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# A New Ligand Scaffold for Catalytic Asymmetric Alkylzinc Additions to Aldehydes

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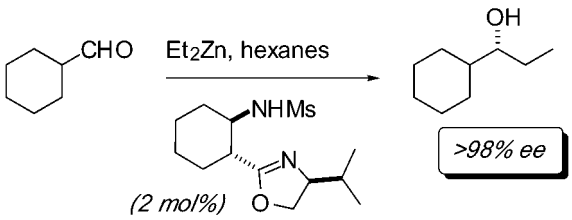
## ABSTRACT




**1,3-Azole derivatives of 2-aminocyclohexanecarboxylic acid represent a new class of bidentate ligands for metal-mediated catalytic asymmetric synthesis. *N*-[2-(4-Isopropyl-4,5-dihydrooxazol-2-yl)cyclohexyl]methanesulfonamide (6) is particularly well suited for the addition of alkylzinc reagents to aliphatic aldehydes in high enantiomeric excess.**

The development of new classes of chiral ligands for metal-catalyzed asymmetric transformations is an important goal of contemporary organic chemistry. While ligands based on the binaphthyl,[1] salen,[2] bisoxazoline,[3] and tartrate[4] scaffolds have been extraordinarily successful in many synthetic transformations,[5] there is still considerable incentive to diversify the family of chiral ligand architectures. Among the most important design criteria for metal ligand development are the spatial orientation of chelating heteroatoms, a ready structural modification, and, of course, convenient access to both enantiomers in high enantioselectivity.

We have recently reported the preparation of aminocyclohexanecarboxylic acids **1** by catalytic asymmetric Diels−Alder methodology (Figure 1).[6,7] While a major application of these compounds lies in the preparation of water-soluble $\beta$-peptide foldamers,[8] we envisioned that the disposition of two neighboring functional groups on the synthetically readily modified cyclohexane scaffold would lend itself to effective metal ligand design. We now report the preparation of several aminooxazoline and -thiazoline congeners based on this motif and the experimental validation of the effectiveness of this new ligand architecture in highly enantioselective diethylzinc additions to aliphatic aldehydes.[9]

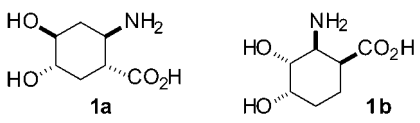



**Figure 1.** Dihydroxylated *cis*- and *trans*-aminocyclohexane $\beta$-amino acid building blocks.

Selective saponification of imide **2**,[6] followed by modified Curtius rearrangement with DPPA,[10] provided carbamate **3** in 80% yield (Scheme 1). Catalytic hydrogenation of the

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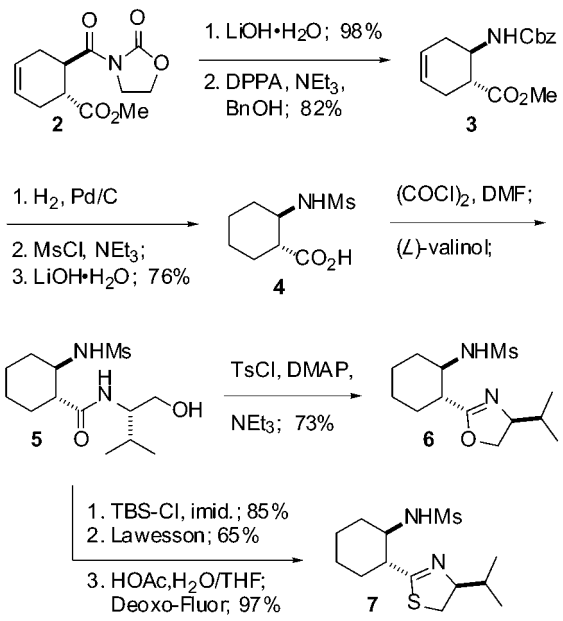
**Scheme 1**




alkene moiety with concomitant removal of the Cbz-group, *N*-mesylation, and hydrolysis of the methyl ester led to carboxylic acid **4** as the precursor for the introduction of heterocyclic substituents. Upon activation of the acid with oxalyl chloride and condensation with (*L*)-valinol, the intermediate amide **5** was cyclodehydrated[11] to give oxazoline **6** in excellent overall yield. Protection of the hydroxy group of **5** with TBS-Cl, formation of the thioamide with Lawesson reagent, cleavage of the silyl ether, and cyclodehydration[12] with Deoxo-Fluor led to thiazoline **7** in 54% yield from acid **4**.

