 41.39 (s), 38.90 (s), 27.37 (s), 26.64 (s), 25.11 (s); ^{19}F NMR (471 MHz, Methanol-d_4) δ −64.07 (s).

Catalyst **Q3**: White solid, m.p. 133–134 °C, yield 91%, $[\alpha]_D^{20} = -185.2°$ (*c* 0.61, $CHCl_3$); ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.59 (d, *J* = 4.7 Hz, 1H), 8.02 (s, 1H), 7.90 (d, *J* = 9.2 Hz, 1H), 7.47 (d, *J* = 4.7 Hz, 1H), 7.38 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.3 Hz, 2H), 6.26 (s, 1H), 5.78–5.67 (m, 1H), 4.99–4.91 (m, 2H), 3.95 (s, 3H), 3.54 (s, 1H), 3.34 (dd, *J* = 17.2, 10.2 Hz, 1H), 3.19 (dd, *J* = 13.7, 10.2 Hz, 1H), 2.80–2.65 (m, 2H), 2.28 (s, 1H), 2.24 (s, 3H), 1.72–1.48 (m, 3H), 1.33 (dd, *J* = 8.2, 5.0 Hz, 1H), 0.83 (dd, *J* = 13.0, 6.4 Hz, 1H); ^{13}C NMR (126 MHz, Methanol-d_4) δ 180.76 (s), 158.22 (s), 146.95 (s), 146.69 (s), 143.80 (s), 141.00 (s), 135.67 (s), 129.88 (s), 128.75 (s), 124.16 (s), 122.40 (s), 120.08 (s), 113.81 (s), 102.92 (s), 60.00 (s), 55.37 (s), 55.18 (s), 55.07 (s), 41.41 (s), 39.22 (s), 27.43 (s), 27.14 (s), 25.49 (s), 19.71 (s).

Catalyst **Q4:** White solid, m.p. 145–147 °C, yield 83%, $[\alpha]_D^{20} = -137.5°$ (*c* 0.80, $CHCl_3$); ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.65 (d, *J* = 4.7 Hz, 1H), 8.06 (s, 1H), 7.92 (d, *J* = 9.2 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.52 (dd, *J* = 11.3, 6.7 Hz, 3H), 7.41 (dd, *J* = 9.2, 2.7 Hz, 1H), 6.31 (d, *J* = 9.9 Hz, 1H), 5.84–5.74 (m, 1H), 5.01–4.94 (m, 2H), 3.99 (s, 3H), 3.53 (s, 1H), 3.35 (dd, *J* = 17.4, 10.2 Hz, 1H), 3.23 (dd, *J* = 13.7, 10.1 Hz, 1H), 2.81–2.71 (m, 2H), 2.31 (s, 1H), 1.67–1.55 (m, 3H), 1.38 (dd, *J* = 13.1, 10.2 Hz, 1H), 0.83 (dd, *J* = 13.5, 6.7 Hz, 1H); ^{13}C NMR (126 MHz, Methanol-d_4) δ 180.82 (s), 158.25 (s), 146.99 (s), 146.62 (s), 143.72 (s), 142.86 (s), 141.06 (s), 129.89 (s), 128.81 (s), 125.47 (q, J_{CF} = 268.38 Hz), 125.37 (s), 124.37 (q, J_{CF} = 32.25 Hz), 122.45 (s), 120.01 (s), 113.83 (s), 109.92 (s), 60.11(s), 55.23 (s), 55.14 (s), 54.66 (s), 41.43 (s), 39.17 (s), 27.37 (s), 27.20 (s), 25.49 (s); ^{19}F NMR (471 MHz, Methanol-d_4) δ −63.22 (s);

Catalyst **Q5**: White solid, m.p.144–145 °C, yield 87%, $[\alpha]_D^{20} = -107.3°$ (*c* 0.51, $CHCl_3$); ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.68 (d, *J* = 4.6 Hz, 1H), 8.10 (s, 3H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.60 (s, 1H), 7.57 (d, *J* = 4.7 Hz, 1H), 7.45 (dd, *J* = 9.2, 2.5 Hz, 1H), 6.37 (d, *J* = 10.4 Hz, 1H), 5.94–5.79 (m, 1H), 5.07–4.95 (m, 2H), 4.03 (s, 3H), 3.61 (s, 1H), 3.42 (dd, *J* = 17.5, 10.1 Hz, 1H), 2.90–2.76 (m, 2H), 2.38 (s, 1H), 1.77–1.61 (m, 3H), 1.47 (dd, *J* = 13.0, 10.4 Hz, 1H), 0.87 (dd, *J* = 12.8, 6.4 Hz, 1H); ^{13}C NMR (126 MHz, Methanol-d_4) δ 181.14 (s), 158.36 (s), 146.93 (s), 146.31 (s), 143.80 (s), 141.72 (s), 141.21 (s), 131.37 (q, J_{CF} = 33.4 Hz), 129.88 (s), 128.85 (s), 123.38 (q, J_{CF} = 271.3 Hz), 122.51 (s), 122.29 (s), 119.85 (s), 116.48 (s), 113.71 (s), 102.80 (s), 60.15 (s), 55.39 (s), 55.19 (s), 41.54 (s), 39.40 (s), 27.45 (s), 27.28 (s), 25.65 (s); ^{19}F NMR (471 MHz, Methanol-d_4) δ −64.39 (s).

