trans-1,2-Diaminocyclopentane-Based Catalyst for the Asymmetric Addition of Alkyl-, Aryl-, and Vinyl Groups to Ketones

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Abstract: The catalytic asymmetric addition of ethyl-, phenyl-, and 1-hexenyl groups to ketones is reported. The new catalyst, generated from titanium *iso*propoxide and a *bis*(sulfonamide) diol ligand based on *trans*-1,2-diaminocyclopentane, gives good to excellent enantioselectivities with a range of substrates.

Key words: alcohols, asymmetric catalysis, ketones, quaternary centers, ligands

A longstanding goal in asymmetric catalysis has been the synthesis of chiral quaternary centers with high levels of enantioselectivity.[1–3] One approach toward this goal is the enantioselective addition of organometallic reagents to ketones.[4] Few catalysts will promote the generation of tertiary alcohols by this means.[5–12] One of the goals of our research has been to develop catalysts capable of promoting asymmetric addition of organozinc reagents to ketones.[4] Our efforts have resulted in development of an efficient and highly enantioselective catalyst for the alkylation, arylation, and vinylation of ketones based on a multidentate *bis*(sulfonamide) diol ligand incorporating *trans*-1,2-diaminocyclohexane **1** (Figure 1).[6–9]

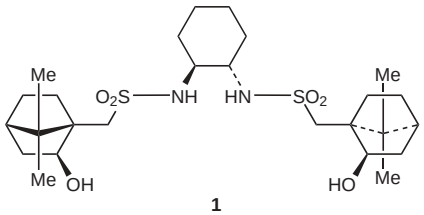

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Figure 1 *Bis*(sulfonamide) diol ligand **1** employed in the asymmetric addition of alkyl-, phenyl-, and vinyl groups to ketones.

In this report we probe the nature of the chiral diamine backbone by preparing an analogous ligand **4** based on *trans*-1,2-diaminocyclopentane **2**. We have examined the reactivity and enantioselectivity of this ligand in the asymmetric alkylation, phenylation, and vinylation of a series of ketones.

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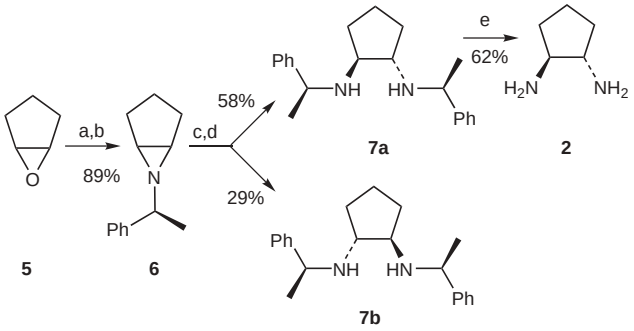
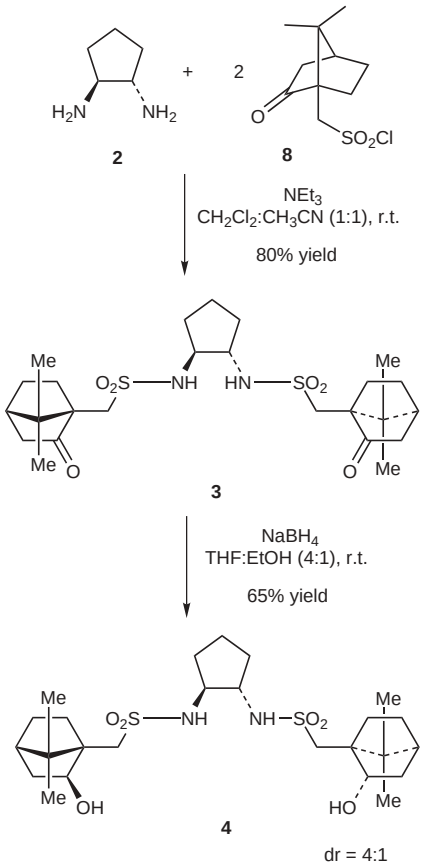
Recently, we reported the synthesis of (1*S*,2*S*)-*trans*-1,2-diaminocyclopentane **2** (Scheme 1).[13] Diamine **2** was prepared from cyclopentene oxide **5**, via the chiral aziridine intermediate **6**. Opening of the aziridine **6** with (*S*)-α-phenylethylamine afforded a 2:1 mixture of the diastereoisomeric *trans*-1,2-diaminocyclopentanes **7a** and **7b** in 87% combined yield. The diastereoisomers were separated by flash chromatography on deactivated silica gel. The major diastereoisomer, **7a**, was debenzylated by hydrogenation affording diamine **2**, which was used immediately as starting material in the preparation of the *bis*(sulfonamide) **3** (Scheme 2).



