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Investigation of ligand loading and asymmetric amplification in CHAOx-catalyzed asymmetric diethylzinc additions

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Abstract—The recently developed (cyclohexylsulfonylamino)oxazoline (CHAOx) ligand was found to provide high ee's and consistent reaction rates in the asymmetric diethylzinc addition to benzaldehyde over a remarkably large loading range of 0.05–10 mol%. Turnover numbers of 1000–2000 can be explained by the absence of a nonlinear effect and the formation of a catalytically active monomer complex. Substituents at the nitrogen donor atoms of the bidentate ligand prevent zinc-complex dimerization.

1. Introduction

The mechanism of diethylzinc addition to aldehydes in the presence of catalytic amounts of chiral amino alcohols has been extensively investigated.[1–6] Kagan's studies[7–10] of the nonlinear correlation of catalyst versus product enantiomeric excess have been particularly valuable for the understanding of mechanistic effects in this system.[11–15] Noyori et al. have developed a model that explains the exceptional nonlinear effect of the chiral amino alcohol catalyst dimethylaminoisoborneol (DAIB), which at 15% ee converts benzaldehyde to (*S*)-1-phenylpropanol in 95% ee.[12] Equilibration of trivalent monomeric Zn catalyst species with tetravalent dimeric complexes produces chiral *d*,*l*- as well as achiral *meso*-complexes; the latter are coordinatively saturated and largely inactive in the nucleophilic addition process (Scheme 1). Moreover, the formation of the stable heterodimeric *meso*-complex enriches the relative concentration of the homochiral, catalytically active species, and a high amplification of chirality is realized when the rate of dissociation of the heterochiral dimer is slow compared to the rate of the reaction. An interesting aspect of nonequilibrium monomer/dimer partitioning was recently discussed by Blackmond et al.:[14] if the Curtin–Hammett condition for equilibrium exchange is not met, strongly binding electron-rich aldehyde substrates may exhibit greater asymmetric amplification in spite of slower reaction rates.

While large nonlinear effects have the practical advantage of allowing the productive use of enantiomerically impure reagents,[16] the effective depletion in the concentration of the catalytically active monomeric catalyst by dimer formation can result in a dramatic decrease in reaction rate as well as the requirement for higher catalyst loadings.[8,17–19] Ligand concentration also similarly effects enantiomeric excess; when 20% ee DAIB was diluted from 8 to 0.4 mM, while mol ratios of reactants were kept constant, the % ee of the addition product of dimethylzinc to benzaldehyde increased from 68 to 83% ee before falling to 65% ee.[12] Consequently, typical loadings of chiral ligands for diethylzinc additions to aldehydes range from 2–20 mol%.[2] Most commonly, 5–10 mol% loadings are utilized, which strongly limits the practical utility of asymmetric zinc additions in fine chemicals production.[20]

Recently, Bräse and Dahmen reported that the [2,2]paracyclophane ligand **6** provided a 92% yield of the diethylzinc addition product to benzaldehyde in 80% ee at 0.05–0.1 mol% loading after 16 h at 0°C,[21,22] which represents a significant improvement over the past state-of-the-art in this process (Fig. 1). The authors did not provide any information about the ability of **6** to form dimeric complexes with diethylzinc and about the occurrence of any nonlinear asymmetric effects, but based on the steric bulk of the paracyclophane backbone it is likely that dimerization is indeed disfavored and thus chiral amplification is suppressed. Planar chiral ferrocenes, for example, show a linear relationship

