Enantioselective Synthesis of Arylamines Through Zr-Catalyzed Addition of Dialkylzincs to Imines. Reaction Development by Screening of Parallel Libraries

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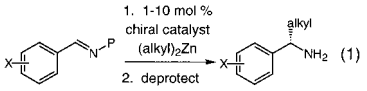
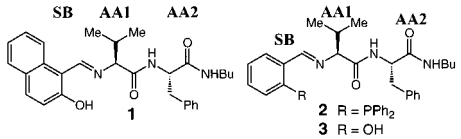
Efficient and asymmetric preparation of amines is an important objective in organic synthesis.[1] Myriad chiral auxiliaries[2] and ligands (stoichiometric)[3] have thus been reported that allow the enantioselective addition of alkylmetals to C═N bonds. The groups of Denmark[4] and Tomioka[5] have accomplished the catalytic addition of alkyllithiums to imines, where appreciable levels of enantioselectivity are detected (up to 82% ee) in the presence of 10−20 mol % of amine chiral ligands. We are interested in the possibility of a catalytic asymmetric approach to the addition of dialkylzincs to imines (eq 1).[6] Our preference



for alkylzincs is partly because of their functional group tolerance. An advantage of the above attribute is that modular peptide-based ligands (e.g., **1**, below) can be used to effect enantioselective catalysis.[7] Herein, we disclose efficient Zr-catalyzed imine alkylations promoted by peptide-based chiral ligands that afford arylimines in 84−98% ee and 60−98% isolated yield.

Parallel libraries were constructed to establish the appropriate reaction parameters. Imines derived from condensation of benzaldehyde and benzylamine, aminodiphenylmethane, aniline, 2-aminophenol, *o*-anisidine, and 2,4-dimethoxyaniline constituted the initial substrate pool. Toluene was chosen as the solvent, since its low volatility leads to more reliable data from ligand screening (minimum concentration variation of library samples). Commercially available Et_2Zn was used as the alkylating agent. The following metal salts were screened: CuCN, $Cu(OAc)_2$, CuOTf, $Ti(O\textit{i}\text{-}Pr)_4$, $Zr(O\textit{i}\text{-}Pr)_4$·HO*i*-Pr, BF_3·Et_2O, $ZnCl_2$, $AlBr_3$, $Sc(OTf)_3$. Since both early and late transition metals were incorporated within our search, the phenol-based Schiff base derived from naphthaldehyde (**1**) and (2-diphenylphosphino) benzaldehyde[8] (**2**) served as preliminary chiral ligands (both aldehydes are commercially available). L-Val was positioned at the AA1 site, and L-Phe served as the AA2, as these two amino acids are relatively inexpensive. We judged that, if necessary, positional optimization would be carried out at the Schiff base and AA1 and AA2 sites for enhanced enantioselectivities.[7b−e]



Screening studies (20 mol % metal and ligand) indicate that the Zr and Ti salts provide higher levels of reactivity and selectivity in conjunction with phenolic Schiff base ligands when *o*-anisidine derivatives are used as substrates (25−98% conversion and 40−75% ee). With the remaining substrates and metal salts, <5% conversion and ee is detected. The phosphine-based ligand provided less conversion and <5% ee with all metals and electrophiles. Further examination of the above parameters indicated that $Zr(O\textit{i}\text{-}Pr)_4$·HO*i*-Pr delivers more selective and efficient additions than $Ti(O\textit{i}\text{-}Pr)_4$ (88% ee, >98% conversion vs 62% ee, 43% conversion).[9] Positional optimizations at the Schiff base, AA1, and AA2 sites (∼20 ligands screened) were carried out subsequently. These studies established that, as shown in entry 1 of Table 1, with 10 mol % **3** and 10 mol % $Zr(O\textit{i}\text{-}Pr)_4$·HO*i*-Pr at 0−22 °C, amine **4** is obtained from the corresponding *o*-anisidyl arylimine[10] in 93% ee and 84% isolated yield. As depicted in entry 2, with 1 mol % **3**, reaction efficiency and selectivity suffer (81% ee, 10% conversion, 24 h). When the amount of the chiral ligand **3** is reduced to 1 mol % but that of the less valuable Zr salt is increased to 20 mol % (entry 3), catalytic alkylation proceeds efficiently and enantioselectively (95% ee, >98% conversion). Remarkably, even in the presence of 0.1 mol % **3** and 20 mol % $Zr(O\textit{i}\text{-}Pr)_4$·HO*i*-Pr, the asymmetric alkylation takes place rapidly to afford **4** in 93% ee (entry 4).[11]