Catalyst **Q6**: White solid, m.p.126–128 °C, yield 82%, $[\alpha]_D^{20} = +152.0°$ (*c* 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.64 (d, *J* = 4.4 Hz, 1H), 8.05 (d, *J* = 33.9 Hz, 3H), 7.97–7.83 (m, 1H), 7.61–7.47 (m, 2H), 7.40 (dd, *J* = 9.1, 2.5 Hz, 1H), 6.36 (d, *J* = 10.4 Hz,

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1H), 5.98–5.84 (m, 1H), 5.21–5.10 (m, 1H), 4.00 (s, 3H), 3.29 (s, 1H), 3.03–2.97 (m, 3H), 2.32 (s, 1H), 1.54 (d, J = 40.4 Hz, 4H), 1.23–1.08 (m, 1H), 1.04–0.92 (m, 1H), 0.89 (t, J = 6.9 Hz, 1H); ^{13}C NMR (126 MHz, Methanol-d_4) δ181.30 (s), 158.31 (s), 146.93 (s), 143.79 (s), 141.72 (s), 140.40 (s), 131.36 (q, J_{CF} = 32.8 Hz), 129.84 (s), 124.45 (s), 122.66 (s), 122.32 (d, J = 7.8 Hz), 116.49 (s), 113.96 (s), 102.64 (s), 60.15 (s), 55.14 (d, J = 16.2 Hz), 48.84 (s), 38.83 (s), 27.32 (s), 26.00 (s), 25.15 (s); ^{19}F NMR (471 MHz, Methanol-d_4) δ −64.35 (s).

4.1.2. Procedure for synthesis of chalcones containing pyridine

Referring to the literature[9b] by a modified method, to a solution of 2-acetyl pyridine (20 mmol) and aldehyde (20 mmol) in methanol (60 mL) was added to KOH (20 mmol) and H_2O (2 mL) at ambient temperature. The resulting solution was stirred at room temperature for 12 h. Then H_2O (1000 mL) was added, filtered under reduced the pressure, dried to obtain the crude product. The crude product was purified by column chromatography over silica gel with EtOAc/n-Hexane (1:10) as eluant, affording the chalcones containing pyridine (**1a**~**1m**).

*4.1.2.1. (E)-3-Phenyl-1-(pyridin-2-yl)-prop-2-en-1-one (**1a**).* Yellow solid, m.p. 68–70 °C, yield 72%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.78 (d, J = 5.0 Hz, 1H), 8.24 (dd, J = 16.5, 1.5 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 8.03 (t, J = 7.5 Hz, 1H), 7.83 (d, J = 16.5 Hz, 1H), 7.79 (t, J = 2.5 Hz, 1H), 7.69 (t, J = 6.0 Hz, 1H), 7.45 (t, J = 2.5 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 189.18 (s), 153.94 (s), 149.66 (s), 144.49 (s), 138.19 (s), 135.14 (s), 131.31 (s), 129.58 (s), 129.24 (s), 129.10 (s), 122.99 (s), 121.35 (s).

*4.1.2.2. (E)-3-(2-fluorophenyl)-1-(pyridin-2-yl)-prop-2-en-1-one (**1b**).* Yellow solid, m.p. 76–78 °C, yield 66%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.78 (d, J = 4.0 Hz, 1H), 8.32 (d, J = 16.5 Hz, 1H), 8.09 (d. J = 8.0 Hz, 1H), 8.03 (td, J = 8.0, 1.5 Hz, 1H), 7.90 (td, J = 8.0, 1.5 Hz, 1H), 7.87 (d, J = 16.5 Hz, 1H), 7.69–7.66 (m, 1H), 7.52–7.48 (m, 1H), 7.31 (d, J = 9.0 Hz, 1H), 7.28 (t, J = 7.0 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 189.14 (s), 161.65 (d, J = 250.0 Hz), 153.65 (s), 149.74 (s), 138.29 (s), 136.38 (d, J = 2.5 Hz), 133.26 (d, J = 8.8 Hz), 130.45 (s), 128.30 (s), 125.68 (d, J = 3.8 Hz), 123.78 (d, J = 6.3 Hz), 123.12 (s), 122.82 (d, J = 10.0 Hz), 116.75 (d, J = 21.3 Hz); ^{19}F NMR (471 MHz, DMSO-d_6) δ −114.85.

*4.1.2.3. (E)-3-(2-trifluoromethylphenyl)-1-(pyridin-2-yl)-prop-2-en-1-one (**1c**).* Yellow solid, m.p. 67–68 °C, yield 82%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.77 (d, J = 4.5 Hz, 1H), 8.26 (d, J = 16.0 Hz, 1H), 8.08 (d. J = 7.5 Hz, 2H), 8.05–8.00 (m, 2H, Ar–H), 7.78 (d, J = 8.0 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 7.68–7.66 (m, 1H), 7.62 (t, J = 7.5 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 188.87 (s), 153.45 (s), 149.72 (s), 138.35 (s), 138.29 (s), 133.61 (s), 133.34 (s), 131.08 (s), 128.86 (s), 128.38 (s), 128.12 (q, J = 29.8 Hz), 126.72 (q, J = 6.0 Hz), 125.55 (s), 124.63 (q, J = 273.0 Hz), 123.19 (s); ^{19}F NMR (471 MHz, DMSO-d_6) δ −57.32.

*4.1.2.4. (E)-3-(2-bromophenyl)-1-(pyridin-2-yl)-prop-2-en-1-one (**1d**).* Yellow solid, m.p. 114–116 °C, yield 63%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.77 (d, J = 4.5 Hz, 1H), 8.23 (d, J = 15.0 Hz, 1H), 8.10–7.96 (m, 4H), 7.72–7.66 (m, 2H), 7.45 (t, J = 7.5 Hz, 1H), 7.45 (td, J = 7.5, 1.5 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 188.97 (s), 153.61 (s), 149.73 (s), 141.79 (s), 138.31 (s), 134.44 (s), 133.92 (s), 132.82 (s), 128.96 (s), 128.91 (s), 128.34 (s), 125.98 (s), 124.20 (s), 123.16 (s).

