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New ligands and structural insights into the catalytic asymmetric addition of organozinc reagents to ketones

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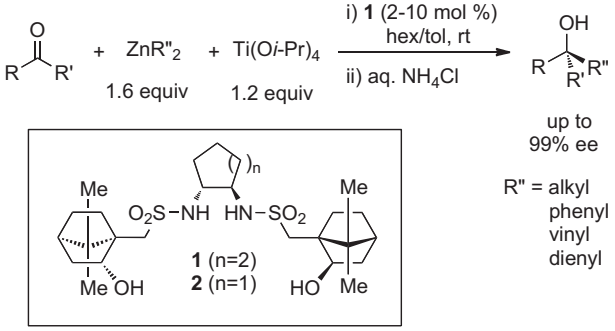
ABSTRACT

The catalytic asymmetric addition of alkyl groups to ketones has received considerable attention. Outlined herein is the synthesis of two new ligands based on the C_2-symmetric 11,12-diamino-9,10-dihydro-9,10-ethanoanthracene. The scope of the new ligands has been evaluated in the catalytic asymmetric addition of diethylzinc to a variety of ketones. Enantioselectivities as high as 99% have been achieved. The structures of two of these ligands have been determined by X-ray crystallography and are compared with related structures. Additionally, the structure of a titanium complex bound to a bis(sulfonamide) diol ligand is reported.

1. Introduction

Despite significant effort, the use of asymmetric catalysts to prepare tetrasubstituted tertiary stereocenters with high enantioselectivity remains challenging.[1–3] One class of reactions that establish such stereocenters is the asymmetric addition of organometallic reagents to ketones, which provides valuable enantioenriched tertiary alcohols.[4–7] Tertiary alcohols are important building blocks for the synthesis of pharmaceuticals and natural products. In 2002 we introduced the first efficient and highly enantioselective catalyst for the addition of alkyl groups to ketones (Scheme 1).[8,9] This catalyst system also promotes the addition of aryl-,[10,11] vinyl-,[12,13] and dienylzinc reagents[13] to ketones with enantioselectivities >90%. Ligand **1** has been applied to tandem enantioselective additions to enones-diastereoselective epoxidation sequences to make epoxy alcohols of high ee and dr.[5,14,15] Other researchers have successfully employed **1** to make tertiary alcohols with high enantioselectivity.[16–22] Recently, a number of highly enantioselective catalysts have been introduced for the addition of organozinc[23–25] and organoaluminum[26–29] reagents to ketones.[6,7,30]



Scheme 1. Asymmetric organozinc additions to ketones with catalyst derived from ligands **1** and **2**.

We are interested in identifying other diamine backbones with the goal of developing catalysts that exhibit high reactivity and enantioselectivity with challenging substrates. In 2004 we synthesized the *trans*-1,2-diaminocyclopentane-based ligand **2** (Scheme 1).[31] Although high enantioselectivities were obtained with ligand **2**, they did not surpass those of the cyclohexane analogue **1**. We hypothesized that the decreased enantioselectivity of **2** was due to the greater conformational flexibility of the cyclopentane backbone.[31] We therefore sought to prepare ligands with more rigid diamine backbones and increased dihedral angles. In this article, we describe the

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synthesis and screening of ligands based on the C_2-symmetric 11,12-diamino-9,10-dihydro-9,10-ethanoanthracene diamine[32] backbone. In some cases, catalysts derived from these ligands are more enantioselective than the original catalyst derived from **1**. Additionally, we present the structural determination of ligand **1** and a dinuclear titanium complex of ligand **1**. Non-linear effects with ligand **1** were examined in the asymmetric addition of diethylzinc to acetophenone.

2. Results and discussion

The efficiency and enantioselectivity of members of a catalyst family are dependent on many factors, including the ligand bite angle.[33,34] It is known that the dihedral angle in diamine-based ligands can have a significant impact on catalyst enantioselectivity and efficiency.[35–37] We therefore decided to alter the bite angle of the diamine backbones of ligands **1** and **2** and examine the impact on the enantioselective alkylation of ketones. The *trans*-1,2-diamino cyclohexane backbone has an N–C–C–N dihedral angle of around 60°. In contrast, the C_2-symmetric 11,12-diamino-9,10-dihydro-9,10-ethanoanthracene diamine[32] has an N–C–C–N dihedral angle over >110° (Fig. 1). We therefore set out to prepare ligands for the asymmetric alkylation of ketones with anthracene-derived diamine backbones.

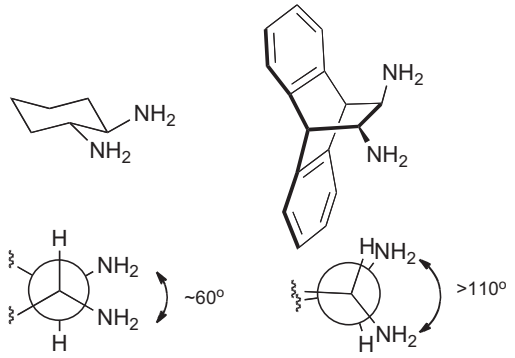


Fig. 1. Dihedral angles for *trans*-1,2-diaminocyclohexane and *trans*-11,12-diamino-9,10-dihydro-9,10-ethanoanthracene.