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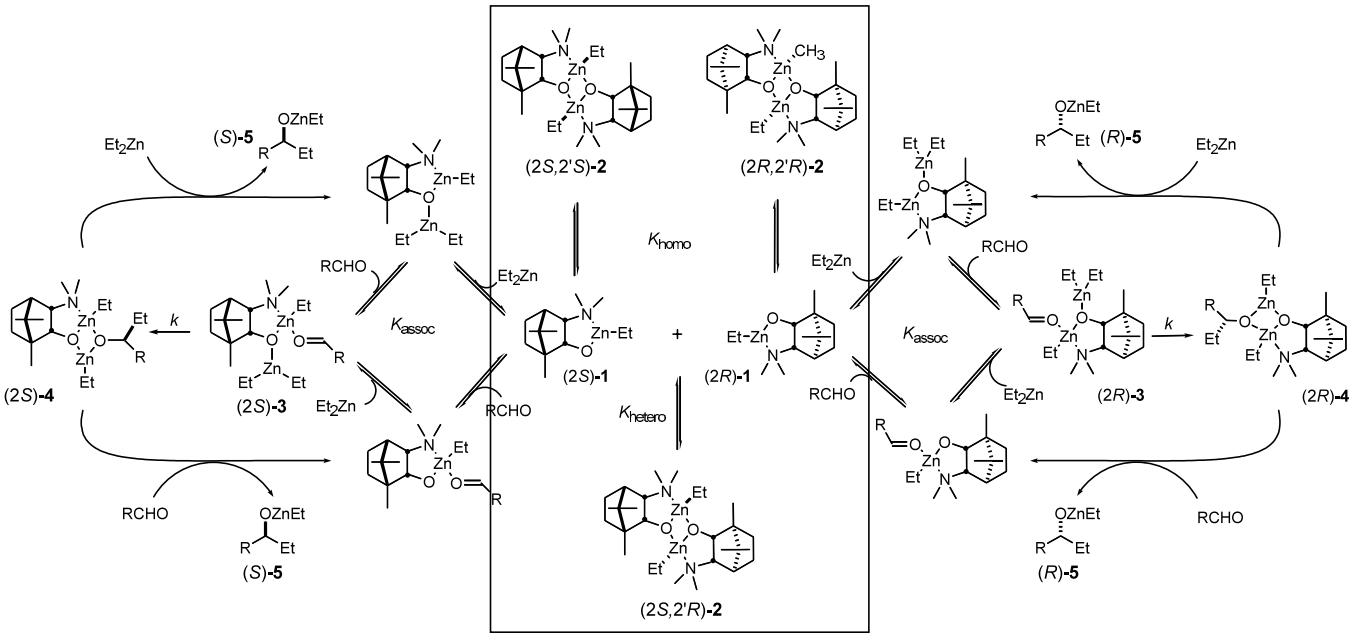


Scheme 1. Noyori mechanism for asymmetric alkylation of aldehydes with diethylzinc.[12]

between the product % ee and ligand ee, due to steric hindrance in the ligand framework.[23,24] However, with the latter planar chiral ligands the effect of loading on reaction rate and asymmetric induction was not investigated, and these catalysts were used at the routine 3–5 mol% level.

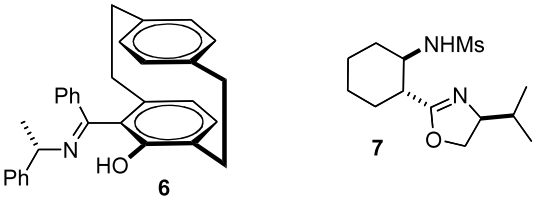


Figure 1. Highly active bidentate ligands for asymmetric diethylzinc additions.

Since the formation of dimeric complex equilibria that accompanies nonlinear effects reduces the concentration of the catalytically active species, we hypothesized that highly active ligands for asymmetric diethylzinc additions to prochiral carbonyl groups could be obtained by restricting the flexibility of the bidentate ligand scaffold in a fashion that would prevent formation of tetrahedral zinc species such as **2**. In order to prevent the general deactivation of the monomeric zinc complex, the use of steric bulk for avoiding dimerization should be kept to a minimum. Specifically, our recently introduced cyclohexylsulfonylaminooxazoline (CHAOx) ligand **7** appeared to be very well suited to test this hypothesis. Due to a 1,5-positional relationship of the two donor nitrogen atoms, which are rigidly held in place by the 1,2-*trans*-disubstituted cyclohexane chair ligand backbone, the N–Zn–N bond angle of 88.4° in the six-membered chelate differs greatly from the ideal[25] 110–120° bond angle in the dinuclear DAIB-Zn crystal structures (Fig. 2). The compression of the N–Zn–N bond angle should increase the reactivity at the Zn atom, while the presence of the methanesulfonyl group on nitrogen precludes the four-membered Zn_2N_2 ring necessary for dimer formation. Based on this structural analysis, ligand **7** was expected to demonstrate a strictly linear relationship between enantiomeric purity and product % ee, and, if our hypothesis was correct, provide high enantiomeric excess of addition product at very low ligand loadings without significant decrease in catalytic efficiency. In preliminary work,[26] we have shown that at 2 mol% loading, ligand **7** provided 86% and >98% ee in the addition of diethylzinc to benzaldehyde and cyclohexanecarboxaldehyde, respectively, thus demonstrating its effectiveness in catalyzing the desired transformation. Herein we report our results on the study of the nonlinear and ligand loading effects of this catalyst.

