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Efficient Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzinc Reagents to Aromatic and Aliphatic Acyclic Nitroalkenes

Dawn M. Mampreian and Amir H. Hoveyda*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467

amir.hoveyda@bc.edu

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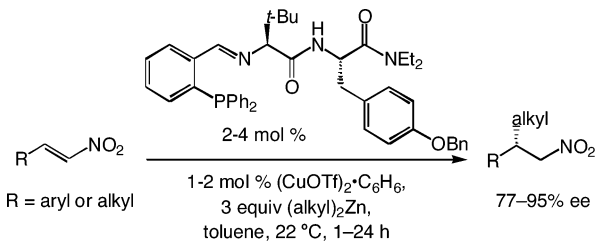
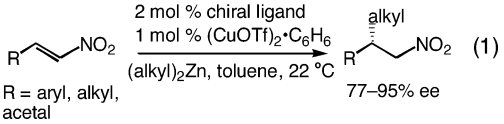
ABSTRACT



An efficient and highly enantioselective (up to 95% ee) Cu-catalyzed method for asymmetric conjugate addition (ACA) of alkylzinc reagents to acyclic disubstituted nitroalkenes is presented. Reactions are typically effected at ambient temperature in the presence of 2 mol % chiral dipeptide phosphine and 1 mol % $(CuOTf)_2 \cdot C_6H_6$. Nitroalkenes bearing aromatic as well as aliphatic substituents readily undergo asymmetric additions.

Optically enriched molecules that contain a nitro group are of considerable significance in synthesis, as they may be converted to a variety of useful N-containing organic molecules.[1] The development of catalytic asymmetric methods that lead to the formation of optically active nitroalkanes has thus been the focus of research in a number of laboratories.[2] In this context, we have reported a highly enantioselective method for Cu-catalyzed conjugate addition (ACA) of alkylzinc reagents to cyclic nitroalkenes.[3,4]

Another important but underdeveloped class of transformations is the catalytic ACA of alkylmetals to acyclic nitroalkenes (eq 1). Several disclosures have focused on this



particular problem, and in limited cases, high asymmetric induction has been observed. One noteworthy example

(1) (a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877−1894. (b) Ono, N. In *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.

(2) For related reviews, see: (a) Krause, N.; Hoffmann-Roder, A. *Synlett* **2001**, 171−196. (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221−3236. (c) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; pp 224−258. For representative recent reports, see: (d) Sewald, N.; Wendisch, V. *Tetrahedron: Asymmetry* **1998**, *9*, 1341−1344. (e) Rimkus, A.; Sewald, N. *Org. Lett.* **2003**, *5*, 79−80. (f) Versleijen, J. P. G.; van Leusen, A. M.; Feringa, B. L. *Tetrahedron Lett.* **1999**, *40*, 5803−5806. (g) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2002**, *58*, 5773−5778. (h) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700−3701. (i) Ongeri, S.; Piarulli, U.; Jackson, R. F. W.; Gennari, C. *Eur. J. Org. Chem.* **2001**, 803−807. (j) Alexakis, A.; Benhaim, C. *Org. Lett.* **2000**, *2*, 2579−2581. (k) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262−5263. (l) Eilitz, U.; Lessmann, F.; Seidelmann, O.; Wendisch, V. *Tetrahedron: Asymmetry* **2003**, *14*, 189−191.

(3) Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192−8193. Also see ref 2k for related examples.

(4) For Rh-catalyzed conjugate additions of arylboronic acids to nitroalkenes, see: (a) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716−10717. (b) Hayashi, T. *Synlett* **2001**, 171−196.

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involves enantioselective Cu-catalyzed ACA to acyclic nitroalkenes that bear an activating α-acetal group (R = $CH(OR)_2$ in eq 1).[2h] The same class of chiral catalysts (derived from a Cu salt and a phosphoramidite) has only been examined with the more reactive Et_2Zn and usually delivers low selectivities in reactions of aryl- or alkyl-substituted acyclic nitroalkenes.[5] Efficient Cu-catalyzed asymmetric hydride additions to trisubstituted acyclic nitroalkenes have been reported;[6] however, stereoisomerically pure trisubstituted nitroolefin substrates must be prepared, and enantioselectivities for reactions of aliphatic substrates can be moderate (66−90% ee).

