Three-Component Catalytic Asymmetric Synthesis of Aliphatic Amines

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Discovery and development of efficient catalytic asymmetric methods for the preparation of nonracemic amines is an important objective in organic synthesis. In this context, there have been notable advances involving catalytic enantioselective hydrogenations and hydrogen transfer reactions involving imine[1] and enamine substrates.[2] Protocols for catalytic enantioselective alkylations of imines have also emerged. Earlier reports include the catalytic enantioselective additions of alkyllithiums,[3] promoted by chiral amines, in up to 82% ee. More recently, Tomioka[4] and co-workers disclosed Cu-catalyzed asymmetric additions of Et_2Zn to *N*-tosylimines, while research in our laboratories has resulted in the development of a method for Zr-catalyzed asymmetric additions of a range of alkylzinc reagents to *o*-anisidyl imines.[5] Nonetheless, the large majority of the above advances (both hydrogenations and alkylations), deals with transformations of *aromatic* imines and enamines.[6] Herein, we report the results of our studies regarding the Zr-catalyzed asymmetric addition of alkylzincs to *aliphatic* imines by a single-vessel, three-component catalytic asymmetric procedure that obviates the need for isolation of unstable imine starting materials (Scheme 1). The requisite chiral ligands are peptide-based[7] and can be synthesized through coupling (and reduction) of commercially available aromatic aldehydes and amino acids valine and phenylalanine.[8]

Our initial attempts to examine the catalytic alkylations of aliphatic *o*-anisidyl imines were thwarted by their lack of stability upon isolation. In contrast to the derived aromatic imines, it is likely that the presence of the acidic α-protons, together with the activating effect of the *o*-anisidyl unit, leads to formation of the enamines and the corresponding homocoupling products (e.g., aldol- and Mannich-type additions).[9] To circumvent the above complication, we set out to examine the possibility of three-component asymmetric amine synthesis involving imine formation from an appropriate aldehyde and *o*-anisidine, followed by in situ catalytic alkylation. The viability of such an approach was first investigated with aromatic aldehydes. As illustrated in entry 1 of Table 1, we established that treatment of benzaldehyde with *o*-anisidine, 10 mol % dipeptide Schiff base ligand **1** and $Zr(Oi\text{-}Pr)_4{\cdot}HOi\text{-}Pr$ and six equiv of Et_2Zn leads to the facile formation of amine **2** in 82% ee and 90% isolated yield.[10] Reaction efficiency and enantioselectivity improved when dipeptide amine **3** was employed (entry 2). Two more examples, involving 2-furaldehyde and 3-pyridine carboxaldehyde[11] are illustrated in Table 1 (entries 3−4). Additional issues regarding the data in Table 1 merit mention: (i) In all cases shown, analysis of the 400 MHz ^{1}H NMR spectra did not indicate any products from alkylations of aldehydes (<2%). (ii) Although appreciable asymmetric induction is observed, the selectivities shown in Table 1 are somewhat lower than those obtained with purified imine substrates.[5]

Since we expected nonselective (noncatalytic) background alkylations to be less favored with the less reactive aliphatic imines, the data in Table 1 proved encouraging despite the lower levels of enantioselectivity (in comparison to the two-vessel procedure[5]). This expectation was substantiated when we estab-

Scheme 1

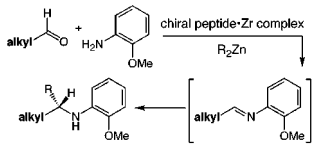
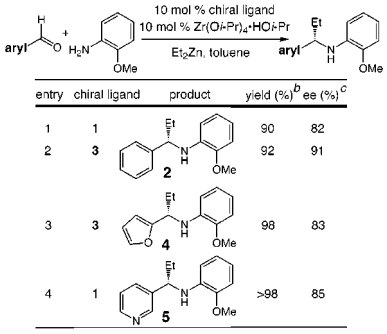
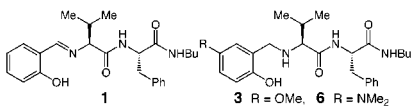


Table 1. Three-Component Catalytic Asymmetric Synthesis of Arylamines[a]



entry	chiral ligand	product	yield (%)[b]	ee (%)[c]
1	1	**2**	90	82
2	**3**		92	91
3	**3**	**4**	98	83
4	1	**5**	>98	85

[a] Conditions: 6 equiv Et_2Zn, toluene, 0 °C→22 °C, 48 h for entry 1−2, 24 h for entry 3, 96 h for entry 4. [b] Isolated yields after silica gel chromatography. [c] Determined by chiral HPLC in comparison with authentic racemic material (Chiralcel OD).