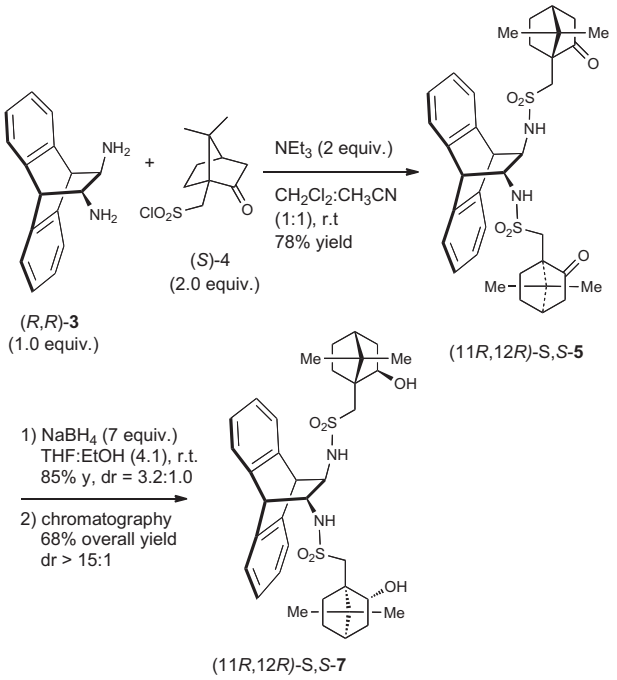
3. Synthesis of the ligands

The ligand syntheses began from resolved 11,12-diamino-9,10-dihydro-9,10-ethanoanthracene diamine[32] (**3**) and (*S*)-camphor sulfonyl chloride, (*S*)-**4**, as outlined in Schemes 2 and 3, respectively. Reaction of the diamine (*R*,*R*)-**3** with 2 equiv of (*S*)-camphor sulfonyl chloride, (*S*)-**4**, in the presence of 2 equiv triethylamine resulted in formation of the dione (11*R*,12*R*)-*S*,*S*-**5** in 78% isolated yield after purification on silica gel (Scheme 2).

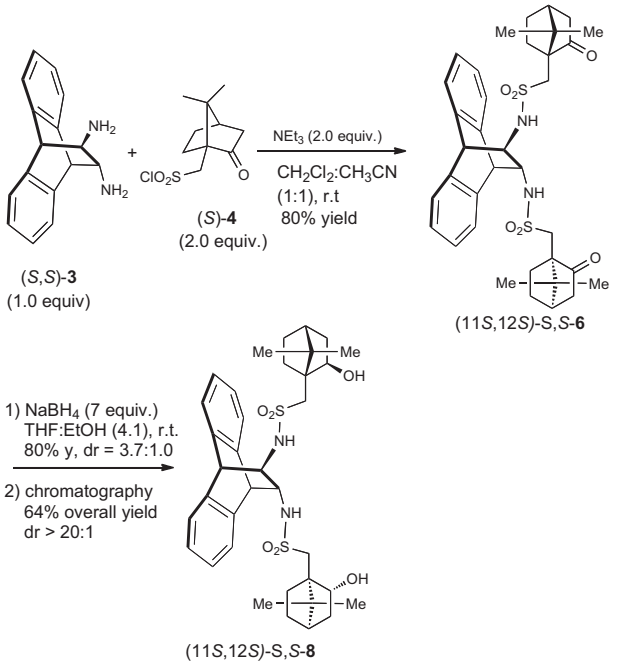
Reduction of the dione ligand (11*R*,12*R*)-*S*,*S*-**5** was accomplished with excess sodium borohydride in THF/ethanol[31] (4:1) to provide diols as a 3.2:1.0 mixture of *exo*–*exo*/*exo*–*endo* diastereomers (85% yield, Scheme 2). The major diastereomer (11*R*,12*R*)-*S*,*S*-**7** was isolated in 68% yield by flash chromatography. Preparation of the diastereomeric diketone (11*S*,12*S*)-*S*,*S*-**6** was performed using diamine (*S*,*S*)-**3** with sulfonyl chloride (*S*)-**4** (Scheme 3). After purification on silica gel, the desired dione (11*S*,12*S*)-*S*,*S*-**6** was isolated in 80% yield. The diketone (11*S*,12*S*)-*S*,*S*-**6** was reduced as above and gave (11*S*,12*S*)-*S*,*S*-**8** with 3.7:1.0 diastereomeric ratio in 80% yield. Similarly, the desired *exo*–*exo* diastereomer was separated from the minor *exo*–*endo* diastereomer by flash chromatography to provide **8** in 64% yield.

3.1. Structural determination of ligands 5, 8, and 1

Crystals of (11*R*,12*R*)-*S*,*S*-**5** were grown from hexanes and dichloromethane and the structure determined by X-ray



Scheme 2. Synthesis of ligand **7**.



Scheme 3. Synthesis of ligand **8**.

crystallography (Fig. 2).[38] An X-ray structural determination of (11*S*,12*S*)-*S*,*S*-**8** was also performed and the structure is shown in Fig. 3.[38] Finally, crystals of **1** were grown from CH_2Cl_2 and benzene (that was not dried) and an ORTEP of **1** is shown in Fig. 4.[38] An earlier structure determination of the ligand **1** was reported as orthorhombic, space group $P2_12_12$.[21,16] We found that the crystal is monoclinic, space group $P2_1$, but with a β angle of 90.008°; it forms a pseudo-merohedral twin by rotation of 180° about the a* (or c*) reciprocal axis that causes it to mimic orthorhombic symmetry. Using a twin matrix of {1 0 0 0 −1 0 0 0 −1}, the twinning parameter refined to a value of 0.1977 (7) and the least squares *R*-factor, *R*1, was