In a series of analogous transformations, oxazolines **8**−**16** were prepared (Figure 2).[13] A preliminary evaluation of the structure−activity relationships in this new class of chiral ligands for asymmetric catalysis was established by the addition of $Et_2Zn$ to benzaldehyde (Scheme 2). [14]

Our initial studies were conducted with the tosyl derivative **8** (Table 1, entries 3−6). Even in the presence of only 2 mol % of **8**, (*R*)-**17** was obtained in 89% yield and 80% ee after a 22 h reaction time at 0 °C. Lowering the reaction temperature had a dramatic effect in decreasing the reaction rate, but the enantioselectivity was essentially temperature independent. In addition, increasing the amount of **8** to 5 mol % loading did not provide a further increase in % ee.

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(13) In all cases, ligand enantiomeric excess exceeded 99%.

(14) In a typical reaction, a solution of benzaldehyde (0.50 mmol) and ligand (0.010 mmol) in hexanes (1.2 mL) was treated with a 1.0 M solution of diethyl zinc in hexanes (1.10 mL, 1.10 mmol) at 0 °C. The reaction mixture was stirred for 20−40 h at 0 °C, quenched by addition of 1 M HCl, and extracted with $CH_2Cl_2$. The combined organic layers were dried ($MgSO_4$), concentrated, and chromatographed on $SiO_2$ (ethyl acetate/hexanes) to give the secondary alcohol as a colorless oil. Toluene could also be used as a reaction solvent, leading to slightly slower reaction rates but similar yields of products and % ee.

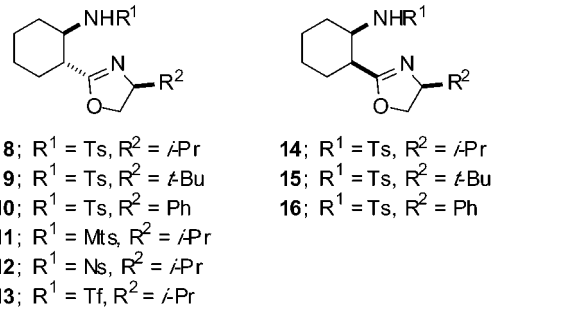


**Figure 2.** *N*-Sulfonated *cis*- and *trans*-aminocyclohexane oxazolines as test ligands for asymmetric catalysis.

Somewhat to our surprise, adding to the bulk of the $R^2$ substituent by replacing the isopropyl group with a *tert*-butyl or a phenyl group (entries 7 and 8, respectively) did not have a noticeable effect on the enantioselectivity either. Accordingly, we decided to investigate the effect of the sulfonyl group. While the 2,4,6-trimethylbenzenesulfonyl (Mts) and the nosyl (Ns) groups in the $R^1$ position lowered the enantiomeric excess, the triflate **13** provided a small increase