(1) For a review on catalytic asymmetric additions to imines, see: (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094.

(2) For representative examples, see: (a) Lee, N. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 5985−5986. (b) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142−5143. (c) Li, W.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 5871−5874.

(3) (a) Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc.* **1994**, *116*, 8797−8798. (b) Denmark, S. E.; Nicaise, O. J.-C. *Chem. Commun.* **1996**, 999−1004. (c) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875−5878. (d) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1991**, *32*, 3095−3098.

(4) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055−12056.

(5) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984−985.

(6) For catalytic asymmetric additions of alkyllithiums to aliphatic imines (in the presence of 20 mol % (−)-sparteine), see: ref 3a. For an example of catalytic asymmetric hydrogenation of imines derived from nonaromatic ketones, see: Hansen, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 713−715.

(7) For other catalytic asymmetric C−C bond forming reactions promoted by this class of peptide-based ligands, see: Ti-catalyzed addition of cyanide to aldehydes: (a) Nitta, H.; Yu, D.; Kudo, M.; Mori, A.; Inoue, S. *J. Am. Chem. Soc.* **1992**, *114*, 7969−7975. Ti-catalyzed cyanide 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 cyanide 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. Cu-catalyzed conjugate additions of dialkylzincs to enones: (f) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755−756. Cu-catalyzed allylic substitutions of allyl phosphates with dialkylzincs: (g) Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1456−1460.

(8) Boc-L-Val and Boc-L-Phe are commercially available at $0.15 and $0.19 per mmol from Advanced Chemtech; the corresponding D-isomers can be purchased at $1.22 and $0.86 per mmol.

(9) This class of aliphatic imines undergo decomposition upon concentration.

(10) See the Supporting Information for the methods used to establish the identity of major enantiomers in this study.

(11) In contrast to reactions with PhCHO (entries 1−2), with 3-pyridine carboxaldehyde, ligand **1** provides superior enantioselectivity and efficiency (77% ee and 64% with **3**).

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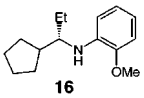
lished that *treatment of 1-pentanal and o-anisidine with 10 mol % **3** and Zr(Oi-Pr)$_4$·HOi-Pr and six equiv of Et$_2$Zn (0 °C→22 °C) leads to the formation of amine **7** in 97% ee and 69% isolated yield after silica gel chromatography* (entry 1, Table 2). Similar results were obtained when heptanal was used as the starting material (→**8**; entry 2, Table 2), and reaction efficiency significantly improved in the catalytic asymmetric synthesis of **9** (>98% yield; entry 3). Synthesis of unsaturated amine **10** (entry 4) proceeds with high enantioselectivity (>98% ee) in 60% isolated yield; ligand screening led us to establish that reaction efficiency improves when dipeptide **6** is used (**10** is obtained in 72% yield and 92% ee). Highly enantioselective syntheses of **11** (entry 5) and cyclopropylamine **12** (entry 6) indicate that the three-component catalytic alkylation is effective with aldehydes bearing an α- or a *β*-alkyl substituent. Zr-catalyzed alkylation with 6-bromo-hexanal, shown in entry 7 of Table 2, proceeds effectively to afford **13** in 95% ee and 57% yield together with 13% of the cyclized product **16** (by addition to imine formed through intramolecular alkylation by the derived enamine).[12] Optically enriched amino alcohols **14** and **15** (entries 8−9) are obtained with excellent enantioselectivity from three-component catalytic alkylations that employ siloxy aldehydes (*tert*-butyldiphenylsilyl and *tert*-butyldimethylsilyl ethers, respectively; 48% and 64% overall yields for two steps).



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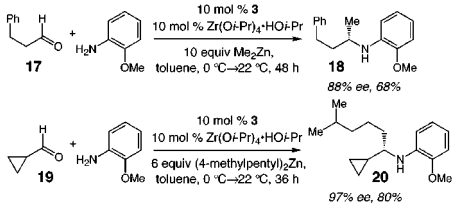
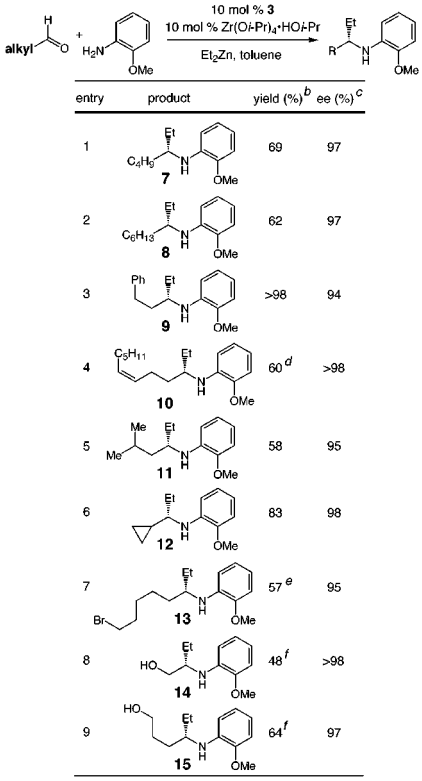
An important attribute of the previously reported Zr-catalyzed alkylations of aromatic imines[5] is that alkylzinc reagents other than Et$_2$Zn can be employed for enantioselective C−C bond formation. As the representative examples in Scheme 2 indicate, this advantage is available to reactions of aliphatic imines as well. The three-component catalytic asymmetric processes involving Me$_2$Zn with aldehyde **17** delivers **18** in 88% ee and 68% isolated yield;[13] in a similar fashion, amine **20** is obtained from the reaction of **19** and (4-methylpentyl)$_2$Zn in 97% ee and 80% yield.