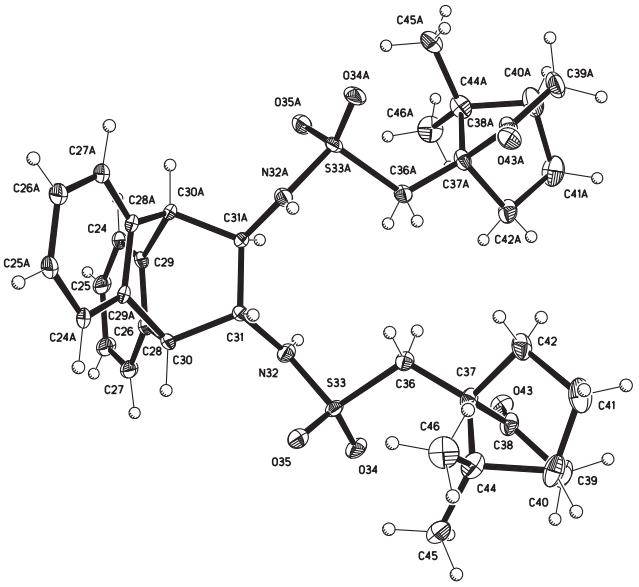


Fig. 2. ORTEP of diketone ligand precursor (11*R*,12*R*)-*S*,*S*-**5**.

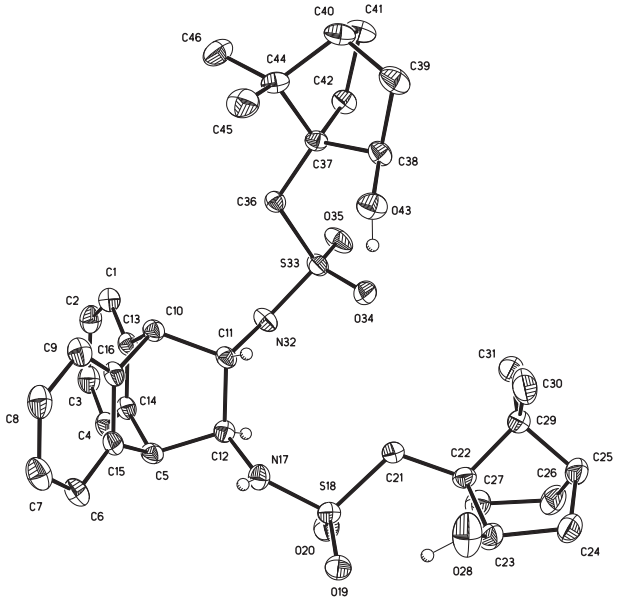


Fig. 3. ORTEP of diol ligand (11*S*,12*S*)-*S*,*S*-**8**.

0.0361. The asymmetric unit consists of four molecules of the ligand plus two benzene molecules and a water molecule.

The N–C–C–N dihedral angle and the N···N distance for ligands **5** (113.9° and 3.415 Å) and **8** (112.7° and 3.485 Å) are listed in Table 1. These can be compared to the same parameters in the structure of ligand **1**, which has an N–C–C–N dihedral angle of 60.8° and average distance between the nitrogen atoms of 2.905 Å.

3.2. Synthesis and structure of the titanium complex of 1

To understand how the ligand **1** binds to titanium, we set out to synthesize and crystallize the titanium–ligand adduct. Both our group[4,39–41] and the Gagné group[42] reported that titanium amide complexes, such as $Ti(NMe_2)_4$ and $Ti(NMe_2)_2(O\text{-}i\text{-}Pr)_2$ readily reacted with bis(sulfonamide) ligands to liberate *N*,*N*-dimethylamine and form bis(sulfonamido)$Ti(NMe_2)_2$ and bis(sulfonamido)$Ti(O\text{-}i\text{-}Pr)_2$ complexes, respectively. In planning for our synthesis of the

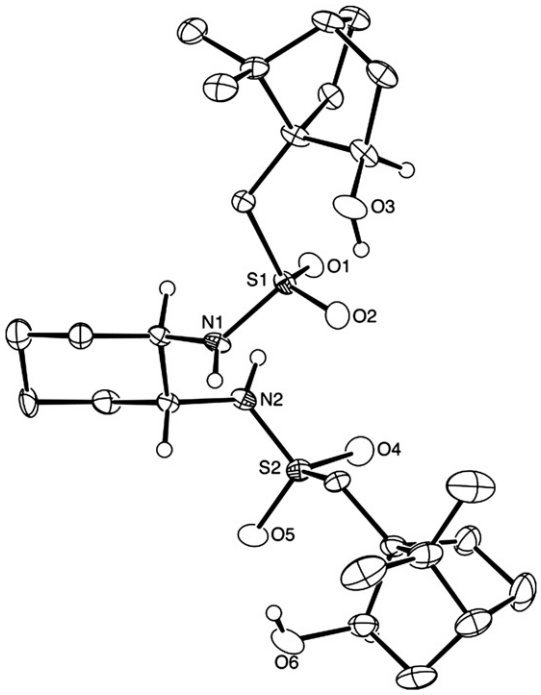


Fig. 4. ORTEP of diol ligand **1**.

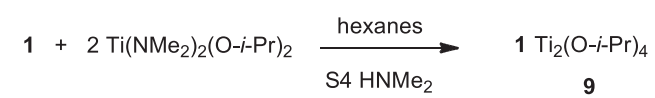
Table 1
Dihedral angles and N···N distances for **5**, **8**, **1**, and **9**

Compound	N–C–C–N (°)	N···N (Å)
5	113.9 (3)	3.415 (4)
8	112.7 (4)	3.485 (5)
1	60.8 (4)[a]	2.900 (10)[a]
9	43.9 (4)	2.702 (3)

[a] Mean value of the four independent molecules of **1**.