*4.1.2.5. (E)-3-(2-methylphenyl)-1-(pyridin-2-yl)-prop-2-en-1-one (**1e**).* Yellow solid, m.p. 72–74 °C, yield 76%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.78 (d, J = 5.0 Hz, 1H), 8.179 (d, J = 16.0 Hz, 1H), 8.10–8.02 (m, 3H), 7.81 (d, J = 7.5 Hz, 1H), 7.69–7.66 (m, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.27 (t, J = 6.0 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 189.13 (s), 153.90 (s), 149.73 (s), 141.68 (s), 138.73 (s), 133.79 (s), 131.47 (s), 131.13 (s), 128.20 (s), 127.13 (s), 123.05 (s), 122.21 (s), 19.90 (s).

*4.1.2.6. (E)-3-(3-methoxyphenyl)-1-(pyridin-2-yl)-prop-2-en-1-one (**1f**).* Yellow solid, m.p. 57–58 °C, yield 87%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.80 (d, J = 4.0 Hz, 1H), 8.25 (d, J = 16.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.04 (t, J = 7.0 Hz, 1H), 7.82 (d, J = 16.0 Hz, 1H), 7.70–7.67 (m, 1H), 7.38–7.35 (m, 3H), 7.03 (d, J = 7.0 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 189.29 (s), 160.20 (s), 153.93 (s), 149.73 (s), 144.61 (s), 138.30 (s), 136.53 (s), 130.65 (s), 128.20 (s), 123.06 (s), 121.63 (s), 117.48 (s), 114.06 (s).

*4.1.2.7. (E)-3-(3-bromophenyl)-1-(pyridin-2-yl)-prop-2-en-1-one (**1g**).* Yellow solid, m.p. 81–83 °C, yield 78%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.77 (d, J = 5.5 Hz, 1H), 8.24 (d, J = 16.0 Hz, 1H), 8.08–7.98 (m, 3H), 7.80–7.75 (m, 2H), 7.68–7.64 (m, 1H), 7.61 (d, J = 9.0 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 189.18 (s), 153.78 (s), 149.73 (s), 142.73 (s), 138.30 (s), 137.64 (s), 133.76 (s), 131.74 (s), 131.63 (s), 128.28 (s), 128.00 (s), 123.09 (s), 122.95 (s).

*4.1.2.8. (E)-3-(4-chlorophenyl)-1-(pyridin-2-yl)-prop-2-en-1-one (**1h**).* Yellow solid, m.p. 97–99 °C, yield 89%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.76 (d, J = 4.5 Hz, 1H), 8.23 (d, J = 16.5 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 8.02 (td, J = 7.5, 2.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 16.5 Hz, 1H), 7.68–7.64 (m, 1H), 7.48 (d, J = 8.0 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 189.14 (s), 153.79 (s), 149.72 (s), 143.07 (s), 138.32 (s), 135.83 (s), 134.06 (s), 130.98 (s), 129.65 (s), 128.26 (s), 123.06 (s), 122.01 (s).

*4.1.2.9. (E)-3-(4-methoxyphenyl)-1-(pyridin-2-yl)-prop-2-en-1-one (**1i**).* Yellow solid, m.p. 81–83 °C, yield 76%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.78 (d, J = 4.0 Hz, 1H), 8.13 (d, J = 16.0 Hz, 1H), 8.08 (d, J = 7.5 Hz, 1H), 8.02 (td, J = 7.5, 1.5 Hz, 1H), 7.81 (d, J = 16.0 Hz, 1H), 7.76 (d, J = 8.5 Hz, 2H), 7.66 (t, J = 6.0 Hz, 1H), 7.00 (d, J = 8.5 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 189.01 (s), 162.07 (s), 154.19 (s), 149.63 (s), 144.58 (s), 138.19 (s), 131.23 (s), 127.96 (s), 127.77 (s), 122.91 (s), 118.77 (s), 115.11 (s), 55.90 (s).

*4.1.2.10. (E)-3-(4-bromophenyl)-1-(pyridin-2-yl)-prop-2-en-1-one (**1j**).* Yellow solid, m.p. 101–102 °C, yield 68%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.78 (dd, J = 4.0, 1.0 Hz, 1H), 8.26 (d, J = 16.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 8.03 (td, J = 7.5, 1.5 Hz, 1H), 7.80 (d, J = 16.0 Hz, 1H), 7.76 (d, J = 8.5 Hz, 2H), 7.70–7.66 (m, 1H), 7.64 (d, J = 8.0 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 189.17 (s), 153.79 (s), 149.75 (s), 143.20 (s), 138.35 (s), 134.39 (s), 132.60 (s), 131.20 (s), 128.30 (s), 124.75 (s), 123.08 (s), 122.07 (s).

*4.1.2.11. (E)-3-(4-methylphenyl)-1-(pyridin-2-yl)-prop-2-en-1-one (**1k**).* Yellow solid, m.p. 94–95 °C, yield 71%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.78 (dd, J = 4.5, 1.5 Hz, 1H), 8.21 (d, J = 16.0 Hz, 1H), 8.09 (d, J = 7.5 Hz, 1H), 8.03 (td, J = 7.0, 2.0 Hz, 1H), 7.81 (d, J = 16.0 Hz, 1H), 7.70–7.65 (m, 3H), 7.26 (d, J = 8.0 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 189.16 (s), 153.99 (s), 149.68 (s), 144.65 (s), 141.54 (s), 138.27 (s), 132.41 (s), 130.26 (s), 129.33 (s), 128.12 (s), 122.98 (s), 120.22 (s), 21.63 (s).

