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Highly efficient asymmetric-axle-supported N–O amides in enantioselective hydrosilylation of ketimines with trichlorosilane☆

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ABSTRACT

A novel asymmetric-axle-supported chiral N–O amide was synthesized and used in catalytic enantioselective hydrosilylation of *N*-aryl ketimines with $HSiCl_3$ at room temperature instead of the typical −20 °C. High conversion yield and high enantioselectivity up to 96% were observed.

1. Introduction

Enantioselective hydrosilylation of C=N with $HSiCl_3$ has been proven to be a powerful method for producing chiral amines.[1] Three major families of organocatalysts have been developed (Fig. 1): *N*-formyl derivative (**1**),[1b,2] picolinamide analog (**2**),[3] and pyridyl-oxazoline (**3**).[1c,4] When classified by catalyst structural characteristics, an axial ligand, such as a BINAM derivative (**4**),[5] a polymer-supported ligand (**5**),[6] a C_2-asymmetric ligand (**6**),[7] and others[8] were also found to have good enantioselectivities. All reactions reported were performed at low temperatures (e.g., −20 °C). Until now, the catalysts with N–O structure have rarely reported in the enantioselective hydrosilylation of C=N with $HSiCl_3$. In our recent study, a biscarboline ester with N–O structure (**7**)[9] was synthesized and used in asymmetric additions of trichlorosilanes to aldehydes to give up corresponding products with up to 99% ee. For the polymer-supported and axial catalyst structures, we have designed and synthesized a series of asymmetric-axle-supported ligands, such as **8**, and investigated their application to hydrosilylation of ketimines with trichlorosilane at room temperature. Catalyst **8** is different from ligand **6**, in which two chiral active moieties are connected via a flexible linear linkage such that no axial conformer can form in solution. While the C–C bond connections in **8** forms an axial asymmetric space, it was anticipated only one chiral molecular residue (e.g., the moiety highlighted in the blue box) catalyzes the reactions.

2. Results and discussion

The synthetic route to **8** is illustrated in Scheme 1. Compound **9** was synthesized as described in our previous study.[9] After hydrolysis of **9**, the intermediate **10**, which was obtained in a yield of 93% was condensed with (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol to form **11** in a yield of 95%, which is oxidized to **8** using 8 equiv of peroxide-urea and TFA at room temperature for 2 days. One major epimer product was obtained with a single step yield of 48% after column chromatography. Bis-N–O products were obtained in a low yield (less than 10%).

Stereochemistry of the major structure was determined using a widely accepted quantum theory.[10] Conformational searches were performed by first using a MMFF94S force field. All stable conformations were then optimized at the B3LYP/6-31G(d) level. Single point energy (SPE) was computed for the low energy conformers (0–2.5 kcal/mol) at the B3LYP/6-311G(d) level. The catalyst

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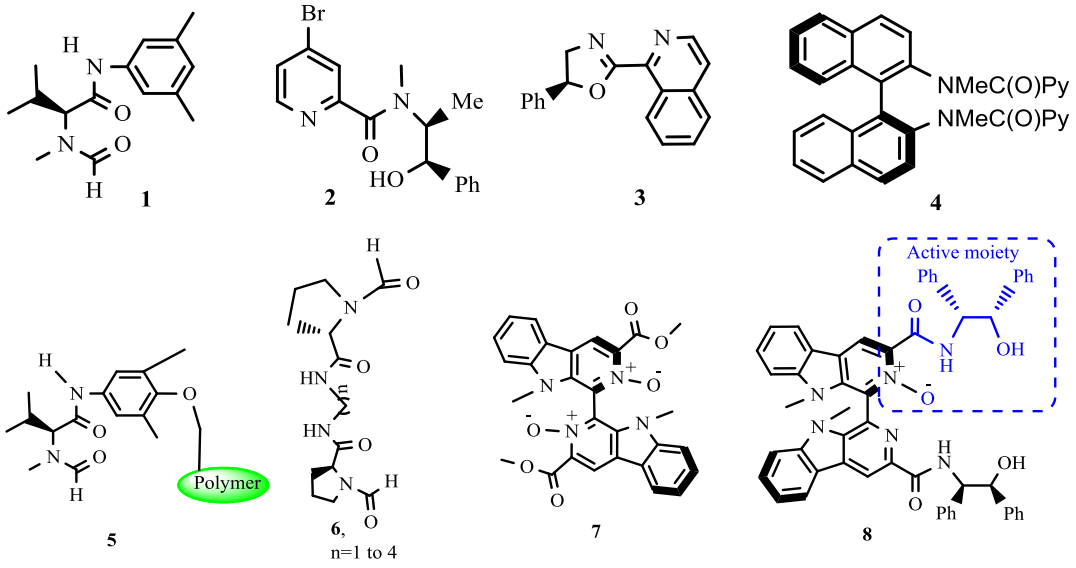
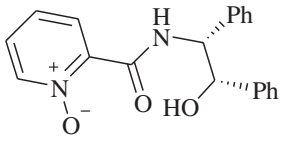


Fig. 1. Effective catalysts designed by us that have been previously reported.

was found to consist of 87% of the major geometry **8a** and 13% of the other epimer (ep-**8a**).