Scheme 1 *Reagents and conditions*: (a) (*S*)-α-Phenylethylamine, $LiClO_4$, MeCN, reflux, 18 h; (b) CH_3SO_2Cl, Et_3N, CH_2Cl_2, r.t., 24 h; (c) (*S*)-α-phenylethylamine, $LiClO_4$, MeCN, reflux, 36 h; (d) flash chromatography on deactivated SiO_2–Et_3N = 2.5% v/v hexanes–EtOAc 50:50; (e) H_2/$Pd(OH)_2$/C 20 mol%, MeOH, 1100 psi, r.t., 3 d.

Reaction of diamine **2** with commercially available (*R*)-camphor sulfonyl chloride (**8**) in the presence of Et_3N yielded the diketone **3**. Reduction of the diketone **3** with sodium borohydride proceeded to give the *bis*(sulfonamide) diols as a mixture of diastereoisomers (4:1 dr). The pure major diastereoisomer **4** was isolated in 65% yield after column chromatography (Scheme 2).

Use of **4** in the asymmetric addition reactions (Scheme 3) resulted in formation of the tertiary alcohol products in 78–98% enantioselectivity. Reactions were performed with catalyst loadings from 2–15 mol%. The addition of diethylzinc proceeded with good enantioselectivities (Table 1, entries 1–6, 78–98% ee). Acetophenone derivatives gave the highest enantioselectivities, although the

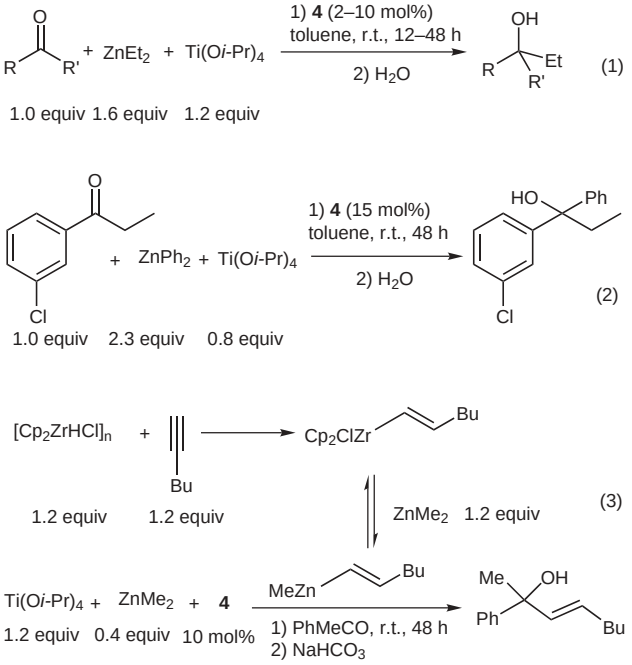


Scheme 2 Synthesis of *bis*(sulfonamide) diol **4**.

yields varied considerably. The cyclic ketone α-tetralone is a difficult substrate for this chemistry, as reflected in the low yield. The low yield arises because the ketone is deprotonated and the resulting enolate undergoes aldol condensation with another equivalent of starting material followed by dehydration. Unsaturated ketones undergo addition with good enantioselectivities (78–85%, entries 5 and 6).