**Scheme 2**

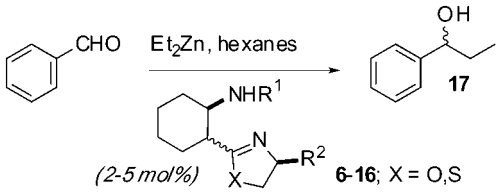


**Table 1.** Ligand-Accelerated Asymmetric $Et_2Zn$ Addition to Benzaldehyde

| entry | ligand (mol %) | temperature | yield (*ee*)[a] |
|---|---|---|---|
| 1 | **6** (2) | 0 °C | 91% (*86%*)[b] |
| 2 | **7** (2) | 0 °C | 89% (*85%*)[b] |
| 3 | **8** (2) | 0 °C | 89% (*80%*)[b] |
| 4 | **8** (2) | −15 °C | 31% (*76%*)[b] |
| 5 | **8** (2) | 22 °C | 93% (*78%*)[b] |
| 6 | **8** (5) | 0 °C | 94% (*80%*)[b] |
| 7 | **9** (2) | 0 °C | 78% (*78%*)[b] |
| 8 | **10** (2) | 0 °C | 90% (*80%*)[b] |
| 9 | **11** (2) | 0 °C | 33% (*58%*)[b] |
| 10 | **12** (2) | 0 °C | 12% (*4%*)[b] |
| 11 | **13** (2) | 0 °C | 54% (*88%*)[b] |
| 12 | **14** (2) | 0 °C | 58% (*48%*)[c] |
| 13 | **14** (2) | −30 °C | 57% (*51%*)[c] |
| 14 | **14** (5) | 0 °C | 88% (*49%*)[c] |
| 15 | **15** (2) | 0 °C | 67% (*3%*)[c] |
| 16 | **16** (2) | 0 °C | 62% (*45%*)[c] |

[a] Determined by chiral HPLC (Chiracell OD) unless noted otherwise. [b] (*R*)-**17** was formed. [c] (*S*)-**17** was formed.

in enantiomeric excess to 88%, but in the presence of this ligand the reaction did not proceed as quickly as with tosylate **8** (entries 9−11).

For comparison, we also tested the *cis*-aminooxazolines **14**−**16**, even though molecular modeling predicted that the geometry for bidentate metal chelation between the sulfonamide and oxazoline nitrogens was not as favorable as in the *trans*-configured congeners. Indeed, the % ee values under a variety of reaction conditions did not exceed 51%, and now (*S*)-**17** was the predominantly formed enantiomer (Table 1, entries 12−16). This change in enantiofacial selectivity in the diethyl zinc addition clearly illustrates the importance of the cyclohexane C(2)-stereocenter but might also be the consequence of a monodentate interaction of chiral ligands **14**−**16** with zinc. In terms of overall yield and enantioselectivity, the *trans*-oxazoline mesylate **6** provided the best results (entry 1), and since the corresponding thiazoline **7** was not superior but required three additional synthetic steps, we decided to further investigate the scope of this process by focusing on ligand **6**.

Substitution at the phenyl ring of the aromatic aldehydes decreased the reaction rate and also led to small decreases in the enantioselectivity of the ethylzinc addition process (Table 2, entries 1 and 2). Cinnamaldehyde only provided a

**Table 2.** Asymmetric $Et_2Zn$ Addition to Aldehydes at 0 °C in the Presence of 2 mol % of Chiral Ligand **6**. In All Cases, the (*R*)-Configuration at the Secondary Alcohol Carbon Was Obtained as the Major Enantiomer

| entry | substrate | time | yield (*ee*)[a] |
|---|---|---|---|
| 1 | (*p*-Cl)PhCHO | 52 h | 79% (*72%*) |
| 2 | (*p*-MeO)PhCHO | 43 h | 81% (*80%*) |
| 3 | (*E*)-PhHC=CHCHO | 45 h | 47% (*41%*) |
| 4 | $BnO(CH_2)_2C{\equiv}CCHO$ | 21 h | 91% (*11%*) |
| 5 | $PhCH_2CH_2CHO$ | 23 h | 97% (*83%*) |
| 6 | *c*-$C_6H_{11}CHO$ | 25 h | 68% (*>98%*)[b] |
| 7 | (*L*)-citronellal | 26 h | 80% (*91%*)[c] |
| 8 | (*R*)-citronellal | 28 h | 80% (*94%*)[c] |
| 9 | *n*-$C_7H_{15}CHO$ | 23 h | 95% (*92%*)[d] |

[a] Determined by chiral HPLC (Chiracell OD) unless noted otherwise. [b] Determined by chiral GC. [c] de determined by GC analysis. [d] Determined by comparison of rotation values with literature data.[15]

47% yield of addition product in 41% ee after 45 h at 0 °C (entry 3). While, in general, low reaction rates were associated with a low enantiomeric excess of the secondary alcohol products, this did not apply to all substrates. 5-Benzyloxypent-2-ynal reacted rapidly, but with no significant enantiofacial differentiation (entry 4). In contrast, aliphatic aldehydes provided the highest enantioselectivities. Hydrocinnamaldehyde led to 83% ee, and the secondary alcohol products from cyclohexanecarboxaldehyde and octanal were formed in >98% and 92% ee, respectively (entries 6 and 9). From the enantiomeric (*L*)- and (*R*)-citronellal, two diastereomeric addition products were formed in 91% and 94% de (entries 7 and 8), thus establishing predominant reagent control over substrate diastereoselectivity in the addition process.