2. Results and discussion

The preparation of (1*R*,2*R*)-*N*-[2-(4-*i*sopropyl-4,5-dihydrooxazol-2-yl)cyclohexyl] methanesulfonamide (CHAOx) **7** was reported previously,[26,27] and the synthesis of (1*S*,2*S*)-*N*-[2-(4-*i*sopropyl-4,5-dihydrooxazol-2-yl)cyclohexyl]methanesulfonamide *ent*-**7** employed an analogous sequence (Scheme 2). A solution of the fumaric acid derivative **8**[28] in toluene was treated with the chiral titanium catalyst[29] prepared from diol **9** to give cyclohexene **10** in 80% yield and >99% ee after recrystallization from *i*-PrOH/hexanes. Saponification of the imide, Curtius rearrangement and quenching of the intermediate isocyanate with benzyl alcohol provided the β-amino ester **11** in 73% yield. Simultaneous catalytic hydrogenation of the alkene and hydrogenolysis of the Cbz group followed by *N*-mesylation and

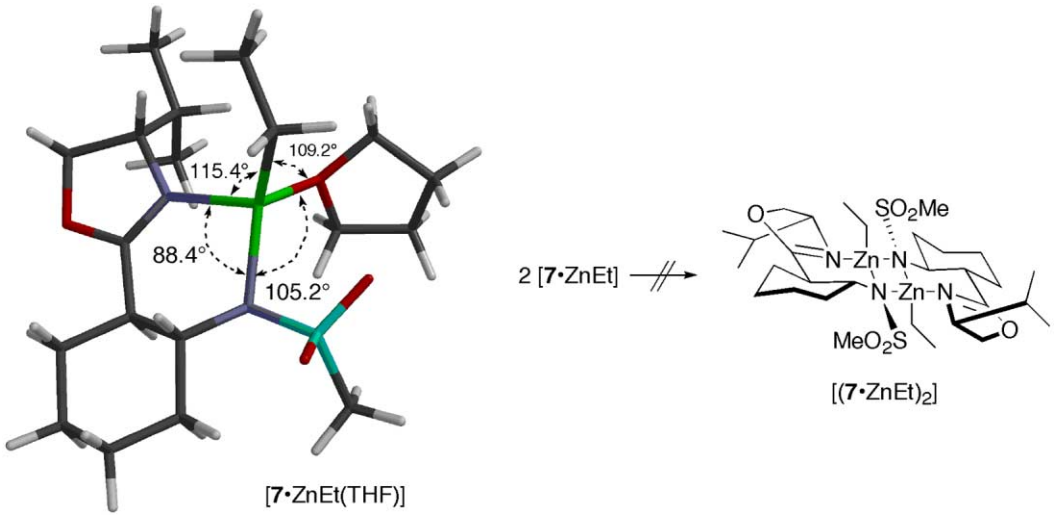
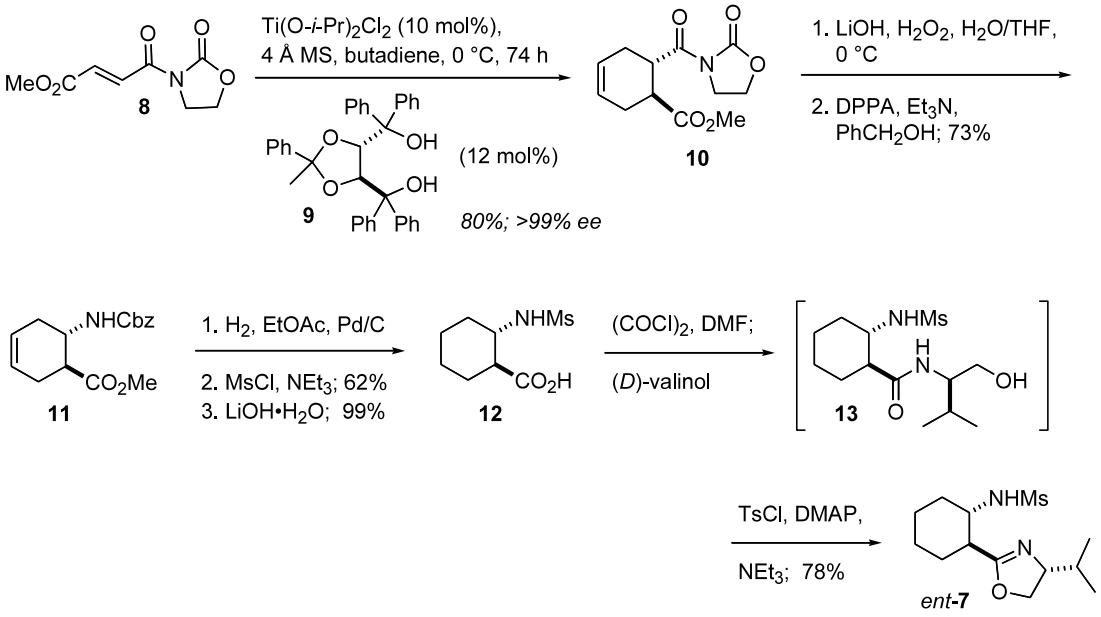