We then examined the phenylation and vinylation of ketones with *bis*(sulfonamide) diol **4**. The phenylation of 3′-chloropropiophenone was performed under the conditions described in Scheme 3, equation 2. The enantioselectivity and yield were improved with a higher catalyst loading (Table 1, entry 7, 82% ee, 70% yield). The vinylation proceeded by hydrozirconation of a terminal alkyne with Schwartz's reagent followed by transmetalation to zinc. The transmetalation to zinc was performed by addition of dimethylzinc to the 1-hexenylzirconocene (Scheme 3, equation 3). The catalyst was prepared in a separate reaction vessel by combining ligand **4** with Ti(O*i*-Pr)$_4$ (Scheme 3, equation 3). The reaction proceeded with good enantioselectivity (Table 1, entry 8, 85% ee).

Although the levels of enantioselectivity with the diaminocyclopentane derived ligand **4** are very high, they are slightly less than the diaminocyclohexane analog **1**. It is also apparent from the data in Table 1 that the catalyst derived from **4** required longer reaction times and resulted



Scheme 3 General protocol for the asymmetric addition of organozinc reagents to ketones.

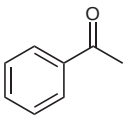
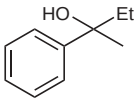
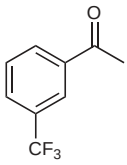
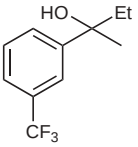
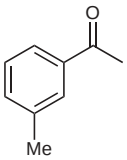
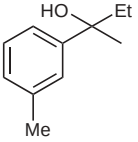
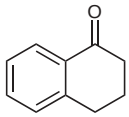
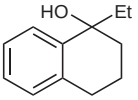
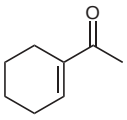
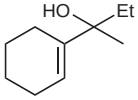
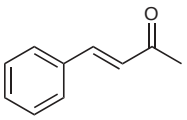
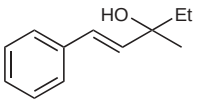
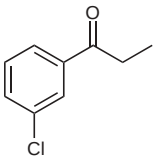
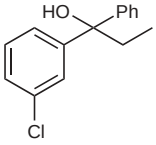
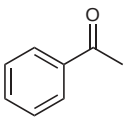
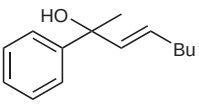
in diminished yields. We speculate that the reason for the lower enantioselectivity of **4** compared to **1** may be due to the greater conformational freedom of *trans*-1,2-disubstituted five member rings.[14]

General Methods. All manipulations involving titanium(IV) *iso*propoxide, diethylzinc, dimethylzinc, diphenylzinc, and Cp_2ZrHCl were carried out under an inert atmosphere using standard Schlenk techniques. NMR spectra were obtained on a Bruker 300 MHz Fourier transform spectrometer at the University of Pennsylvania NMR facility. ^{1}H NMR spectra were referenced to tetramethylsilane; ^{13}C{^{1}H} NMR spectra were referenced to residual solvent. Titanium(IV) *iso*propoxide and all liquid ketone substrates were distilled prior to use. Solutions of diethylzinc (1.0 M), dimethylzinc (2.0 M), and titanium(IV) *iso*propoxide (1.0 M) in toluene were prepared and stored in a Vacuum Atmospheres dry box. Diamine **2** was prepared according to literature procedure.[13]

Preparation of *Bis*(sulfonamide) Dione 3. To a solution of 100 mg (1.0 mmol) of (1*S*,2*S*)-*trans*-1,2-diaminocyclopentane (**2**) and 202 mg (2.0 mmol) Et_3N in 10 mL of MeCN was slowly added a solution of 502 mg (2.0 mmol) of (*R*)-(–)-10-camphorsulfonyl chloride in 10 mL of CH_2Cl_2. The resulting mixture was stirred at r.t. for 24 h. The mixture was then washed with 25 mL of 10% aq Na_2SO_4, extracted with 3 × 25 mL of CH_2Cl_2, and the combined organic phase was dried with $MgSO_4$. The solvent was then removed under reduced pressure. The pale yellow solid obtained was purified by column chromatography on silica gel (hexanes–EtOAc 50:50 as eluent) to yield 423 mg (80%) of **3**.