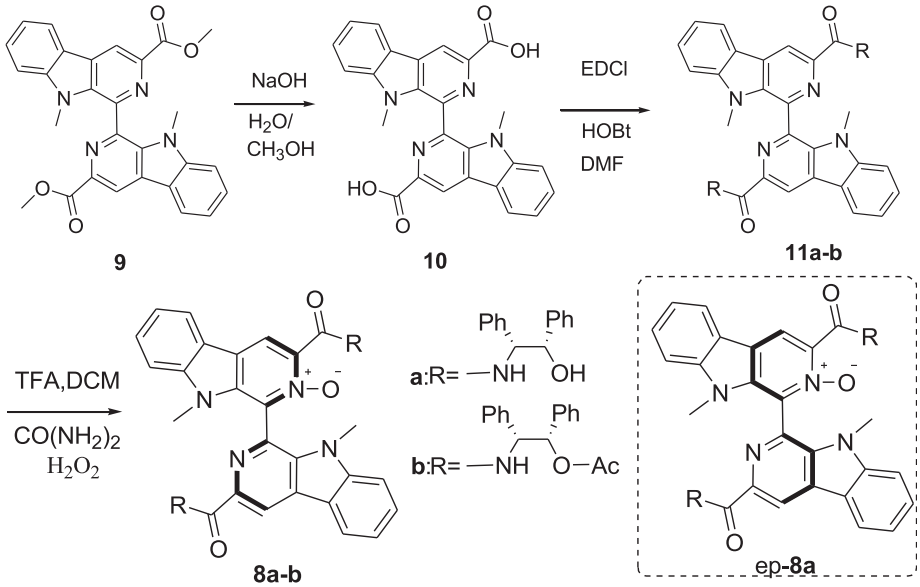
Our initial attempt with 10 mol % of catalyst **8a** gave a 74% ee in enantioselective hydrosilylations of ketimine **13** (R^1=Ph, R^2=Ph, R^3=Me) with $HSiCl_3$ at 0 °C in CH_2Cl_2. We then investigated the effects of temperature (from −20–40 °C) and solvent (CH_2Cl_2, $CHCl_3$ or toluene) on the enantioselectivity. The optimized reaction condition was found to be 20 mol % of **8** in $CHCl_3$ at room temperature for 4 h (Table 1, entry 1). Finally, we examined a series of ketimines and the results are summarized in Table 1. All substrates were converted to the corresponding amines in high yields (≥94%) and good ee% values (up to 96%). The *N*-(1-phenylethyl)aniline has an OR of −13.5° in CH_3OH.

The effect of different moiety of the catalyst on the hydrosilylation was investigated. The loss of the free −OH (e.g., ligand **8b**) led to a decrease in ee% from 93% to 30%. Once the −O on *N* was removed, as in **11a**, the ee% decreased to 7%. If the asymmetric-axle-supported moiety and indol were absent as in **12**, only 26% ee was achieved. The results showed that the active moiety (N–O-containing residue) is crucial in efficiently catalyzing the enantioselective hydrosilylation.



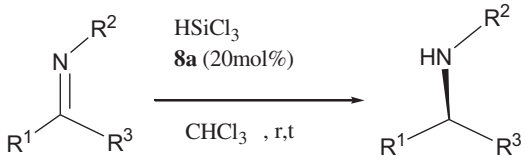
3. Conclusion

In conclusion, we prepared a novel asymmetric-axle-supported chiral N–O amide **8a** as highly efficient Lewis basic organocatalyst



Scheme 1. Synthesis of catalyst **8**.