titanium complex of ligand **1**, we reflected on our structural and mechanistic study of (BINOLate)Ti-based catalysts for the asymmetric alkylation of aldehydes. We had shown that in the presence of $Ti(O\text{-}i\text{-}Pr)_4$ that di- and trinuclear adducts $(BINOLate)Ti_2(O\text{-}i\text{-}Pr)_6$ and $(BINOLate)Ti_3(O\text{-}i\text{-}Pr)_{10}$ were formed.[43] We presented evidence that dinuclear $(BINOLate)Ti_2(O\text{-}i\text{-}Pr)_6$ was catalytically active in the asymmetric addition of alkylzinc reagents to aldehydes,[44] consistent with Nakai's proposed mechanism.[45] Given that both the BINOL-based asymmetric additions to aldehydes[45,46] and the addition of alkyl groups to ketones with catalyst formed from **1** (Scheme 1) are both conducted in the presence of superstoichiometric titanium tetraisopropoxide, we decided to examine reaction of 2 equiv of $Ti(NMe_2)_2(O\text{-}i\text{-}Pr)_2$ with **1**. The reaction was performed in hexanes at room temperature as outlined in Scheme 4. The reaction flask was then subjected to reduced pressure to remove the liberated *N*,*N*-dimethyl amine. Fresh hexanes was added and the volatiles removed two more times to insure the *N*,*N*-dimethylamine was removed to prevent the coordination to titanium.[4,47] The resulting oil was dissolved in dichloromethane and layered with diethyl ether. Upon cooling to −30 °C, crystals of **9** formed and were isolated for X-ray analysis.[38]

The structure of the ligand adduct is shown in Fig. 5 along with a simplified representation. In the drawing, the bicyclic framework



Scheme 4. Synthesis of **9**.

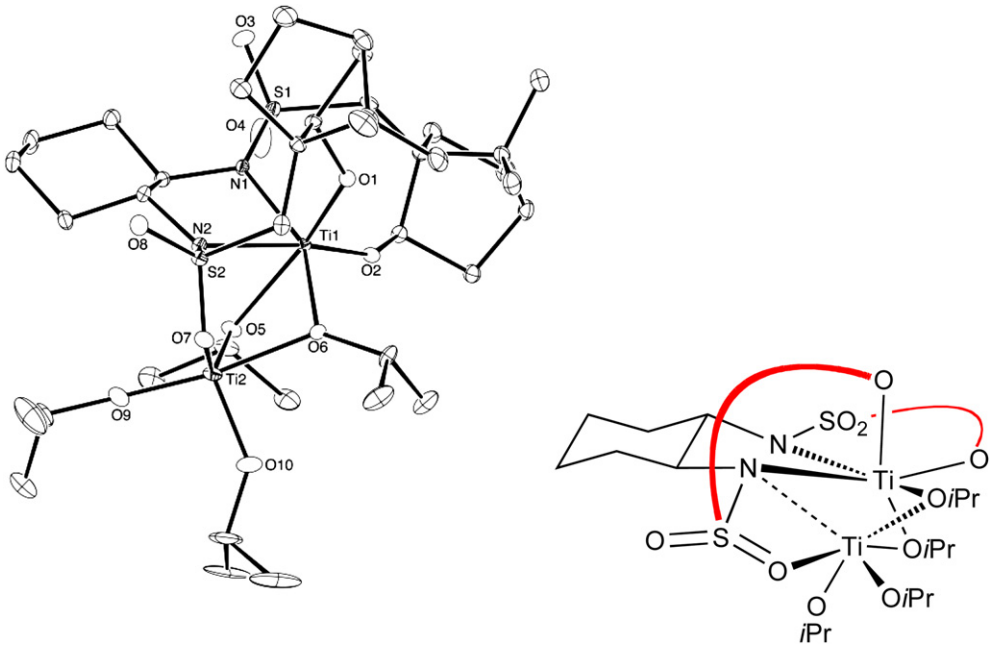


Fig. 5. ORTEP of **9** and simplified drawing. The bicyclic camphor moieties have been replaced with red curves in the drawing.

of the camphor-derived moieties has been replaced with red curves. The structure consists of two titanium centers, one in the pocket of the chiral ligand and the second bridging to the ligand through a sulfonyl oxygen and a sulfonamido nitrogen. There are two bridging isopropoxy groups connecting the titanium centers. The central titanium exhibits dissimilar bond lengths to the sulfonamido nitrogens [Ti1–N1, 2.038 (2) Å and Ti1–N2, 2.259 (3) Å], with the distance to N1 in line with related structures.[41] The Ti1–N2 distance is likely elongated due to a weak interaction of Ti2 with N2 [2.371 (3) Å]. The sum of the angles around N2 is 351°, indicating a small distortion from planarity due to interaction with Ti2. The Ti–O bond lengths of the terminal alkoxides range from 1.775 (2)–1.842 (2) Å. As expected, the bridging alkoxides exhibit longer distances [1.913 (2)–2.186 (2) Å] and the bridges are unsymmetrical with the central titanium Ti1 closer to O6 and the peripheral Ti2 closer to O5. The titanium interaction with the sulfonyl (Ti2–O7) is 2.128 (2) Å, which is less then in mononuclear bis(sulfonamido)Ti(*O*-*i*-Pr)$_2$ complexes.[41] Interestingly, the N–C–C–N dihedral angle of **9** in the coordinated ligand is 43.9°, notably less than in the structure of the free ligand **1** (60.8°) and quite different from unligated **8** (112.7°). The N···N distance of 2.70 Å in **9** is similar to that found in the free ligand **1** (2.90 Å, Table 1).

After we obtained the structure of the dinuclear titanium adduct **9**,[48] Yus reported NMR studies of **1** with varying equivalents of titanium tetraisopropoxide.[16,21] Although the NMR spectra are complex, it was proposed that they provide evidence for a dinuclear adduct, such as **9**.