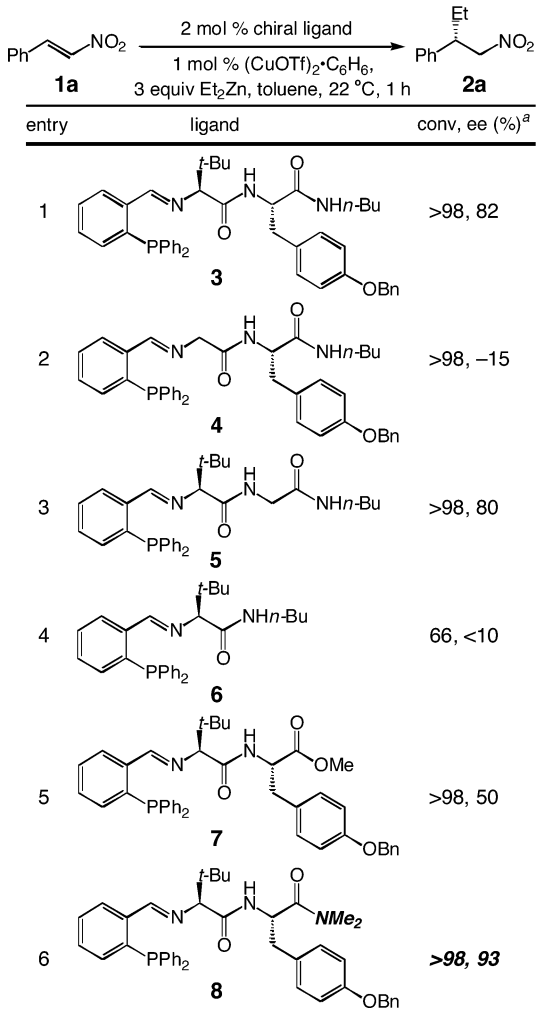
Herein, we report a general method for efficient and highly enantioselective synthesis of *β*,*β*′-arylalkyl and *β*,*β*′-dialkyl nitroalkanes by Cu-catalyzed ACA of alkylzincs to acyclic nitroalkenes, promoted by a readily available dipeptide phosphine (**9**); catalytic alkylations are typically carried out at room temperature (low temperatures required in some cases) in the presence of 1−4 mol % catalyst.[7] The requisite substrates are easily prepared (>98% *trans*) in two steps from commercially available nitromethane and various aromatic and aliphatic aldehydes (by the Henry reaction in ∼60% overall yield). The aliphatic and aromatic nitroalkanes can be readily converted to various optically enriched amines that can be used in the enantioselective synthesis of biologically important compounds. Moreover, we disclose the unexpected observation that a subtle modification of the chiral ligand structure leads to significant improvement in asymmetric induction. Use of the chiral ligand employed in related additions to cyclic nitroalkenes[3] affords products in significantly lower enantioselectivities.

Our studies commenced with screening[8] of different amino acid based ligands in order to examine their ability to promote ACA of Et_2Zn to aryl nitroalkene **1a**. As illustrated in entry 1 of Table 1, we established that dipeptide phosphine **3**, the ligand used to promote additions to cyclic nitroalkenes, initiates the formation of the desired product **2a**, but only in 82% ee. To understand the origin of enantioselectivity better and hopefully obtain improved levels of asymmetric induction, we set out to alter the structure of the chiral ligand in a systematic fashion. Selected results of our investigation are summarized in Table 1.

The data illustrated in entries 2−5 of Table 1 suggest that the presence of a second amino acid moiety (AA2) is critical to efficiency and enantioselectivity (entry 1 vs 4, in Table 1). Comparison of the data in entries 1 and 2 indicate that chirality at the AA1 site (amino acid that forms the Schiff base through its amine site), although not required to ensure high conversion, is necessary for achieving high asymmetric induction. As illustrated by the catalytic ACA with phosphine **5**, chirality at the AA2 site has a minimal influence on enantioselectivity (entry 1 vs 3, Table 1). We also included in our screening studies dipeptide phosphines bearing different carboxyl termini. Accordingly, as depicted in entries 5 and 6 of Table 1, we discovered that, whereas the derived methyl ester **7** leads to efficient but less enantioselective additions (50% vs 82% ee with **3**), dimethylamide **8** provides significantly enhanced asymmetric induction (93% ee).

The identity of the optimal amide terminus was established by examination of the ability of various chiral phosphines in promoting the synthesis of **2a**. Representative results from these studies are summarized in Table 2. These findings indicate that chiral phosphine ligand **9** bearing a diethylamide terminus provides the highest level of enantioselectivity.[9] Thus, as indicated in entry 1 of Table 3, in the presence of 2 mol % **9**, 1 mol % $(CuOTf)_2{\cdot}C_6H_6$, and 3 equiv of Et_2Zn,

Table 1. Cu-Catalyzed ACA with Various Chiral Ligands



entry	ligand	conv, ee (%)[a]
1	**3**	>98, 82
2	**4**	>98, –15
3	**5**	>98, 80
4	**6**	66, <10
5	**7**	>98, 50
6	**8**	***>98, 93***

[a] Determined by chiral GLC (betadex column).

