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Enantioselective conjugate hydrosilylation of α,β-unsaturated ketones†

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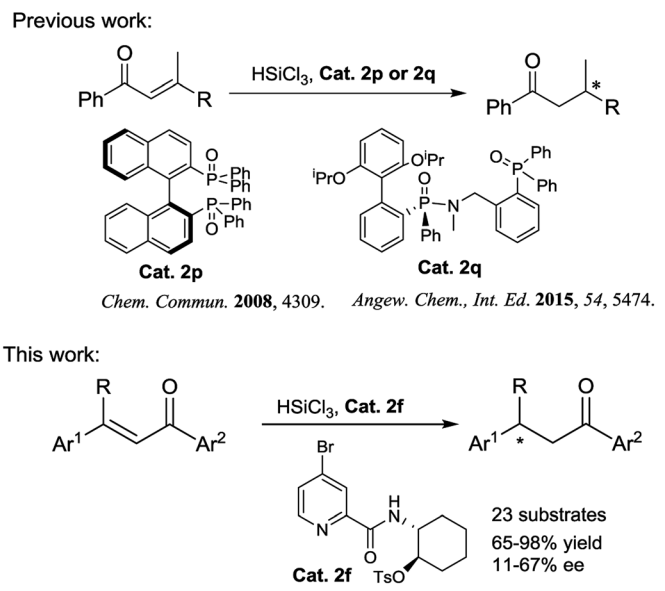
Enantioselective conjugate hydrosilylation of β,β-disubstituted α,β-unsaturated ketones was realized. In the presence of a chiral picolinamide–sulfonate Lewis base catalyst, the reactions provided various chiral ketones bearing a chiral center at the β-position in up to quantitative yields with moderate enantioselectivities.

Chiral ketones are important intermediates for the synthesis of natural products or chiral drugs, and some themselves are useful chiral drugs.[1] Asymmetric conjugate reduction of α,β-unsaturated carbonyl compounds is an attractive and challenging transformation for the construction of chiral ketones. During the past few decades, many groups have devoted considerable efforts to this area and made great improvement, for instance, transition metal catalyzed asymmetric hydrogenation of α,β-unsaturated carbonyl compounds, including palladium,[2] iridium,[3] copper,[4] ruthenium,[5] rhodium[6] and cobalt.[7] Besides, some organocatalyzed asymmetric conjugate transfer hydrogenations using Hantzsch ester[8] or pinacolborane[9] as the hydride source have also been reported. However, very few examples about chiral Lewis base catalyzed conjugate hydrosilylation of α,β-unsaturated carbonyl compounds have been reported and only chiral phosphine oxide Lewis base catalysts were used in these reactions (Scheme 1).[10] Therefore, exploration of the application of other kinds of chiral Lewis base catalysts in this reaction is still highly desirable.

Recently, we developed a kind of easily accessible chiral picolinamide–sulfonate Lewis base catalysts and used them in asymmetric hydrosilylation of α-acyloxy-β-enamino esters,[11] one of them exhibiting excellent reactivity, diastereoselectivity and enantioselectivity. Herein we present the enantioselective conjugate hydrosilylation of β,β-disubstituted α,β-unsaturated ketones using this kind of Lewis base as catalysts, leading to various chiral ketones bearing a chiral center at β-position (Fig. 1).

First, various chiral Lewis base catalysts **2** were screened in the enantioselective hydrosilylation of (*E*)-1,3-diphenylbut-2-en-1-one **1a** in acetonitrile at 0 °C. As shown in Fig. 2, L-piperazine-2-carboxylic acid derived *N*-formamide **2a**,[12a] *R*-(+)-*tert*-butylsulfinamide derived catalyst **2b**[12b] and picolinamide **2c**[12c] were found to be totally inactive for the reaction. Meanwhile picolinamide–tosylate catalyst **2d** was highly active to afford the product with excellent yield in moderate ee value. Afterwards, several picolinamide–tosylate catalysts **2f–2h** bearing electron-withdrawing group in 4-position of pyridine were employed in the reaction and 4-bromo picolinamide **2f** delivered a slightly higher ee value. 5-Methoxy picolinamide **2i** gave the product with the same ee value as that of **2d** but in much lower yield. Lower enantioselectivities were observed with 4-phenyl picolinamide **2j** and 3-methyl picolinamide **2k**. When (*R*)-1-(2-



Scheme 1 Enantioselective conjugate hydrosilylation of α,β-unsaturated ketones by chiral Lewis base catalysts.

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aminonaphthalen-1-yl)naphthalen-2-ol derived catalyst **2l** was used, no product was observed. When (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol derived catalyst **2m** gave the product in both poor yield and ee value. Moreover, two picolinamide–sulfonamide catalysts **2n** and **2o** were also used in the reaction and almost racemic products were obtained. Hence, **2f** was determined as the optimal catalyst and was used through out our study.

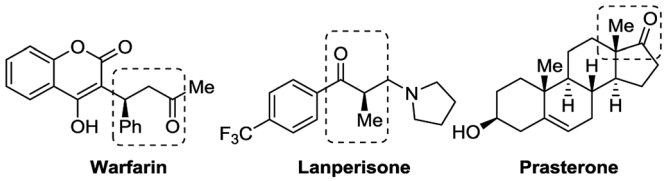


Fig. 1 Three typical chiral drugs containing chiral ketone moiety.

