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Enantioselective Synthesis of Propargylamines through Zr-Catalyzed Addition of Mixed Alkynylzinc Reagents to Arylimines

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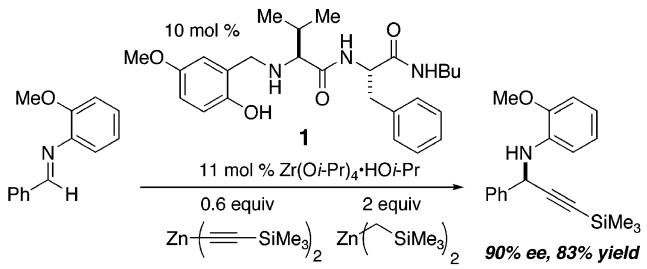
ABSTRACT



Addition of mixed alkynylzinc reagents to various arylimines is catalyzed by chiral amino acid-based ligand 1 and Zr(O*i*-Pr)$_4$·HO*i*-Pr to afford chiral propargylamines in up to 90% ee. Oxidative removal of the *o*-anisidyl group affords the free amine, which can then be acylated.

Recent efforts in these laboratories have focused on the development of a general class of readily available and easily modifiable amino acid-based chiral ligands that can be used to effect a variety of synthetically important C−C bond-forming reactions enantioselectively.[1] One objective of this program is to design protocols for the asymmetric synthesis of nonracemic chiral aryl-[2] and alkylamines. In this context, we have reported methods that allow access to aryl-[3] and alkylamines[4] efficiently and with high optical purity through three-component syntheses. These Zr-catalyzed transformations[5] involve enantioselective addition of alkylzinc reagents to different imines promoted by peptidic chiral ligands (e.g., **1** shown in eq 1). After the above studies, we set out to develop methods for the asymmetric synthesis of alkynylamines.[6] In principle, such a task may involve two different types of C−C bond-forming reactions (Scheme 1): catalytic

(1) For representative examples, see: (a) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668−1671. (b) 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. (c) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755−756. (d) Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1456−1460. (e) Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 1009−1012. (f) Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192−8193. (g) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018−4019. (h) Murphy, K. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4690−4691.

(2) For reviews 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.

(3) (a) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984−985. For related studies involving catalytic asymmetric alkylations of imines, see: (b) Denmark, S. E.; Stiff, C. M. *J. Org. Chem.* **2000**, *65*, 5875−5878 and references therein. (c) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055−12056. (d) Zhang, X.-M.; Zhang, H.-L.; Lin, W.-Q.; Gong, L.-Z.; Mi, A.-Q.; Cui, X.; Jiang, Y.-Z.; Yu, K.-B. *J. Org. Chem.* **2003**, *68*, 4322−4330. (e) Dahmen, S.; Brase, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940−5941. (f) Boezio, A. A.; Charrette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 1692−1693.

(4) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409−10410.

(5) For a review of Zr-catalyzed asymmetric transformations, see: Hoveyda, A. H. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; VCH−Wiley: Weinheim, 2002; pp 180−229.

(6) For a review of asymmetric syntheses of propargylamines, see: Blanchet, J.; Bonin, M.; Micouin, L. *Org. Prep. Proced. Int.* **2002**, *34*, 459.

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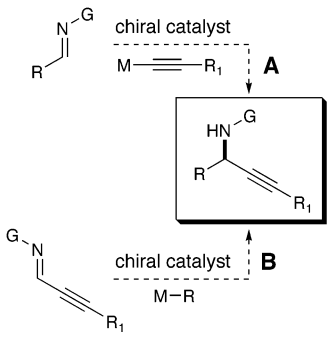
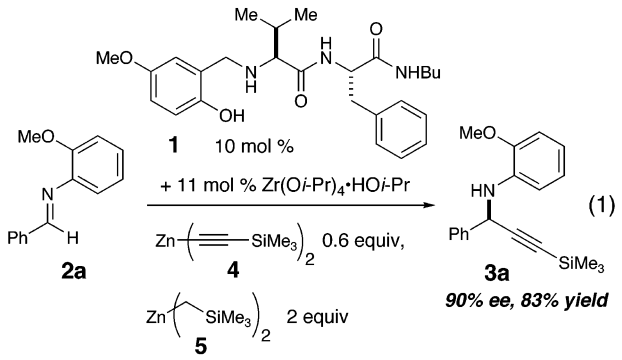
Scheme 1. Two C−C Bond-Forming Routes toward Alkynylamines.



asymmetric addition of alkynylmetals to an imine (pathway **A**) or the addition of an alkylmetal to an alkynylimine (pathway **B**).[7] Two catalytic enantioselective approaches for the synthesis of propargylamines have been reported that proceed along pathway **A**.[8] One disclosure by Li[8a] involves additions to various arylimines in the presence of 10 mol % Cu-pybox; reactions proceed in high enantioselectivity but are limited to phenylacetylene (78−96% ee), and protocols for conversion of the *N*-arylamines to the corresponding free amines were not outlined. The other procedure, also Cu-catalyzed (Quinap as a chiral ligand), is by Knochel;[8b,c] this method delivers aliphatic alkynylamines, bearing *N*-allyl or *N*-Bn groups, through asymmetric addition of alkynes to enamine substrates (54−90% ee).