*4.1.2.12. (E)-3-(furan-2-yl)-1-(pyridin-2-yl)-prop-2-en-1-one (**1l**).* Yellow solid, m.p. 48–50 °C, yield 78%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.25–7.75 (m, 4H), 7.64 (d, J = 18.5 Hz, 2H), 7.09 (s, 1H), 6.68 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 188.73 (s), 153.81 (s), 151.79 (s), 149.72 (s), 147.02 (s), 138.26 (s), 130.77 (s), 128.13 (s), 122.87 (s), 118.27 (s), 118.21 (s), 113.74 (s).

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*4.1.2.13. (E)-3-(thiophen-2-yl)-1-(pyridin-2-yl)-prop-2-en-1-one (**1m**).* Yellow solid, m.p. 73–75 °C, yield 67%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.77 (d, J = 4.5 Hz, 1H), 8.08–7.94 (m, 4H), 7.77 (d, J = 5.0 Hz, 1H), 7.67–7.63 (m, 2H), 7.18 (t, J = 4.5 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 188.55 (s), 153.76 (s), 149.69 (s), 140.59 (s), 138.23 (s), 137.30 (s), 134.26 (s), 131.03 (s), 129.42 (s), 128.13 (s), 122.89 (s), 119.64 (s).

4.1.3. Typical procedure for the preparation of racemic compounds

To the chalcone (0.2 mmol, **1**) and the nitroalkane (2.0 mmol, **2**) in THF (2 mL) were added to NaH (0.4 mmol). Then the mixture was stirred until completion. The products were isolated after filtration and column chromatography.

4.1.4. General procedure for asymmetric synthesis of γ-nitroketones containing pyridine

Chalcones containing pyridine (0.2 mmol, **1**) and nitromethane (2.0 mmol, **2**) was added in capped vials containing the catalyst (0.02 mmol, **Q5**). The resulting reaction mixture was stirred at room temperature. After completion of the reaction as monitored by TLC, the mixture was purified by column chromatography on silica gel (EtOAc/hexane as eluant = 2/1) affording the product (*S*)-**3a**~**3m**. However, the products (*R*)-**3a**~**3m** were obtained using **Q6** catalyst. Enantiomeric excess of the product was determined by chiral stationary phase HPLC analysis using chiral IA column.

*4.1.4.1. (S)-4-Nitro-3-phenyl-1-(pyridin-2-yl)-butan-1-one (**3a**).* White solid, m.p. 72–74 °C, $[\alpha]_D^{20}$ = +39.2° (*c* 0.51, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 (ddd, J = 4.7, 1.6, 0.9 Hz, 1H), 7.96 (td, J = 7.7, 1.7 Hz, 1H), 7.88 (dt, J = 7.9, 1.1 Hz, 1H), 7.64 (ddd, J = 7.5, 4.8, 1.3 Hz, 1H), 7.35 (dt, J = 2.8, 1.8 Hz, 2H), 7.30–7.25 (m, 2H), 7.20 (ddd, J = 7.3, 3.9, 1.3 Hz, 1H), 5.01 (dd, J = 13.0, 5.8 Hz, 1H), 4.92 (dd, J = 13.0, 9.6 Hz, 1H), 4.10–4.02 (m, 1H), 3.80 (dd, J = 18.3, 8.0 Hz, 1H), 3.55 (dd, J = 18.3, 6.3 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 199.11 (s), 152.85 (s), 149.69 (s), 140.61 (s), 138.13 (s), 128.99 (s), 128.50 (s), 128.27 (s), 127.70 (s), 121.88 (s), 80.18 (s), 41.13 (s), 39.57 (s); IR (thin film, cm^{-1}): 3058 (s), 3030 (s), 2919 (s), 1699 (s), 1601 (s), 1582 (s), 1550 (s), 1495 (s), 1453 (s), 1436 (s), 1402 (s), 1387 (s), 1369 (s), 1349 (s), 1327 (s), 1299 (s), 1220 (s), 1200 (s), 996 (s), 977 (s), 776 (s), 763 (s); HRMS (ES) *m*/*z* for $C_{15}H_{14}N_2O_3$ $[M+H]^+$ cacld. 271.1077, found. 271.1071; Elemental analysis for $C_{15}H_{14}N_2O_3$: calcd. C 66.66, H 5.22, N 10.36; found C 66.50, H 4.95, N 10.41. HPLC analysis: IA, hexane: EtOH = 95%:5%, 1.0 mL/min, 20 °C, 254 nm, t_R = 23.263 min (major, *S*), 28.035 min (minor, *R*).

*4.1.4.2. (S)-4-Nitro-3-(2-fluorophenyl)-1-(pyridin-2-yl)-butan-1-one (**3b**).* White solid, m.p. 76–77 °C, $[\alpha]_D^{20}$ = +26.3° (*c* 0.48, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.71 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 7.97 (td, J = 7.7, 1.7 Hz, 1H), 7.88 (dt, J = 7.8, 1.1 Hz, 1H), 7.65 (ddd, J = 7.5, 4.7, 1.2 Hz, 1H), 7.48 (td, J = 7.6, 1.6 Hz, 1H), 7.31–7.21 (m, 1H), 7.18–7.05 (m, 2H), 5.01 (dd, J = 13.1, 5.8 Hz, 1H), 4.92 (dd, J = 13.1, 9.4 Hz, 1H), 4.41–4.29 (m, 1H), 3.78 (dd, J = 18.3, 8.1 Hz, 1H), 3.63 (dd, J = 18.3, 6.2 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 198.85 (s), 161.78 (s), 159.83 (s), 152.75 (s), 149.70 (d, J = 22.6 Hz), 138.12 (d, J = 3.5 Hz), 129.70 (d, J = 23.9 Hz), 128.53 (d, J = 66.5 Hz), 127.28 (d, J = 14.3 Hz), 125.12 (d, J = 35.8 Hz), 121.89 (s), 116.01 (dd, J = 36.9, 21.4 Hz), 79.17 (t, J = 38.3 Hz), 40.44 (s), 32.85 (d, J = 16.8 Hz); ^{19}F NMR (487 MHz, DMSO-d_6) δ −117.36; IR (thin film, cm^{-1}): 3060 (s), 2991 (s), 2910 (s), 1691 (s), 1614 (s), 1580 (s), 1543 (s), 1490 (s), 1435 (s), 1384 (s), 1369 (s), 1330 (s), 1218 (s), 1106 (s), 1003 (s), 984 (s), 844 (s), 769 (s); HRMS (ES) *m*/*z* for $C_{15}H_{13}FN_2O_3$ $[M+H]^+$ cacld. 289.0983, found. 289.0974; Elemental analysis for $C_{15}H_{13}FN_2O_3$: calcd. C 62.50, H 4.55, N 9.72; found C 62.25, H 4.23, N 9.78; HPLC analysis: IA, hexane: EtOH = 95%:5%, 1.0 mL/min, 20 °C, 254 nm, t_R = 17.274 min (major, *S*), 18.969 min (minor, *R*).