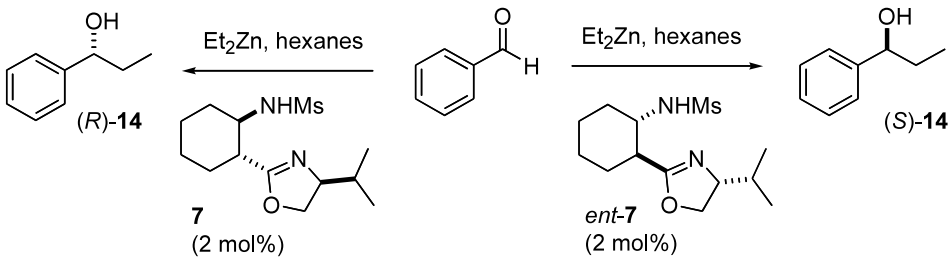
Figure 2. Calculated structure of the THF complex of ethylzinc and ligand **7**. Complex geometry was optimized at the B3LYP/6-31G* level using Spartan. *N*-Mesylation prevents Zn_2N_2 dimer formation.

ester hydrolysis led to the carboxylic acid **12**. Oxalyl chloride in CH_2Cl_2 in the presence of a catalytic amount of DMF was used to activate the acid, and in situ trapping of the acid chloride with (D)-valinol followed by cyclodehydration to the oxazoline gave the desired *ent*-**7** (Scheme 2).

With both enantiomers of ligand **7** in hand, the nonlinear effect in the diethylzinc addition to benzaldehyde could be evaluated (Scheme 3). As shown in Figure 3, the enantiomeric excess of 1-phenyl-1-propanol **14** depended in a strictly linear fashion on the enantiomeric excess of ligand **7**; no asymmetric amplification



Scheme 2. Preparation of *ent*-**7** by catalytic asymmetric Diels–Alder reaction and Curtius rearrangement.



Scheme 3. Asymmetric addition of diethylzinc to benzaldehyde in the presence of mixtures of chiral ligands **7** and *ent*-**7**.

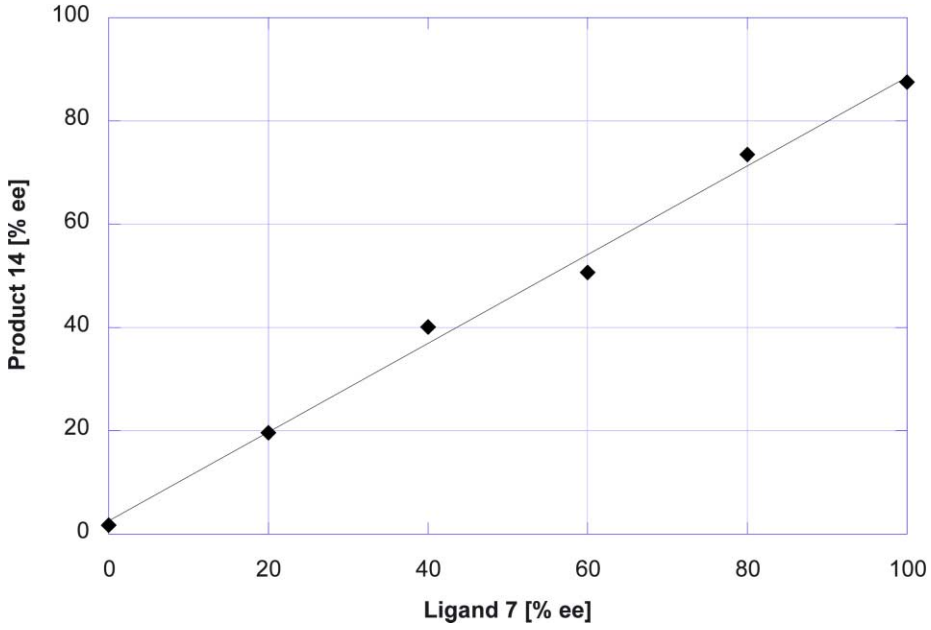


Figure 3. Linear correlation between the enantiomeric excess of diethylzinc addition product **14** and the enantiomeric excess of ligand **7**.

was observed. The correlation coefficient for the linear curve fitting of the ee of **14**, determined by chiral HPLC analysis, was very high ($R^2 = 0.997$). A maximum ee of 88% was obtained with enantiomerically pure chiral ligand, and for all % ee combinations of **7** a 2 mol% catalyst loading was employed in these studies.

