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Chiral amino alcohols derived from (*S*)-6-chloronicotine as catalysts for asymmetric synthesis

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ABSTRACT

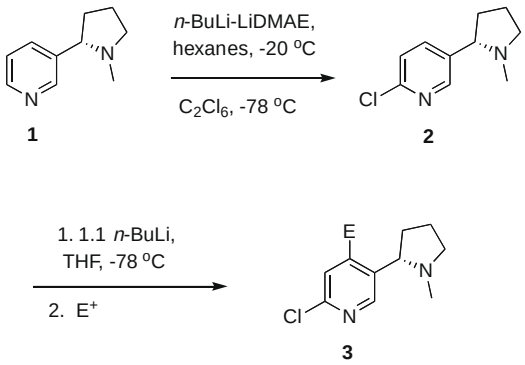
Commercially available (*S*)-nicotine was converted in two or three synthetic steps to various chiral amino alcohols. These nicotine derivatives were evaluated as potential chiral ligands for metal-catalyzed asymmetric reactions by using the addition of diethylzinc to aldehydes as a screen. Several reactions proceeded with a high degree of enantioselectivity providing good yields of secondary alcohols of high enantiopurity.

Currently there is considerable interest in the synthesis of chiral ligands for metal-catalyzed asymmetric reactions.[1] Although numerous enantiopure chelating ligands have been prepared, there is still a need for new types obtainable by concise syntheses from inexpensive starting materials. (*S*)-Nicotine is a commercially available enantiopure amine that has been underutilized in organic synthesis. Recently in our laboratories,[2] we have been developing methods for the substitution of natural nicotine with the goal of producing analogues as potential therapeutics for central nervous system (CNS)-related disorders.[3] As a spin-off of this program, a study on the application of our nicotine substitution methods to the preparation of novel ligands for asymmetric synthesis was initiated. Since amino alcohols are well established as an effective class of ligands for asymmetric reactions,[4] they were chosen as our first synthetic targets. Herein is reported the preparation of novel chiral amino alcohols in two to three steps from natural (*S*)-nicotine.

(*S*)-Nicotine (1) can be converted to 6-chloronicotine (2) in one step by directed lithiation[5] using *n*-BuLi-LiDMAE.[6] Subsequent metalation at C-4 of 2 with *n*-BuLi gives a 4-lithio intermediate which on addition of electrophiles affords the desired 4,6-disubstituted nicotines[7] (Scheme 1). This methodology can be used to provide C-4 substituted amino-alcohol ligands in two steps from nicotine. The addition of an aryl aldehyde to 6-chloro-4-lithionicotine gave approximately a 1:1 mixture of diastereomers **5** and **6** as shown in Table 1 (entries 1–4). The diastereomers were separated by silica gel chromatography to afford pure alcohols in moderate yields. The relative stereochemistry of **5a** was determined by single crystal X-ray analysis.[7] The use of symmetrical ketones (**4**) as electrophiles avoided diastereomer separation and provided an increase in yield of the desired amino alcohols **7** (entries 5–8).

In addition to the above ligands, the C-2 tertiary alcohol **9** was prepared from iodide **8**[8], and the C_2 symmetric alcohol **11** was prepared from aldehyde **10**[8] as shown in Scheme 2.

With the synthesized ligands in hand, their ability to transfer chirality was screened using the asymmetric addition of diethylzinc to benzaldehyde.[9] Initially, reactions were run with 20% catalyst loading in toluene at 0 °C for 24 h (Table 2). The C-4 secondary alcohol **5a** (entry 2) provided both a better yield and enantioselectivity for the asymmetric reaction than the C-2-substituted ligand **9** (entry 1). Both diastereomers of the secondary alcohol ligands (**5** and **6**) were examined as catalysts in the diethylzinc reaction as shown in entries 2–9. Interestingly, only the nicotine ligands containing a C-4 phenylmethanol unit of the *R* configuration provided good enantioselectivity. Compound **6d** gave the highest enantiomeric excess for this class of ligands (entry 9); however, the 1-naphthyl-substituted ligand **6c** provided a similar ee of 76% with an 83% yield. In the case of **6d**, the electron-withdrawing effect of



Scheme 1. Directed lithiation of nicotines **1** and **2**.