*4.1.4.3. (S)-4-Nitro-3-(2-bromophenyl)-1-(pyridin-2-yl)-butan-1-one (**3d**).* White solid, m.p. 23–25 °C, $[\alpha]_D^{20}$ = +30.8° (*c* 0.63, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 (d, J = 4.1 Hz, 1H), 7.99–7.92 (m, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.63 (ddd, J = 7.4, 4.8, 1.4 Hz, 1H), 7.58 (dd, J = 8.0, 1.3 Hz, 2H), 7.33 (td, J = 7.6, 1.2 Hz, 1H), 7.19–7.10 (m, 1H), 5.00 (d, J = 7.4 Hz, 2H), 4.62–4.57 (m, 1H), 3.72 (qd, J = 18.4, 7.1 Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 198.80 (s), 152.70 (s), 149.66 (s), 139.44 (s), 138.07 (s), 133.47 (s), 129.60 (s), 128.88 (s), 128.61 (s), 128.51 (s), 124.83 (s), 121.91 (s), 78.80 (s), 40.67 (s), 38.20 (s); IR (thin film, cm^{-1}): 3060 (s), 2916 (s), 1693 (s), 1583 (s), 1551 (s), 1472 (s), 1437 (s), 1377 (s), 1024 (s), 996 (s), 759 (s); HRMS (ES) *m*/*z* for $C_{15}H_{13}BrN_2O_3$ $[M+H]^+$ cacld. 349.0182, found. 349.0176; Elemental analysis for $C_{15}H_{13}BrN_2O_3$: calcd. C 51.60, H 3.75, N 8.02; found C 51.41, H 3.89, N 8.22; HPLC analysis: IA, hexane: EtOH = 85%:15%, 1.0 mL/min, 20 °C, 254 nm, t_R = 17.644 min (major, *S*), 19.492 min (minor, *R*).

*4.1.4.4. (S)-4-Nitro-3-(2-methylphenyl)-1-(pyridin-2-yl)-butan-1-one (**3e**).* White solid, m.p. 76–77 °C, $[\alpha]_D^{20}$ = +48.9° (*c* 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 (d, J = 4.7 Hz, 1H), 7.96 (td, J = 7.7, 1.7 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.64 (ddd, J = 7.5, 4.7, 1.2 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.16–7.03 (m, 3H), 4.98 (dd, J = 13.1, 6.3 Hz, 1H), 4.91 (dd, J = 13.1, 9.2 Hz, 1H), 4.40–4.31 (m, 1H), 3.81 (dd, J = 18.1, 8.1 Hz, 1H), 3.50 (dd, J = 18.2, 6.1 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 199.32 (s), 152.82 (s), 149.69 (s), 139.00 (s), 138.15 (s), 136.72 (s), 130.85 (s), 128.52 (s), 127.33 (s), 126.80 (s), 126.58 (s), 121.90 (s), 79.88 (s), 41.51 (s), 34.43 (s), 19.67 (s); IR (thin film, cm^{-1}): 3055 (s), 3011 (s), 1699 (s), 1580 (s), 1550 (s), 1466 (s), 1437 (s), 1404 (s), 1376 (s), 1404 (s), 1376 (s), 1357 (s), 1276 (s), 1222 (s), 1043 (s), 995 (s), 775 (s); HRMS (ES) *m*/*z* for $C_{16}H_{16}N_2O_3$ $[M+H]^+$ cacld. 285.1234, found. 285.1228; Elemental analysis for $C_{16}H_{16}N_2O_3$: calcd. C 67.59, H 5.67, N 9.85; found C 67.64, H 5.51, N 10.05; HPLC analysis: IA, hexane: EtOH = 85%:15%, 1.0 mL/min, 20 °C, 254 nm, t_R = 9.374 min (major, *S*), 11.577 min (minor, *R*).