Most significantly, we found that ligand **7** was indeed capable of providing a high level of enantioenriched addition product over an exceptionally broad concentration range (Fig. 4). Over a 50-fold range from 5 to 0.1 mol% loading, the chiral ligand maintained a consistent 85–88% product ee. At 0.05% loading, the % ee dropped to 70%, but product **14** was still formed in 85% yield. In these studies, the concentrations of benzaldehyde and diethylzinc were kept constant at 0.2 and 0.4 mM, respectively, and the reaction was always quenched after 21 h at 0°C. Yields of isolated products varied from 85 to 94% in the 0.05–10 mol% loading range. However, at 0.02% loading of **7**, the yield of **14** markedly decreased to 14%, and essentially racemic product was isolated.

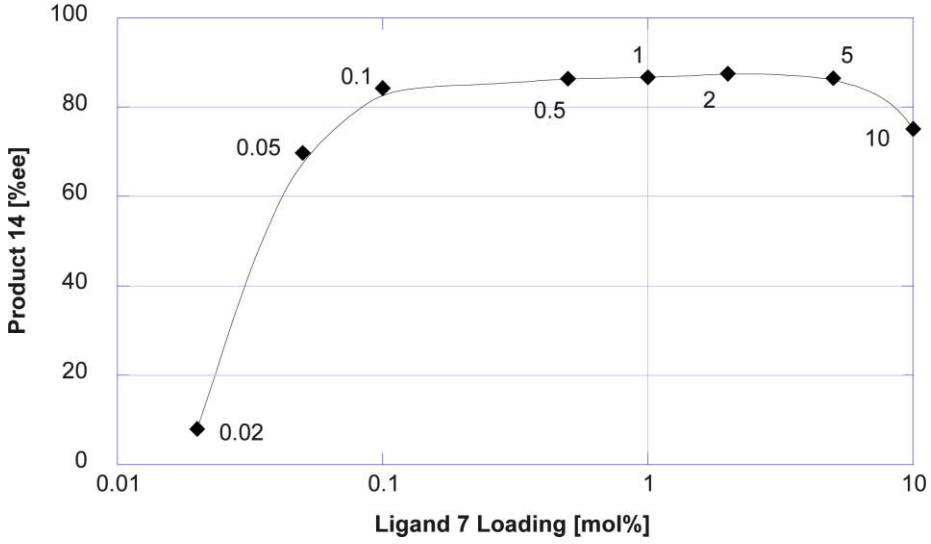


Figure 4. The enantiomeric excess of diethylzinc addition product **14** as a function of the loading of enantiomerically pure ligand **7**.

In a series of control experiments, we also determined if the product % ee in this process changed as a function of reaction time, in order to eliminate the possibility for asymmetric autocatalysis.[1] After 4, 21, and 40 h, the enantiomeric excess of isolated **14** was consistently determined to be 85±3% (Fig. 5). Accordingly, autocatalysis does not appear to effect the conclusions of this study. This result was confirmed by performing the diethylzinc addition reaction in the presence of 2 mol% of (*S*)-**14**: With additional 2 mol% of chiral ligand **7**, product (*S*)-**14** was formed as usual. In contrast, in the absence of any added ligand **7**, no product was obtained, thus demonstrating both the need for the chiral ligand to accelerate the addition reaction and the inability of product to substitute for this function.

3. Conclusions

Our studies provide for the first time a quantitative illustration of the limits of ligand loading as a function of chiral amplification phenomena. We were able to apply rational design principles to obtain a bidentate ligand that does not lead to zinc complex dimer formation and preserves catalytic efficiency at unusually low loadings of 0.05–0.1 mol%, thus allowing turnover numbers in excess of 1000. For potential industrial applications it is also important to note that the dynamic range of this catalytic system spans a 50–100 fold loading range without any major deterioration of product % ee or yield, which is remarkable for organozinc additions to prochiral substrates. This study supports the hypothesis that catalytic efficiency can be significantly increased if nonlinear effects are eliminated by catalyst design.