Scheme 2



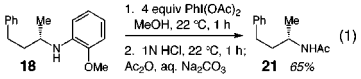
Although optically enriched *o*-anisidylamines are of potential utility in synthesis, facile and efficient removal of the N-activating group to yield the unfunctionalized amines is important as well. Toward this end, we discovered that the protocol employed previously for unmasking of aromatic amines yields[5] the desired aliphatic products in <35% yield. Accordingly, the oxidative method represented in eq 1 was developed,[14] where the optically enriched acylated amine is obtained with higher efficiency and without any detectable loss of enantiopurity (chiral GLC and HPLC).[15]

Table 2. Three-Component Catalytic Asymmetric Synthesis of Alkylamines[a]



entry	product	yield (%)[b]	ee (%)[c]
1	**7**	69	97
2	**8**	62	97
3	**9**	>98	94
4	**10**	60[d]	>98
5	**11**	58	95
6	**12**	83	98
7	**13**	57[e]	95
8	**14**	48[f]	>98
9	**15**	64[f]	97

[a] Conditions: 6 equiv Et$_2$Zn, toluene, 0 °C→22 °C, 24 h (48 h for entry 9). [b] >98% conv in all cases. Isolated yields after silica gel chromatography. [c] Determined by chiral HPLC in comparison with authentic racemic material (Chiralcel OD). [d] With **6** as the chiral ligand, **10** is obtained in 78% yield and 92% ee. [e] 13% **16** was also isolated. [f] Overall yields after alkylation and deprotection of silyl ethers (see Supporting Information for details).



(1)

We thus disclose a general catalytic asymmetric method for alkylations of aliphatic imines, where prior isolation of imines is not necessary. The metal salts employed are inexpensive and the chiral ligands can be easily prepared and modified. The use of dialkylzinc reagents other than Et$_2$Zn is effective and allows for the preparation of aliphatic amines of high optical purity that are not otherwise readily available. The above factors, together with the significance of three-component approaches[16] to combinatorial synthesis,[17] collectively render the present technology of notable utility. Future studies will involve study of mechanism and applications to target-oriented synthesis.[18]

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

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(12) Amine **16** is formed in 53% ee. The reason for the lower level of enantioselectivity is unclear and will be addressed in the course of upcoming mechanistic studies.

(13) Lower reactivity of Me$_2$Zn requires that larger amounts of this alkylmetal reagent be employed.

(14) For related oxidative procedures, see: (a) Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677−680. (b) Barret, R.; Daudon, M. *Tetrahedron Lett.* **1990**, *31*, 4871−4872. (c) Kinugawa, M.; Masuda, Y.; Arai, H.; Nishikawa, H.; Ogasa, T.; Tomioka, S.; Kasai, M. *Synthesis* **1996**, 633−636. (d) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S.; Sugita, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 2145−2149.

(15) The present procedure is more effective for the unmasking of alkylation products of aromatic imines as well. For example, **2** was deprotected in 75% isolated yield (vs 65% by protocol in ref 5).

(16) For representative recent reports regarding multicomponent asymmetric catalysis, see: (a) Ikeda, S.; Cui, D.-M.; Sato, Y. *J. Am. Chem. Soc.* **1999**, *121*, 4712−4713. (b) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron* **1999**, *55*, 8857−8867. (c) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450−5458. (d) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762−766. (e) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336−9337. For a related nonasymmetric example, see: (f) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2001**, *123*, 5122−5123.

(17) (a) Lutz, W.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366−374. (b) Lee, D.; Sello, J. K.; Schreiber, S. L. *Org. Lett.* **2000**, *2*, 709−712.

(18) Financial support was provided by the NIH (GM-57212).