3.3. Examination of catalyst enantioselectivity as a function of the ee of 1

Evaluation of enantioenriched catalysts for non-linear behavior is a powerful mechanistic probe.[34,49] We therefore varied the ee of the ligand **1** in the asymmetric addition of diethylzinc to acetophenone and examined the ee of the product by chiral stationary phase HPLC. The results of this study are illustrated in Fig. 6 and clearly indicate that there is no non-linear behavior. The absence of non-linear

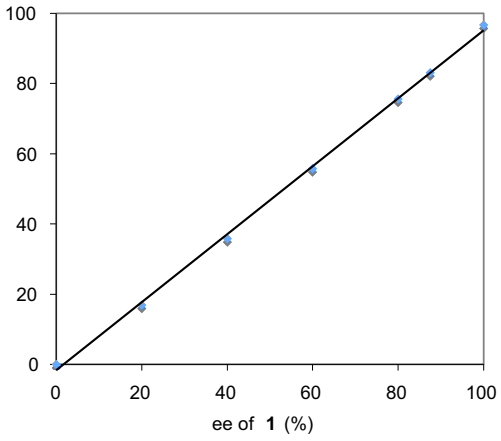


Fig. 6. A plot of ee of **1** against product ee in the asymmetric addition of diethylzinc to acetophenone (Scheme 1).

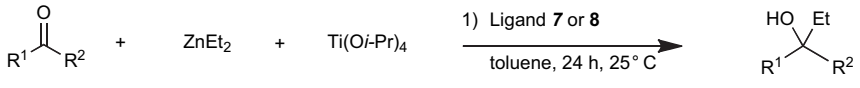
behavior suggests that the central titanium in the pocket of the chiral ligand does not interact with another titanium adduct of **1**.

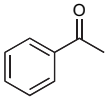
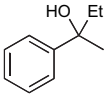
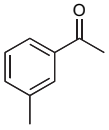
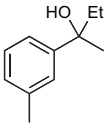
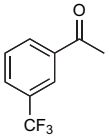
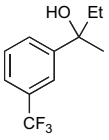
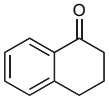
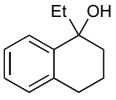
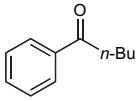
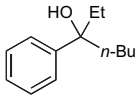
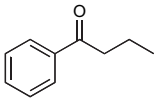
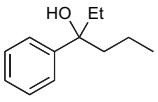
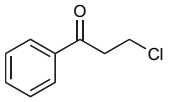
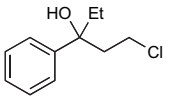
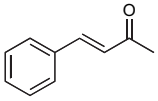
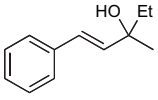
3.4. Enantioselective additions of diethylzinc to ketones with ligands 7 and 8

The diastereomeric bis(sulfonamide) diols **7** and **8** were employed in the asymmetric addition of diethylzinc to various ketones at 2 and 5 mol % ligand loading. As shown in Table 2, the ketone substrates were combined with 1.2 equiv titanium tetraisopropoxide and 1.6 equiv diethylzinc in toluene. Reactions were performed at room temperature for 24 h then quenched with water. These conditions are very close to those used with ligand **1**,[8] facilitating comparison.

Diastereomeric ligands **7** and **8** were employed with acetophenone (entry 1) and derivatives. With acetophenone, **7** exhibited greater conversion after 24 h at both 2 and 5 mol % ligand loading, but **8** exhibited higher enantioselectivity, reaching 99% enantioselectivity at 5 mol % catalyst. It is noteworthy that both

Table 2
Enantioselectivities using ligands **7** and **8** with various ketones substrates. Enantioselectivities and yields with ligand **1** are given for the purpose of comparison and are previously reported[8]



Entry	Substrate	Product	2 mol % **7** ee (config)[a] [% yield][b]	5 mol % **7** ee (config)[a] [% yield][b]	2 mol % **8** ee (config)[a] [% yield][b]	5 mol % **8** ee (config)[a] [% yield][b]	**1** ee [% yield]
1			89 (*S*) [60]	89 (*S*) [75]	94 (*S*) [32]	99 (*S*) [50]	96 [71]
2			92 (*S*) [58]	92 (*S*) [98]	96 (*S*) [82]	96 (*S*) [91]	99 [78]
3			99 (*S*) [70]	99 (*S*) [78]	99 (*S*) [82]	99 (*S*) [88]	98 [56]
4			—	—	99 (*R*) [65]	99 (*R*) [98]	99 [35]
5			—	61 (*R*) [78]	19 (*R*) [61]	23 (*R*) [85]	88 [79]
6			—	53 (*R*) [62]	—	24 (*R*) [98]	—
7			—	65 (*R*) [16]	—	76 (*R*) [20]	89 [82]
8			40 (S) [25]	37 (*S*) [68]	—	53 (*S*) [51]	90 [80]

[a] The enantiomeric excess was determined by HPLC using a Chiralcel OD-H or AD-H. The absolute configuration or the sign of the predominant enantiomer is indicated in parentheses.
[b] The yields were obtained after column chromatography on deactivated silica gel (SiO_2/Et_3N=2.5% v/v; hexanes/EtOAc 95%).

diastereomeric catalysts gave the (*S*)-enantiomer of the tertiary alcohol product with high ee. Thus, it is clear that the stereochemistry of the bicyclic alkoxide moiety bound to titanium, that is, largely responsible for the control of asymmetric induction and the stereocenters of the diamine play a secondary role. When 2 mol % catalyst derived from ligand **1** (Scheme 1) was used in the asymmetric addition of diethylzinc to acetophenone, the (*S*)-product was formed with 96% enantioselectivity and 96% yield after 29 h.[8] The diastereomer of **1**, derived from (*S*,*S*)-*trans*-diaminocyclohexane, also gave the (*S*)-tertiary alcohol, however, the ee was only 31% and the reaction conversion after 24 h was only 15%.[48] Thus, the diamine in **1** has a larger impact on the enantioselectivity and activity than the diamine in **7** and **8**.