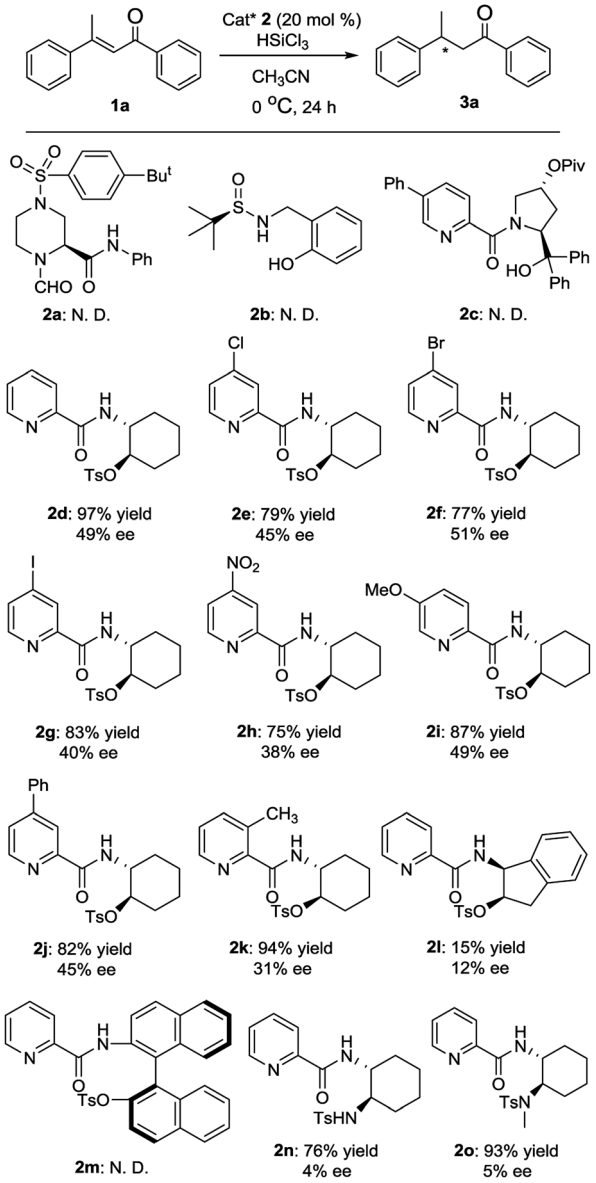
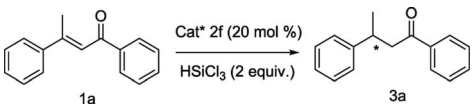


Fig. 2 Evaluation of the chiral Lewis base catalysts **2** in conjugate hydrosilylation of (*E*)-1,3-diphenylbut-2-en-1-one **1a**. Unless otherwise specified, the reactions were carried out with **1a** (0.1 mmol), trichlorosilane (0.2 mmol) and catalyst 2 (0.02 mmol) in 1 mL of acetonitrile at 0 °C for 24 hours. Isolated yield based on **1a**. The ee values were determined by using chiral HPLC.

Subsequently, the other reaction conditions were optimized. The results are summarized in Table 1. First, various solvents were evaluated. Surprisingly, reactions in some polar solvents generated R-products (Table 1, entries 1–4), while S-products were obtained in some non-polar solvents (Table 1, entries 6, 9, 10 and 13) with the exception of 1,2-dichloroethane (Table 1, entry 7). Reaction in toluene delivered the product in excellent yield with the best ee value (Table 1, entry 10). However, no product was detected in xylene or mesitylene (Table 1, entries 11 and 12). Hence, toluene was determined as the optimal solvent for the reaction. In order to improve the enantioselection, we tried to perform the reaction at lower temperatures. Lowering the temperature to −10 °C led to an increased ee value (Table 1, entry 14). However, further lowering the temperature to −20 and −40 °C did not provide better results (Table 1, entries 15 and 16). Therefore, −10 °C was determined as the optimal temperature for the reaction.

With the optimized conditions in hand, the scope and limitations of the reaction were explored. The results are summarized in Fig. 3. In the presence of 20 mol% of chiral Lewis base catalyst **2f** and 2 equivalents of trichlorosilane, various α,β-unsaturated ketones were hydrosilylated. We first tested the effect of various 3-aryl groups of **1**. 3-(4-Methoxyphenyl) substrate **3e** (Fig. 3) and 3-(naphthalen-2-yl) substrate **3i** (Fig. 3) underwent the reaction to give the products with good

Table 1 Optimization of the reaction[a]



Entry[a]	Solvent	T (°C)	Time [h]	Yield[b] [%]	ee[c,d] [%]
1	CH_3CN	0	24	77	51 (*R*)
2	CH_3CH_2CN	0	24	84	50 (*R*)
3	C_6H_5CN	0	24	83	24 (*R*)
4	THF	0	24	92	11 (*R*)
5	1,4-Dioxane	0	24	63	5 (*R*)
6	$CHCl_3$	0	24	92	25 (*S*)
7	CH_2Cl_2	0	24	96	3
8	$ClCH_2CH_2Cl$	0	24	90	10 (*R*)
9	CCl_4	0	24	95	35 (*S*)
10	Toluene	0	24	95	55 (*S*)
11	Xylene	0	24	N.R.	—
12	Mesitylene	0	24	N.R.	—
13	$C_6H_5CF_3$	0	24	95	31 (*S*)
14	Toluene	−10	48	97	64 (*S*)
15	Toluene	−20	60	92	65 (*S*)
16	Toluene	−40	72	N.R.	—

[a] Unless otherwise specified, the reactions were carried out with **1a** (0.1 mmol), trichlorosilane (0.2 mmol) and catalyst **2f** (0.02 mmol) in 1 mL of solvent. [b] Isolated yield based on **1a**. [c] The ee values were determined by using chiral HPLC. [d] The absolute configuration of **3a** was determined by comparison of the retention times of the two enantiomers on the stationary phase with those in the literatures.