*4.1.4.5. (S)-4-Nitro-3-(3-methoxyphenyl)-1-(pyridin-2-yl)-butan-1-one (**3f**).* White solid, m.p. 113–115 °C, $[\alpha]_D^{20}$ = +35.3° (*c* 0.51, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.71 (d, J = 3.9 Hz, 1H), 7.97 (td, J = 7.7, 1.7 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.65 (ddd, J = 7.5, 4.8, 1.3 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 6.93 (t, J = 2.0 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 6.77 (ddd, J = 8.3, 2.6, 0.8 Hz, 1H), 4.99 (dd, J = 13.0, 5.9 Hz, 1H), 4.92 (dd, J = 13.0, 9.4 Hz, 1H), 4.06–3.98 (m, 1H), 3.79 (dd, J = 18.3, 7.9 Hz, 1H), 3.70 (s, 3H), 3.52 (dd, J = 18.3, 6.4 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 199.13 (s), 159.75 (s), 152.87 (s), 149.71 (s), 142.19 (s), 138.16 (s), 130.03 (s), 128.52 (s), 121.91 (s), 120.47 (s), 114.14 (s), 112.86 (s), 80.05 (s), 55.48 (s), 41.06 (s), 39.55 (s); IR (thin film, cm^{-1}): 3040 (s), 3020 (s), 1693 (s), 1609 (s), 1581 (s), 1547 (s), 1489 (s), 1456 (s), 1437 (s), 1404 (s), 1363 (s), 1292 (s), 1275 (s), 1246 (s), 1219 (s), 1157 (s), 1048 (s), 995 (s), 868 (s), 791 (s), 777 (s); HRMS (ES) *m*/*z* for $C_{16}H_{16}N_2O_4$ $[M+H]^+$ cacld. 301.1183, found. 301.1175; Elemental analysis for $C_{16}H_{16}N_2O_4$: calcd. C 63.99, H 5.37, N 9.33; found C 63.82, H 5.11, N 9.37; HPLC analysis: IA, hexane: EtOH = 90%:10%, 1.0 mL/min, 20 °C, 254 nm, t_R = 21.313 min (major, *S*), 24.080 min (minor, *R*).

*4.1.4.6. (S)-4-Nitro-3-(3-bromophenyl)-1-(pyridin-2-yl)-butan-1-one (**3g**).* White solid, m.p. 59–61 °C, $[\alpha]_D^{20}$ = +24.5° (*c* = 0.49, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 (d, J = 4.0 Hz, 1H), 7.97 (td, J = 7.7, 1.7 Hz, 1H), 7.89 (dt, J = 7.9, 1.1 Hz, 1H), 7.69–7.61 (m, 2H), 7.42–7.35 (m, 2H), 7.24 (t, J = 7.8 Hz, 1H), 5.03 (dd, J = 13.2, 5.8 Hz, 1H), 4.96 (dd, J = 13.2, 9.5 Hz, 1H), 4.07–4.01 (m, 1H), 3.80 (dd, J = 18.5, 8.1 Hz, 1H), 3.57 (dd, J = 18.5, 6.1 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 198.93 (s), 152.76 (s), 149.69 (s), 143.50 (s), 138.15 (s), 131.09 (s), 130.65 (s), 128.56 (s), 127.62 (s), 122.24 (s),

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121.89 (s), 79.74 (s), 40.98 (s), 39.22 (s); IR (thin film, cm^{-1}): 3061 (s), 3028 (s), 1697 (s), 1596 (s), 1580 (s), 1565 (s), 1546 (s), 1465 (s), 1435 (s), 1384 (s), 1363 (s), 1277 (s), 1221 (s), 1193 (s), 1066 (s), 995 (s), 792 (s), 773 (s); HRMS (ES) *m/z* for $C_{15}H_{13}BrN_2O_3$ $[M+H]^+$ cacld. 349.0182, found. 349.0176; Elemental analysis for $C_{15}H_{13}BrN_2O_3$: calcd. C 51.60, H 3.75, N 8.02; found C 51.68, H 3.57, N 8.21; HPLC analysis: IA, hexane: EtOH = 85%:15%, 1.0 mL/min, 20 °C, 254 nm, t_R = 23.449 min (major, *S*), 25.525 min (minor, *R*).

*4.1.4.7. (S)-4-Nitro-3-(4-chlorophenyl)-1-(pyridin-2-yl)-butan-1-one (**3h**).* White solid, m.p. 68–69 °C, $[\alpha]_D^{20}$ = +36.7° (*c* = 0.45, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6) δ 8.70 (d, *J* = 4.0 Hz, 1H), 7.96 (td, *J* = 7.5, 1.5 Hz, 1H), 7.88 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.65 (ddd, *J* = 7.5, 4.7, 1.3 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 5.02 (dd, *J* = 13.1, 5.7 Hz, 1H), 4.93 (dd, *J* = 13.1, 9.7 Hz, 1H), 4.09–4.01 (m, 1H), 3.79 (dd, *J* = 18.4, 8.2 Hz, 1H), 3.56 (dd, *J* = 18.4, 6.1 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 198.97 (s), 152.78 (s), 149.69 (s), 139.67 (s), 138.14 (s), 132.32 (s), 130.28 (s), 128.93 (s), 128.54 (s), 121.88 (s), 79.93 (s), 40.99 (s), 38.99 (s); IR (thin film, cm^{-1}): 3060 (s), 1699 (s), 1583 (s), 1546 (s), 1487 (s), 1438 (s), 1382 (s), 1367 (s), 1221 (s), 1091 (s), 1011 (s), 996 (s), 976 (s), 821 (s), 774 (s); HRMS (ES) *m/z* for $C_{15}H_{13}ClN_2O_3$ $[M+H]^+$ cacld. 305.0688, found. 305.0682; Elemental analysis for $C_{15}H_{13}ClN_2O_3$: calcd. C 59.12, H 4.30, N 9.19; found C 58.93, H 4.11, N 9.32; HPLC analysis: IA, hexane: EtOH = 85%:15%, 1.0 mL/min, 20 °C, 254 nm, t_R = 21.187 min (major, *S*), 24.255 min (minor, *R*).