The high enantioselectivity obtained with ligand **6** and α-branched as well as linear aliphatic aldehydes compares well to the frequently low to modest asymmetric inductions reported for this class of substrates in the literature.[9] Most comparable to **6**−**16** are Bolm's ferrocenyl oxazolines that combine planar and central chirality elements and catalyze the addition of diethylzinc to heptanal in 87% ee at 5 mol % ligand loading.[16] In contrast, Hou's bidentate ferrocenyl oxazolines only provided a 71% ee for diethylzinc addition to cyclohexanecarboxaldehyde.[17] From a structural point of view, sulfonylaminooxazoline and -thiazoline ligands **6**−**16** are most closely related to the chiral (2-sulfonylamino)-phenyloxazolines reported by Fujisawa[18] and Mikami[19] that have been employed for enantioselective Diels−Alder, cyclopropanation, and C−H bond activation reactions. However, the latter ligands have not yet been explored for asymmetric zinc additions and do not offer the same level of control in scaffold configurations, metal complex bite angles, and substitution patterns as ligands **6**−**16**.

The facial selectivity of the ligand **6**/diethyl zinc reagent can be explained by coordination of the aldehyde substrate *syn* to the oxazoline isopropyl group of a distorted tetrahedral zinc complex (Figure 3). This leaves the *re*-face of the

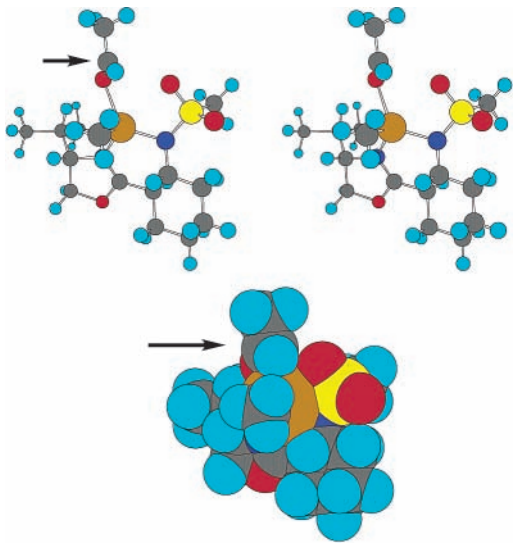

**Figure 3.** Stereoview and CPK model of an acetaldehyde complex with the methylzinc adduct to ligand **6**. Complex geometry was optimized semiempirically with PM3 parametrization using Spartan.

carbonyl group relatively open to nucleophilic attack, and addition would accordingly occur opposite to the sulfonamide


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substituent. If the oxazoline substituents or the sulfonamide functions become too sterically demanding, the reaction rate is expected to decrease and the selectivity drops, as was experimentally observed. The presence of the cyclohexane backbone and the sterically demanding environment around the zinc atom leads to a conformational rigidity that is essential for high asymmetric induction and blocks intermolecular aggregation. The latter effect is most likely what allows catalyst loadings to remain relatively small at 2 mol % in comparison with standard asymmetric zinc additions to aldehydes and explains the lack of dependence of product % ee on catalyst loadings.

In conclusion, the new *pseudo*-$C_2$-symmetric bidentate ligand **6** is well suited for accelerating the catalytic asymmetric addition of diethylzinc to aldehydes. The high enantiomeric excess that was obtained with aliphatic aldehydes and the low level of ligand loading clearly validate the efficacy of the newly designed and structurally readily modified family of aminocyclohexane azoles **6**−**16** for asymmetric catalysis. Further applications of these chiral ligands in metal-mediated synthetic methodology are currently under investigation and will be reported in due course.

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**Supporting Information Available:** Experimental procedures and spectral data for ligands **6** and **7**, including copies of $^1H$ and $^{13}C$ NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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