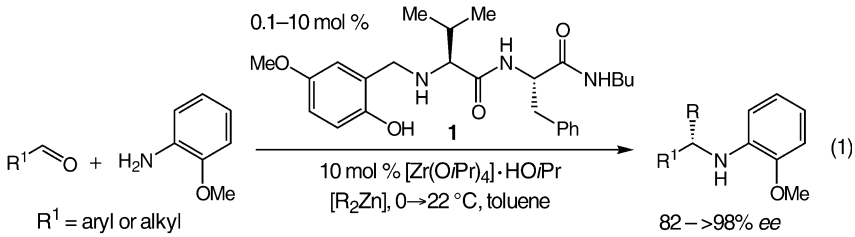
Synthesis of Propargylamines

Three-Component Enantioselective Synthesis of Propargylamines through Zr-Catalyzed Additions of Alkyl Zinc Reagents to Alkynylimines**

Laura C. Akullian, Marc L. Snapper, and Amir H. Hoveyda**

Design and development of new methods for the synthesis of enantiomerically enriched amines is a critical objective in modern organic chemistry. We recently disclosed efficient catalytic methods for enantioselective alkylation of aryl- and alkylimines with alkyl zinc reagents promoted by chiral ligand **1** and $[Zr(OiPr)_4]\cdot HOiPr$ [Eq. (1)].[1,2] These asymmetric



amine syntheses do not require initial preparation of the imine substrates, which are typically difficult to isolate. The Zr-catalyzed asymmetric processes are effected by treatment of an aromatic or aliphatic aldehyde with *o*-methoxyaniline and an alkyl zinc reagent, as well as 1–10 mol % of **1** and the Zr salt.

Another class of chiral N-containing compounds are propargylamines. Several approaches involving chiral controllers[3] and auxiliaries[4,5] have been developed for the preparation of these synthetically[6] and biologically[3,7] important compounds. Two catalytic methods have been outlined involving addition of alkynyl nucleophiles to imines. One protocol is by Knochel and co-workers,[8] regarding Cu-catalyzed addition of alkynes to enamines (bearing *N*-allyl or *N*-Bn groups). Starting materials that contain larger substituents (i.e., Cy) can be converted into products with up to 90 % *ee*, whereas enantioselectivities range from 55–86 % *ee* with substrates bearing *n*-alkyl substituents. Another method was disclosed by Wei and Li,[9] in which addition of phenylacetylene to various arylimines in the presence of 10 mol % of

[*] Prof. Dr. M. L. Snapper, Prof. Dr. A. H. Hoveyda, L. C. Akullian
Department of Chemistry
Merkert Chemistry Center, Boston College
Chestnut Hill, MA 02467 (USA)
Fax: (+1) 617-552-1442
E-mail: marc.snapper@bc.edu
amir.hoveyda@bc.edu

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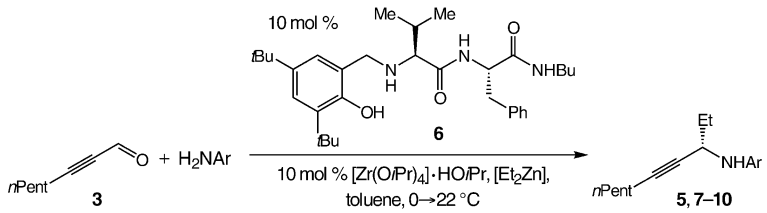
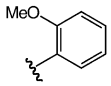
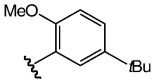
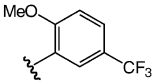
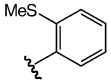
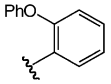
a chiral Cu complex proceeds in 78–96% *ee*; however, reactions are limited to a single nucleophile and methods for conversion of the *N*-arylamines into the corresponding free amines were not described.