As the data summarized in Table 1 illustrate, Zr-catalyzed addition of an Et group to a variety of imines proceeds to >98% conversion within 24 h (except for entries 4−6, requiring 48 h) to afford the desired chiral amines in >88% ee and >62% yield.A number of additional issues merit mention: (1) As the result in entry 7 indicates, where the Schiff base from 2-naphthalene carboxaldehyde is used as the electrophile, reactions involving

(1) Federsel, H.-J.; Collins, A. N.; Sheldrake, G. N.; Crosby, J. *Chirality in Industry II*; John Wiley and Sons: Chichester, 1997; pp 225−244.

(2) For example, see: Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc*. **1999**, *121,* 268−269.

(3) For representative examples of addition of dialkylzincs to imines (stoichiometric ligand), see: (a) Soai, K.; Hatanaka, T.; Miyazawa, T. *J. Chem. Soc., Chem. Commun*. **1992**, 1097−1098. (b) Andersson, P. G.; Guijarro, D.; Tanner, D. *J. Org. Chem*. **1997**, *62*, 7364−7375. (c) Franz, D. E.; Faessler, R.; Carreira, E. M. *J. Am. Chem. Soc*. **1999**, *121*, 11245−11246. (d) Jimeno, C.; Reddy, K. S.; Sola, L.; Moyano, A.; Pericas, M. A.; Riera, A. *Org. Lett*. **2000**, *2*, 3157−3159. For related processes involving other alkylmetals, see: (e) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc*. **1989**, *111*, 8266−8268. (f) Weber, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl*. **1992**, *31*, 84−86. (g) Itsuno, S.; Sasaki, M.; Kuroda, S.; Ito, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1507−1510. (h) Inoue, I.; Shindo, M.; Koga, K.; Kanai, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2527−2533. For related reviews, see: (i) Bloch, R. *Chem. Rev*. **1998**, *98*, 1407−1438. (j) Denmark, S. E.; Nicaise, O. J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; pp 924−958.

(4) (a) Denmark, S. E.; Stiff, C. M. *J. Org. Chem*. **2000**, *65*, 5875−5878. (b) Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc*. **1994**, *116*, 8797−8798. For a related review, see: (c) Denmark, S. E.; Nicaise, O. J.-C. *Chem. Commun*. **1996**, 999−1004.

(5) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett*. **1991**, *32*, 3095−3098.

(6) For a review on catalytic asymmetric additions to imines, see: Kobayashi, S.; Ishitani, H. *Chem. Rev*. **1999**, *99*, 1069−1094.

(7) For other catalytic asymmetric C−C bond-forming processes promoted by peptidic Schiff base ligands, see the following. Ti-catalyzed addition of CN to aldehydes: (a) Nitta, H.; Yu, D.; Kudo, M.; Mori, A.; Inoue, S. *J. Am. Chem. Soc*. **1992**, *114*, 7969−7975. Ti-catalyzed CN addition to epoxides: (b) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 1668−1671. (c) Shimizu, K. D.; Cole, B. M.; Krueger, C. A.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 1704−1707. Ti-catalyzed CN addition to imines: (d) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1999**, *121*, 4284−4285. (e) Porter, J. R.; Wirschun, W. G.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2000**, *122*, 2657−2658.

(8) This class of peptide-based phosphine ligands promotes catalytic enantioselective conjugate addition of dialkylzincs to cyclic enones: Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.*, in press.

(9) Use of other Zr-based salts (e.g., $Zr(OEt)_4$ led to lower selectivity.