Table 1
Asymmetric hydrosilylation of various ketimines catalyzed by **8a**



13 **14**

Entry[a]	R^1, R^2, R^3	Yield %[b]	ee (%)[c]	OR
1(**a**)	Ph, Ph, Me	95	93	−13.5
2(**b**)	4-F−Ph, Ph, Me	98	95	−17.1
3(**c**)	4-Cl−Ph, Ph, Me	97	94	−12.1
4(**d**)	4-Br−Ph, Ph, Me	96	93	−17.1
5(**e**)	4-F_3C−Ph, Ph, Me	95	84	−40.0
6(**f**)	4-NO_2−Ph, Ph, Me	95	78	+16.5
7(**g**)	4-Br−Ph, PMP, Me	98	76	+11.7
8(**h**)	4-MeO−Ph, Ph, Me	94	77	−13.9
9(**i**)	Ph, PMP, Me	97	96	−2.0[d]
10(**j**)	Ph, 4-EtO−Ph, Me	95	94	−18.2
11(**k**)	Ph, 4-Me−Ph, Me	95	93	+5.7
12(**l**)	Ph, 4-Et−Ph, Me	95	89	−1.74
13(**m**)	Ph, 4-Br−Ph, Me	98	75	+26.6
14(**n**)	Ph, Ph, Et	95	94	+40

Unless specified, reactions were carried out with 2 equiv of $HSiCl_3$ and 20% of **8a** in 2 mL of $CHCl_3$ at room temperature for 4 h.

[a] The bold letter in bracket represents the number for compound **14**, e.g., a means **14a**.

[b] Isolated yield.

[c] Determined using HPLC.

[d] The sign of OR was not very stable during measurement due to resolution limitation of the polarimeter.

to promote hydrosilylation of *N*-aryl ketimines with $HSiCl_3$. *N*-oxide pyridine compounds has been used in this model reaction for the first time. Instead of typical low temperature, this reaction can be carried out at room temperature within only 4 h in good excellent yields and ee values.

4. Experimental section

4.1. General method

Thin layer chromatography was performed on TLC plates (GF254). Flash column chromatography was performed with silica gel (300−400 mesh). Enantiomeric excess was determined using a Waters HPLC with a 2695 pump and a 2996 diode array detector. Optical rotations were performed on an Optical Activity AA-55 polarimeter using a 10 cm cell with a Na 589 nm filter. IR spectra were obtained with an FTIR spectrometer (Bruker Tensor 27). ^{1}H NMR and ^{13}C NMR were recorded on a Bruker AV-400 or Bruker DRX-600 spectrometer. The mass spectra were measured on an API QSTAR Pulsar. All solvents for the reactions were of reagent grade and were dried and distilled before use.

4.2. General procedure for preparation of catalysts

*4.2.1. 9,9′-Dimethyl-9H,9′H-1,1′-bipyrido[3,4-b]indole-3,3′-dicarboxylic acid (**10**).* To a solution of **9** (5 mmol in CH_3OH (40 mL)) NaOH (4 mL, 5 mol/L) was added at 0 °C, the mixture was heated to 60 °C, and refluxed for 12 h, then HCl solution (1 M) was added to adjust its pH to 3−4. The precipitate was filtered, and washed with water, then dried in vacuum oven. Light yellow powder **10** was obtained. MS-ESI, *m*/*z* 473 $[M+Na]^+$. HRMS *m*/*z* calcd for $C_{26}H_{18}N_4O_4Na$ $[M+Na]^+$ 473.1225, found 473.1230. ^{1}H NMR (400 MHz, DMSO) δ 3.47 (3H×2, s, NCH_3), 7.42 (1H×2, t, *J*=7.4 Hz), 7.66−7.78 (2H×2, m), 8.58 (1H×2, d, *J*=7.9 Hz), 9.16 (1H×2, s). ^{13}C NMR (100 MHz, DMSO) δ 32.6, 110.8, 117.4, 120.7, 120.8, 122.3, 129.2, 129.8, 136.3, 136.7, 139.6, 142.6, 166.8.