Herein we report a Zr-catalyzed protocol for the enantioselective synthesis of propargylamines which, in contrast to the previous approaches, involves addition of alkyl metal reagents to alkynylimines [Eq. (2); G = *o*-methoxyphenyl].[10] Peptidic ligands, composed of commercially available and inexpensive amino acids, can be used to promote an efficient, three-component, and enantioselective (82→98% *ee*) synthesis of α-alkynylamines. Asymmetric synthesis of products obtained by the present method have not been covered by the previously mentioned reports.[8,9]

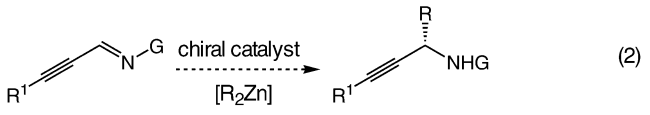
Initially, we examined the ability of **1**, the chiral ligand used in asymmetric additions to aliphatic and aromatic imines [Eq. (1)], in promoting similar transformations involving alkynyl substrates. As the representative examples in Equation (3) indicate, we discovered that although the desired propargylamines form efficiently, low levels of enantioselectivity are attained.

Table 1: Effect of arylamine structure on the enantioselectivity and efficiency of propargylamine formation.[a]

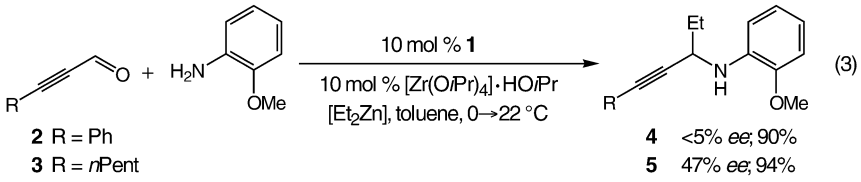


Entry	Ar	Product	*ee* [%]	Yield [%]
1		**5**	68	n.d.
2		**7**	54	n.d.
3		**8**	70	n.d.
4		**9**	92	61
5		**10**	94	84

[a] Conditions: alkyl zinc reagent (6 equiv), 4 h. [b] Enantioselectivities determined by HPLC (chiralcel OD). [c] Yields of products isolated after silica-gel chromatography; >98% conversion in all cases. n.d. = not determined.



(2)

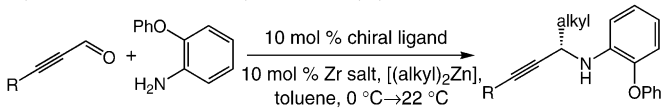


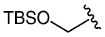
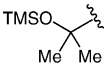
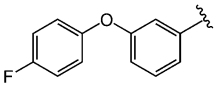
(3)

To improve asymmetric induction, we turned to modifications of the chiral ligand. Since the amino acid units in **1** are among the most readily available and inexpensive,[11] we decided to focus on altering other structural features of the peptidic system. Accordingly, a brief survey of chiral ligands varying in the structure of the aromatic terminus was carried out.[12] These studies established that, as illustrated in entry 1 of Table 1, dipeptide **6** catalyzes formation of **5** with improved enantioselectivity (68% *ee* versus 47% *ee*; >98% conversion). Next, we varied the structure of the aryl group in the imine substrate. This was based on our prior investigations [cf. Eq. (1)], which indicated that the structure of the aryl group attached to the imine can exert a strong influence on reaction outcomes. For example, in contrast to transformations involving *o*-anisidyl imines, the derived phenyl or *p*-methoxy derivatives are inert under the same reaction conditions. As the data in Table 1 illustrate, in the reaction of imines derived from aldehyde **3** in the presence of 10 mol% **6** and [Et_2Zn], levels of enantiofacial selectivity vary significantly as a function of the nature of the arylimine, with the phenoxyphenyl-bearing imine proving to be optimal (entry 5; 94% *ee*, 84%).

