J. Am. Chem. Soc. **1998,** *120,* 445−446

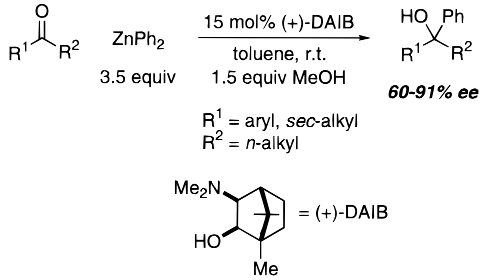
Catalytic Asymmetric Addition of $ZnPh_2$ to Ketones: Enantioselective Formation of Quaternary Stereocenters

Peter I. Dosa and Gregory C. Fu*

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

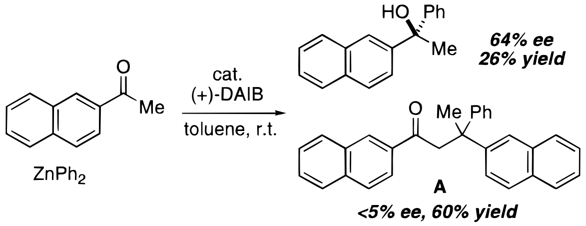
Received September 10, 1997

A wide array of highly effective catalysts have been developed for the enantioselective addition of organometallic reagents to aldehydes.[1,2] However, to the best of our knowledge there have been no reports of efficient catalytic asymmetric addition of organometallic reagents to ketones.[3] In this communication, we provide an example of such a process, establishing that 3-*exo*-(dimethylamino)isoborneol (DAIB)[1b] serves as an effective catalyst for the enantioselective addition of $ZnPh_2$ to a range of aryl−alkyl and dialkyl ketones, thereby producing a quaternary stereocenter with good to excellent stereocontrol (eq 1).



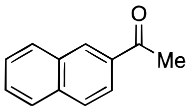
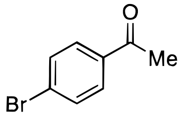
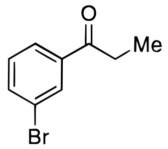
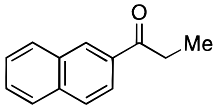
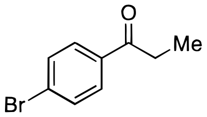
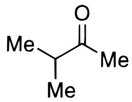
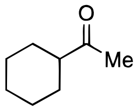
(1)

In pioneering studies, Noyori has demonstrated that DAIB is a remarkably efficient catalyst for the asymmetric addition of $ZnEt_2$ to aldehydes.[1b,d] We sought to expand the scope of DAIB-catalyzed processes to include reactions of ketones, and we focused our initial efforts on the addition of $ZnPh_2$[4] to 2-acetonaphthone. Although we observed a promising level of enantiomeric excess in the desired tertiary alcohol (64% ee), the yield was disappointing (26% yield; eq 2). The predominant reaction product was ketone **A**, which is formed via an aldol-dehydration−conjugate addition sequence.[5]



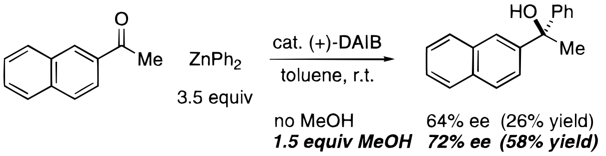
(2)

Table 1. Enantioselective Addition of $ZnPh_2$ to Ketones Catalyzed by (+)-DAIB (eq 1)

entry	substrate	% ee[a]	yield (%)
1		72 (+)	58
2		80 (-)	53
3		91 (-)	91
4		86 (-)	79
5		90 (-)	83
6		60 (+)	63
7		75 (+)	76

[a] The sign of rotation of the predominant enantiomer is indicated in parentheses. For entries 1, 4, and 7, the R isomer is formed preferentially.

With the expectation that an additive would alter the nature of the zinc species in solution, we introduced MeOH to the reaction mixture.[6] We were pleased to discover that the addition of 1.5 equiv of MeOH results in enhanced enantioselectivity and in an improved yield of the desired tertiary alcohol (eq 3).[7]



(3)

We have explored the scope of DAIB-catalyzed reactions of $ZnPh_2$ with ketones, and we have established that for an array of substrates the additions proceed with good to excellent enantio-

---

(1) For reactions of organozinc reagents, see: (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) Soai, K.; Niwa, S. *Chem. Rev. (Washington, D.C.)* **1992**, *92*, 833−856. (d) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; Chapter 5.

(2) *Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: New York, 1996; Part D, Section 1.3.

(3) For examples of efficient asymmetric additions of organometallic reagents to ketones in the presence of a *stoichiometric* quantity of an enantiopure magnesium alkoxide, see: Weber, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 84−86.

(4) We are aware of only one report of catalytic asymmetric addition of $ZnPh_2$ to a carbonyl group: Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444-445 (addition of ZnPh2 to 4-chlorobenzaldehyde in 57% ee).

(5) For precedent, see: (a) Aldol-dehydration: Henrich, F.; Wirth, A. *Monatsh. Chem.* **1904**, *25*, 423−442. (b) Conjugate addition: Soai, K.; Okudo, M.; Okamoto, M. *Tetrahedron Lett.* **1991**, *32*, 95−96.

(6) MeOH reacts rapidly with $ZnPh_2$ to form benzene and a zinc alkoxide.

(7) In these DAIB-catalyzed addition processes, enolization of the ketone is a key side reaction that is detrimental from the standpoints of yield *and* enantioselectivity. Thus, whereas $ZnPh_2$ reacts with 2-acetonaphthone to produce the tertiary alcohol in 58% yield and 72% ee (eq 3), it reacts with 2-acetonaphthone-d_3 to afford the tertiary alcohol in 87% yield and 86% ee.