*4.2.2. N,N′-Bis(1R,2S-2-hydroxy-1,2-diphenylethyl) 9,9′-dimethyl-9H,9′H-1,1′-bipyrido[3,4-b]indole-3,3′-dicarboxamide (**11a**).* To a solution of **10** and 1-hydroxybenzotriazole (HOBT, 2.2 equiv) in DMF kept under nitrogen at 0 °C, DMF solution of 1-[3-(dimethylamino) propyl]-3-ethylcarbodiimine hydrochloride (EDC, 2.2 equiv) was added, stirred for 0.5 h, then (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol was added. The mixture solution was warmed to room temperature and stirred overnight. After quenched with ice water, the precipitate was filtered, washed with water, and then dried in oven. Light yellow powder **11a** was obtained. $[\alpha]_D^{11}$ +189.47 (*c* 0.38, $CHCl_3$), MS-ESI, *m*/*z* 863 $[M+Na]^+$. HRMS-EI *m*/*z*, calcd for $C_{54}H_{44}N_6O_4$ $[M]^+$ 840.3432, found 840.3438. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.02 (s, 1H, N*H*), 8.95 (s, 1H, N*H*), 8.66 (d, *J*=7.5 Hz, 1H), 8.32 (d, *J*=7.9 Hz, 1H), 8.18 (d, *J*=7.9 Hz, 1H), 7.70 (t, *J*=7.6 Hz, 1H), 7.64 (t, *J*=7.6 Hz, 1H), 7.49−7.38 (m, 2H), 7.30 (t, *J*=7.5 Hz, 1H), 7.18−7.06 (m, 8H), 7.03−6.95 (m, 6H), 6.86 (dt, *J*=15.3, 9.3 Hz, 6H), 6.73 (d, *J*=6.9 Hz, 2H), 5.56 (dd, *J*=7.6, 5.0 Hz, 1H, PhC*H*OH), 5.48−5.37 (m, 1H, PhC*H*OH), 5.06 (d, *J*=4.9 Hz, 1H, PhC*H*N), 4.96 (s, 1H, PhC*H*N), 3.28 (s, 3H, NCH_3), 3.26 (s, 3H, NCH_3)/^{13}C NMR (150 MHz, $CDCl_3$) δ 165.28, 164.67, 143.11, 143.08, 139.88, 139.48, 138.23, 138.06, 137.81, 137.49, 137.29, 137.20, 131.29, 129.56, 129.44, 128.33, 128.12, 127.83, 127.79, 127.70, 127.58, 127.29, 127.25, 126.88, 126.21, 122.23, 122.21, 121.33, 121.29, 121.15, 121.02, 115.09, 114.88, 110.06, 110.03, 79.50, 77.51, 77.32, 77.11, 76.89, 75.71, 59.91, 59.65, 32.85, 32.57.

*4.2.3. N,N′-Bis(1R,2S-2-acetoxyl-1,2-diphenylethyl) 9,9′-dimethyl-9H,9′H-1,1′-bipyrido[3,4-b]indole-3,3′-dicarboxamide (**11b**).* To a solution of **11a** in DCM, 1.2 equiv acetic anhydride and 5 mol % DMAP were added then stirred at room temperature for 3 h, after wash with water, and purification through silicon gel, it can gives **11b**. $[\alpha]_D^{11}$ +167.1 (*c* 0.07, $CHCl_3$). MS-ESI, *m*/*z* 947 $[M+Na]^+$. HRMS-EI *m*/*z* calcd for $C_{58}H_{48}N_6O_6$ $[M]^+$ 924.3635, found 924.3652. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H, N*H*), 9.09 (s, 1H, N*H*), 8.76 (d, *J*=9.2 Hz, 1H), 8.60 (d, *J*=9.1 Hz, 1H), 8.37 (t, *J*=7.7 Hz, 2H), 7.74 (t, *J*=7.7 Hz, 2H), 7.55 (d, *J*=8.4 Hz, 1H), 7.45 (dt, *J*=23.4, 8.1 Hz, 3H), 7.28 (d, *J*=1.8 Hz, 2H), 7.20 (s, 6H), 7.15−7.11 (m, 2H), 7.01−6.91 (m, 6H), 6.80 (t, *J*=7.7 Hz, 2H), 6.67 (t, *J*=7.6 Hz, 1H), 6.56 (t, *J*=7.4 Hz, 1H), 6.15 (dd, *J*=11.2, 5.0 Hz, 1H×2, PhC*H*OH), 5.76 (dt, *J*=8.9, 6.4 Hz, 1H×2, PhC*H*N), 3.35 (s, 3H, NCH_3), 3.30 (s, 3H, NCH_3), 1.91 (s, 3H, COCH_3), 1.79 (s, 3H, COCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.92, 169.55, 164.33, 164.23, 143.13, 143.03, 138.27, 138.24, 138.16, 138.10, 137.79, 137.14, 137.12, 135.91, 134.82, 131.55, 131.23, 129.53, 129.36, 128.32, 128.24, 128.19, 128.05, 127.97, 127.61, 127.19, 126.98, 122.13, 122.06, 121.45, 121.31, 121.14, 114.91, 114.61, 110.07, 110.02, 77.62, 77.21, 56.48, 56.45, 32.72, 32.61, 20.93, 20.68.