(10) For use of *o*-anisidyl imines in other transformations, see: Saito, S.; Hatanaka, K.; Yamamoto, H. *Org. Lett*. **2000**, *2*, 1891−1894. (b) Adrian, J. C., Jr.; Barkin, J. L.; Hassib, L. *Tetrahedron Lett*. **1999**, *40*, 2457−2460.

(11) Similar effects have been observed in the Ti-catalyzed enantioselective addition of alkylzinc reagents to aldehydes: Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691−5700.

10.1021/ja003747y CCC: $20.00
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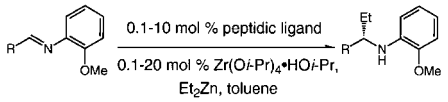
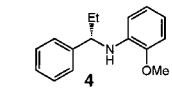
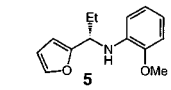
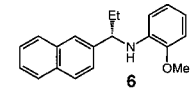
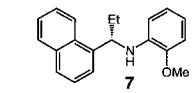
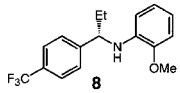
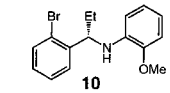
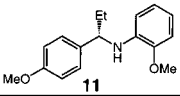
Table 1. Zr-Catalyzed Enantioselective Ethyl Addition to Arylimines[a]



entry	product	ligand; mol %	Zr salt mol %	conv (%);[b] yield (%)[c]	ee (%);[d] config
1	 **4**	**3**; 10	10	>98; 84	93; *S*
2		**3**; 1	1	10; --	81; *S*
3		**3**; 1	20	>98; 81	95; *S*
4		**3**; 0.1	20	>98; 82	93; *S*
5	 **5**	**3**; 1	20	>98; 87	97; *S*
6	 **6**	**3**; 1	20	95; 67	92; *S*
7	 **7**	**3**; 10	10	>98; 86	91; *S*
8	 **8**	**9**; 10	11	95;[e] 87	88; *S*
9	 **10**	**9**; 10	11	95;[e] 62	90; *S*
10	 **11**	**3**, 10	11	57; 38	82; *S*
11		**9**; 10	11	95; 71	91; *S*

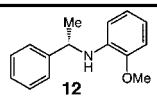
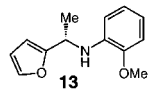
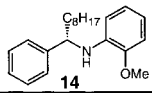
[a] Conditions: 3 equiv of Et_2Zn, toluene, 0 → 22 °C, 24 h except for entries 4 and 6 (48 h); 5 equiv of Et_2Zn used in entry 4. [b] By ^1H NMR analysis. [c] Isolated yield. [d] By chiral HPLC in comparison with authentic material (Chiralcel OD for entries 1−8, 10, 11; Chiralcel OJ for entry 9). [e] Carried out at +4 °C.

more sterically demanding substrates occur efficiently and with high asymmetric induction. (2) In contrast to reactions illustrated in entries 1−7 of Table 1, when ligand **3** is employed in the catalytic alkylation of electron-deficient imines (entries 8, 9), the reduced amine product is formed predominantly (10−50%). This finding suggests that the active chiral ligand may be the derived peptidic *amine* and not the original Schiff base. That is, an EtZr or EtZn complex might undergo rapid β-H elimination to afford a metal hydride that effects C=N bond reduction. We surmised that competitive reduction of the highly reactive substrate imine might preclude the in situ generation of the active amine ligand.[12] Accordingly, *amine* ligand **9** was prepared and used in the catalytic alkylations depicted in entries 8 and 9 (Table 1). In the presence of 10 mol % **9** and 11 mol % Zr(O*i*-Pr)$_4$·HO*i*-Pr (+4 °C), ethyl addition products **8** and **10** are generated efficiently (95% conversion) in 88% and 90% ee, respectively. (3) As depicted in entry 10 (Table 1), catalytic formation of **11** from the corresponding electron-rich imine, promoted by ligand **3**, takes place selectively (82% ee) but slowly (57% conversion, 24 h). When amine ligand **9** is used, however (entry 11), reaction efficiency is enhanced (95% conversion, 24 h) and enantioselectivity is increased to 91% ee.[13]