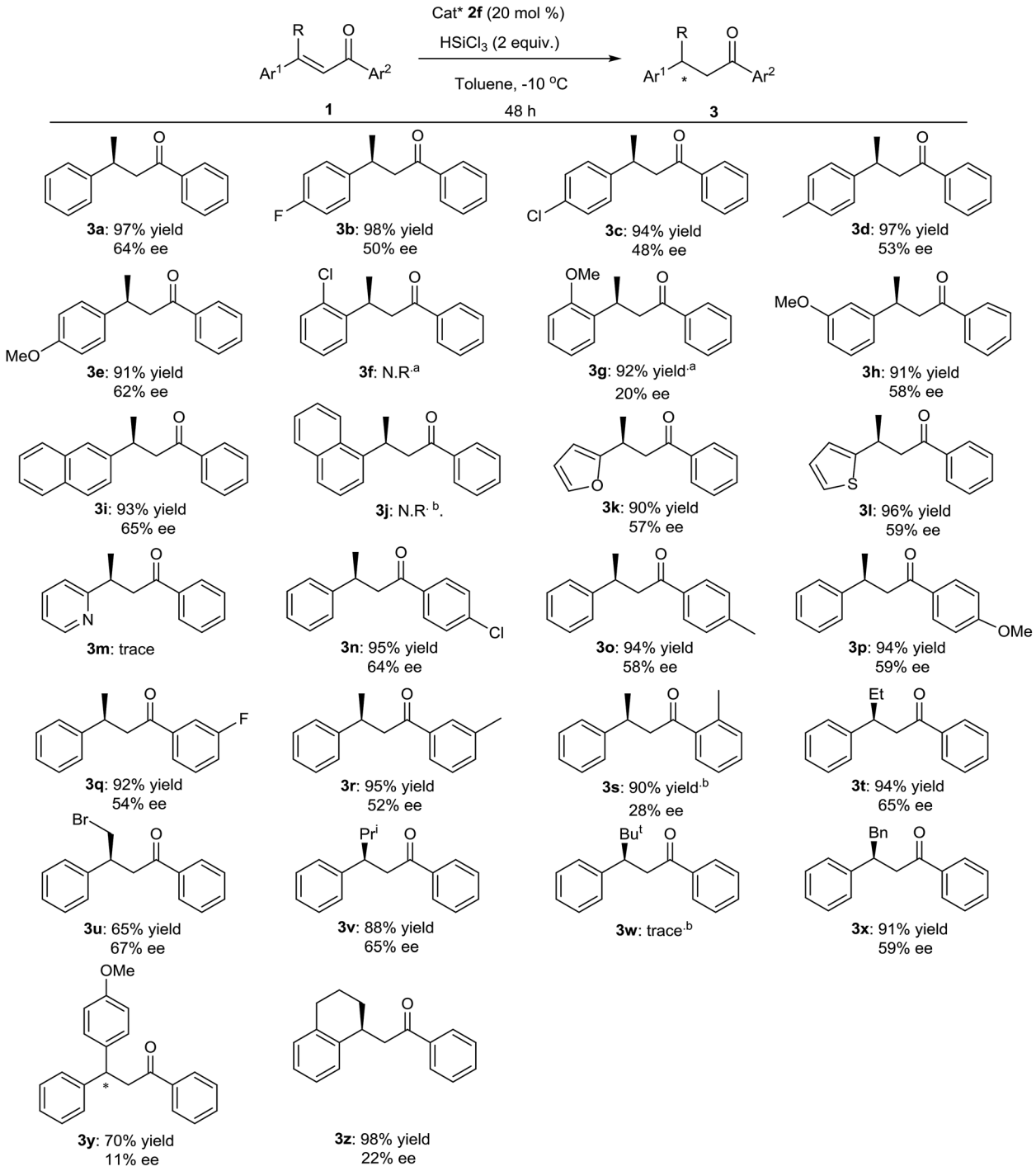


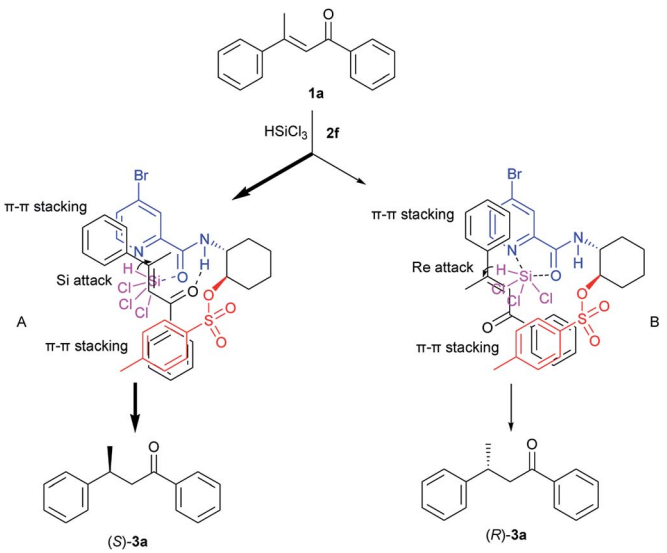
Fig. 3 Substrate scope of the reaction. Unless otherwise specified, the reactions were carried out with **1** (0.1 mmol), trichlorosilane (0.2 mmol) and catalyst **2f** (0.02 mmol) in 1 mL of toluene at −10 °C for 48 hours. Isolated yield based on **1**. The ee values were determined by using chiral HPLC. The absolute configuration of **3a** was determined by comparison of the retention times of the two enantiomers on the stationary phase with the literatures. The absolute configurations of other products were determined in analogy. [a]The reaction time was 60 hours. [b]The reaction time was 72 hours.

yields in enantioselectivities close to **3a**, while lower ee values were observed with **3b–3d**, **3h**, **3k** and **3l** (Fig. 3). No product was obtained with 3-(2-chloro-phenyl) substrate **3f** and 3-(naphthalen-1-yl) substrate **3j**, perhaps due to the high steric hindrance (Fig. 3). When 3-(2-methoxy-phenyl) substrate **3g** was used, by prolonging the reaction time to 60 hours, the product was obtained with good yield but very poor enantioselection (Fig. 3). Trace amount of the product was detected with 3-(pyridin-2-yl) substrate **3m** (Fig. 3). Next, some 3-phenyl-but-2-en-1-ones with different 1-aryl groups were also employed in the reaction. The 4-substituted or 3-substituted substrates delivered good yields of the products with similar or slightly

lower enantioselectivities (Fig. 3), while much lower ee value was observed with 2-substituted substrate **3s** (Fig. 3). For some other 3-alkyl chalcones, moderate to good yields and moderate ee values were obtained (Fig. 3), except for the bulkier tertiary butyl substituted **3w** that gave trace amount of the product (Fig. 3). Reaction of **3y** with two different 3,3-aryl groups afforded the product with moderate yield in very low enantioselectivity (Fig. 3). Finally, cyclic substrate **3z** was subjected in the reaction and provided the product with excellent yield but in poor ee value (Fig. 3).