*4.2.4. 3,3′-Bis[(1R,2S-2-hydroxy-1,2-diphenylethyl)aminocarbonyl]-9,9′-dimethyl-9H,9′H-1,1′-bipyrido[3,4-b]indole-2-oxide (**8a**).* Peroxide-urea (8 equiv) and TFA (8 equiv) were added to the solution of **11a**, and stirred at room temperature for 48 h. After purified by silicon column and Chiralpak IC column, yellow powder **8a** was obtained. $[\alpha]_D^{11}$ −211.05 (*c* 0.16, $CHCl_3$). MS-ESI, *m*/*z* 879 $[M+Na]^+$. HRMS-EI *m*/*z* calcd for $C_{54}H_{44}N_6O_5$ $[M]^+$, 856.3373, found 856.3401. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.08 (s, 1H, N*H*), 8.91 (s, 1H, N*H*), 8.35 (d, *J*=7.6 Hz, 1H), 7.86 (d, *J*=7.3 Hz, 1H), 7.70 (dt, *J*=14.4, 7.4 Hz, 2H), 7.53 (d, *J*=8.3 Hz, 1H), 7.50−7.43 (m, 2H), 7.15 (dt, *J*=22.9, 7.3 Hz, 8H), 7.04 (d, *J*=7.3 Hz, 2H), 6.98 (d, *J*=6.9 Hz, 6H), 6.92 (d, *J*=6.6 Hz, 4H), 6.68 (d, *J*=3.3 Hz, 2H), 6.37 (d, *J*=55.1 Hz, 1H), 5.47 (s, 1H, PhC*H*OH), 5.37 (d, *J*=6.4 Hz, 1H, PhC*H*OH), 5.18 (d, *J*=6.4 Hz, 1H, PhC*H*N), 4.49 (s, 1H, PhC*H*N), 3.64 (s, 3H, NCH_3), 3.08 (s, 3H, NCH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.48, 160.56, 144.23, 142.95, 140.35, 140.27, 139.11, 138.78, 138.16, 138.14, 136.00, 132.77, 131.69, 131.04, 130.46, 129.79, 129.51, 128.68, 128.39, 127.87, 127.71, 127.62, 127.38, 127.20, 127.06, 126.40, 126.18, 123.12, 122.84, 122.37,

122.13, 121.51, 121.46, 120.96, 120.16, 116.31, 110.31, 109.95, 74.97, 74.56, 60.67, 60.45, 32.03, 29.86.

*4.2.5. 3,3′-Bis[(1R,2S-2-acetoxyl-1,2-diphenylethyl)aminocarbonyl]-9,9′-dimethyl-9H,9′H-1,1′-bipyrido[3,4-b]indole-2-oxide (**8b**).* Following procedure to give **8a**, starting from **11b**, light yellow powder **8b** was obtained. MS-ESI, *m*/*z* 963 $[M+Na]^+$. HRMS-EI *m*/*z* calcd for $C_{58}H_{48}N_6O_7$ $[M]^+$ 940.3584, found 940.3519. $[\alpha]_D^{11}$ +405.56 (*c* 0.36, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ 9.30 (s, 1H, N*H*), 9.08 (s, 1H, N*H*), 8.44 (d, *J*=9.1 Hz, 1H), 8.32 (d, *J*=7.9 Hz, 1H), 8.26 (d, *J*=7.9 Hz, 1H), 7.74 (t, *J*=7.7 Hz, 1H), 7.68 (t, *J*=7.7 Hz, 1H), 7.55 (t, *J*=7.1 Hz, 1H), 7.45 (qd, *J*=12.6, 8.7 Hz, 4H), 7.24–7.15 (m, 16H), 6.97 (d, *J*=7.4 Hz, 3H), 6.92 (t, *J*=7.4 Hz, 1H), 6.75 (t, *J*=7.7 Hz, 2H), 6.22 (t, *J*=7.0 Hz, 1H, Ph*CH*OH), 6.11 (d, *J*=6.1 Hz, 1H, Ph*CH*OH), 5.72 (td, *J*=9.3, 6.5 Hz, 2H, Ph*CH*N), 3.53 (s, 3H, NCH_3), 2.95 (s, 3H, NCH_3), 1.88 (s, 3H, COCH_3), 1.78 (s, 3H, COCH_3). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.87, 169.59, 163.92, 160.19, 144.01, 142.83, 138.68, 138.62, 137.84, 137.74, 137.32, 137.05, 136.09, 132.19, 131.81, 130.81, 130.08, 129.74, 129.29, 128.25, 128.19, 128.14, 127.98, 127.72, 127.33, 127.05, 122.91, 122.33, 122.24, 121.74, 121.29, 121.27, 121.15, 120.18, 116.26, 109.99, 109.83, 77.07, 76.85, 57.79, 56.55, 31.88, 29.75, 20.95, 20.79.

