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

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A B S T R A C T
A novel asymmetric-axle-supported chiral N–O amide was synthesized and used in catalytic enantioselective hydrosilylation of N-aryl ketimines with HSiCl3 at room temperature instead of the typical −20 °C. High conversion yield and high enantioselectivity up to 96% were observed.

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1. Introduction

Enantioselective hydrosilylation of C=N with HSiCl3 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,c 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 C2-asymmetric ligand (6),7 and others8 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 been reported in the enantioselective hydrosilylation of C=N with HSiCl3. In our recent study, a bisscarboline 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 (1S,2R)-(−)-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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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 (R1=Ph, R2=Ph, R3=Me) with HSiCl3 at 0°C in CHCl3. We then investigated the effects of temperature (from −20 to 40°C) and solvent (CH2Cl2, CHCl3 or toluene) on the enantioselectivity. The optimized reaction condition was found to be 20 mol % of 8 in CHCl3 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 CH3OH.

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-

3. Conclusion

In conclusion, we prepared a novel asymmetric-axle-supported chiral N–O amide 8a as highly efficient Lewis basic organocatalyst
4.2.1. 9,9'-Dimethyl-9H,9'H-11'-bipyrano[3,4-b]indole-3,3'-dicarboxylic acid (10). To a solution of 9 (5 mmol in CH$_2$OH (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 calcld for C$_{20}$H$_{18}$N$_{13}$O$_{6}$Na [M- Na$^+$] 473.2125, found 473.2130. 1H NMR (400 MHz, DMSO) $\delta$ 3.47 (3H, d, J=7.6 Hz, 1H), 3.74 (2H, t, J=7.4 Hz), 7.66–7.78 (2H, m, 8.18 (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), 7.49–7.68 (3m, 2H), 7.67 (t, J=7.5 Hz, 1H), 7.18–7.30 (6H), 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=7.0, 5.0 Hz, 1H, PhCHO), 5.48–5.37 (m, 1H, PhCHO), 5.06 (d, J=4.9 Hz, 1H, PhCH$_2$), 4.56 (s, 1H, PhCH$_2$), 3.28 (s, 3H, NCH$_3$), 3.26 (s, 3H, NCH$_3$) [13]C NMR (150 MHz, CDCl$_3$) $\delta$ 165.28, 164.67, 143.11, 143.08, 139.95, 139.85, 139.23, 138.06, 137.81, 137.49, 137.29, 137.20, 131.29, 129.56, 129.44, 128.33, 128.12, 128.73, 127.99, 127.58, 127.59, 127.25, 126.88, 126.21, 122.23, 122.11, 123.11, 122.9, 121.15, 121.02, 115.09, 114.88, 110.06, 110.03, 79.50, 77.51, 77.32, 77.11, 76.89, 75.71, 75.91, 69.55, 32.85, 32.57.

4.2.2. NN'-Bis[1R,2S-2-hydroxy-1,2-diphenylethyl]-9,9'-dimethyl-9H,9'H-11'-bipyrano[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 gives 11b [m/z] 856.3373, found 856.3380. 1H NMR (400 MHz, CDCl$_3$) $\delta$ 15.12 (s, 1H, NH), 9.09 (s, 1H, NH), 8.76 (d, J=2.9 Hz, 1H), 8.60 (d, J=1.0 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, Ph), 7.09 (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, PhCHO), 5.76 (dt, J=8.9 Hz, 6H, 1H, PhCHO), 5.35 (s, 3H, NCH$_3$), 3.30 (s, 3H, NCH$_3$), 1.91 (s, 3H, CO$_2$H), 1.79 (s, 3H, CO$_2$H). [13] C NMR (101 MHz, CDCl$_3$) $\delta$ 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, 133.91, 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, 203.93, 206.88.