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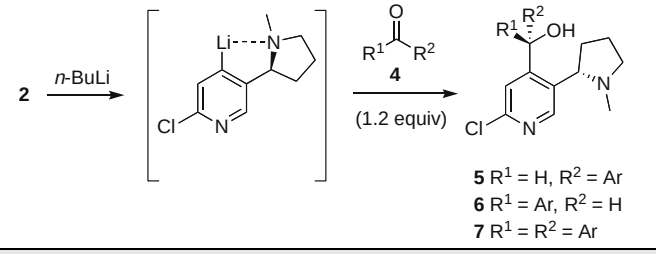
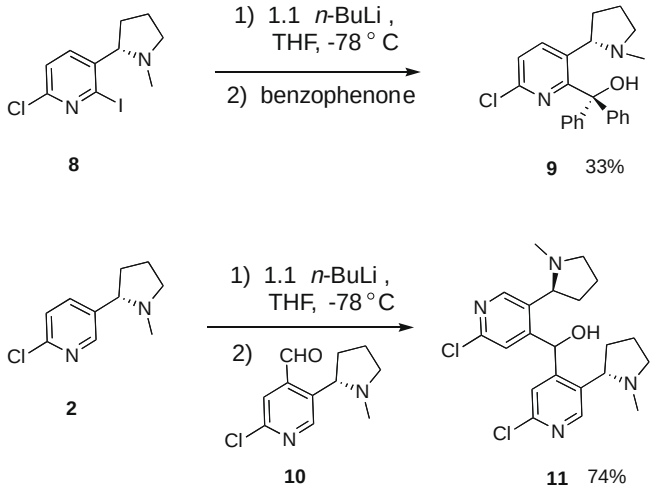
Table 1
Formation of secondary and tertiary alcohols at the C-4 position of **2**



5 R^1 = H, R^2 = Ar
6 R^1 = Ar, R^2 = H
7 R^1 = R^2 = Ar

Entry	4	Yield **5** (%)	Yield **6** (%)	Yield **7** (%)
1	Benzaldehyde	**5a**[a], 31	**6a**[a], 37	—
2[b]	2-Naphthaldehyde	**5b**, 21	**6b**, 25	—
3[b]	1-Naphthylaldehyde	**5c**, 12	**6c**, 14	—
4[b]	Pentafluorobenzaldehyde	**5d**, 25	**6d**. 35	—
5	Benzophenone	—	—	**7a**, 68
6	Di-naphthalen-2-yl methanone	—	—	**7b**, 50
7	Bis-(4-*tert*-butylphenyl) methanone	—	—	**7c**, 39
8	Decafluorobenzophenone	—	—	**7d**. 51

[a] Known compound.
[b] The absolute stereochemistry at the C-4 position of **5** and **6** was determined by the X-ray diffraction of and comparison to **5a**.



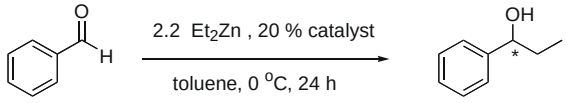
Scheme 2. Synthesis of ligands **9** and **11**.

the fluorines on the aromatic ring created an increase in chirality transfer as compared to the phenyl derivative **6a**.

In general, the C-4 tertiary alcohols (entries 10–13) enhanced the enantioselectivity of the catalytic asymmetric reaction more than the secondary alcohols. The decafluoro tertiary alcohol **7d** provided the best enantioselectivity (95% ee) overall. Surprisingly, the increased bulkiness of the *tert*-butyl groups on compound **7c** did not improve the selectivity over that afforded by **7a** and even caused a decrease in asymmetric induction.

After discovering that **7d** was the most effective catalyst at 20 mol % loading, the asymmetric reaction parameters were optimized by varying the amount of catalyst (Table 3). When going from 20% to 10% of catalyst (**7d**), only a slight change in yield and ee was observed. Much to our delight, the reaction was more efficient and successful when 5% of catalyst **7d** was employed in the reaction; however, when lowering to 2% of **7d** a decrease in selectivity was observed (Table 3, entry 4). Using the optimized conditions, **7d** was used to catalyze the addition of diethylzinc to other aldehyde substrates as shown in Table 3.

Table 2
Screening of nicotine-derived ligands in the catalytic asymmetric addition of diethylzinc to benzaldehyde



Entry	Catalyst	Yield (%)	ee[a] (%)
1	**9**	42	2 (*R*)
2	**5a**	82	14 (*R*)
3	**6a**	64	64 (*R*)
4	**5b**	13	2 (*S*)
5	**6b**	73	64 (*R*)
6	**5c**	90	10 (*S*)
7	**6c**	83	76 (*R*)
8	**5d**	64	7 (*R*)
9	**6d**	48	79 (*R*)
10	**7a**	78	79 (*R*)
11	**7b**	83	83 (*R*)
12	**7c**	72	66 (*R*)
13	**7d**	66[b]	**95 (*R*)**
14	**11**	91	67 (*R*)