*4.2.6. 2-[(1R,2S-2-Hydroxy-1,2-diphenylethyl)aminocarbonyl]pyridine oxide (**12**).* To a solution of picolinic acid and 1-hydroxybenzotriazole (HOBT 1.1 equiv) in DMF kept under nitrogen at 0 °C, DMF solution of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimine hydrochloride (EDC·HCl, 1.1 equiv) was added, stirred for 0.5 h, then (1*S*,2*R*)-(+)-2-amino-1,2-diphenylethanol was added. The mixture was warmed to room temperature and overnight, then quenched with ice water. The precipitate was filtered, and washed with water. Dried in vacuum oven. Light yellow powder can be obtained. The powder was dissolved in DCM, 8 equiv peroxide-urea, and 8 equiv TFA were added and stirred at room temperature for 48 h. After silicon column chromatography, **12** was obtained. $[\alpha]_D^{11}$ +52.63 (*c* 0.19, $CHCl_3$) MS-ESI, *m*/*z* 357 $[M+Na]^+$. HRMS-EI *m*/*z* calcd for $C_{20}H_{18}N_2O_3$ $[M]^+$ 334.1317, found 334.1312. ^1H NMR (600 MHz, $CDCl_3$), 8.35–8.36 (d, *J*=2.1 Hz, 1H), 8.23–8.20 (m, 1H), 7.45–7.40 (m, 1H), 7.38–7.34 (m, 1H), 7.26–7.20 (m, 7H), 7.17–7.14 (m, 2H), 7.14–7.10 (m, 2H), 5.48 (dd, *J*=8.1, 4.9 Hz, 1H), 5.14 (d, *J*=4.8 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.56, 140.73, 140.64, 140.04, 137.27, 129.19, 128.42, 128.28, 128.23, 128.10, 127.92, 127.73, 127.61, 126.94, 77.18, 60.57.

4.3. General procedure for preparation of imines

A mixture of $NaHCO_3$ (50 mmol), and the corresponding amine (10 mmol) and ketone (10 mmol) plus activated molecular 4 Å sieves (8.0 g) in anhydrous toluene (10 mL) was heated at 80 °C for 12 h under an argon atmosphere. The mixture was filtered through Celite. The filtrate was then evaporated in vacuum and the product was crystallized from appropriate solvents or purified by distillation to give pure imine. Only the ^1H NMR data of two new imines were listed here.

*4.3.1. Compound **13j**.* MS-ESI, *m*/*z* 240 $[M+H]^+$ ^1H NMR (400 MHz, $CDCl_3$) δ 8.02–7.94 (m, 2H), 7.45 (dd, *J*=5.2, 1.9 Hz, 3H), 6.96–6.89 (m, 2H), 6.76 (dd, *J*=6.6, 2.2 Hz, 2H), 4.04 (q, *J*=7.0 Hz, 2H), 2.26 (s, 3H), 1.44 (t, *J*=7.0 Hz, 3H).

*4.3.2. Compound **13l**.* MS-ESI, *m*/*z* 224 $[M+H]^+$ ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (m, 2H), 7.51 (dd, *J*=8.0, 2.3 Hz, 3H), 7.05 (d, *J*=8.1 Hz, 2H), 6.67 (d, *J*=8.2 Hz, 2H), 2.63 (m, 2H), 2.29 (s, 3H), 1.26 (t, *J*=7.6 Hz, 3H).

4.4. General procedure for the hydrosilylation of ketimines

Under an argon atmosphere, 2 equiv trichlorosilane was added dropwise to a stirred solution of imine **13** and catalyst **8a** (20 mol %) in anhydrous $CHCl_3$ at 27 °C. The mixture was allowed to stir at the same temperature for 4 h. The reaction was quenched with saturated aqueous solution of $NaHCO_3$ and was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$ and the solvents were evaporated. Purification by column chromatography (silica gel, hexane/EtOAc) afforded pure amine **14**. The ee% values were determined using established HPLC techniques with chiral stationary phases.

*4.4.1. N-Phenyl-N-(1-phenylethyl)amine (**14a**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.28 (m, 17H), 7.22 (dd, *J*=29.8, 22.9 Hz, 7H), 7.10 (d, *J*=7.4 Hz, 6H), 6.68 (t, *J*=7.3 Hz, 4H), 6.55 (d, *J*=7.8 Hz, 8H), 4.50 (q, *J*=6.7 Hz, 5H), 1.54 (d, *J*=6.7 Hz, 13H). Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/2-propanol=98/2, 1 mL/min), t_{minor}=10.7 min; t_{major}=12.9 min, 93% ee. $[\alpha]_D^{14}$ −13.5 (*c* 0.85, CH_3OH).

*4.4.2. N-Phenyl-N-[1-(4-fluorophenyl)ethyl]amine (**14b**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.26 (m, 2H), 7.15–6.90 (m, 4H), 6.71 (t, *J*=7.3 Hz, 1H), 6.55 (d, *J*=7.8 Hz, 2H), 4.47 (dd, *J*=13.4, 6.6 Hz, 1H), 1.53 (d, *J*=6.7 Hz, 3H). Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/2-propanol=98/2, 0.5 mL/min), t_{minor}=19.9 min; t_{major}=22.7 min, 95% ee. $[\alpha]_D^{14}$ −17.1 (*c* 0.002, CH_3OH).