*4.1.4.8. (S)-4-Nitro-3-(4-methoxyphenyl)-1-(pyridin-2-yl)-butan-1-one (**3i**).* White solid, m.p. 68–69 °C, $[\alpha]_D^{20}$ = +35.5° (*c* 0.51, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6) δ 8.70 (d, *J* = 4.0 Hz, 1H), 7.96 (td, *J* = 7.7, 1.7 Hz, 1H), 7.88 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.64 (ddd, *J* = 7.6, 4.8, 1.3 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 4.97 (dd, *J* = 12.8, 5.8 Hz, 1H), 4.86 (dd, *J* = 12.8, 9.7 Hz, 1H), 4.04–3.96 (m, 1H), 3.77 (dd, *J* = 18.2, 8.1 Hz, 1H), 3.68 (s, 3H), 3.50 (dd, *J* = 18.2, 6.2 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 199.22 (s), 158.79 (s), 152.89 (s), 149.71 (s), 138.15 (s), 132.32 (s), 129.35 (s), 128.50 (s), 121.89 (s), 114.34 (s), 80.45 (s), 55.46 (s), 41.22 (s), 38.92 (s); IR (thin film, cm^{-1}): 3015 (s), 1691 (s), 1610 (s), 1580 (s), 1546 (s), 1516 (s), 1437 (s), 1396 (s), 1375 (s), 1249 (s), 1230 (s), 1181 (s), 1113 (s), 1024 (s), 995 (s), 827 (s), 780 (s), 762 (s); HRMS (ES) *m/z* for $C_{16}H_{16}N_2O_4$ $[M+H]^+$ cacld. 301.1183, found. 301.1176; Elemental analysis for $C_{16}H_{16}N_2O_4$: calcd. C 63.99, H 5.37, N 9.33; found C 64.14, H 5.23, N 9.54; HPLC analysis: IA, hexane: EtOH = 85%:15%, 1.0 mL/min, 20 °C, 254 nm, t_R = 27.259 min (major, *S*), 37.695 min (minor, *R*).

*4.1.4.9. (S)-4-Nitro-3-(4-bromophenyl)-1-(pyridin-2-yl)-butan-1-one (**3j**).* White solid, m.p. 101–102 °C, $[\alpha]_D^{20}$ = +32.3° (*c* 0.33, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6) δ 8.70 (d, *J* = 4.1 Hz, 1H), 7.97 (td, *J* = 7.7, 1.7 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.65 (ddd, *J* = 7.5, 4.7, 1.2 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 5.02 (dd, *J* = 13.1, 5.7 Hz, 1H), 4.92 (dd, *J* = 13.1, 9.6 Hz, 1H), 4.10–3.98 (m, 1H), 3.79 (dd, *J* = 18.4, 8.2 Hz, 1H), 3.56 (dd, *J* = 18.4, 6.0 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 198.93 (s), 152.77 (s), 149.67 (s), 140.08 (s), 138.12 (s), 131.82 (s), 130.61 (s), 128.51 (s), 121.85 (s), 120.83 (s), 79.84 (s), 40.90 (s), 39.02 (s); IR (thin film, cm^{-1}): 3062 (s), 1698 (s), 1583 (s), 1546 (s), 1484 (s), 1437 (s), 1398 (s), 1383 (s), 1366 (s), 1302 (s), 1286 (s), 1221 (s), 1008 (s), 997 (s), 976 (s), 821 (s), 774 (s); HRMS (ES) *m/z* for $C_{15}H_{13}BrN_2O_3$ $[M+H]^+$ cacld. 349.0182, found. 349.0176; Elemental analysis for $C_{15}H_{13}BrN_2O_3$: calcd. C 51.60, H 3.75, N 8.02; found C 51.52, H 3.58, N 8.20; HPLC analysis: IA, hexane: EtOH = 85%:15%, 1.0 mL/min, 20 °C, 254 nm, t_R = 24.386 min (major, *S*), 29.186 min (minor, *R*).

*4.1.4.10. (S)-4-Nitro-3-(4-methylphenyl)-1-(pyridin-2-yl)-butan-1-one (**3k**).* White solid, m.p. 59–61 °C, $[\alpha]_D^{20}$ = +30.7° (*c* 0.45, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6) δ 8.70 (d, *J* = 3.9 Hz, 1H), 7.96 (td, *J* = 7.7, 1.8 Hz, 1H), 7.88 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.64 (ddd, *J* = 7.5, 4.7, 1.3 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 4.98 (dd, *J* = 12.9, 5.8 Hz, 1H), 4.88 (dd, *J* = 12.9, 9.6 Hz, 1H), 4.05–3.98 (m, 1H), 3.77 (dd, *J* = 18.2, 8.1 Hz, 1H), 3.51 (dd, *J* = 18.2, 6.2 Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 199.17 (s), 152.89 (s), 149.71 (s), 138.15 (s), 137.52 (s), 136.83 (s), 129.58 (s), 128.52 (s), 128.16 (s), 121.91 (s), 80.33 (s), 41.15 (s), 39.26 (s), 21.12 (s); IR (thin film, cm^{-1}): 3058 (s), 1696 (s), 1582 (s), 1546 (s), 1520 (s), 1437 (s), 1376 (s), 1230 (s), 995 (s), 816 (s), 761 (s); HRMS (ES) *m/z* for $C_{16}H_{16}N_2O_3$ $[M+H]^+$ cacld. 285.1234, found. 285.1227; Elemental analysis for $C_{16}H_{16}N_2O_3$: calcd. C 67.59, H 5.67, N 10.05; found C 67.54, H 5.54, N 9.96; HPLC analysis: IA, *n*-Hexane: *i*-PrOH = 90%:10%, 1.0 mL/min, 20 °C, 254 nm, t_R = 27.825 min (major, *S*), 30.634 min (minor, *R*).

