Bis(ethylsulfonamide)amines via nucleophilic ring-opening of chiral aziridines. Application to Ti-mediated addition of diethylzinc to benzaldehyde

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Abstract: Homochiral bis(*N*-triflyl-2-alkyl-2-aminoethyl)amines, obtained from *N*-triflyl-2-alkylaziridines via reaction with benzylamine, catalyze the titanium-mediated addition of diethylzinc to benzaldehyde to yield 1-phenylpropanol in up to 78% ee in the presence of molecular sieves. Use of tetradentate analogs prepared by reaction of the aziridine with 2-(aminomethyl)pyridine or 2-aminophenol resulted in lower enantioselectivity. © 1997 Elsevier Science Ltd

Introduction

Asymmetric metal catalysis constitutes one of the most efficient methods to obtain enantiopure chiral compounds.[1] Extensive efforts are therefore devoted to the catalytic reactions.[2]

Chiral aziridines may serve as convenient starting materials for a variety of chiral ligands. The chiral aziridines are easily prepared from chiral amino alcohols,[3] which in turn are obtained by reduction of amino acids.[4] When activated by the presence of a Lewis acid or by an electron-withdrawing substituent on nitrogen, the heterocyclic ring undergoes smooth ring opening upon reaction with nucleophiles.[5] Ring opening of unsubstituted *N*-sulfonylaziridines with primary amines was early shown to yield achiral diethylenetriamine derivatives,[6] whereas chiral analogs were obtained by treatment of chiral enantiopure aziridines with ammonia or primary amines.[7] We have recently shown that ammonia reacts with three equivalents of aziridines in methanol to yield C_3-symmetric tetradentate tripodal trisamidoamines.[8] *N*-Alkylation followed by removal of the sulfonyl group, which is readily achieved when the *p*-nitrobenzenesulfonyl (nosyl) group is employed,[9] gives access to alkyl-substituted amines.

We have now extended this methodology to include reactions with primary amines, such as benzylamine, 2-(aminomethyl)pyridine and 2-aminophenol, as nucleophiles, thus providing a facile route to a variety of tridentate C_2-symmetric and tetradentate C_1-symmetric ligands. The products obtained have been assessed as catalysts for the addition of diethylzinc to benzaldehyde in the presence of titanium tetraisopropoxide.[10]

Results and Discussion

Preparation of ligands

Aminoalcohols **1a–1c** were reacted with triflic anhydride in methylene chloride in the presence of triethylamine to yield, in one step, aziridines **2a–2c** in high (89–100%) yields (Scheme 1). Subsequent treatment of the aziridines with benzylamine **3** in methanol at room temperature gave C_2-symmetric triamines **4a–4c** in 65–68% yield. Compound **1a** was used as a commercial mixture (ca. 85:15) of the *R* and *S* enantiomers, and **4a** was therefore formed along with its stereoisomers. The ^{1}H NMR spectrum of the product showed the presence of two diastereomers in a ratio (ca. 80:20) which is close to the expected statistical distribution of isomers. This ratio remained the same after chromatography of the product.

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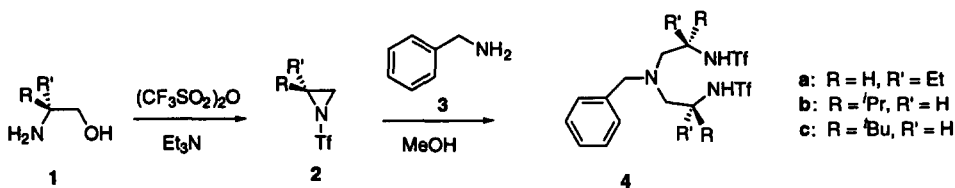
Scheme 1.

This methodology allows for extensive structural modifications, since a large number of primary amines can be used as nucleophiles in the ring opening reaction. Thus, reaction of aziridine **2b** with 2-(aminomethyl)pyridine (**5**) and 2-aminophenol (**6**) yielded **7** and **8**, respectively (Scheme 2). Compound **7** was obtained in a mere 20% yield, probably due to competing quaternization of the pyridine nitrogen.
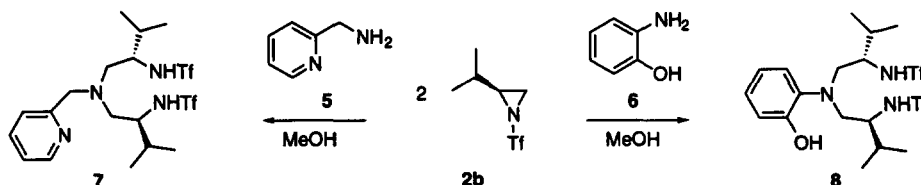
Scheme 2.