*4.4.3. N-Phenyl-N-[1-(4-chlorophenyl)ethyl]amine (**14c**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.28 (m, 17H), 7.22 (dd, *J*=29.8, 22.9 Hz, 7H), 7.10 (d, *J*=7.4 Hz, 6H), 6.68 (t, *J*=7.3 Hz, 4H), 6.55 (d, *J*=7.8 Hz, 8H), 4.50 (q, *J*=6.7 Hz, 5H), 1.54 (d, *J*=6.7 Hz, 13H). Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/2-propanol=98/2, 0.5 mL/min), t_{minor}=26.3 min; t_{major}=29.6 min, 94% ee. $[\alpha]_D^{14}$ −12.1 (*c* 0.03, CH_3OH).

*4.4.4. N-Phenyl-N-[1-(4-bromophenyl)ethyl)amine] (**14d**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J*=8.4 Hz, 2H), 7.16 (d, *J*=8.2 Hz, 2H), 7.01 (t, *J*=7.9 Hz, 2H), 6.59 (t, *J*=7.3 Hz, 1H), 6.40 (d, *J*=7.7 Hz, 2H), 4.34 (dd, *J*=13.4, 6.7 Hz, 1H), 1.41 (d, *J*=6.7 Hz, 3H). Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/2-propanol=95/5, 1 mL/min), t_{minor}=10.7 min; t_{major}=12.1 min, 90% ee. $[\alpha]_D^{14}$ −17.1 (*c* 0.02, CH_3OH).

*4.4.5. N-Phenyl-N-[1-(4-trifluoromethylphenyl)ethyl]amine (**14e**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 6H), 7.53 (dd, *J*=29.2, 8.1 Hz, 29H), 7.28 (s, 2H), 7.15 (dd, *J*=37.7, 29.8 Hz, 26H), 6.72 (t, *J*=7.3 Hz, 9H), 6.54 (d, *J*=7.6 Hz, 16H), 4.53 (dd, *J*=13.4, 6.7 Hz, 12H), 1.56 (d, *J*=6.7 Hz, 35H). Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/2-propanol=90/10, 1 mL/min), t_{minor}=8.7 min; t_{major}=9.8 min, 84% ee. $[\alpha]_D^{14}$ −40 (*c* 0.015, CH_3OH).

*4.4.6. N-Phenyl-N-[1-(4-nitrophenyl)ethyl)amine] (**14f**).* ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J*=8.7 Hz, 4H), 7.56 (d, *J*=8.6 Hz, 4H), 7.11 (dd, *J*=8.5, 7.4 Hz, 4H), 6.71 (t, *J*=7.3 Hz, 2H), 6.48 (d, *J*=7.7 Hz, 4H), 4.57 (dd, *J*=13.5, 6.8 Hz, 3H), 1.56 (d, *J*=6.8 Hz, 6H). Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/2-propanol=98/2, 0.5 mL/min), t_{minor}=20.4 min; t_{major}=22.1 min, 78% ee. $[\alpha]_D^{14}$ +16.5 (*c* 0.03, CH_3OH).

*4.4.7. N-Methoxyphenyl-N-[1-(4-bromophenyl)ethyl]amine (**14g**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J*=8.4 Hz, 2H), 7.25 (d, *J*=9.2 Hz, 2H), 6.74–6.66 (m, 2H), 6.50 (d, *J*=8.7 Hz, 2H), 4.36 (dd, *J*=13.2, 6.6 Hz, 1H), 3.69 (d, *J*=6.0 Hz, 3H), 1.51 (d, *J*=6.7 Hz, 3H). Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/2-propanol=98/2, 1 mL/min), t_{major}=19.8 min; t_{minor}=26.2 min, 80% ee. $[\alpha]_D^{14}$ +11.69 (*c* 0.03, CH_3OH).

*4.4.8. N-Phenyl-N-[1-(4-methoxyphenyl)ethyl]amine (**14h**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J*=12.4 Hz, 2H), 7.17–6.99 (m, 2H), 6.99–6.79

(m, 2H), 6.73–6.46 (m, 3H), 4.47 (q, *J*=6.7 Hz, 1H), 3.79 (s, 3H), 1.52 (d, *J*=6.7 Hz, 3H). Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/2-propanol=98/2, 1 mL/min), t_{minor}=13.2 min; t_{major}=14.1 min, 79% ee. $[\alpha]_D^{14}$ −13.93 (*c* 0.01, CH_3OH).