4.2.3. 3,3'-Bis[(1R,2S-2-hydroxy-1,2-diphenylethyl)aminocarbonyl]-9,9'-dimethyl-9H,9'H-11'-bipyrano[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. [m/z] 879 [M+Na$^+$]. HRMS-ESI, m/z calcld for C$_{20}$H$_{18}$N$_{13}$O$_{6}$Na [M+Na$^+$] 856.3373, found 856.3340. 1H NMR (600 MHz, CDCl$_3$) 9.08 (s, 1H, NH), 8.91 (s, 1H, NH), 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=5.5 Hz, 1H), 5.47 (s, 1H, PhCHO), 5.37 (d, J=6.4 Hz, 1H, PhCHO), 5.18 (d, J=4.6 Hz, 1H, PhCH$_2$), 4.49 (s, 1H, PhCHO), 3.64 (s, 3H, NCH$_3$), 3.08 (s, 3H, NCH$_3$) [13] C NMR (151 MHz, CDCl$_3$) $\delta$ 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, 123.37.
in anhydrous CHCl₃ 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 NaHCO₃ and was extracted with CH₂Cl₂. The combined organic layers were washed with brine and dried over anhydrous MgSO₄ 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). [4]H NMR (400 MHz, CDCl₃) 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, 3H). Enantiomeric excess was determined by HPLC with a chiral OD-H column (hexane/2-propanol=98/2, 0.5 ml/min), t_minor=10.7 min; t_major=12.9 min, 93% ee. [α]D³⁰ = −13.5 (c = 0.85, CH₃OH).

4.4.2. N-Phenyl-N-[1-(4-fluorophenyl)ethyl]amine (14b). [4]H NMR (400 MHz, CDCl₃) 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 chiral OD-H column (hexane/2-propanol=98/2, 0.5 ml/min), t_minor=19.5 min; t_major=22.7 min, 95% ee. [α]D³⁰ = −171 (c = 0.002, CH₂OH).

4.4.3. N-Phenyl-N-[1-(4-chlorophenyl)ethyl]amine (14c). [4]H NMR (400 MHz, CDCl₃) 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, 3H). Enantiomeric excess was determined by HPLC with a chiral OD-H column (hexane/2-propanol=98/2, 0.5 ml/min), t_minor=26.3 min; t_major=29.6 min, 94% ee. [α]D³⁰ = −12.1 (c = 0.03, CH₂OH).

4.4.4. N-Phenyl-N-[1-(4-bromophenyl)ethyl]amine (14d). [4]H NMR (400 MHz, CDCl₃) 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 chiral OD-H column (hexane/2-propanol=95/5, 1 ml/min), t_minor=10.7 min; t_major=12.1 min, 90% ee. [α]D³⁰ = −171 (c = 0.02, CH₂OH).

4.4.5. N-Phenyl-N-[1-(4-trifluoromethyl)phenyl]ethyl]amine (14e). [4]H NMR (400 MHz, CDCl₃) 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 chiral OD-H column (hexane/2-propanol=90/10, 0.1 ml/min), t_minor=8.8 min; t_major=9.8 min, 84% ee. [α]D³⁰ = −40 (c = 0.015, CH₃OH).

4.4.6. N-Phenyl-N-[1-(4-nitrophenyl)ethyl]amine (14f). [4]H NMR (400 MHz, CDCl₃) 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 chiral OD-H column (hexane/2-propanol=98/2, 0.5 ml/min), t_minor=20.4 min; t_major=22.1 min, 78% ee. [α]D³⁰ = +16.5 (c = 0.03, CH₃OH).

4.4.7. N-Methoxyphenyl-N-[1-(4-bromophenyl)ethyl]amine (14g). [4]H NMR (400 MHz, CDCl₃) 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 chiral OD-H column (hexane/2-propanol=98/2, 1 ml/min), t_minor=19.8 min; t_major=26.2 min, 80% ee. [α]D³⁰ = +11.69 (c = 0.03, CH₃OH).


4. General procedure for the hydroisolation of ketimines

Under an argon atmosphere, 2 equiv trichlorosilane was added dropwise to a stirred solution of imine 13 and catalyst 8a (20 mol %)
4.4.4. N-Methoxyphenyl-N-[(1-phenyl)ethyl]amine (14i). 1H NMR (400 MHz, CDCl₃) 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 chiral AD-H column (hexanec/2-propanol=98/2, 1 mL/min), tminor=13.0 min; tmajor=15.2 min, 94 ee% [%]d = +40 (c 0.01, CH₃OH).

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References and notes