Although detailed structural and mechanistic studies remain to be carried out, based on the absolute configuration of the product **3a**, we propose a mechanism shown in Scheme 2. First, the nitrogen atom of the pyridine ring and the carbonyl oxygen atom of catalyst **2f** are coordinated to Cl_3SiH to create an activated hydrosilylation species. Substrate **1a** may approache the Cl_3SiH-catalyst complex to generate two transition states A and B. In transition state A, the N–H of catalyst **2f** activates the carbonyl group of **1a** through H-bonding. In addition, there could be π–π stackings between the two aromatic systems of the catalyst and the substrate. Then Si-face conjugate attack of the hydride to **1a** generate (*S*)-product **3a**. On the contrary, in transition state B through which (*R*)-product will be obtained, the carbonyl group of **1a** can not be connected with the N–H of catalyst **2f**. Thus the fact that (*S*)-enriched product **3a** was obtained is consistent with the suggestion that the hydrosilylation predominantly proceeds through the pathway involving transition state A rather than transition state B.

In conclusion, we have developed a facile, metal-free and mild enantioselective conjugate hydrosilylation of β,β-disubstituted α,β-unsaturated ketones. By using chiral picolinamide–sulfonate Lewis base as catalyst, the reactions provided various optically active ketones bearing a chiral center at β-position with moderate to good yields in moderate enantioselectivities. Comparing with the chiral phosphine oxide Lewis base catalysts, the chiral picolinamide–sulfonate is cheaper and easier accessible. The absolute configuration of one product was determined by comparison of the retention times of the two enantiomers on the stationary phase with those in the literature.



Scheme 2 A plausible reaction mechanism for hydrosilylation of **1a** catalyzed by **2f**.

Experimental section

General procedure of enantioselective conjugate hydrosilylation of α,β-unsaturated ketones

A solution of trichlorosilane (21 μL, 0.2 mmol, 2.0 equiv.) in 0.5 mL of toluene was added to a stirred solution of the corresponding α,β-unsaturated ketones (0.1 mmol) and the catalyst **2f** (0.02 mmol) in toluene (2.0 mL) at −10 °C. The mixture was stirred at the same temperature for 48 hours. The reaction mixture was then treated with saturated aqueous solution of $NaHCO_3$ at room temperature for 20 minutes. Then the mixture was extracted with EtOAc. The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure. The residue was purified by silica-gel chromatography with ethyl acetate/petroleum ether to give the pure product. The ee values were determined using established HPLC techniques with chiral stationary phases.

