Planar−Chiral Heterocycles as Ligands in Metal-Catalyzed Processes: Enantioselective Addition of Organozinc Reagents to Aldehydes

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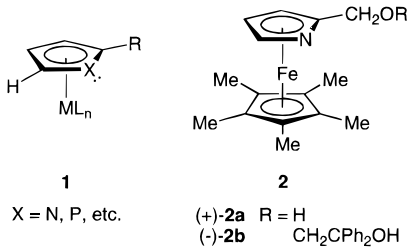
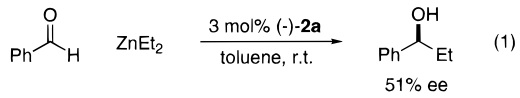
As part of a program directed toward the development of new families of chiral nucleophilic catalysts and new classes of chiral ligands, we have begun to explore the chemistry of 2-substituted heterocycles that are π-bound to transition metals (e.g., **1**).[1] Such complexes are chiral by virtue of the presence of ML_n and the differentiation of R from H, and the asymmetric environment around the Lewis-basic heteroatom can readily be "tuned" by varying the steric bulk either of the metal fragment or of R. We recently demonstrated that enantiopure planar−chiral heterocycles function as efficient nucleophilic acylation catalysts for the kinetic resolution of secondary alcohols.[1] In this paper, we report that they also serve as effective chiral ligands,[2] catalyzing the enantioselective addition of organozinc reagents to aldehydes.



1 X = N, P, etc. **2** (+)-**2a** R = H; (−)-**2b** CH_2CPh_2OH

Because an array of β-amino alcohols are known to catalyze the asymmetric addition of diethylzinc to aldehydes,[3] we focused our initial efforts in this area on planar−chiral β-amino alcohol **2a**. Treatment of benzaldehyde with 3 mol % of (−)-**2a** and 1.2 equiv of $ZnEt_2$ results in the formation of (*S*)-1-phenyl-1-propanol with modest enantioselectivity (51% ee; eq 1).



(1)

We next chose to follow the lead of Hoshino, who has established that *O*-alkylation of a chiral β-amino alcohol with 1,1-diphenyloxirane can enhance the stereoselectivity observed for organozinc additions to aldehydes.[4]

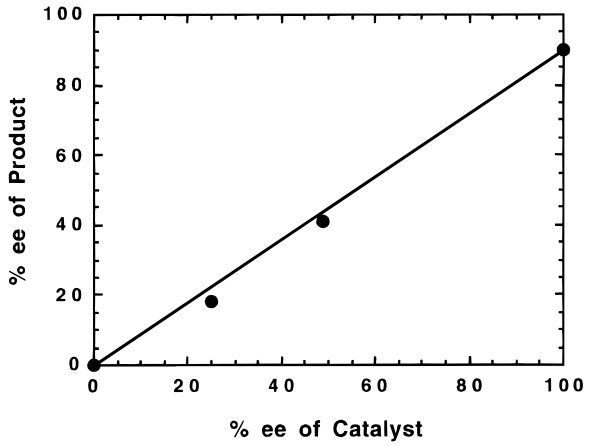
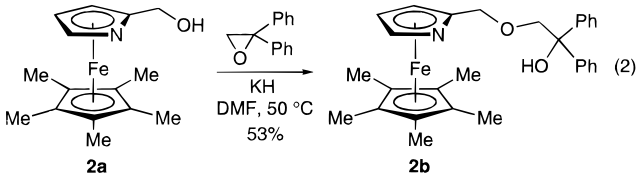
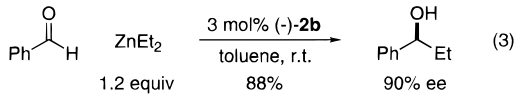


Figure 1. Product ee as a function of catalyst ee for the reaction of benzaldehyde with $ZnEt_2$ in the presence of 3 mol % of **2b**.

Alkylation of the potassium salt of **2a** affords tridentate ligand **2b** (eq 2), which has indeed proved to be a more



(2)



(3)

effective asymmetric catalyst than **2a**. Thus, reaction of benzaldehyde with $ZnEt_2$ in the presence of 3 mol % of (−)-**2b** produces (*S*)-1-phenyl-1-propanol in 90% ee (eq 3; cf. eq 1).[5,6] Several striking examples of asymmetric amplification have been reported for amino alcohol-catalyzed additions of organozinc reagents to aldehydes;[7] in the case of **2b**, however, the relationship between the ee of the catalyst and the ee of the product is essentially linear (Figure 1).

A study of the addition of $ZnEt_2$ to 4-substituted benzaldehydes reveals that catalyst **2b** provides high enantioselectivity regardless of the electronic character of the aromatic ring (eq 4[8]). However, consistent with other amino alcohol-catalyzed $ZnEt_2$ reactions,[3c] some-

(1) (a) Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230−7231. (b) Ruble, J. C.; Latham, H. A.; Fu, G. C., in press.