The data in Table 2 illustrate that three-component asymmetric alkylations can be performed with a variety of alkynylimines and alkyl zinc reagents to afford propargylamines (**15**–**19**, **21**, and **23**–**26**) efficiently and enantioselectively. Several important issues in connection with the data in Table 2 deserve mention: With the more reactive [Et_2Zn] (Table 1 and Table 2, entries 4–6 and 8) higher selectivity is obtained when [Zr(O*i*Pr)$_4$]·HO*i*Pr is used. With the less reactive [Me_2Zn] and longer chain dialkyl zinc reagents (Table 2, entries 1–3, 7, and 9–10), significantly higher enantioselectivities are attained with [Zr(O*t*Bu)$_4$].[13] As an example, in the reaction shown in entry 7 in Table 2, under otherwise identical conditions but in the presence of [Zr(O*i*Pr)$_4$]·HO*i*Pr, propargylamine **23** is obtained with only 40% *ee* (>98% conversion); in the presence of [Zr(OEt)$_4$], racemic product is formed (>98% conversion). It should be noted that in reactions of [Et_2Zn], use of [Zr(O*t*Bu)$_4$] does not result in improved selectivity. In spite of the diminished Lewis basicity of the *o*-phenoxy group (versus *o*-methoxy used previously), preliminary evidence suggests that the aryloxy heteroatom may be involved in metal chelation. Attempted catalytic alkylation of **27** with [Et_2Zn] in the presence of 10 mol% of **6** and [Zr(O*i*Pr)$_4$]·HO*i*Pr (identical conditions as shown in

Table 2: Zr-catalyzed enantioselective alkylation of alkynylamines.[a]

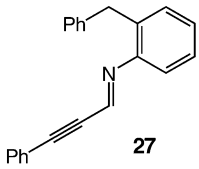


Entry	R		[(alkyl)$_2$Zn]	Zr salt	Product	Chiral ligand	Yield [%]	*ee* [%]
1	*n*Pent	**3**	[Me_2Zn]	[Zr(O*t*Bu)$_4$]	**15**	**6**	87	82
2	*n*Pent	**3**	[{$Me_2CH(CH_2)_3$}$_2$Zn]	[Zr(O*t*Bu)$_4$]	**16**	**6**	60	98
3		**11**	[Me_2Zn]	[Zr(O*t*Bu)$_4$]	**17**	**6**	75	92
4		**11**	[Et_2Zn]	[Zr(O*i*Pr)$_4$]·HO*i*Pr	**16**	**6**	70	>98
5		**12**	[Et_2Zn]	[Zr(O*i*Pr)$_4$]·HO*i*Pr	**19**	**20**	86	84
6		**13**	[Et_2Zn]	[Zr(O*i*Pr)$_4$]·HO*i*Pr	**21**	**22**	89	86
7	Ph	**2**	[Me_2Zn]	[Zr(O*t*Bu)$_4$]	**23**	**6**	84	80
8	Ph	**2**	[Et_2Zn]	[Zr(O*i*Pr)$_4$]·HO*i*Pr	**24**	**6**	85	>98
9	Ph	**2**	[{$Me_2CH(CH_2)_3$}$_2$Zn]	[Zr(O*t*Bu)$_4$]	**25**	**6**	81	91
10		**14**	[Me_2Zn]	[Zr(O*t*Bu)$_4$]	**26**	**6**	75	93

[a] Conditions: alkyl zinc reagent (6 equiv), 4 h for reactions with [Et_2Zn], 24 h for other alkyl zinc reagents. [b] Yields of product isolated after silica-gel chromatography; >98% conversion in all cases. [c] Enantioselectivities determined by HPLC (chiralcel OD).

Table 2) leads to the formation of a mixture of unidentified compounds.

In the majority of cases shown in Table 2 dipeptide amine **6** delivers the highest *ee* values. However, in two instances, propargylamines **19** (Table 2, entry 5) and **21** (Table 2, entry 6) are obtained with 70 and 74% *ee*, respectively, when ligand **6** is used. In search of enhanced selectivity, we again took advantage of the modular character of this class of ligands to screen additional structures. These studies indicated that **19** can be obtained with 84% *ee* (versus 70% *ee*) when dipeptide amine **20** is employed (Table 2, entry 5); moreover, with Schiff base **22**, propargylamine **21** is isolated with 86% *ee* (versus 74% *ee*).