4. Experimental

4.1. General

^{1}H NMR spectra were measured in $CDCl_3$, unless otherwise noted (chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, b = broad, m = multiplet), integration, and coupling constants (Hz)). Optical rotations were measured on a Perkin–Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $[\alpha]_D$ (*c* g/100 mL). Analysis of the enantiomeric excess was performed by chiral HPLC (Daicel Chiracel OD-H column, flow rate 1.0 mL/min, 2% *i*-PrOH, 98% hexane, T_r 12.5 and 16.5 min). Oven or flame dried glassware was used for all experiments. The experiments were carried out under a nitrogen atmosphere and used the standard inert atmosphere techniques for introducing reagents and solvents. All solvents were freshly distilled from CaH_2 under a nitrogen atmosphere. All other commercial reagents were used as received.

4.2. (1*S*,6*S*)-6-(2-Oxooxazolidine-3-carbonyl)-cyclohex-3-enecarboxylic acid methyl ester 10[30]

A solution of $Ti(O\textit{i}\text{-}Pr)_2Cl_2$ (362 mg, 1.52 mmol) and chiral diol **9** (888 mg, 1.68 mmol) in toluene (57.0 mL) was stirred at room temperature for 1 h and then added to a suspension of 4 Å MS (3.0 g) in toluene (57.0 mL). The reaction mixture was cooled to 0°C. A solution of fumaric acid derivative **8** (2.79 g, 14.0 mmol) in toluene (78.0 mL) was added followed by addition of hexane (96 mL, distilled) and butadiene (40 mL). The reaction mixture was stirred at 0°C for 24 h, then additional butadiene (40 mL) was added. Stirring was continued at 0°C for another 49 h. The solution was quenched with H_2O and extracted with EtOAc, the organic layers were dried ($MgSO_4$) and concentrated, and the residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 15:85) to give **10** (2.71 g, 80%, after recrystallization from *i*-PrOH/hexanes) as a colorless solid: $[\alpha]_D = +186$ (*c* 1.28, CH_2Cl_2); ^{1}H NMR δ 5.69 (AB, 2H, $J = 1.76$, 1.76 Hz), 4.46–4.36 (m, 2H), 4.09–3.95 (m, 3H), 3.66 (s, 3H), 3.03 (dt, 1H, $J = 5.58$, 11.5 Hz), 2.55–2.43 (m, 2H), 2.12–1.95 (m, 2H); ^{13}C NMR δ 176.1, 175.5, 153.2, 125.0, 124.9, 62.0, 51.9, 42.7, 41.2, 39.8, 28.2, 28.1.

4.3. (1*S*,6*S*)-6-Benzyloxycarbonylaminocyclohex-3-enecarboxylic acid methyl ester 11

To a solution of Diels–Alder adduct **10** (2.00 g, 7.90 mmol) in THF (105 mL, stabilized by BHT) and H_2O (30.0 mL) was added 30% H_2O_2 (1.80 g, 52.9 mmol)

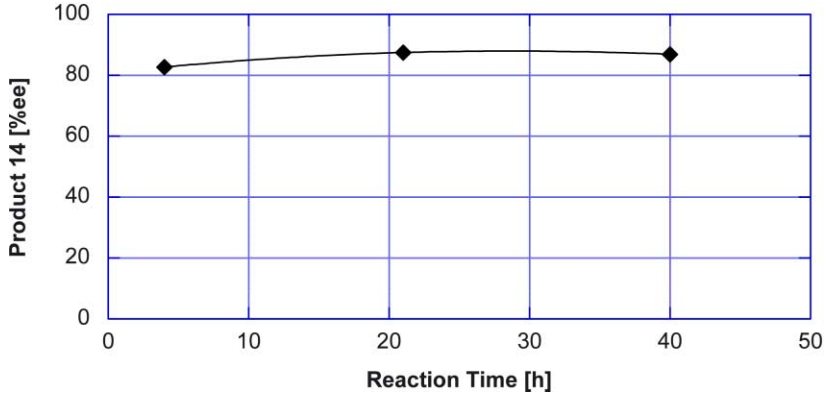


Figure 5. The enantiomeric excess of diethylzinc addition product **14** as a function of reaction time in the presence of 2 mol% of enantiomerically pure ligand **7**. (*S*)-**14** was isolated in 14, 91, and 91% after 4, 21, and 40 h reaction times, respectively.