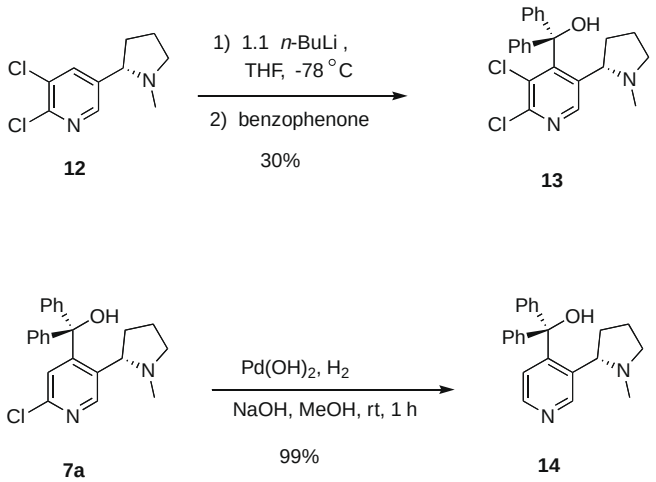
[a] Determined by chiral HPLC on column Chiralcel OD, 10% *i*-propanol/hexanes as the eluent and a flow rate of 1.00 mL/min.
[b] Lower yield due to difficulties in purification.

The –Cl and –OCH_3 substituents on the aromatic ring did not seem to have a significant effect on the enantioselectivity of the reaction (entries 5 and 6) and afforded similar results; however, the yield of the reaction was lower with chlorobenzaldehyde as the substrate. When cinnamaldehyde and hydrocinnamaldehyde

Table 3
Et_2Zn addition to aldehydes catalyzed by **7d**

Entry	RCHO	**7d**, mol %	Yield[a] (%)	ee[b] (%) (*R*)
1	Benzaldehyde	20	66	96
2	Benzaldehyde	10	55	95
3	Benzaldehyde	5	89	95
4	Benzaldehyde	2	83	89
5	*p*-Chlorobenzaldehyde	5	57	94
6	*p*-Methoxybenzaldehyde	5	78	94
7	Hydrocinnamaldehyde	5	43	69
8	Cinnamaldehyde	5	88	72

[a] Lower yield due to difficulties in purification.
[b] Determined by chiral HPLC on column Chiralcel OD with λ = 219 nm, 2–10% *i*-propanol/hexanes as the eluent and a flow rate of 0.8–1.00 mL/min.



Scheme 3. Preparation of ligands **13** and **14**.

Table 4
Effect of chlorine substituents[a]

Entry	Catalyst	mol %	Yield (%)	ee (%)
1	**7a**	20	78	79 (*R*)
2	**13**	20	61	95 (*R*)
3	**13**	5	91	92 (*R*)
4	**14**	20	69	63 (*R*)
5	**14**	5	36	60 (*R*)

[a] Reactions were run at 0 °C for 24 h in toluene.

were employed in the reaction, a decrease in enantioselectivity occurred. In an attempt to discover a way to bring the selectivity up for these aldehydes, a few different reaction conditions were tested but no improvement was observed. Overall, the novel nicotine-based decafluorocatalyst demonstrates good yields and high enantioselectivities when employed in the catalytic asymmetric addition of diethylzinc to aromatic aldehydes.

Finally, to investigate the effect of the C-6 chlorine substituent on the nicotine-based catalysts during the asymmetric reaction, compounds **13** and **14** were synthesized from **12** and **7a** as shown in Scheme 3 and compared to **7a**. This comparison was intended to provide insight as to whether or not the C-4 substituted nicotine-based catalysts could be modified to enhance enantioselectivity in the asymmetric reaction by adding or removing chlorine substituents on the pyridine ring. Addition of a chlorine substituent to the C-5 position of the catalyst, as shown with compound **13**, increased the selectivity from 79% to 95% ee at 20 mol %, but at 5 mol % a slight decrease in selectivity was observed (Table 4, entries 2 and 3). In contrast, catalyst **14**, with no chlorine substituents, effected a decrease in observed selectivity as compared to ligand **7a** (entries 4 and 5). This study showed that it is necessary to have at least one chlorine substituent on the pyridine portion of the catalyst in order to maintain adequate enantioselectivity in the asymmetric addition of organozinc reagents to aldehydes.

Although further study is needed to understand how the substituents affect the degree of chirality transfer, it appears that a C-6 electron-withdrawing group may be needed to reduce the basicity, and thus the coordinating ability, of the pyridyl nitrogen.

In summary, novel chiral amino alcohol catalysts have been prepared in two to three steps from natural (*S*)-nicotine.[10] The ability of these catalysts to transfer chirality was determined by using the asymmetric addition of diethylzinc to aldehydes as a screen. A high degree of enantioselectivity was obtained in several examples. The effectiveness of these catalysts in other asymmetric reactions and the synthesis of other types of ligands from commercially available (*S*)-nicotine are under study in our laboratories.