(2) (a) First report of *N*-coordination of an azaferrocene to a transition metal: Pyshnograeva, N. I.; Setkina, V. N.; Kursanov, D. N. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1984**, 2778−2780. (b) Review of σ,π-complexes of five-membered monoheterocycles: Sadimenko, A. P.; Garnovskii, A. D.; Retta, N. *Coord. Chem. Rev.* **1993**, *126*, 237−318.

(3) (a) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823−2824. (b) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071−6072. (c) Comprehensive review of the enantioselective addition of organozinc reagents to aldehydes: Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856.

(4) Ishizaki, M.; Fujita, K.-i.; Shimamoto, M.; Hoshino, O. *Tetrahedron: Asymmetry* **1994**, *5*, 411−424.

(5) Representative procedure: $ZnEt_2$ (31 μL, 0.30 mmol) was added dropwise by syringe to a solution of (+)-**2b** (3.6 mg, 0.0074 mmol) and benzaldehyde (26.5 mg, 0.25 mmol) in 3.0 mL of toluene. After being stirred for 24 h at room temperature, the reaction was quenched by the addition of 2.5 mL of 1 N HCl. The resulting mixture was extracted with Et_2O, and the organic layer was concentrated. Purification by flash chromatography (20% Et_2O/pentane) afforded 28.8 mg (92%) of 1-phenyl-1-propanol, which was acylated with acetic anhydride. Chiral GC analysis of the acetate revealed a 90% ee of the *R* isomer. Note: The data reported for eqs 1 and 3−7 are the average of two runs, one with each enantiomer of the catalyst.

(6) Benzaldehyde is the only substrate for which optimization studies have been performed. The enantioselectivity is not sensitive to changes in catalyst loading, temperature, concentration, stoichiometry of $ZnEt_2$, or solvent (hexane, 1:1 toluene:hexane, Et_2O, or $PhCF_3$).

(7) (a) Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877−7878. (b) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M. *Pure Appl. Chem.* **1988**, *60*, 1597−1606.

(8) The absolute configuration of 1-(4-fluorophenyl)propanol has not been determined (no literature data are available).

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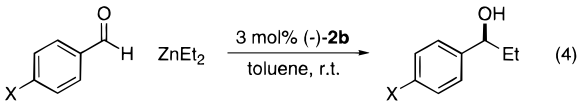
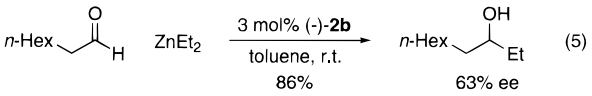
what lower stereoselectivity is observed when the aromatic ring is replaced with an *n*-alkyl group (63% ee; eq 5).



(4)

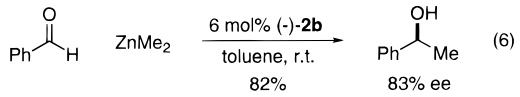
X	% ee	Yield (%)
F	89	91
Cl	90	94
H	90	88
OMe	86	94



(5)

We have also explored the reactions of $ZnMe_2$ and $ZnPh_2$ with aldehydes in the presence of catalyst (−)-**2b**. In the case of $ZnMe_2$, addition to benzaldehyde provides (*S*)-1-phenylethanol in good enantiomeric excess (83% ee; eq 6), while the reaction of $ZnPh_2$ with 4-chlorobenzaldehyde proceeds with moderate stereoselectivity (57% ee; eq 7).[9]

In conclusion, we have established that 2-substituted heterocycles that are chiral by virtue of π-complexation to a metal serve as effective catalysts for the enantioselective addition of organozinc reagents to aldehydes. To the best of our knowledge, this is the first application of this family of ligands in asymmetric catalysis, and our current efforts are focused on extending their utility to an array of transition metal-catalyzed reactions.



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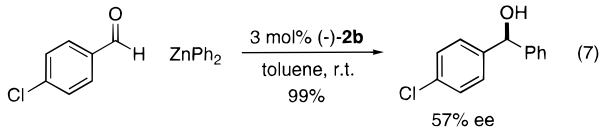

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Supporting Information Available: Experimental procedures and compound characterization data (9 pages).

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(9) Crystalline $ZnPh_2$ (Strem) was used in these reactions. To the best of our knowledge, this is the first example of the catalytic enantioselective addition of $ZnPh_2$ to an aldehyde. The few previous reports of asymmetric catalysis with "$ZnPh_2$," prepared by mixing phenylmagnesium halide and zinc chloride, appear not to involve $ZnPh_2$. For a discussion, see ref 3c, pp 846−847.