Data for 3: mp 172.0–172.3 °C; $[\alpha]_D^{20}$ –28.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 6 H), 0.96 (s, 6 H), 1.32–1.42 (m, 2 H), 1.48–1.62 (m, 2 H), 1.72–1.89 (m, 2 H), 1.91–2.32 (m, 14 H), 2.92 (d, *J* = 15.1 Hz, 2 H), 3.47 (d, *J* = 15.1 Hz, 2 H), 3.59–3.65 (m, 2 H), 5.52 (d, *J* = 4.6 Hz, 2 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 19.7, 20.0, 26.6, 27.2, 27.3, 30.1, 42.8, 43.1, 48.9, 50.3, 59.3, 60.4, 216.8. IR (film): 3331, 3213, 2954, 2884, 1743, 1467, 1449, 1414, 1326, 1278, 1243, 1214, 1143, 1114, 1049, 967, 920,

Table 1 Comparison of Results Obtained with Ligands **1** vs. **4** in the Asymmetric Addition of Organometallic Reagents to Ketones

Entry	Substrate[a]	Product	mol%	Ligand **4** ee (yield)[b]	Ligand **1** ee (yield)[c]
1			2	91 (62)	96 (71)
2			2	90 (45)	98 (56)
3			2	94 (63)	99 (82)
4			10	98 (11)	99 (35)
5			2	85 (25)	96 (56)
6			2	78 (70)	90 (80)
7			15	82 (70)	99 (92)
8			10	85 (51)	93 (85)

[a] All reactions were performed using 0.1–0.5 mmol of ketones.
[b] The analyses for determining ee were performed after purification by flash chromatography on deactivated silica gel (SiO_2–Et_3N = 2.5% v/v; hexanes–EtOAc 95:5) either by HPLC using a Chiralcel OD-H column or by GC using a Supelco β-dex column under conditions reported previously,[7–9] and were confirmed by optical rotation.
[c] See ref.[7–9]

855, 761, 679, 594, 573 cm^{-1}. HRMS-ES$^+$: *m/z* $[M + Na]^+$ calcd for $C_{25}H_{40}N_{26}ONaS_2$: 555.2225; found: 551.2255.

Preparation of *Bis*(sulfonamide) Diol 4. *Bis*(sulfonamide) dione **3** (423 mg, 0.8 mmol, 1 equiv) was charged to the reaction vessel with a 4:1 mixture of THF and EtOH (20 mL). $NaBH_4$ (212 mg, 5.6 mmol, 7 equiv) was added over 5 min. The reaction mixture was stirred at r.t. for 1 h and quenched with sat. NH_4Cl (5 mL). The organic solvents were removed from the two-phase mixture under reduced pressure. To the resulting aqueous mixture CH_2Cl_2 (25 mL) was added, and the organic layer was extracted with CH_2Cl_2 (3 × 25 mL), the combined organic layer was washed with H_2O (25 mL), dried over $MgSO_4$, and concentrated in vacuo. The product was purified by column chromatography on silica gel (hexanes–EtOAc 70:30 as eluent) to yield 277 mg (65%) of **4**.

Data for 4: mp 114.0–114.5 °C; $[\alpha]_D^{20}$ +35.4 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.77 (s, 6 H), 0.93 (m, 1 H), 1.00 (s, 6 H), 1.05 (d, *J* = 7.9 Hz, 2 H), 1.38–1.53 (m, 5 H), 1.61–1.72 (m, 12 H), 2.06–2.12 (m, 2 H), 2.85 (d, *J* = 13.7 Hz, 2 H), 3.41–3.49 (m, 6 H), 4.01 (m, 2 H), 5.48 (m, 2 H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 19.4, 20.0, 20.7, 27.5, 30.4, 30.7, 39.2, 44.5, 48.9, 50.6, 53.6, 60.1, 76.7. IR (film): 3519, 3284, 2954, 2884, 1472, 1449, 1390, 1372, 1314, 1261, 1237, 1138, 1114, 1067, 1027, 901, 758, 703, 573 cm^{-1}. HRMS-ES$^+$: *m/z* $[M + Na]^+$ calcd for $C_{25}H_{44}N_2O_6NaS_2$: 555.253851; found: 555.256407.