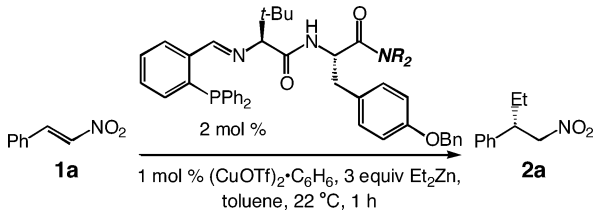
(5) In two instances, with Et_2Zn as the alkylating agent, enantioselectivities >80% ee have been reported (R = Cy, 96% ee and R = Ph, 84% ee). See ref 2g,h.

(6) Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4793−4795.

(7) For other Cu-catalyzed ACA of alkylzincs to unsaturated carbonyls promoted by related amino acid-based chiral phosphines, see: (a) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755−756. (b) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779−781. (c) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 13362−13363. (d) Hird, A. W.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1276−1279. (e) Cesati, R. R., III; de Armas, J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 96−101.

(8) For screening strategies and significant attributes of the amino acid based ligands, see: Hoveyda, A. H. In *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH: Weinheim, 2002; pp 991−1016.

Table 2. Examination of Chiral Ligands with Different Termini



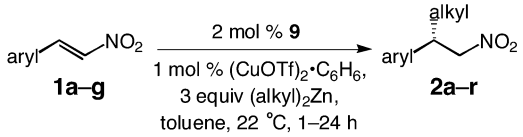
entry	NR_2		ee (%)
1	NEt_2	**9**	95
2	NBn_2	**10**	85
3	NHBn	**11**	85
4		**12**	91
5		**13**	93

catalytic ACA to **1a** proceeds to completion (1 h, 22 °C) to afford **2a** in 79% yield and 95% ee.

As the data in Table 3 demonstrate, the Cu-catalyzed ACA can be used efficiently to synthesize readily a range of chiral nitroalkanes in high optical purity. Other important aspects regarding the data presented in Table 3 merit discussion: (i) The positive effect of the dialkylamide terminus is not limited to the reaction shown in entry 1. For example, when ligand **3** is used to promote the Cu-catalyzed ACA, additions in entries 4, 8, and 12 in Table 3 afford the desired products in only 78%, 70%, and 77% ee, respectively. (ii) Alkylzinc reagents other than Et_2Zn can be readily employed. Unlike some other C−C bond forming reactions involving this class of amino acid based ligands,[10] even with the less reactive Me_2Zn, reactions readily proceed to >98% conversion (24 h) in the presence of 2 mol % catalyst without the need for a larger excess of the alkylmetal. (iii) Regardless of the substitution pattern of the aromatic substituent (e.g., the sterically demanding **1e**) or whether the substituent is electron-donating (e.g., entries 5−7) or electron-withdrawing (e.g., entries 8−12, Table 3), catalytic ACA reactions occur efficiently and with high enantioselectivity (78−95% ee).

One of the most noteworthy and unique attributes of the present method is that substrates bearing aliphatic substituents (entries 1−4, Table 4) can be used in efficient Cu-catalyzed

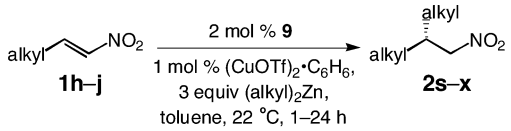
Table 3. Cu-Catalyzed Enantioselective Conjugate Additions of Alkylzincs to Acyclic Aromatic Nitroalkenes[a]



entry	R		$(alkyl)_2Zn$	product	yield (%)[b]	ee (%)[c]
1	Ph	**a**	Et_2Zn	**2a**	79	95
2	Ph	**a**	Me_2Zn	**2b**	78	92
3	Ph	**a**	$[(Me_2HCCH_2)_3]_2Zn$	**2c**	70	95
4	Ph	**a**	$[AcO(CH_2)_4]_2Zn$	**2d**	60	89
5	*p*-$OMeC_6H_4$	**b**	Et_2Zn	**2e**	72	95
6	*p*-$OMeC_6H_4$	**b**	Me_2Zn	**2f**	75	95
7	*p*-$OMeC_6H_4$	**b**	$[(CH_2)_4OAc]_2Zn$	**2g**	57	93
8	*p*-ClC_6H_4	**c**	Et_2Zn	**2h**	84	93
9	*p*-ClC_6H_4	**c**	Me_2Zn	**2i**	70	94
10	*p*-ClC_6H_4	**c**	$[(Me_2HCCH_2)_3]_2Zn$	**2j**	78	90
11	*p*-$CF_3C_6H_4$	**d**	Et_2Zn	**2k**	65	79
12	*p*-$CF_3C_6H_4$	**d**	Me_2Zn	**2l**	70	95
13	*o*-MeC_6H_4	**e**	Et_2Zn	**2m**	65	94
14	*o*-MeC_6H_4	**e**	Me_2Zn	**2n**	65	88
15[d]	*o*-BrC_6H_4	**f**	Et_2Zn	**2o**	68	81
16[e]	*o*-BrC_6H_4	**f**	Me_2Zn	**2p**	67	78
17	2-furyl	**g**	Et_2Zn	**2q**	78	95
18	2-furyl	**g**	Me_2Zn	**2r**	75	92