Catalytic reactions

The ligands thus obtained were tested as catalysts in the addition of diethylzinc to benzaldehyde **9** in the presence of titanium tetraisopropoxide to yield (*R*)- and (*S*)-1-phenylpropanol [(*R*)-**10** and (*S*)-**10**] (Scheme 3).
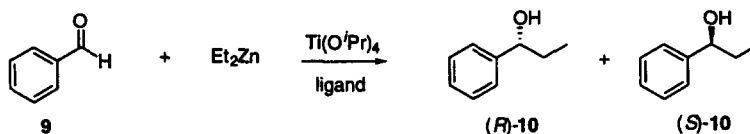
Scheme 3.

In order to study the influence of the reaction conditions on the selectivity of the catalytic reaction, ligand **4a** (as a mixture of stereoisomers) was first employed as a catalyst. The reaction was slow and resulted in poor selectivity. Upon addition of powdered 4Å molecular sieves (100 mg/mmol of substrate), a higher yield as well as a somewhat higher selectivity (18% ee) was observed (entry 1, Table 1). Doubling the amount of sieves had a beneficial effect on the selectivity (28% ee, entry 2), whereas a further increase had no influence. The amount of titanium isopropoxide also proved to be important, as an increase from 0.4 to 1.35 equiv. resulted in a substantially higher selectivity (51% ee).

These conclusions were corroborated using ligand **4b** as catalyst (73 and 78% ee[11] using 100 and 250 mg, respectively, of molecular sieves per mmol of substrate, entries 4 and 5). With this ligand it was found that a further increase of the amount of titanium alcoholate did not afford improved results. Use of the sterically bulkier ligand **4c**, under those conditions affording best results for **4b**, resulted in lower selectivity (63% ee, entry 7).

The tetradentate ligands **7** and **8** (entries 8 and 9) were both found to be inferior catalysts than the tridentate analogs, **7** exhibiting no selectivity at all.

Table 1. Titanium-mediated addition of diethylzinc to benzaldehyde

Entry	Ligand	Ti(O^{i}Pr)$_4$ (equiv)	MS (mg/mmol of 9)	time (h)	yield (%)	ee (%) abs.config
1	4a	0.40	100	36	73	18 R
2	4a	0.40	250	36	74	28 R
3	4a	1.35	100	36	70	51 R
4	4b	1.35	100	102	68	73 S
5	4b	1.35	250	102	74	78 S
6	4b	2.15	250	102	74	75 S
7	4c	1.35	250	62	51	63 S
8	7	1.35	250	62	11	0
9	8	1.35	250	96	47	39 S

Conditions: Benzaldehyde (1 equiv), diethylzinc (1.2 equiv), ligand (0.125 equiv), and toluene (2 mL). A titanium complex was prepared from the ligand and 1 equiv of Ti(O^{i}Pr)$_4$ in the presence of molecular sieves. The reagents were then mixed at -78 °C, new molecular sieves were added (the amount indicated in the table), whereafter the reactions were run at -30 °C.

Molecular sieves[12] have previously been shown to favor ligand exchange on Ti(IV) and thus formation of the active catalyst.[13] The titanium complex obtained from ligands 4 turned out not to be sensitive to exposure to air, since filtering in air gave the same result as use of Schlenck equipment.

Conclusion

Use of ligands 4 as catalysts for the titanium-mediated addition of diethylzinc to benzaldehyde resulted in a moderate stereoselectivity, lower than that observed with analogous disulfonamides.[14] However, the method presented for the preparation of ligands allows for large structural variations and new derivatives will be explored for catalytic applications.

Experimental Section

General

Chemicals were purchased from Aldrich and Lancaster and used as received unless otherwise stated. (S)-*tert*-Leucinol[15] was prepared according to a literature procedure and (R)-2-aminobutan-1-ol (70% ee) was purchased from Tokyo Kasei. Benzylamine, benzaldehyde and Ti(O^{i}Pr)$_4$ were distilled before use. CH$_2$Cl$_2$ was distilled from P$_2$O$_5$ and diethyl ether from benzophenone ketyl. MPLC (Medium Pressure Liquid Chromatography) and flash chromatography were carried out using Merck silica gel 60H. Melting points are uncorrected. Enantiomeric excesses were determined by GLC using a chiral column (Supelco γ-DEX 120). The assignment of the absolute configuration of compounds (R)-10 and (S)-10 was made by optical rotation measurements and comparison with literature data.[16] ^{1}H NMR spectra were recorded at 400 MHz in CDCl$_3$ with the solvent as reference. Powdered 4Å molecular sieves were used. Compound 2b was prepared as previously described.[8]