(1*R*,2*R*)-2-(4-Phenylpicolinamido)cyclohexyl 4-methyl-benzenesulfonate (2j)

White solid, mp: 124–125 °C, 32% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J = 5.1 Hz, 1H), 8.34 (d, J = 1.5 Hz, 1H), 8.04 (d, J = 7.9 Hz, 1H), 7.74–7.64 (m, 5H), 7.55–7.48 (m, 3H), 7.03 (d, J = 8.3 Hz, 2H), 4.62–4.53 (m, 1H), 4.14–4.04 (m, 1H), 2.21 (s, 3H), 2.16–2.13 (m, 2H), 1.83–1.67 (m, 3H), 1.48–1.32 (m, 3H). ^{13}C NMR (100 MHz, DMSO) δ 163.3, 150.8, 149.2, 148.9, 144.2, 137.1, 134.3, 131.3, 130.1, 129.9, 128.5, 127.4, 125.9, 124.0, 119.4, 84.5, 51.3, 33.1, 31.3, 24.3, 24.0, 21.4. $[\alpha]_D^{20.0} = -27.6$ (c = 0.5, CH_2Cl_2); HRMS (ESI): calcd for $[C_{25}H_{26}N_2O_4S + H]^+$ 451.1613, found 451.1686.

(1*R*,2*R*)-2-(3-Methylpicolinamido)cyclohexyl 4-methylbenzenesulfonate (2k)

White solid, mp: 75–76 °C, 45% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35–8.33 (m, 1H), 8.09 (d, J = 9.5 Hz, 1H), 7.66 (d, J = 8.3 Hz, 2H), 7.58–7.55 (m, 1H), 7.30 (dd, J = 4.6 Hz, 1H), 7.01 (d, J = 8.0 Hz, 2H), 4.57–4.49 (m, 1H), 4.07–3.96 (m, 1H), 2.66 (s, 3H), 2.26 (s, 3H), 2.19–2.04 (m, 2H), 1.80–1.69 (m, 3H), 1.45–1.26 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 146.8, 145.2, 144.0, 140.7, 135.5, 134.3, 129.4, 127.5, 125.6, 83.1, 51.6, 32.4, 31.7, 24.0, 24.0, 21.6, 20.6. $[\alpha]_D^{20.0} = -53.6$ (c = 0.5, CH_2Cl_2); HRMS (ESI): calcd for $[C_{20}H_{24}N_2O_4S + H]^+$ 389.1457, found 389.1530.

(1*S*,2*R*)-1-(Picolinamido)-2,3-dihydro-1*H*-inden-2-yl 4-methylbenzene-sulfonate (2l)

White solid, mp: 123–124 °C, 57% yield. ^{1}H NMR (300 MHz, DMSO) δ 8.68 (d, J = 4.1 Hz, 1H), 8.38 (d, J = 9.6 Hz, 1H), 8.09–8.04 (m, 1H), 8.02–7.94 (m, 1H), 7.83–7.52 (m, 3H), 7.50–7.14 (m, 4H), 7.10 (d, J = 8.0 Hz, 2H), 5.72–5.67 (m, 1H), 5.33–5.30 (m, 1H), 3.40 (d, J = 4.6 Hz, 1H), 3.10 (d, J = 17.2 Hz, 1H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 149.2, 148.2, 144.5,

139.5, 138.5, 137.2, 133.3, 129.5, 128.6, 127.9, 127.5, 126.4, 125.3, 123.6, 122.3, 83.6, 55.9, 38.5, 21.6. $[\alpha]_D^{20.0} = -4.8$ ($c = 0.5$, CH_2Cl_2); HRMS (ESI): calcd for $[C_{22}H_{20}N_2O_4S + H]^+$ 409.1144, found 409.1217.

(*R*)-1-(2-(Picolinamido)naphthalen-1-yl)naphthalen-2-yl 4-methyl-benz-enesulfonate (2m)

White solid, mp: 211–212 °C, 40% yield. ^{1}H NMR (300 MHz, *d*-DMSO) δ 9.64 (s, 1H), 8.61 (d, $J = 9.1$ Hz, 1H), 8.29 (d, $J = 9.0$ Hz, 1H), 8.17–8.11 (m, 3H), 8.07–7.93 (m, 3H), 7.66 (d, $J = 9.1$ Hz, 1H), 7.55–7.43 (m, 3H), 7.36–7.24 (m, 2H), 7.13 (d, $J = 8.3$ Hz, 2H), 7.01 (t, $J = 9.8$ Hz, 3H), 6.84 (d, $J = 8.7$ Hz, 1H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 149.5, 147.8, 146.1, 144.6, 137.3, 134.8, 133.1, 132.7, 132.6, 132.4, 130.8, 130.6, 129.4, 129.2, 128.2, 127.8, 127.5, 127.4, 126.6, 126.5, 126.3, 126.1, 125.8, 124.7, 124.5, 12.0, 121.9, 120.1, 119.7, 21.6. $[\alpha]_D^{20.0} = -87.6$ ($c = 0.5$, CH_2Cl_2); HRMS (ESI): calcd for $[C_{33}H_{24}N_2O_4S + H]^+$ 545.1547, found 545.1530.

N-((1*R*,2*R*)-2-(4-Methylphenylsulfonamido)cyclohexyl)picolinamide (2n)

White solid, mp: 173–174 °C, 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (d, $J = 4.5$ Hz, 1H), 8.11 (d, $J = 7.8$ Hz, 1H), 7.91–7.85 (m, 1H), 7.63 (d, $J = 8.0$ Hz, 1H), 7.53 (d, $J = 8.2$ Hz, 2H), 7.47–7.43 (m, 1H), 6.75 (d, $J = 9.0$ Hz, 2H), 5.97 (d, $J = 5.3$ Hz, 1H), 3.85–3.74 (m, 1H), 3.04–2.94 (m, 1H), 2.25 (d, $J = 13.9$ Hz, 1H), 2.12 (s, 3H), 1.99–1.95 (m, 1H), 1.77–1.72 (m, 2H), 1.52–1.39 (m, 1H), 1.37–1.25 (m, 3H). $[\alpha]_D^{20.0} = -8.6$ ($c = 0.5$, CH_2Cl_2); HRMS (ESI): calcd for $[C_{19}H_{23}N_3O_3S + H]^+$ 374.1460, found 374.1533.