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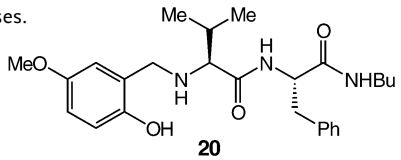
That a different ligand might be required for optimal selectivity with a particular substrate should not be viewed as a shortcoming of this or any other method. With less easily modifiable systems, although a single chiral ligand is utilized (and such could be the case here as well), levels of selectivity at times vary significantly and cannot be easily improved.[14]

Propargylamines accessible through Zr-catalyzed alkylation can be functionalized in a variety of ways to afford chiral cyclic and acyclic N-containing compounds in high enantiomeric purity. Several representative examples are depicted in Scheme 1.



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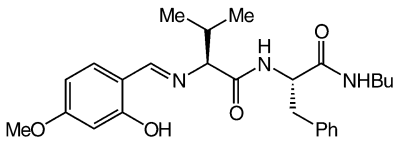

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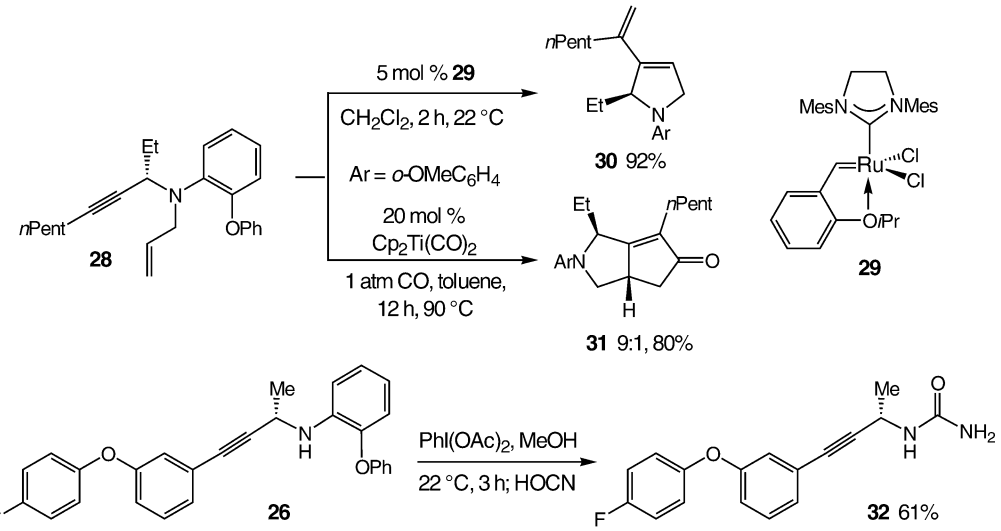

Scheme 1. Representative functionalization of nonracemic propargylamines. Mes = mesityl = 2,4,6-trimethylphenyl.

Optically enriched enyne **28**, obtained from allylation of propargylamine **10** (Table 1, entry 5), readily undergoes Ru-catalyzed ring closure in the presence of 5 mol% of **29**[15] to afford diene **30**, a compound that may be further functionalized through [4+2] cycloaddition with dienophiles. Efficient and diastereoselective formation of bicycle **31** is achieved through a Ti-catalyzed intramolecular Pauson–Khand[16] reaction. The propargyl amines are unmasked and functionalized through oxidative cleavage of the N–aryl bond (e.g., **26**→**32**).[1b]

In summary, we have disclosed an efficient method for alkylation of alkynylimines that lead to a range of chiral enantiomerically enriched propargylamines. Several of the products (e.g., **15**–**17**, **23**, and **26**) obtained cannot be accessed readily or with high enantioselectivity by existing catalytic protocols. The chiral catalyst can be prepared conveniently from commercially available and inexpensive amino acids and Zr salts in significant quantities. Such attributes, together with the significance of propargylamines in the synthesis of compounds of therapeutic importance, render the present approach of notable synthetic utility.

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Keywords: alkyl zinc reagents · asymmetric catalysis · enantioselectivity · propargylamines · zirconium

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