followed by addition at 0°C of $LiOH \cdot H_2O$ (347 mg, 8.27 mmol). The reaction mixture was stirred at room temperature for 17 h, cooled to 0°C and treated with a 1.35N solution of Na_2SO_3 in H_2O (35.0 mL) followed by a 0.5N solution of $NaHCO_3$ in H_2O (62.1 mL). The organic solvent was evaporated in vacuo, and the aqueous residue was diluted with H_2O and extracted with CH_2Cl_2 (4×). The aqueous layer was acidified with 5N HCl to pH 1 and extracted with EtOAc (4×). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 ($MeOH/CH_2Cl_2$, 5:95) to give a colorless oil. A solution of this oil (1.25 g, 6.77 mmol) in toluene (30.0 mL) was treated with DPPA (1.87 g, 6.77 mmol) and Et_3N (0.69 g, 6.77 mmol) at room temperature. The mixture was stirred at room temperature for 3 h, quenched with cold H_2O, extracted with Et_2O (3×) and dried ($MgSO_4$). After concentration the residue was dried further under vacuum (20 min) and dissolved in toluene (30 mL). The crude acyl azide was heated at reflux for 1.5 h. Benzyl alcohol (0.69 g, 15.0 mmol) was added at 85°C, and the reaction mixture was stirred at 88°C overnight (12 h). The solvent was removed in vacuo, and the residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 20:80) to give **11** (1.43 g, 73%) contaminated with a trace of benzyl alcohol as a colorless oil that was used without further purification.

4.4. (1*S*,2*S*)-2-Methanesulfonylaminocyclohexanecarboxylic acid 12

A solution of carbamate **11** (1.43 g, 4.94 mmol) in EtOAc (54.0 mL) was treated with 10% Pd/C (175 mg, 1.64 mmol) under a hydrogen atmosphere for 3 h, then passed through a pad of Celite. The solvent was removed in vacuo and the residue was diluted in CH_2Cl_2 (54.0 mL). The solution was treated at 0°C with Et_3N (1.68 g, 16.6 mmol) and methane sulfonyl chloride (0.342 g, 2.99 mmol). The resulting mixture was stirred at room temperature for 19 h, then the solvent was removed in vacuo. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 30:70) to give (1*S*,2*S*)-2-methanesulfonylaminocyclohexanecarboxylic acid methyl ester (0.713 g, 62%) contaminated with a trace of MsCl as a white solid that was used without further purification. A THF–water (17.6 mL, 10:1) solution of the methyl ester (713 mg, 3.03 mmol) was treated with $LiOH \cdot H_2O$ (376 mg, 8.96 mmol) at room temperature for 26 h. The THF was evaporated in vacuo, and the residue was diluted with H_2O, acidified to pH 1 with 5N HCl and extracted with EtOAc (3×). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 ($MeOH/CH_2Cl_2$, 8:92) to give **12** (687mg, 65% over three steps) as a white solid: Mp 163.5–164.2°C ($MeOH/CH_2Cl_2$); $[\alpha]_D = +74.2$ (*c* 0.95, MeOH); IR (neat) 3295, 2936, 1725, 1294, 1218, 1148, 1120 cm^{-1}; ^1H NMR (CD_3OD) δ 3.54–3.44 (m, 1H), 3.00 (s, 3H), 2.36 (dt, 1H, $J = 3.2$, 10.9 Hz), 2.23–2.21 (m, 1H), 2.12–2.07 (m, 1H), 1.91–1.80 (m, 2H), 1.69–1.30 (m, 5H); ^{13}C NMR δ (CD_3OD) 178.0, 55.2, 51.0, 41.6, 35.5, 30.7, 25.9, 25.5.

4.5. (1*S*,2*S*)-2-Methanesulfonylaminocyclohexanecarboxylic acid (1-hydroxymethyl-2-methylpropyl)-amide 13