N-((1*R*,2*R*)-2-(*N*,4-Dimethylphenylsulfonamido)cyclohexyl)picolinamide (2o)

White solid, mp: 108–109 °C, 43% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (d, $J = 4.6$ Hz, 1H), 8.12 (t, $J = 9.3$ Hz, 2H), 7.86–7.80 (m, 1H), 7.62 (d, $J = 8.2$ Hz, 2H), 7.44–7.40 (m, 1H), 7.06 (d, $J = 8.1$ Hz, 2H), 4.13–3.99 (m, 1H), 3.89–3.80 (m, 1H), 2.77 (s, 3H), 2.30 (s, 3H), 2.22–2.18 (m, 1H), 1.86–1.69 (m, 2H), 1.53–1.50 (m, 1H), 1.46–1.23 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 149.8, 148.2, 142.8, 137.4, 137.1, 129.4, 127.0, 126.0, 122.1, 60.0, 49.0, 33.4, 29.3, 28.6, 25.2, 24.7, 21.5. $[\alpha]_D^{20.0} = -12.4$ ($c = 0.5$, CH_2Cl_2); HRMS (ESI): calcd for $[C_{20}H_{25}N_3O_3S + H]^+$ 388.1617, found 388.1689.

(*S*)-1,3-Diphenylbutan-1-one (3a)

White solid, 97% yield, 65% ee. HPLC conditions: IC column, hexane/iPrOH = 98/2, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, $tr_{major} = 6.43$ min, $tr_{minor} = 6.82$ min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95–7.92 (m, 2H), 7.58–7.52 (m, 1H), 7.47–7.42 (m, 2H), 7.34–7.29 (m, 4H), 7.23–7.17 (m, 1H), 3.57–3.45 (m, 1H), 3.35–3.15 (m, 2H), 1.34 (d, $J = 6.9$ Hz, 3H).

(*S*)-3-(4-Fluorophenyl)-1-phenylbutan-1-one (3b)

Colorless oil, 98% yield, 50% ee. HPLC conditions: AD-H column, hexane/iPrOH = 95/5, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, $tr_{minor} = 6.96$ min, $tr_{major} = 8.26$ min; ^{1}H NMR (300 MHz, *d*-DMSO) δ 7.93–7.90 (m, 2H), 7.58–7.53 (m, 1H), 7.47–7.42 (m, 2H), 7.26–7.20 (m, 2H), 7.01–6.93 (m, 2H), 3.56–3.44 (m, 1H), 3.31–3.13 (m, 2H), 1.32 (d, $J = 6.9$ Hz, 3H).

(*S*)-3-(4-Chlorophenyl)-1-phenylbutan-1-one (3c)

Colorless oil, 94% yield, 48% ee. HPLC conditions: AD-H column, hexane/iPrOH = 95/5, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, $tr_{minor} = 7.01$ min, $tr_{major} = 8.80$ min; ^{1}H NMR (300 MHz, *d*-DMSO) δ 7.93–7.90 (m, 2H), 7.58–7.53 (m, 1H), 7.47–7.42 (m, 2H), 7.28–7.27 (m, 1H), 7.25–7.19 (m, 3H), 3.55–3.44 (m, 1H), 3.31–3.13 (m, 2H), 1.32 (d, $J = 6.9$ Hz, 3H).

(*S*)-1-Phenyl-3-(*p*-tolyl)butan-1-one (3d)

White solid, 97% yield, 53% ee. HPLC conditions: AD-H column, hexane/iPrOH = 95/5, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, $tr_{minor} = 5.88$ min, $tr_{major} = 7.24$ min; ^{1}H NMR (300 MHz, *d*-DMSO) δ 7.93 (d, $J = 7.5$ Hz, 2H), 7.55 (t, $J = 7.3$ Hz, 1H), 7.44 (t, $J = 7.6$ Hz, 2H), 7.16–7.10 (m, 4H), 3.53–3.41 (m, 1H), 3.32–3.13 (m, 2H), 2.32 (s, 3H), 1.32 (d, $J = 6.9$ Hz, 3H).

(*S*)-3-(4-Methoxyphenyl)-1-phenylbutan-1-one (3e)

Colorless oil, 91% yield, 62% ee. HPLC conditions: AD-H column, hexane/iPrOH = 95/5, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, $tr_{minor} = 8.92$ min, $tr_{major} = 11.47$ min; ^{1}H NMR (300 MHz, *d*-DMSO) δ 7.94–7.91 (m, 2H), 7.58–7.52 (m, 1H), 7.47–7.42 (m, 2H), 7.21–7.17 (m, 2H), 6.87–6.82 (m, 2H), 3.78 (s, 3H), 3.54–3.41 (m, 1H), 3.31–3.11 (m, 2H), 1.31 (d, $J = 6.9$ Hz, 3H).