*4.1.4.11. (S)-4-Nitro-3-(furan-2-yl)-1-(pyridin-2-yl)-butan-1-one (**3l**).* White solid, m.p. 60–62 °C, $[\alpha]_D^{20}$ = +19.1° (*c* 0.37, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6) δ 8.73 (d, *J* = 4.7 Hz, 1H), 8.00 (td, *J* = 7.6, 1.7 Hz, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.67 (ddd, *J* = 7.4, 4.7, 1.3 Hz, 1H), 7.53 (d, *J* = 1.8 Hz, 1H), 6.33 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.21 (d, *J* = 3.2 Hz, 1H), 4.95 (dd, *J* = 13.1, 5.4 Hz, 1H), 4.86 (dd, *J* = 13.1, 8.5 Hz, 1H), 4.23–4.16 (m, 1H), 3.80 (dd, *J* = 18.3, 7.6 Hz, 1H), 3.55 (dd, *J* = 18.3, 6.3 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 198.78 (s), 153.59 (s), 152.77 (s), 149.77 (s), 142.88 (s), 138.20(s), 128.61 (s), 122.00 (s), 111.02 (s), 107.00 (s), 78.36 (s), 38.77 (s), 33.22 (s); IR (thin film, cm^{-1}): 3058 (s), 1702 (s), 1583 (s), 1553 (s), 1501 (s), 1437 (s), 1380 (s), 1290 (s), 1215 (s), 1186 (s), 1135 (s), 1071 (s), 1014 (s), 988 (s), 913 (s), 806 (s), 775 (s), 754 (s); HRMS (ES) *m/z* for $C_{13}H_{12}N_2O_4$ $[M+H]^+$ cacld. 261.0870, found. 261.0863; Elemental analysis for $C_{13}H_{12}N_2O_4$: calcd. C 60.00, H 4.65, N 10.76; found C 60.20, H 4.41, N 10.91; HPLC analysis: IA, *n*-Hexane: EtOH = 85%:15%, 1.0 mL/min, 20 °C, 254 nm, t_R = 16.986 min (major, *S*), 40.015 min (minor, *R*).

*4.1.4.12. (S)-4-Nitro-3-(thiophene-2-yl)-1-(pyridin-2-yl)-butan-1-one (**3m**).* White solid, m.p. 61–63 °C, $[\alpha]_D^{20}$ = +30.7° (*c* 0.45, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6) δ 8.72 (d, *J* = 4.3 Hz, 1H), 7.99 (td, *J* = 7.7, 1.7 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.67 (ddd, *J* = 7.4, 4.8, 1.3 Hz, 1H), 7.35 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.01 (d, *J* = 3.4 Hz, 1H), 6.92 (dd, *J* = 5.1, 3.5 Hz, 1H), 5.02 (dd, *J* = 13.1, 5.4 Hz, 1H), 4.89 (dd, *J* = 13.1, 9.2 Hz, 1H), 4.40–4.34 (m, 1H), 3.86 (dd, *J* = 18.3, 8.0 Hz, 1H), 3.59 (dd, *J* = 18.3, 6.0 Hz, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 198.75 (s), 152.78 (s), 149.77 (s), 143.25 (s), 138.21 (s), 128.63 (s), 127.50 (s), 125.83 (s), 125.32 (s), 122.00 (s), 80.71 (s), 41.89 (s), 34.73 (s); IR (thin film, cm^{-1}): 3056 (s), 1697 (s), 1582 (s), 1546 (s), 1438 (s), 1377 (s), 1226 (s), 1136 (s), 1003 (s), 994 (s), 853 (s), 841 (s), 763 (s); HRMS (ES) *m/z* for $C_{13}H_{12}N_2O_3S$ $[M+H]^+$ cacld. 277.0641, found. 277.0635; Elemental analysis for $C_{13}H_{12}N_2O_3S$: calcd. C 56.51, H 4.38, N 10.14; found C 56.54, H 4.18, N 10.36; HPLC analysis: IA, *n*-Hexane: EtOH = 85%:15%, 1.0 mL/min, 20 °C, 254 nm, t_R = 17.265 min (major, *S*), 26.148 min (minor, *R*).

4.2. Biological assays

The antibacterial activities against rice bacterial leaf blight of chiral products from our reactions were evaluated via the turbid meter test according to the reported method.[29] The chiral compounds were dissolved in 150 μL of DMF and diluted with water containing Tween-20 (0.1%) to obtain final concentrations of 200 and 100 μg/mL respectively. DMF in sterile distilled water served as a blank control, whereas bismerthiazol served as a positive control. Then, approximately 40 μL NB containing rice bacterial leaf blight was added to 4 mL NB (1.5 g of beef extract, 2.5 g of peptone, 0.5 g of yeast powder, 5.0 g of glucose, and 500 mL of distilled water, pH 7.0 to 7.2) containing the test compounds or thiodiazole-copper (1 mL).

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The inoculated test tubes were incubated at 30 ± 1 °C with continuous shaking at 180 rpm until OD_{600} of a blank control was monitored to 0.6–0.8 with a spectrophotometer. Accordingly, the relative inhibitory rate (%) of testing compounds was calculated as follows: $(OD_{control} - OD_{sample})/OD_{control} \times 100$; $OD_{control}$ is the corrected turbidity value of bacterial growth of a blank control), and OD_{sample} is the corrected turbidity value of bacterial growth of testing compounds.

4.3. Computer calculation

Structural optimizations and subsequent frequency calculations for all systems were performed using the B3LYP[30] hybrid functional in combination with the all-electron 6-31G(d) basis set[31] for all atoms implemented in the Gaussian 09 package.[32] Computational data for optimized structures **Cat**, **El**, **Nu, Cat-El** and **Cat-Nu** at the B3LYP/6-31G(d) level was shown in Table 1 in support information. The binding energy of **Cat-El** is defined as $E_{Cat\text{-}Ei} = E_{Cat\text{-}El}\text{-}E_{Cat}\text{-}E_{El}$; The binding energy of **Cat**–**Nu** is defined as $E_{Cat\text{-}Nu} = E_{Cat\text{-}Nu}\text{ -}E_{Cat}\text{-}E_{Nu}$.

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra for all products. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.11.063. These data include MOL files and InChiKeys of the most important compounds described in this article.

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