To a suspension of acid **12** (787 mg, 3.11 mmol) in CH_2Cl_2 (15.6 mL) was added dimethyl formamide (29.5 mg, 0.404 mmol) and oxalyl chloride (590 mg, 4.64 mmol) at 0°C. The resulting mixture was stirred at room temperature for 19 h. The solvent was removed in vacuo and the residue was re-dissolved in CH_2Cl_2 (10.9 mL). A solution of D-valinol (401 mg, 3.88 mmol) in CH_2Cl_2 (4.3 mL) was treated with Et_3N (941.8 mg, 9.33 mmol) and the solution of the acid chloride in CH_2Cl_2 (10.9 mL) at 0°C. The reaction mixture was stirred at room temperature for 6 h and purified by chromatography on SiO_2 (acetone/CH_2Cl_2, 40:60) to give **13** (0.782 g) as an off-white solid contaminated with a trace of D-valinol that was used without further purification: ^1H NMR (CD_3OD) δ 3.78–3.76 (m, 1H), 3.69–3.65 (m, 2H), 3.55–3.51 (m, 1H), 3.00 (s, 3H), 2.34–2.25 (m, 2H), 2.07–1.96 (m, 2H), 1.89–1.82 (m, 2H), 1.69–1.28 (m, 4H), 1.09–1.04 (m, 6H); ^{13}C NMR (CD_3OD) δ 176.7, 63.0, 57.8, 54.9, 52.8, 41.9, 35.8, 31.6, 29.6, 26.3, 25.9, 20.0, 19.1; MS (EI) *m*/*e* (relative intensity) 288 ([M–H_2O]$^+$, 2.4), 275 (80), 245 (20), 227 (16), 204 (89), 176 (26), 150 (32), 140 (50), 127 (22), 109 (58), 81 (69), 72 (100), 56 (32); HRMS (EI) *m*/*z* calculated for $C_{13}H_{24}N_2O_3S$ (M–H_2O) 288.1508, found 288.1499.

4.6. (1*S*,2*S*)-*N*-[2-(4-Isopropyl-4,5-dihydrooxazol-2-yl)-cyclohexyl methanesulfonamide *ent*-7

A suspension of amide alcohol **13** (739 mg, 2.41 mmol) and 4-(dimethylamino)pyridine (73.8 mg, 0.604 mmol) in CH_2Cl_2 (35 mL) was treated with Et_3N (855 mg, 8.45 mmol) and a solution of *p*-toluenesulfonyl chloride (781 mg, 4.09 mmol) in CH_2Cl_2 (15 mL). The resulting mixture was stirred at room temperature for 41 h, quenched with saturated aqueous NH_4Cl, and extracted with EtOAc (3×). The combined organic layers were dried ($MgSO_4$), concentrated and purified by chromatography on SiO_2 (EtOAc/hexanes, 90:10) to give *ent*-**7** (543 mg, 78% over two steps) as a colorless solid: Mp 93.0–94.0°C (EtOAc/hexanes); $[\alpha]_D = +81.5$ (*c* 0.9, CH_2Cl_2); IR (neat) 3282, 2934, 2866, 1664, 1320, 1149, 997, 895, 753 cm^{-1}; ^1H NMR δ 4.89 (d, 1H, $J = 7.04$ Hz), 4.23 (dd, 1H, $J = 0.71$, 8.93 Hz), 4.00–3.91 (m, 2H), 3.49–3.39 (m, 1H), 2.94 (s, 3H), 2.41 (dt, 1H, $J = 3.4$, 11.0 Hz), 2.36–2.25 (m, 1H), 2.05–1.94 (m, 2H), 1.85–1.55 (m, 2H), 1.42–1.20 (m, 4H), 0.97 (d, 3H, $J = 6.7$ Hz), 0.89 (d, 3H, $J = 6.7$ Hz); ^{13}C NMR δ 167.9, 71.3, 70.1, 54.6, 44.5, 41.5, 34.8, 32.6, 29.6, 25.0, 24.7, 18.7, 18.1; MS (EI) *m*/*z* (relative intensity) 288 ([M]$^+$, 1.8), 245 (14), 209 (47), 150 (28), 140 (33), 129 (22), 97 (22), 81 (48), 69 (100), 57 (95); HRMS (EI) *m*/*z* calculated for $C_{13}H_{24}N_2O_3S$ 288.1508, found 288.1498.

4.7. 1-Phenylpropan-1-ol 14

A solution of benzaldehyde (159.3 mg, 1.5 mmol) and ligand **7** (8.70 mg, 0.03 mmol) in hexane (3.60 mL) was treated at 0°C with a 1.0 M solution of diethyl zinc in hexanes (3.30 mL, 3.30 mmol). The reaction mixture

was stirred at 0°C for 21 h, quenched with a 1.0 M solution of HCl in H_2O, and extracted with CH_2Cl_2 (3×). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (EtOAc/hexanes, 15:85) to give **14** (194 mg, 94%) as a colorless oil: ^{1}H NMR δ 7.41–7.27 (m, 5H), 4.64 (t, 1H, $J=6.9$ Hz), 1.95–1.70 (m, 3H), 0.96 (t, 3H, $J=7.2$ Hz).

Acknowledgements

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