In this report, we outline catalytic enantioselective additions of alkynylzinc reagents to a variety of *o*-anisidyl imines (pathway **A**). Transformations are promoted by chiral ligand **1** in the presence of Zr(O*i*-Pr)$_4$·HO*i*-Pr to afford the derived alkynylamines in up to 90% ee and ≥69% isolated yield. Products bearing a variety of alkyne substituents can be readily accessed by the present protocol. Moreover, the *o*-anisidyl group may be removed efficiently to afford the corresponding amines or other related derivatives.



Our investigations began with screening for optimal amino acid-based ligands and metal salts to effect the enantioselective addition of dialkynylzinc reagent **4** to imine **2a** (eq 1). In all cases, only 5−10% conversion to the desired **3a** occurred under a variety of conditions. To address this reactivity problem,[9] we investigated reactions in the presence of mixed organozinc reagents formed upon addition of bis-[(trimethylsilyl)methyl]zinc **5**.[10] Such a modification led to significant improvement in reaction efficiency: in certain cases, >98% conversion to **3a** was observed after 48 h at 22 °C.[11,12] These studies illustrated that dipeptide amine **1** and Zr(O*i*-Pr)$_4$·HO*i*-Pr, a system that had proven to be optimal in previous studies, again is the combination of choice. Subsequent optimization led us to establish that, as illustrated in eq 1, addition of only 0.6 equiv of **4** to **2a** affords alkynylamine **3a** in 90% ee and 83% isolated yield in a 2 mmol scale process. It should be noted that there is only 5−10% conversion in the absence of **1**. Moreover, when the Zr-catalyzed reaction is carried out at elevated temperatures, lower enantioselectivity as well as reduced yields are obtained. The lower yields are due in part to competing side reactions at higher temperatures, for example at 55 °C, only 25% of **3a** is obtained after 24 h. Lower catalyst loadings may be used to promote enantioselective additions. With 5 mol % **1** and 10 mol % of the metal alkoxide, **3a** is isolated in 88% ee and 86% isolated yield; identical conditions, except with 2.5 mol % **1**, delivers the desired unsaturated amine in 86% ee and 90% yield after purification (48 h in both cases). Any further reduction in the loading of the chiral ligand significantly diminishes reaction efficiency and the level of asymmetric induction. Use of 1 mol % **1** and 10 mol % Zr(O*i*-Pr)$_4$·HO*i*-Pr leads to the formation of **3a** in 63% ee and 61% yield (after 48 h).

As the data summarized in Table 1 indicate, a variety of aryl imines with different steric and electronic attributes can be converted to nonracemic alkynylamines. Electron-poor **2b** (entry 1, Table 1) as well as electron-rich **2c** (entry 2, Table 1) are alkylated to afford the corresponding unsaturated amines in 81 and 86% ee, respectively. The presence of an ortho substituent in **2d** (entry 3, Table 1) can cause a

(7) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, in press.

(8) (a) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638−5639. (b) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem. Eur. J.* **2003**, *9*, 2797−2811. (c) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535−2538. For enantioselective synthesis of propargylamines through the use of chiral controllers and auxiliaries, see: (d) Huffman, M. A.; Yasuda, N.; DeCamp, A. E.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, *60*, 1590−1594. (e) Kolb, M.; Barth, A. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 725−726. (f) Hattori, K.; Miyata, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 1151−1152. (g) Enders, D.; Schankat, J. *Helv. Chim. Acta* **1995**, *78*, 970−992. (h) Blanchet, J.; Bonin, M.; Chiaroni, A.; Micouin, L.; Riche, C.; Husson, H.-P. *Tetrahedron Lett.* **1999**, *40*, 2935−2938. (i) Fassler, R.; Frantz, D. E.; Oetiker, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3054−3056. (j) Blanchet, J.; Bonin, M.; Micouin, L.; Husson, H.-P. *J. Org. Chem.* **2000**, *65*, 6423−6426. For an example regarding synthesis of optically pure propargylamines through enzymatic resolution, see: (k) Messina, F.; Botta, M.; Corelli, F.; Schneider, M. P.; Fazio, F. *J. Org. Chem.* **1999**, *64*, 3767−3769.

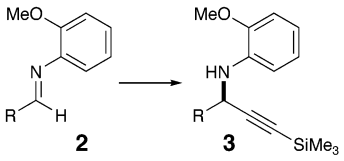
(9) It is likely that such a lack of reactivity is partly due to the low solubility of dialkynylzinc reagents in toluene. Initial studies indicated that catalytic alkylations in THF, a solvent that more effectively dissolves alkynylzincs, lead to significantly lower enantioselectivity.