[a] Times: 1 h with Et_2Zn, 24 h with Me_2Zn, 12 h otherwise. [b] Isolated yields. [c] Determined by chiral GLC and HPLC (see SI for details). [d] 4 mol % **9** and 2 mol % $(CuOTf)_2$•C_6H_6 was used. [e] Reaction run with 4 mol % **9** and 2 mol % $(CuOTf)_2$•C_6H_6 at −30 °C.

Table 4. Cu-Catalyzed Enantioselective Conjugate Additions of Alkylzincs to Acyclic Aliphatic Nitroalkenes[a]

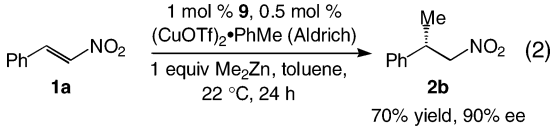


entry	R		$(alkyl)_2Zn$	product	yield (%)[b]	ee (%)[c]
1	*n*-C_7H_{15}	**h**	Et_2Zn	**2s**	72	93
2	*n*-C_7H_{15}	**h**	Me_2Zn	**2t**	68	85
3	Cy	**i**	Et_2Zn	**2u**	52	95
4	Cy	**i**	Me_2Zn	**2v**	58	87
5[d]	$CH(OMe)_2$	**j**	Et_2Zn	**2w**	64	84
6[e]	$CH(OMe)_2$	**j**	Me_2Zn	**2x**	60	77

[a−d] See Table 3. [e] Reaction run at −55 °C (24 h).

ACA reactions with high enantioselectivity (85−95% ee). Furthermore, as shown by the examples in entries 5 and 6 of Table 4, albeit less effectively than a previous protocol disclosed by Feringa,[2h] the present method can also be used for asymmetric alkylations of acetal substrates.

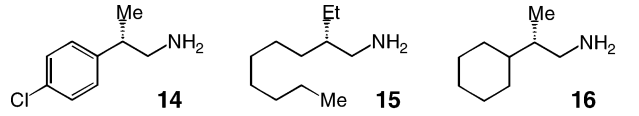
It should be noted that although all catalytic ACA were carried out with 3 equiv of alkylzincs, reactions can proceed efficiently with only 1 equiv of alkylmetal. Moreover, commercially available $(CuOTf)_2$•PhMe (Aldrich) can be used to obtain the desired products in high yield and optical purity. The example shown in eq 2 is illustrative. Cu-



catalyzed addition to **1a** is carried out in the presence of 1

equiv of Me_2Zn, 1 mol % commercially available $(CuOTf)_2 \cdot PhMe$ (unpurified), and 1 mol % phosphine **9** to afford **2b** in 70% isolated yield and 90% ee.

As mentioned before, optically enriched nitroalkanes are precursors to a wide range of N-containing compounds. The optically enriched amines **14**−**16** shown in Figure 1 can be



93% from **2i** (94% ee) 89% from **2s** (93% ee) 91% from **2v** (87% ee)

Figure 1. Optically enriched amines available through reduction of Cu-catalyzed ACA products. Conditions: 10% Pd(C), 1 atm H_2, MeOH, 22 °C, 12 h.

easily synthesized through Pd-catalyzed reductions of Cu-catalyzed ACA products in high yield. Furthermore, as illustrated previously,[2h] nitroacetals **2w** and **2x** (entries 5 and 6, Table 4) can be converted to the corresponding β^2-amino acids.

In summary, we present a method for catalytic enantioselective alkylation of acyclic nitroalkenes that allows efficient access to β-alkylnitroalkanes and the derived amines in high optical purity. Considering the versatility of nitroalkanes, the present general protocol should prove to be of notable utility in asymmetric organic synthesis.

Design and development of new chiral catalysts and enantioselective methods for olefin alkylation, as well as applications to the synthesis of biologically active molecules, are in progress in our laboratories.

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

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(9) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018−4019 and references therein.

(10) For example, see: (a) Reference 7d. (b) Murphy, K. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4690−4691.