General Procedure for Ethylation of Ketones. The *bis*(sulfonamide) diol **4** (2–10 mol%, 4.5–22.5 mg) was weighed into the reaction vessel, and diethylzinc (1.0 M toluene, 1.6 equiv, 1.6 mL) and titanium(IV) *iso*propoxide (1.0 M toluene, 1.2 equiv, 1.2 mL) were added at r.t. After 10 min, the substrate ketone (1.0 equiv, 0.42 mmol) was added neat or as a solution in toluene (1 mL). The homogeneous reaction mixture was stirred at r.t. After 12–48 h the reaction was quenched with H_2O (5 mL), diluted with EtOAc, filtered through Celite, and the layers separated. The aqueous layer was extracted with EtOAc (2 × 40 mL) and the combined organic layers washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on deactivated silica gel (Et_3N–SiO_2 = 2.5% v/v, hexanes–EtOAc 95:5) to afford the ethyl addition products, which were fully characterized and compared with the data reported in the literature.[7]

Procedure for Phenylation of 3′-Chloropropiophenone. The *bis*(sulfonamide) diol **4** (11.7 mg, 15 mol%), was weighed into a dried Schlenk flask. Diphenylzinc was added (20% toluene solution, 0.32 mmol, 2.3 equiv, 0.39 mL) followed by titanium(IV) *iso*propoxide (1.0 M toluene solution, 1.2 mmol, 0.8 equiv, 0.12 mL). The homogenous reaction mixture was stirred at r.t. for 15 min. 3′-Chloropropiophenone (24.1 mg, 0.14 mmol, 1.0 equiv) was added dissolved in toluene (1.0 mL). The reaction mixture was stirred at r.t. for 48 h. The reaction was quenched with H_2O (5 mL), diluted with EtOAc, filtered through Celite, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 40 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on deactivated silica gel (Et_3N–SiO_2 = 2.5% v/v, hexanes–EtOAc 95:5) to afford the product, which was fully characterized and compared with the data reported in the literature.[8]

Procedure for Vinylation of Acetophenone. To a solution of Cp_2ZrHCl (155 mg, 0.60 mmol, 1.2 equiv) in CH_2Cl_2 (2.0 mL) under N_2 was added 1-hexyne (70 μL, 0.60 mmol, 1.2 equiv). The reaction mixture was stirred for 10 min at r.t., after which it was a homogeneous yellow solution. The solvent was removed in vacuo and the residue was dissolved in dry toluene (2.0 mL), cooled to –78 °C, and treated with Me_2Zn (0.30 mL, 2.0 M in toluene, 0.60 mmol, 1.2 equiv) for 10 min. In another Schlenk flask were mixed ligand **4** (27.2 mg, 0.05 mmol, 10 mol%) in 1.0 mL toluene, and titanium(IV) *iso*propoxide (0.29 mL, 0.3 mmol, 1.0 M toluene solution, 1.2 equiv), Me_2Zn (0.10 mL, 2.0 M in toluene, 0.20 mmol) at r.t. and stirred for 15 min. The resulting solution was added to the Schlenk flask containing the vinylzirconocene and dimethylzinc at –78 °C. After the addition, the solution was warmed to 0 °C and acetophenone (59 μL, 0.50 mmol, 1 equiv) was added. The reaction mixture was warmed to r.t. and stirred during 48 h. The reaction was quenched with sat. aq $NaHCO_3$ (5 mL), diluted with EtOAc, filtered through Celite, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 40 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on deactivated silica gel (Et_3N–SiO_2 = 2.5% v/v, hexanes–EtOAc 95:5) to afford the product, which was fully characterized and compared with the data reported in the literature.[9]

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