Acknowledgments

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10. *General procedure for the preparation of the nicotine-derived ligands*: To a solution of (*S*)-6-chloronicotine (**2**, 200 mg, 1.02 mmol) in THF (2 mL) was added *n*-BuLi (0.68 mL, 1.12 mmol) at −78 °C. After 1 h, a solution of the aldehyde or ketone (1.2 equiv) in toluene (2 mL) kept over molecular sieves was cannulated into the reaction. The mixture was stirred for 30–60 min at −78 or −42 °C after which it was quenched with aqueous saturated sodium bicarbonate (2 mL). After warming to room temperature, the organic layer was separated. The aqueous layer was extracted with methylene chloride (2 × 10 mL). The combined organic layers were dried over potassium carbonate, filtered, and concentrated in vacuo. The crude product was purified by radial PLC (silica gel).
Spectral data: *[5-((2S)-1-Methylpyrrolidin-2-yl)-2-chloro(4-pyridyl)]bis(2,3,4,5,6-pentafluorophenyl)methan-1-ol* (**7d**). The crude product was purified using radial PLC (5% TEA/hexanes; then CH_2Cl_2) to afford 146 mg (51%) of **7d** as a white solid, mp 38–40 °C; $[\alpha]_D^{32}$ −16.9 (*c* 1.1, CH_2Cl_2); IR (thin film) 3380, 2963, 2924, 2856, 1650, 1578, 1524, 1484, 1122, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.82 (s, 1H), 8.36 (s, 1H), 6.93 (s, 1H), 3.54–3.49 (m, 1H), 3.35–3.30 (m, 1H), 2.49–2.41 (m, 1H), 2.27 (s, 3H), 2.24–2.17 (m, 1H), 2.13–1.96 (m, 2H), 1.93–1.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 153.2, 152.5, 146.7, 143.4, 142.9, 139.8, 139.7, 136.7, 136.5, 132.6, 125.3, 79.5, 71.4, 56.3, 39.7, 32.7, 22.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −133.2 (d, *J* = 18.6 Hz, 2F), −133.9 (d, *J* = 18.6 Hz, 2F), −149.7 (m, 2F), −157.4 (m, 4F); HRMS calcd for $C_{23}H_{13}ClF_{10}N_2O$ ($[M+H]^+$) 559.0635, found 559.0654.
Bis[5-((2S)-1-methylpyrrolidin-2-yl)-2-chloro-4-pyridyl]methan-1-ol (**11**). The crude product was purified using radial PLC (1% TEA/30% EtOAc/hexanes) to afford 249 mg (74%) of **11** as a white solid, mp 80–82 °C; $[\alpha]_D^{31}$ −101 (*c* 0.95, CH_2Cl_2); IR (thin film) 3238, 2967, 2876, 2840, 2787, 1582, 1455, 1372, 1146, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.54 (s, 1H), 8.24 (s, 1H), 7.67 (s, 1H), 6.41 (s, 1H), 6.31 (s, 1H), 3.46–3.42 (m, 1H), 3.38–3.32 (m, 1H), 3.10–3.06 (m, 1H), 2.89–2.85 (m, 1H), 2.51–2.41 (m, 2H), 2.33–2.20 (m, 4H), 2.16–2.03 (m, 3H), 1.98 (s, 3H), 1.92–1.79 (m, 1H), 1.69–1.56 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 152.4, 151.6, 151.3, 150.7, 135.1, 133.6, 123.6, 122.7, 69.8, 67.0, 66.3, 57.3, 57.1, 40.7, 40.6, 34.5, 31.9, 24.6, 22.9; HRMS calcd for $C_{21}H_{26}Cl_2N_4O$ (M^+) 421.1556, found 421.1554.
5-((2S)-1-Methylpyrrolidin-2-yl)-2,3-dichloro(4-pyridyl)diphenylmethan-1-ol (**13**). The crude product was purified using radial PLC (1% TEA/2% EtoAc/hexanes; then CH_2Cl_2) to afford 46 mg (30%) of **13** as a white solid, mp 170–172 °C; $[\alpha]_D^{32}$ −164.5 (*c* 1.1, CH_2Cl_2); IR (thin film) 3321, 3057, 3027, 2957, 2784, 1550, 1489, 1447, 1310, 1219, 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 8.30 (s, 1H), 7.41–7.31 (m, 5H), 7.26–7.21 (m, 3H), 7.12–7.10 (m, 2H), 3.48–3.43 (m, 1H), 3.12–3.08 (m, 1H), 2.64–2.55 (m, 1H), 2.34–2.28 (m, 1H), 2.26–2.19 (m, 1H), 2.12–2.00 (m, 1H), 1.89–1.83 (m, 1H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 150.4, 147.4, 143.2, 136.7, 129.0, 128.2, 128.0, 127.9, 127.8, 127.1, 84.8, 73.2, 56.5, 39.4, 34.8, 22.0; HRMS calcd for $C_{23}H_{22}Cl_2N_2O$ (M^+) 413.1181, found 413.1173.