(R)-N-Triflic-2-ethylaziridine (2a)

A solution of (R)-2-aminobutan-1-ol (1a, 482 mg, 5.40 mmol) and triethylamine (1.51 mL, 10.82 mmol) in 35 mL of dry CH$_2$Cl$_2$ under N$_2$ was cooled to −78°C and triflic anhydride (2.00 mL, 11.9 mmol) was added dropwise during 1 h. The mixture was stirred at this temperature for 2 h and then at −30°C overnight. The cold solution was diluted with cold CH$_2$Cl$_2$ (40 mL) and washed with cold HCl (0.1 M, 2×55 mL) and cold sat. aq. NaHCO$_3$ (2×55 mL). The organic phase was dried (MgSO$_4$) and the solvent was evaporated to give 975 mg (89%) of 2 as a slightly yellow oil, which was used without further purification. ^{1}H NMR δ 3.05 (1H, app tt, J=7.0 and 4.9 Hz), 2.89 (1H, d, J=7.0 Hz), 2.43 (1H, d, J=4.3 Hz), 1.77 (1H, dqd, J=14.5, 7.3 and 5.0 Hz), 1.58 (1H, dqd, J=14.5, 7.3 and 7.3 Hz), 1.05 (3H, t, J=7.3 Hz).

*(S)-N-Triflic-2-*tert-*butylaziridine (2c)*

Aziridine **2c** (100%) was prepared as described above from *(S)-tert*-leucinol (**1c**, 314 mg, 2.7 mmol). ^{1}H NMR δ 2.97 (1H, dd, *J*=7.0 and 5.3 Hz), 2.79 (1H, d, *J*=7.0 Hz), 2.51 (1H, dd, *J*=5.6 and 1.0 Hz), 0.97 (9H, s).

General procedure for the ring-opening of aziridines 2a–2c with benzylamine

A mixture of benzylamine and the appropriate aziridine (2 equiv) in MeOH (1 mL) was stirred under N_2 at 20–45°C for 1–3 days. The MeOH was evaporated and the residue purified by MPLC (continuous gradient from pure hexane to pure EtOAc) to give the desired products **4**.

(2R,6R)-4 Benzyl-1,7-ditriflic-2,6-diethyl-1,4,7-triazaheptane (4a)

Colorless oil, 68%; [α]$_D^{20}$ −51 (*c* 1.00, MeOH); ^{1}H NMR δ 7.35–7.26 (5H, m), 5.22 (2H, br s), 3.95 (1H, d, *J*=13.1 Hz), 3.67–3.60 (2H, m), 3.35 (1H, d, *J*=13.1 Hz), 2.63 (2H, dd, *J*=13.6 and 8.7 Hz), 2.50 (2H, dd, *J*=13.7 and 4.9 Hz), 1.78–1.64 (2H, m), 1.62–1.45 (2H, m), 0.89 (6H, t, *J*=7.6 Hz); ^{13}C NMR δ 137.1, 129.7, 128.6, 127.7, 119.4 (q, *J*$_{CF}$=320 Hz), 58.7, 58.5, 55.1, 26.4, 9.4.

(2S,6S)-4-Benzyl-1,7-ditriflic-2,6-diisopropyl-1,4,7-triazaheptane (4b)

Colorless solid, 65%, mp 112°C; [α]$_D^{20}$ −50 (*c* 1.00, MeOH); ^{1}H NMR δ 7.37–7.26 (5H, m), 5.38 (2H, br s), 3.92 (1H, d, *J*=13.1 Hz), 3.58 (2H, app dt, *J*=8.3 and 4.9 Hz), 3.41 (1H, d, *J*=13.1 Hz), 2.66 (2H, dd, *J*=13.6 and 8.4 Hz), 2.51 (2H, dd, *J*=13.7 and 5.5 Hz), 1.97 (2H, d septet, *J*=7.0 and 4.6 Hz), 0.87 (6H, d, *J*=7.0 Hz), 0.83 (6H, d, *J*=7.0 Hz); ^{13}C NMR δ 137.1, 129.7, 128.6, 127.7, 119.4 (q, *J*$_{CF}$=320 Hz), 58.7, 58.6, 55.4, 29.8, 18.1, 17.3.