(*S*)-3-(2-Methoxyphenyl)-1-phenylbutan-1-one (3g)

Colorless oil, 92% yield, 20% ee. HPLC conditions: IC column, hexane/iPrOH = 98/2, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, $tr_{major} = 9.91$ min, $tr_{minor} = 10.69$ min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, $J = 7.3$ Hz, 2H), 7.56 (t, $J = 7.3$ Hz, 1H), 7.45 (t, $J = 7.5$ Hz, 2H), 7.26–7.18 (m, 2H), 6.94 (t, $J = 7.4$ Hz, 1H), 6.87 (d, $J = 8.1$ Hz, 1H), 3.91–3.79 (m, 4H), 3.41–3.01 (m, 2H), 1.31 (d, $J = 6.9$ Hz, 3H).

(*S*)-3-(3-Methoxyphenyl)-1-phenylbutan-1-one (3h)

Colorless oil, 91% yield, 58% ee. HPLC conditions: IC column, hexane/iPrOH = 95/5, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, $tr_{major} = 7.54$ min, $tr_{minor} = 9.19$ min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95–7.92 (m, 2H), 7.58–7.53 (m, 1H), 7.47–7.42 (m, 2H), 7.22 (d, $J = 7.9$ Hz, 1H), 6.88 (d, $J = 7.7$ Hz, 1H), 6.83 (t, $J = 2.1$ Hz, 1H), 6.77–6.73 (m, 1H), 3.80 (s, 3H), 3.56–3.43 (m, 1H), 3.34–3.14 (m, 2H), 1.33 (d, $J = 6.9$ Hz, 3H).

(*S*)-3-(Naphthalen-2-yl)-1-phenylbutan-1-one (3i)

White solid, 97% yield, 65% ee. HPLC conditions: AD-H column, hexane/iPrOH = 95/5, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, $tr_{minor} = 8.00$ min, $tr_{major} = 9.24$ min; ^{1}H NMR (300 MHz, *d*-DMSO) δ 7.99–7.96 (m, 2H), 7.86–7.78 (m, 4H), 7.65–7.60 (m, 1H), 7.55–7.40 (m, 5H), 3.57–3.40 (m, 3H), 1.33 (d, $J = 6.5$ Hz, 3H).

(*S*)-3-(Furan-2-yl)-1-phenylbutan-1-one (3k)

White solid, 90% yield, 57% ee. HPLC conditions: AD-H column, hexane/iPrOH = 98/2, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, tr_{minor} = 6.97 min, tr_{major} = 8.03 min; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90–7.87 (m, 2H), 7.52–7.46 (m, 1H), 7.41–7.36 (m, 2H), 7.23–7.22 (m, 1H), 6.21–6.19 (m, 1H), 6.02 (d, J = 3.2 Hz, 1H), 3.65–3.5 (m, 1H), 3.39–2.97 (m, 2H), 1.26 (d, J = 6.9 Hz, 3H).

(*S*)-1-Phenyl-3-(thiophen-2-yl)butan-1-one (3l)

White solid, 96% yield, 59% ee. HPLC conditions: AD-H column, hexane/iPrOH = 98/2, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, tr_{minor} = 8.23 min, tr_{major} = 9.34 min; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96–7.94 (m, 2H), 7.57 (t, J = 7.3 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 7.14–7.12 (m, 1H), 6.94–6.87 (m, 2H), 3.92–3.80 (m, 1H), 3.42–3.17 (m, 2H), 1.43 (d, J = 6.9 Hz, 3H).

(*S*)-1-(4-Chlorophenyl)-3-phenylbutan-1-one (3n)

Colorless oil, 95% yield, 64% ee. HPLC conditions: AD-H column, hexane/iPrOH = 98/2, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, tr_{minor} = 9.05 min, tr_{major} = 10.71 min; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88–7.84 (m, 2H), 7.43–7.39 (m, 2H), 7.34–7.27 (m, 3H), 7.25–7.17 (m, 1H), 3.55–3.43 (m, 1H), 3.31–3.11 (m, 2H), 1.34 (d, J = 6.9 Hz, 3H).

(*S*)-3-Phenyl-1-(*p*-tolyl)butan-1-one (3o)

White solid, 94% yield, 58% ee. HPLC conditions: AD-H column, hexane/iPrOH = 98/2, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, tr_{minor} = 10.13 min, tr_{major} = 13.40 min; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 8.2 Hz, 2H), 7.33–7.28 (m, 4H), 7.25–7.17 (m, 3H), 3.56–3.44 (m, 1H), 3.31–3.12 (m, 2H), 2.40 (s, 3H), 1.33 (d, J = 6.9 Hz, 3H).

(*S*)-1-(4-Methoxyphenyl)-3-phenylbutan-1-one (3p)

White solid, 94% yield, 59% ee. HPLC conditions: AD-H column, hexane/iPrOH = 98/2, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, tr_{minor} = 20.17 min, tr_{major} = 27.94 min; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93–7.90 (m, 2H), 7.33–7.28 (m, 4H), 7.22–7.16 (m, 1H), 6.91 (d, J = 8.9 Hz, 2H), 3.86 (s, 3H), 3.56–3.43 (m, 1H), 3.28–3.09 (m, 2H), 1.33 (d, J = 6.9 Hz, 3H).