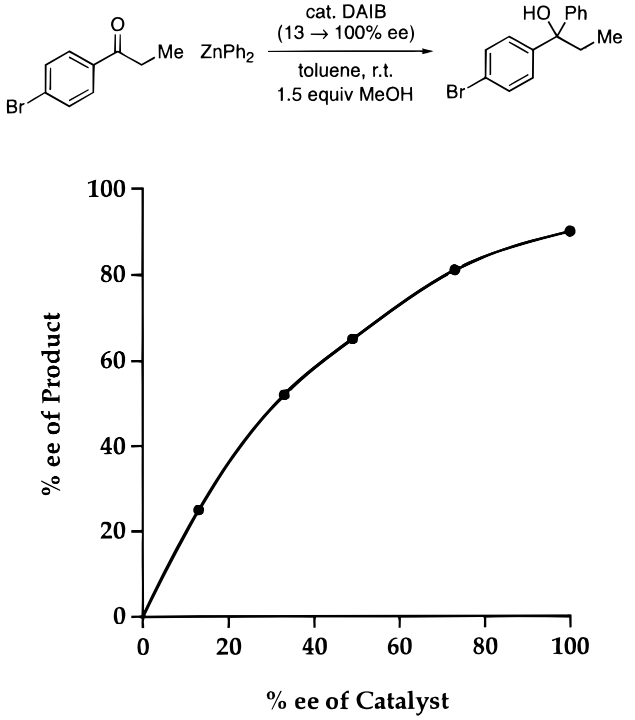
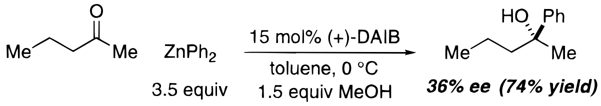


Figure 1. DAIB-catalyzed addition of $ZnPh_2$ to 4-bromopropiophenone: Nonlinear dependence of product ee on catalyst ee.

selectivity (Table 1).[8] In the case of aryl−alkyl ketones (entries 1−5), increasing the steric bulk of the alkyl substituent leads to both greater enantiomeric excess and higher yield (entries 1 vs 4 and entries 2 vs 5). With respect to dialkyl ketones, we have determined that DAIB is an effective chiral catalyst for the addition of $ZnPh_2$ to isopropyl methyl ketone (entry 6) and to cyclohexyl methyl ketone (entry 7). We have observed more modest, but appreciable, enantioselectivity in the catalytic asymmetric addition of $ZnPh_2$ to 2-pentanone, a particularly challenging substrate (*n*-propyl vs methyl; eq 4).



(4)

Noyori has reported that when the addition of $ZnEt_2$ to benzaldehyde is conducted in the presence of DAIB catalyst of only 15% ee, the product alcohol is nevertheless generated with very high enantiomeric excess (95% ee); he attributed this nonlinear effect to the formation of a relatively unreactive dinuclear zinc complex that sequesters a 1:1 mixture of DAIB enantiomers.[9] We have observed an analogous, albeit less dramatic, nonlinear dependence of product ee on catalyst ee in DAIB-catalyzed additions of $ZnPh_2$ to ketones (Figure 1).

In conclusion, we have established that in the presence of MeOH, DAIB serves as an effective chiral catalyst for the addition of $ZnPh_2$ to a variety of aryl−alkyl and dialkyl ketones, providing good to excellent enantioselectivity in the formation of a new quaternary stereocenter. As far as we are aware, this represents the first method for the catalytic asymmetric addition of an organometallic reagent to a ketone. Additional studies of the scope and mechanism of this process are underway.

Acknowledgment. We thank Prof. Stephen L. Buchwald and Prof. Stephen J. Lippard for generously sharing their HPLC, GC, and X-ray facilities, Dr. Peter Fuhrmann (Lippard group) for solving an X-ray crystal structure, and Diego A. Hoic for a helpful suggestion. Support has been provided by the Alfred P. Sloan Foundation, the American Cancer Society, the Camille and Henry Dreyfus Foundation, Eli Lilly, Firmenich, Glaxo Wellcome, the National Science Foundation (Young Investigator Award to G.C.F., with funding from Procter & Gamble, Merck, Bristol-Myers Squibb, DuPont, Pfizer, Rohm & Haas, and Bayer), Pharmacia & Upjohn (fellowship to P.I.D.), and the Research Corporation. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the ACS, for partial support of this research. Dedicated to Professor Satoru Masamune on the occasion of his 70th birthday.

Supporting Information Available: Experimental procedures and compound characterization data (35 pages). See any current masthead page for ordering and Internet access instructions.

JA973169U

---

(8) **Sample experimental (Table 1, entry 4):** Toluene (1.5 mL) was added by syringe to a vessel containing (−)-DAIB (7.5 mg, 0.038 mmol) and $ZnPh_2$ (193 mg, 0.877 mmol). After the mixture was stirred for 5 min at room temperature, MeOH (16 μL, 0.40 mmol) was added dropwise by syringe. Ten minutes later, a solution of 2-propionaphthone (46.7 mg, 0.253 mmol) in toluene (1.5 mL) was added by syringe. After the mixture was stirred for 48 h at room temperature, the reaction was exposed to air, and 1 N HCl (3.0 mL) was added. The mixture was extracted three times with Et_2O, and the organic layer was concentrated and purified by flash chromatography (15% Et_2O/pentane), which afforded 53.2 mg (80%) of (+)-1-(2-naphthyl)-1-phenylpropanol. HPLC analysis (Chiralcel OD) revealed an 86% ee.

(9) (a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028−4036. (b) Reference 1d. (c) See also: Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877−7878.