(2S,6S)-4-Benzyl-1,7-ditriflic-2,6-ditertbutyl-1,4,7-triazaheptane (4c)

Colorless oil, 67%; ^{1}H NMR δ 7.37–7.26 (5H, m), 4.18 (1H, d, *J*=14.0 Hz), 3.53–3.47 (3H, m), 2.81 (2H, dd, *J*=13.9 and 9.0 Hz), 2.59 (2H, dd, *J*=13.9 and 4.3 Hz), 0.92 (18H, s).

(2S,6S)-4-(2-Pyridyl)-1,7-ditriflic-2,6-diisopropyl-1,4,7-triazaheptane (7)

This compound was prepared in the same way as compounds **4** from aziridine **2b** and 2-(aminomethyl)pyridine. The reaction mixture turned bright red, probably due to quarternization of the pyridine nitrogen. Yield: 20% (colorless oil); [α]$_D^{20}$ −19 (*c* 3.0, MeOH); ^{1}H NMR δ 8.52 (1H, ddd, *J*=5.0, 1.8 and 0.9 Hz), 7.70 (1H, dt, *J*=7.7 and 1.8 Hz), 7.26–7.23 (1H, m), 7.21 (1H, d, *J*=7.9), 4.05 (1H, d, *J*=16.2 Hz), 3.86 (1H, d, *J*=16.2 Hz), 3.55 (2H, dt, *J*=6.7 and 4.8 Hz), 2.82 (4H, d, *J*=6.7 Hz), 2.06 (2H, d of septet, *J*=6.9 and 4.6 Hz), 0.90 (6H, d, *J*=7.0 Hz), 0.84 (6H, d, *J*=6.7 Hz); ^{13}C NMR δ 158.0, 148.2, 137.5, 122.8, 122.7, 119.6 (q, *J*$_{CF}$=321 Hz), 59.4, 59.2, 55.9, 29.4, 17.8, 17.3.

(2S,6S)-4-(2-Hydroxyphenyl)-1,7-ditriflic-2,6-diisopropyl-1,4,7-triazaheptane (8)

This compound was prepared in the same way as compounds **4** from aziridine **2b** and *o*-aminophenol. Yield: 42% (colorless oil; [α]$_D^{20}$ −21 (*c* 2.4, MeOH); ^{1}H NMR δ 7.14–7.09 (2H, m), 6.97 (1H, dd, *J*=8.5 and 1.5 Hz), 6.92 (1H, dt, *J*=7.6 and 1.6 Hz), 6.56 (1H, br s), 5.60 (2H, br s), 3.53 (2H, m), 3.10 (2H, dd, *J*=13.7 and 4.0 Hz), 2.95 (2H, dd, *J*=13.7 and 9.8 Hz), 1.99 (2H, d of septet, *J*=7.0 and 4.3 Hz), 0.95 (6H, d, *J*=7.0 Hz), 0.92 (6H, d, *J*=6.7 Hz); ^{13}C NMR δ 151.7, 136.0, 127.3, 122.3, 120.9, 119.3 (q, *J*$_{CF}$=320 Hz), 116.2, 58.6, 56.0, 30.6, 17.9, 17.3.

General procedure for the preparation of titanium(IV) complexes

The ligand (1 equiv), distilled Ti(O^{i}Pr)$_4$ (1.2 equiv) and powdered molecular sieves (4 Å, 500 mg/mmol of ligand) in dry toluene (10 mL/mmol of ligand) was stirred under N_2 at 40°C overnight and at 60°C for 3 h. The molecular sieves were filtered off and washed with toluene. Evaporation of the solvent left the crude titanium(IV) complex, which was used directly.

General procedure for the catalytic reaction

The titanium(IV) complex (0.13 equiv) was dissolved in dry toluene (1 mL/mmol of benzaldehyde) and the molecular sieves (Table 1) were added. The suspension was stirred under N_2,Ti(O^{i}Pr)$_4$ (Table 1)

was added and the stirring was continued for 10 min. The mixture was cooled to −78°C before Et_2Zn (1.20 equiv) in toluene (1 mL) was added and the stirring continued for another 15 min. Benzaldehyde (1.00 equiv) was added and the mixture was stirred at −78°C for 2 h and then at −30°C for 36–102 h. The reaction was quenched by adding some HCl (2 M), the molecular sieves were filtered off and the filtrate was extracted with ether. The combined organic phases were dried ($MgSO_4$) and the solvent evaporated to leave a yellow oil, which after flash chromatography through a micro column (4×1 cm of silica, eluent hexane:EtOAc 95:5) gave a mixture of (R)-10 and (S)-10 as a pale yellow oil.

Acknowledgements

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