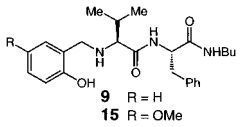
As the data in entries 1 and 2 of Table 2 illustrate, with 10 mol % **9** and Zr(O*i*-Pr)$_4$·HO*i*-Pr, asymmetric addition of Me_2Zn affords **12** and **13** in 88% ee (79% yield) and 84% ee (98% yield), respectively. Under identical conditions, but with ligand **3**, the

(12) Preliminary studies indicate that Schiff base ligands are partially reduced in situ in the presence of Et_2Zn and the Zr salt (<2% Et addition to the C=N bond of ligands).

Table 2. Zr-Catalyzed Enantioselective Additions to Arylimines Promoted by Amine-Peptide Ligands[a]

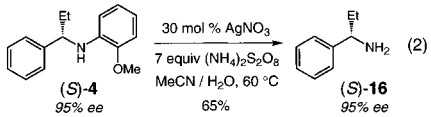
entry	product	ligand	conv (%);[b] yield (%)[c]	ee (%)[d] config
1	 **12**	**9**	85; 79	88; *S*
2	 **13**	**9**	>98; 98	84; *S*
3	 **14**	**15**	>98; 63	98; *S*

[a] Conditions: (entries 1, 2) 15 equiv of Me_2Zn, toluene, 10 mol % Zr(O*i*-Pr)$_4$·HO*i*-Pr and ligand, 0 → 22 °C, 48 h; (entry 3) 6 equiv of (octyl)$_2$Zn at +4 °C. [b] By ^1H NMR analysis. [c] Isolated yield. [d] By chiral HPLC in comparison with authentic material (Chiralcel OD).



aforementioned transformations proceed to <15% conversion. These observations are consistent with the proposed role of metal hydrides in the in situ formation of ligands such as **9**.[14] As shown in entry 3 of Table 2, catalytic asymmetric addition of (octyl)$_2$Zn can be carried out efficiently and enantioselectively (98% ee) in the presence of **15**. When ligands **9** and **3** are employed to promote the formation of **14**, ~65% of the reaction mixture again consists of the reduced amine product.

The resulting *o*-anisidine amines constitute a building block in a number of medicinally important agents.[15,16] Moreover, as the representative example in eq 2 illustrates,[17] optically enriched



arylamines can be accessed through oxidative removal of the anisido group.[18]

Acknowledgment. This work is dedicated to the memory of our late colleague Professor George Vogel. Financial support was provided by the NIH (GM-57212) and DuPont (to A. H. H.). We are grateful to Professor J. C. Adrian, Jr., K. W. Kuntz, and Dr. H. Mizutani for helpful suggestions. M.L.S. is a Camille Dreyfus Tecaher-Scholar and a Glaxo-Wellcome Young Investigator.

Supporting Information Available: Experimental procedures and spectral and analytical data for all recovered starting materials and reaction products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) In entries 10, 11, <2% reduced products are detected.

(14) Metal hydride generation likely requires the presence of a β-hydride within the alkylmetal precursor; use of Me_2Zn thus preempts the generation of such hydrides. Generation of metal hydrides is less facile with β-methylenes (vs β-Me). For example, see: Negishi, E.; Nguyen, T.; Maye, J. P.; Choueiri, D.; Suzuki, N.; Takahashi, T. *Chem. Lett.* **1992**, 2367−2370.

(15) While this paper was under review, a report concerning catalytic asymmetric addition of Et_2Zn to imines appeared: Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 0000.

(16) For example, see: Annunziata, R.; Cinquini, M.; Cozzi, F.; Molteni, V.; Schupp, O. *Tetrahedron* **1997**, *53*, 9715−9726.

(17) (a) Bhattarai, K.; Cainelli, G.; Panunzio, M. *Synlett* **1990**, 229−230. (b) Reference 10a.

(18) Significantly lower yields (<20%) are observed when CAN is used as the oxidant. Kobayashi, S.; Ishitani, H. Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431−432.