Substituted acetophenones also proved to be good substrates (entries 2 and 3). Thus, 3-methyl acetophenone underwent addition promoted with ligands **7** and **8** with enantioselectivities of 92 and 96%, respectively. With 3-trifluoromethyl acetophenone, both ligands were highly enantioselective and provided ethyl addition product with 99% ee. α-Tetralone underwent addition of diethylzinc with catalyst derived from **1** with >99% ee, but the yield was only 35% due to competitive aldol condensation.[8] Catalysts derived from **7** and **8** also exhibited excellent enantioselectivities (99%) with α-tetralone and up to 98% yield with ligand **8**.

Alkyl aryl ketones with alkyl groups larger than methyl are more challenging substrates. The catalysts must differentiate the two lone pairs of the carbonyl group to achieve high enantioselectivity. When the size of the alkyl and aryl substituents is similar, the differentiation becomes more difficult. With valerophenone, catalysts derived from **7** and **8** gave 61 and 23% enantioselectivity, respectively. These values are lower than the 88% enantioselectivity observed with catalyst derived from ligand **1**. Similar enantioselectivities were observed with ligands **7** and **8** with butyrophenone.

The chlorinated substrate 3-chloropropiophenone also proved challenging for catalysts derived from **7** and **8**, which gave enantioselectivities of 65 and 76%, respectively (entry 7). Catalyst derived from **1** gave higher enantioselectivity (89%) but required 10 mol % ligand loading and longer reaction time (44 h) to achieve 82% yield. With catalyst derived form **1**, *trans*-4-phenyl-3-buten-2-one also gave higher enantioselectivity (90%) than with **7** or **8** (37% and 53% enantioselectivity, respectively, entry 8). Thus, while catalysts derived from **7** and **8** perform very well with acetophenone derivatives, **1** gave better results overall.

4. Summary and outlook

In this study we report the synthesis and characterization of two new diastereomeric ligands for the asymmetric addition of organozinc reagents to ketones. These ligands are based on the enantioenriched 11,12-diamino-9,10-dihydro-9,10-ethanoanthracene, which has a large N–C–C–N dihedral angle and larger bite angle than *trans*-1,2-diaminocyclohexane. These ligands were examined in the asymmetric addition of diethylzinc to a variety of ketones. Surprisingly, it was found that the configuration of the diamine played only a minor role in the catalyst enantioselectivity with the best substrates and a more significant role with more challenging substrates. In some cases, the catalysts derived from **7** and **8** outperformed the catalyst formed from **1**. In cases where the enantioselectivities were comparable, the new ligands exhibited improved yields (up to 60% higher than **1** with α-tetralone). We also report the structure of a dinuclear titanium complex employing ligand **1**. Under catalytic conditions, catalyst derived from **1** exhibited no non-linear effects.

We continue to search for new ligands for ketone substrates that remain challenging.

5. Experimental section

5.1. General methods

All manipulations involving titanium tetraisopropoxide, diethyl-zinc, were carried out under an inert atmosphere. NMR spectra were obtained on a Varian 200 MHz, Fourier transform spectrometer. ^{1}H NMR spectra were referenced to tetramethylsilane and ^{13}C{H} NMR spectra were referenced to residual solvent. Titanium tetraisopropoxide and all liquid ketone substrates were distilled prior to use. Diamine **3** was prepared according to literature procedure.[32] Proton and carbon NMR spectra for the alcohol products matched those in the literature for entries 1–5, 7, and 8[8] and entry 6.[50]

5.2. Preparation of (11*R*,12*R*)-*N*,*N*′-bis[(*S*)-camphorsulfonyl]-11,12-diamino-9,10-dihydro-9,10-ethanoanthracene dione

To a solution of 300 mg (1.27 mmol) of *trans*-11*R*,12*R*-diamino-9,10-dihydro-9,10-ethanoanthracene and 260 mg (2.5 mmol) Et_3N in 10 mL of MeCN was slowly added a solution of 640 mg (2.54 mmol) of (*S*)-(+)-10–camphorsulfonyl chloride in 10 mL of CH_2Cl_2. The resulting mixture was stirred at room temperature for 24 h. The mixture was then washed with 25 mL of 10% aqueous Na_2SO_4, extracted with 3×25 mL of CH_2Cl_2, and the combined organic phase was dried over $MgSO_4$. The solvent was then removed under reduced pressure. The white solid obtained was purified by column chromatography on silica gel (hexanes/EtOAc 80:20 as eluent).

*5.2.1. Data for (11R,12R)-S,S-**5**.* White solid (450 mg 78% yield) mp=325 °C; $[\alpha]_D^{20}$ −9.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ=7.24–7.38 (m, 4H), 7.16–7.20 (m, 4H), 4.75 (d, *J*=8.2 Hz, 2H), 4.44 (d, *J*=2.6 Hz, 2H), 3.55 (m, 4H), 3.00 (d, *J*=15.0 Hz, 2H), 2.21–2.43 (m, 4H), 1.76–2.11 (m, 8H), 1.36–1.48 (m, 2H), 1.03 (s, 6H), 0.89 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ=214.6, 140.0, 137.4, 126.9, 126.8, 126.1, 124.6, 62.0, 59.2, 51.7, 50.6, 48.9, 43.2, 27.6, 26.3, 20.6, 20.3. IR (film): 3279, 2958, 1736, 1457, 1429, 1417, 1392, 1375, 1331, 1268, 1201, 1145, 1115, 1102, 1066, 1051, 1025, 967, 924, 907, 869, 855, 762, 734, 701 cm^{-1}. FAB$^+$: *m/z* $[M+1]^+$ calcd for $C_{36}H_{45}O_6N_2S_2$: 665.2707; found: 665.2719. Compound **5** was recrystallized from hexanes/CH_2Cl_2 (8:1), colorless prism 0.444×0.172×0.172 mm^3; $C_{36}H_{44}N_2O_6S_2$, monoclinic, *I* 2 *a*=16.743 (2) Å, *b*=, 19.508 (3) Å *c*=11.430 (2) Å, *Z*=4, δ_{calcd}=1.189 mg/m^3, *V*=3713.6 (9) Å^3 μ=0.187 mm^{-1} *F*(000)=1416. A set of 12,599 reflections was collected at 298 (2) K, 6684 independent reflections [R_{int}=0.0283]. Brüker Smart diffractometer, APEX AXS CCD area detector, omega scans.