(10) (a) Berger, S.; Langer, F.; Lutz, C.; Knochel, P.; Mobley, T. A.; Kishan Reddy, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1496−1498. (b) Bertz, S. H.; Eriksson, M.; Snyder, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 10906−10907.

(11) See Supporting Information for details.

(12) Reactions involving terminal alkynes and Me_2Zn or those in the presence of dialkynylzincs and Me_2Zn resulted in the formation of amines derived from predominant or exclusive addition of a Me group. See: Li, Z.; Upadhyay, V.; DeCamp, A. E.; DiMichele, L.; Reider, P. J. *Synthesis* **1999**, 1453−1458.

Table 1. Zr-Catalyzed Enantioselective Addition of Alkynylzincs to Imines



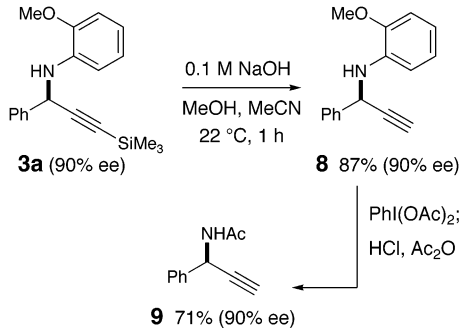
entry	R		yield (%)[b]	ee (%)[c]
1	*p*-ClC_6H_4	**b**	90	81
2	*p*-$OMeC_6H_4$	**c**	69	86
3	*o*-BrC_6H_4	**d**	84	69[d]
4	1-naph	**e**	77	86[d]
5	2-naph	**f**	85	81
6	2-furyl	**g**	72	82[d]

[a] Conditions: 10 mol % **1**, 11 mol % Zr(O*i*-Pr)$_4$, 0.6 equiv of **4**, 2 equiv of **5**, toluene, 22 °C, 72 h (entries 1, 2, and 4), 48 h (entries 3 and 5), 24 h (entry 6). [b] Isolated yield after silica gel chromatography. [c] Determined by HPLC (chiralcel OD). [d] Determined through analysis of the derived desilylated product (HPLC; chiralcel OD).

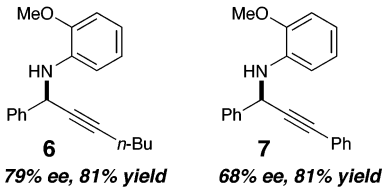
significant reduction in asymmetric induction (69% ee). Sterically hindered naphthylimines **2e** and **2f** (entries 4 and 5, Table 1) are converted to propargylamines in 86 and 81% ee, respectively. As the example in entry 6 of Table 1 illustrates (**2g** → **3g**), products bearing heterocyclic aromatic substituents can be obtained by the present method (entry 6, Table 1).

The decision to focus our studies on the utility of silylalkyne reagent **4** was largely based on the principle that removal of the $SiMe_3$ unit (e.g., **3a** → **8** in Scheme 2) can

Scheme 2. Optically Enriched Alkynylamines through Oxidative Removal of the *o*-Anisidyl Group.



be easily effected and the resulting terminal alkyne can be converted to a wide range of other nonracemic acetylenic amines through a number of alkylation or cross coupling reactions.[13] Alkynylzinc reagents bearing aliphatic substituents may also be used in the Zr-catalyzed reactions, albeit with some reduction in enantioselectivity.[14] As an example, amine **6** can be prepared by the protocol outlined above in 79% ee and 81% isolated yield. The diminution in asymmetric induction is higher when aryl-substituted alkynylzincs are utilized; synthesis of unsaturated amine **7** in 68% ee and 81% yield is illustrative.



Optically enriched secondary alkynylamines can be prepared through oxidative removal of the *o*-anisidyl activating group;[4] the example shown in Scheme 2, which proceeds in 71% overall yield, via the corresponding unprotected amine, is illustrative.

In summary, we report a Zr-catalyzed method for the enantioselective addition of a range of mixed alkynylzinc reagents to various arylimines to afford optically enriched secondary propargylamines in up to 90% ee. The present protocol demonstrates the utility of Si-containing mixed alkynylzincs. In addition, this study extends the utility of amino acid-based ligands such as **1**, which is prepared from inexpensive and commercially available amino acids and 5-methoxysalicylaldehyde, to include the asymmetric preparation of another class of biologically important organic building blocks.[15]

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

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(13) For representative examples, see: (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731−1769. (b) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979−2017.

(14) Alkynylzincs 1−2 equiv vs 0.6 equiv) derived from 1-hexyne and phenylacetylene are required for efficient Zr-catalyzed alkynylations (see Supporting Information for details). For example, with 0.6 equiv of the alkynylzinc reagent, **6** is obtained in 50−58% yield (vs 81%).

(15) For example, see: (a) Shirota, F. N.; DeMaster, E. G.; Nagasawa, H. T. *J. Med. Chem.* **1979**, *22*, 463−464. (b) Yu, P. H.; Davis, B. A.; Boulton, A. A. *J. Med. Chem.* **1992**, *35*, 3705−3713.