(*S*)-1-(3-Fluorophenyl)-3-phenylbutan-1-one (3q)

White solid, 91% yield, 54% ee. HPLC conditions: IC column, hexane/iPrOH = 98/2, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, tr_{major} = 6.18 min, tr_{minor} = 6.56 min; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74–7.65 (m, 1H), 7.62–7.57 (m, 1H), 7.45–7.38 (m, 1H), 7.33–7.27 (m, 4H), 7.25–7.17 (m, 2H), 3.55–3.44 (m, 1H), 3.32–3.11 (m, 2H), 1.34 (d, J = 6.9 Hz, 3H).

(*S*)-3-Phenyl-1-(*m*-tolyl)butan-1-one (3r)

White solid, 95% yield, 52% ee. HPLC conditions: IC column, hexane/iPrOH = 98/2, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, tr_{major} = 7.23 min, tr_{minor} = 7.89 min; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 6.8 Hz, 2H), 7.35–7.28 (m, 6H), 7.22–7.14 (m, 1H), 3.36–3.44 (m, 1H), 3.32–3.13 (m, 2H), 2.40 (s, 3H), 1.34 (d, J = 6.9 Hz, 3H).

(*S*)-3-Phenyl-1-(*o*-tolyl)butan-1-one (3s)

Colorless oil, 90% yield, 28% ee. HPLC conditions: AD-H column, hexane/iPrOH = 98/2, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, tr_{minor} = 6.15 min, tr_{major} = 6.90 min; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 7.8 Hz, 1H), 7.39–7.28 (m, 2H), 7.25–7.15 (m, 6H), 3.51–3.40 (m, 1H), 3.25–3.07 (m, 2H), 2.35 (s, 3H), 1.32 (d, J = 6.9 Hz, 3H).

(*S*)-1,3-Diphenylpentan-1-one (3t)

White solid, 94% yield, 65% ee. HPLC conditions: AD-H column, hexane/iPrOH = 98/2, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, tr_{minor} = 7.95 min, tr_{major} = 10.16 min; ^1H NMR (300 MHz, $CDCl_3$) δ 7.91–7.89 (m, 2H), 7.56–7.41 (m, 1H), 7.45–7.40 (m, 2H), 7.31–7.27 (m, 2H), 7.26–7.15 (m, 3H), 3.34–3.19 (m, 3H), 1.86–1.57 (m, 2H), 0.80 (t, J = 7.3 Hz, 3H).

(*S*)-4-Bromo-1,3-diphenylbutan-1-one (3u)

Colorless oil, 76% yield, 67% ee. HPLC conditions: IC column, hexane/iPrOH = 98/2, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, tr_{major} = 13.06 min, tr_{minor} = 13.84 min; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03–7.93 (m, 2H), 7.66–7.43 (m, 4H), 7.36–7.27 (m, 3H), 7.25–7.23 (m, 1H), 3.84–3.78 (m, 1H), 3.76–3.66 (m, 2H), 3.62 (d, J = 6.1 Hz, 1H), 3.47–3.39 (m, 1H).

(*R*)-4-Methyl-1,3-diphenylpentan-1-one (3v)

White solid, 88% yield, 65% ee. HPLC conditions: IC column, hexane/iPrOH = 98/2, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, tr_{major} = 8.68 min, tr_{minor} = 10.42 min; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90–7.87 (m, 2H), 7.56–7.50 (m, 1H), 7.45–7.39 (m, 2H), 7.28–7.27 (m, 2H), 7.25–7.12 (m, 3H), 3.37 (d, J = 7.0 Hz, 2H), 3.20–3.13 (m, 1H), 2.00–1.89 (m, 1H), 0.99 (d, J = 6.7 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H).

(*S*)-1,3,4-Triphenylbutan-1-one (3x)

White solid, 91% yield, 59% ee. HPLC conditions: IC column, hexane/iPrOH = 98/2, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, tr_{major} = 11.40 min, tr_{minor} = 11.99 min; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96–7.83 (m, 2H), 7.58–7.49 (m, 1H), 7.44–7.33 (m, 2H), 7.31–7.14 (m, 8H), 7.10–7.07 (m, 2H), 3.72–3.62 (m, 1H), 3.40–3.24 (m, 2H), 3.05–2.86 (m, 2H).

3-(4-Methoxyphenyl)-1,3-diphenylpropan-1-one (3y)

White solid, 70% yield, 11% ee. HPLC conditions: OD-H column, hexane/iPrOH = 90/10, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, tr_{minor} = 7.17 min, tr_{major} = 7.99 min; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96–7.93 (m, 2H), 7.59–7.531 (m, 1H), 7.47–7.42 (m, 2H), 7.32–7.25 (m, 4H), 7.21–7.15 (m, 3H), 6.83–6.81 (m, 2H), 4.79 (t, J = 7.3 Hz, 1H), 3.76 (s, 3H), 3.72 (d, J = 7.3 Hz, 2H).

1-Phenyl-2-(1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-one (3z)

White solid, 98% yield, 22% ee. HPLC conditions: OD-H column, hexane/iPrOH = 95/5, flow rate 1.0 mL min^{-1}, UV detection at 254 nm, tr_{minor} = 6.22 min, tr_{major} = 6.61 min; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00–7.98 (m, 2H), 7.61–7.55 (m, 1H), 7.50–7.47 (m, 2H), 7.20–7.08 (m, 4H), 3.68–3.60 (m, 1H), 3.39–3.23 (m, 2H), 2.86–2.71 (m, 2H), 1.99–1.90 (m, 1H), 1.86–1.66 (m, 3H).

Conflicts of interest

There are no conflicts to declare.

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