*5.2.2. Data for (11S,12S)-S,S-**6**.* White solid (1.0 g, 80% yield) mp=328 °C; $[\alpha]_D^{20}$ +37.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ=7.24–7.39 (m, 4H), 7.17–7.21 (m, 4H), 5.05 (d, *J*=8.8 Hz, 2H), 4.45 (d, *J*=2.6 Hz, 2H), 3.72 (m, 4H), 3.52 (d, *J*=14.6 Hz, 2H), 3.01 (d, *J*=15 Hz, 2H), 2.05–2.27 (m, 8H), 1.81–1.91 (m, 4H), 1.00 (s, 6H), 0.87 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ=215.1, 139.8, 137.7, 126.9, 126.8, 126.1, 124.7, 61.3, 59.5, 52.7, 51.0, 49.1, 43.3, 27.6, 27.0, 20.6, 20.3. IR (film): 3278, 2958, 1739, 1549, 1525, 1456, 1416, 1392, 1375, 1331, 1270, 1216, 1146, 1115, 1101, 1066, 1052, 1026, 967, 923, 869, 855, 834, 796, 763, 733, 702, 680 cm^{-1}. FAB$^+$: *m/z* $[M+1]^+$ calcd for $C_{36}H_{45}O_6N_2S_2$: 665.2719; found: 665.2715.

5.3. Preparation of bis(sulfonamide) diol

Bis(sulfonamide) dione (450 mg 1 equiv) was charged to the reaction vessel with a 4:1 mixture of THF and EtOH (20 mL). $NaBH_4$ (5.6 mmol, 7 equiv) was added over 5 min. The reaction mixture was stirred at room temperature for 1 h and quenched with saturated NH_4Cl (5 mL). The organic solvents were removed from the two-phase mixture under reduced pressure. To the resulting aqueous mixture was added CH_2Cl_2 (25 mL), 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).

*5.3.1. Data for (11R,12R)-S,S-**7**.* White solid (680 mg 68% yield) mp=270 °C; $[\alpha]_D^{20}$ −60.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ=7.35–7.39 (m, 4H), 7.19–7.24 (m, 4H), 4.37 (d, *J*=2.6 Hz, 2H), 4.23 (d, *J*=9.0 Hz, 2H), 4.00 (m, 2H), 3.55 (m, 4H), 3.07 (b, 2H), 2.92 (d, *J*=13.6 Hz, 2H), 1.71 (m, 8H), 1.20–1.31 (m, 4H), 1.04 (s, 6H), 0.90 (m, 2H), 0.81 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ=139.6, 137.0, 127.2, 127.1, 126.1, 124.8, 61.8, 54.7, 51.1, 51.0, 49.3, 44.8 39.6, 31.1, 28.0, 21.3, 20.6. IR (film): 3533, 3255, 2955, 2933, 2880, 1549, 1456, 1390, 1371, 1324, 1262, 1142, 1115, 1101, 1074, 1059, 1027, 982, 881, 855, 761, 701 cm^{-1}. FAB$^+$: *m/z* $[M+1]^+$ calcd for $C_{36}H_{49}O_6N_2S_2$: 669.3032; found: 669.3025.

*5.3.2. Data for (11S,12S)-S,S-**8**.* White solid (277 mg 64% yield) mp=255 °C; $[\alpha]_D^{20}$ −19.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ=7.36–7.40 (m, 4H), 7.19–7.24(m, 4H), 4.38 (d, *J*=2.6 Hz, 2H), 4.20 (d, *J*=9.2 Hz, 2H), 3.99 (m, 2H), 3.59 (m, 4H), 3.47 (d, *J*=14 Hz, 2H), 3.08 (m, 2H), 1.74 (m, 8H), 1.35 (m, 6H), 1.04 (s, 6H), 0.81 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ=139.5, 137.1, 127.2, 127.1, 126.0, 125.0, 61.9, 54.7, 51.0, 51.1, 49.3, 44.9, 39.6, 31.1, 28.0, 21.3, 20.6. IR (film): 3531, 3251, 2956, 2880, 1721, 1621, 1596, 1549, 1525, 1456, 1389, 1371, 1324, 1263, 1236, 1212, 1141, 1114, 1101, 1073, 1058, 1027, 1012, 982, 923, 881, 855, 834, 795, 761, 736, 701 cm^{-1}. FAB$^+$: *m/z* $[M+1]^+$ calcd for $C_{36}H_{49}O_6N_2S_2$: 669.3032; found: 669.3036. Recrystallized from hexanes/CH_2Cl_2 (5:1), colorless prism 0.376×0.178×0.136 mm^3;

$C_{37}H_{50}Cl_2N_2O_6S_2$, orthorhombic, $P\,2_12_12_1$ a=11.510 (2) Å, b=13.536 (2) Å, c=24.506 (4) Å, Z=4, δ_{calcd}=1.311 mg/m^3, V=3818.1 (10) Å^3 μ=0.326 mm^{-1} F(000)=1600. A set of 31,224 reflections was collected at 298 (2) K, 7000 independent reflections [R_{int}=0.0856]; Brüker Smart diffractometer, APEX CCD area detector, omega scans.