*4.4.9. N-Methoxyphenyl-N-[(1-phenyl)ethyl]amine (**14i**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.57–7.28 (m, 4H), 7.31–7.14 (m, 1H), 6.82–6.66 (m, 2H), 6.51 (d, *J*=8.9 Hz, 2H), 4.44 (dd, *J*=13.3, 6.6 Hz, 1H), 3.72 (s, 3H), 1.53 (d, *J*=6.7 Hz, 3H). Enantiomeric excess was determined by HPLC with a chiralcel AD-H column (hexane/2-propanol=98/2, 1 mL/min), t_{major}=10.7 min; t_{minor}=12.3 min, 96% ee. $[\alpha]_D^{14}$ −2.03 (*c* 0.013, CH_3OH).

*4.4.10. N-Ethoxyl-N-[(1-phenyl)ethyl]amine (**14j**).* MS-ESI, *m*/*z* 242 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.56–7.10 (m, 5H), 6.92–6.58 (m, 2H), 6.51 (d, *J*=8.6 Hz, 2H), 4.42 (dd, *J*=13.2, 6.6 Hz, 1H), 3.91 (dd, *J*=13.9, 7.0 Hz, 2H), 1.53 (d, *J*=6.7 Hz, 3H), 1.34 (t, *J*=7.0 Hz, 3H). Enantiomeric excess was determined by HPLC with a chiralcel AD-H column (hexane/2-propanol=98/2, 1 mL/min), t_{major}=9.9 min; t_{minor}=11.5 min, 92% ee. $[\alpha]_D^{14}$ −18.2 (*c* 0.015, CH_3OH).

*4.4.11. N-Methylphenyl-N-[(1-lphenyl)ethyl]amine (**14k**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.46–7.30 (m, 4H), 7.25 (s, 1H), 6.93 (d, *J*=8.1 Hz, 2H), 6.48 (d, *J*=8.4 Hz, 2H), 4.48 (q, *J*=6.7 Hz, 1H), 2.22 (s, 3H), 1.54 (d, *J*=6.7 Hz, 3H). Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/2-propanol=99/1, 1 mL/min), t_{major}=11.3 min; t_{minor}=13.1 min, 93% ee. $[\alpha]_D^{14}$ +3.6 (*c* 0.025, CH_3OH).

*4.4.12. N-Ethylphenyl-N-[(1-phenyl)ethyl]amine (**l4l**).* MS-ESI, *m*/*z* 226 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.60–7.09 (m, 5H), 6.95 (d, *J*=8.0 Hz, 2H), 6.51 (d, *J*=8.0 Hz, 2H), 4.47 (dd, *J*=12.9, 6.3 Hz, 1H), 2.51 (dd, *J*=14.9, 7.4 Hz, 2H), 1.54 (d, *J*=6.6 Hz, 3H), 1.16 (t, *J*=7.5 Hz, 3H). Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/2-propanol=97/3+0.1% Et_3N, 1 mL/min), t_{major}=8.2 min; t_{minor}=8.8 min, 93% ee. $[\alpha]_D^{14}$ −1.74 (*c* 0.025, CH_3OH).

*4.4.13. N-4-Bromophenyl-N-[(1-phenyl)ethyl]amine (**14m**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.29 (m, 4H), 7.29–7.22 (m, 1H), 7.16 (d, *J*=8.8 Hz, 2H), 6.40 (d, *J*=8.8 Hz, 2H), 4.44 (q, *J*=6.7 Hz, 1H), 1.53 (d, *J*=6.7 Hz, 3H). Enantiomeric excess was determined by HPLC with a chiralcel OD-H column (hexane/2-propanol=99/1, 1 mL/min), t_{major}=15.3 min; t_{minor}=20.5 min, 76% ee. $[\alpha]_D^{14}$ 26.6 (*c* 0.008, CH_3OH).

*4.4.14. N-phenyl-N-(1-lphenylpropyl)amine (**14n**).* ^1H NMR (400 MH z, $CDCl_3$) δ 7.54–7.17 (m, 5H), 7.09 (t, *J*=7.3 Hz, 2H), 6.64 (dd, *J*=41.1, 6.7 Hz, 3H), 4.22 (t, *J*=6.4 Hz, 1H), 1.88 (dd, *J*=13.1, 6.5 Hz, 2H), 0.92 (dd, *J*=19.6, 12.4 Hz, 3H). Enantiomeric excess was determined by HPLC with a chiralcel AD-H column (hexane/2-propanol=98/2, 1 mL/min), t_{minor}=13.0 min; t_{major}=15.2 min, 94% ee. $[\alpha]_D^{14}$ +40 (*c* 0.01, CH_3OH).

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