5.4. General procedure for ethylation of ketones

The bis(sulfonamide) diol **7** or **8** (5 mol %, 33 mg) was weighed into the reaction vessel and diethylzinc (1.0 M toluene, 1.6 equiv, 1.6 mL) and titanium(IV) isopropoxide (1.2 equiv, 1.2 mL) were added at room temperature. After 10 min, the substrate ketone (1.0 equiv, 1 mmol) was added neat or as a solution in toluene (1 mL). The homogeneous reaction mixture was stirred at room temperature. After 24 h the reaction was quenched with H_2O (5 mL), diluted with EtOAc, filtered through Celite, and layers 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 under reduced pressure. The resulting 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. These alcohols were fully characterized and compared with the data reported in the literature. The ee value was determined by HPLC on a Daicel OD-H or AD-H column.

5.4.1. Probing non-linear behavior. The reactions were performed using 10 mol % of ligand **1** to facilitate accurate weighing of the enantiomeric ligands. The enantiomeric ligands were individually weighted and combined in the reaction vessel. The diethylzinc solution (1.0 M in toluene, 1.6 equiv) and the titanium(IV) isopropoxide (1.4 M toluene solution, 1.2 equiv) were added at room temperature. After 5–10 min, the acetophenone (1.0 equiv) was added neat. The homogeneous reaction mixture was stirred at room temperature for 18 h. After completion, the reaction mixture was quenched with saturated aqueous solution NH_4Cl, extracted into CH_2Cl_2, concentrated under reduced pressure, and purified by column chromatography. The ee was determined by GC using Supelco β-Dex 120 column and nitrogen carrier gas (t_1=25.8 min, t_2=26.7 min, 110 °C, 1.0 mL/min).

5.4.2. Preparation of 2-phenylbutan-2-ol. (1)In the presence of ligand **7**: 75% yield, 89% ee (*S*) as an oil, HPLC Chiralcel column OD-H, v(hexane)/v(*i*-propanol)=95:5, flow rate 0.5 mL/min, 254 nm UV detector, retention time t_1: 14.5 min, t_2: 15.9 min. (2) In the presence of ligand **8**: 50% yield, 99% ee. The racemic alcohols were prepared by addition of ethylmagnesium bromide to the corresponding ketone.

5.4.3. Preparation of m-tolylbutan-2-ol. (1) In the presence of ligand **7**: 98% yield, 92% ee as an oil, HPLC, Chiralcel column OD-H, v(hexane)/v(*i*-propanol)=99:1, flow rate 0.5 mL/min, 254 nm UV detector, retention time t_1: 17.4 min, retention time t_2: 18.6 min. (2) In the presence of ligand **8**: 91% yield, 96% ee.

5.4.4. Preparation of (3-trifluoromethylphenyl)-butan-2-ol. (1) In the presence of ligand **7**: 78% yield, 98% ee as an oil, HPLC, Chiralcel column OD-H, v(hexane)/v(*i*-propanol)=99:1, flow rate 0.5 mL/min, 254 nm UV detector, retention time t_1: 16.9 min retention time t_2: 17.8 min. (2) In the presence of ligand **8**: 99% yield, 88% ee.

5.4.5. Preparation of 1-ethyl-1,2,3,4-tetrahydro-naphthalen-1-ol. (1) In the presence of ligand **7**: 65% yield, 99% ee as an oil, HPLC, Chiralcel column OD-H, v(hexane)/v(*i*-propanol)=99:1, flow rate 0.5 mL/min, 254 nm UV detector, retention time t_1: 19.3 min, retention time t_2: 20.7 min. (2) In the presence of ligand **8**: 98% yield, 99% ee.

5.4.6. Preparation of 3-phenylheptan-3-ol. (1) In the presence of ligand **7**: 78% yield, 61% *ee* as an oil, HPLC, Chiralcel column AD-H, v(hexane)/v(*i*-propanol)=98:2, flow rate 0.5 mL/min, 254 nm UV detector, retention time t_1: 28.9 min, retention time t_2: 32.0 min. (2) In the presence of ligand **8**: 85% yield, 23% *ee*.

5.4.7. Preparation of 3-phenylhexan-3-ol. (1) In the presence of ligand **7**: 62% yield, 53% ee as an oil, HPLC, Chiralcel column OD-H, v(hexane)/v(*i*-propanol)=95:5, flow rate 0.5 mL/min, 254 nm UV detector, retention time t_1: 21.4 min, retention time t_2: 22.4 min. (2) In the presence of ligand **8**: 98% yield, 24% ee.

5.4.8. Preparation of 1-cloro-3-phenylpentan-3-ol. (1) In the presence of ligand **7**: 16% yield, 65% ee as an oil, HPLC, Chiralcel column AD-H, v(hexane)/v(*i*-propanol)=99:1, flow rate 0.5 mL/min, 254 nm UV detector, retention time t_1: 27.2 min, retention time t_2: 28.5 min. (2) In the presence of ligand **8**: 20% yield, 76% ee.

5.4.9. Preparation of (1E)-3-methyl-1-phenylpent-1-en-3-ol. (1) In the presence of ligand **7**: 68% yield, 37% ee as an oil, HPLC, Chiralcel column AD-H, v(hexane)/v(*i*-propanol)=99:1, flow rate 0.5 mL/min, 254 nm UV detector, retention time t_1: 9.6 min, retention time t_2: 11.5min. (2) In the presence of ligand **8**: 51% yield, 53% ee.

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