Chiral Nitroalkanes

Catalytic Enantioselective Conjugate Reduction of β,β-Disubstituted Nitroalkenes**

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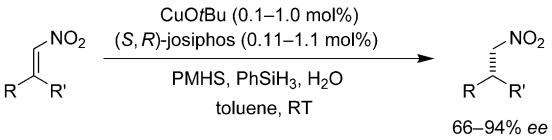
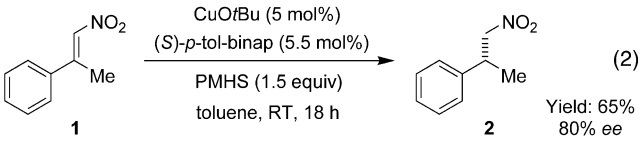
Optically active nitroalkanes are versatile precursors for a wide range of useful building blocks for fine-chemical synthesis. However, only a few effective methods for their preparation are available.[1–3] Despite recent advances in the addition of dialkyl zinc reagents to α,β-unsaturated nitroolefins, the complementary method involving metal-catalyzed enantioselective reduction of β,β-disubstituted nitroalkenes has not been reported.[2] Herein we document such an approach in which bisphosphane–Cu complexes (with tol-binap or josiphos[4]) catalyze the enantioselective reduction of β,β-disubstituted nitroalkenes, giving optically active β,β-disubstituted nitroalkanes in useful yields and selectivities [Eq. (1)].[5] Of additional mechanistic and practical importance is the observation we have made regarding the inhibitory effect of halides; thus, in their absence the reductions can be carried out with as little as 0.1 mol% of complex, rendering the process among one of the more efficient methods for conjugate addition chemistry.



(1)

We had previously reported that a complex prepared from tol-binap and CuO*t*Bu effectively catalyzes the addition of dienolates to aldehydes involving a metalloenolate intermediate.[6] A related complex derived from tol-binap, CuCl, and NaO*t*Bu mediates the enantioselective reduction of α,β-unsaturated esters and ketones.[7,8] As part of our ongoing investigations of copper–phosphane complexes for asymmetric synthesis, we have tested such systems in the reduction of β,β-disubstituted nitroalkenes, which are not only easily prepared (i.e., addition of N_2O_4 to alkenes and subsequent elimination[1,9]) but also whose reductions are unprecedented in small-molecule catalysis.[10]

In our initial investigations on the reduction of (*E*)-1-nitro-2-phenyl-1-propene (**1**) with PMHS, we employed the published procedure for the preparation of the catalyst formed between CuCl, tol-binap, and NaO*t*Bu. Under these conditions, the reaction proceeded rather sluggishly: 5 mol% of catalyst led to 18% conversion after 22 h at 25°C. Additionally, isomerization of **1** to the β,γ-unsaturated nitroalkene (14%) was observed. We then investigated the catalyst prepared from tol-binap and CuO*t*Bu which we had originally formulated for mechanistic studies in aldol addition chemistry. In the presence of 5 mol% of this catalyst, full conversion of **1** into **2** (65% yield, 80% *ee*) within 18 h at room temperature was observed [Eq. (2)].[11] Interestingly, at this stage the reduction appeared to be quite general as 2-methyl-3-nitro-prop-2-en-1-ol provided the corresponding nitroalkane in 58% yield and 56% *ee*.[12]



(2)

These results along with subsequent investigations led us to the significant conclusion that the presence of NaCl inhibits the activity of the Cu–phosphane complex, a premise which is supported by the finding that the addition of various inorganic salts (e.g. LiCl, NEt_4Cl, KCN) always leads to diminished reaction rates.

We subsequently looked to variation of the silane component in the reaction in an effort to increase turnover frequency and lower catalyst loading.[13] We found that the use of diphenylsilane or phenylsilane in the reaction resulted in increased reaction rates, with the highest acceleration observed when a combination of PMHS (0.1 equiv) and phenylsilane (1.2 equiv) was employed. Nevertheless, under these conditions, substantial amounts of 2-phenyl-propional-dehydeoxime (38%) were isolated.[14] However, the addition of 1.2 equivalents of water to the reaction mixture resulted in complete suppression of this overreduction.[15] An important consequence of these conditions is the fact that in the presence of tol-binap and josiphos, the catalyst loadings can be further substantively decreased to the level of 0.1 mol% [Eq. (1), Table 1].

As shown in Table 1 aromatic and aliphatic substrates are reduced to give adducts in useful selectivity. Both protected and unprotected alcohol functionalities as well as heterocyclic substrates are tolerated. The reduction of *E* and *Z* olefins (Table 1, entries 7 and 8) resulted in the formation of opposite enantiomers with similar high levels of enantioselectivity.[17] This observation is in accordance with those in conjugate reductions of unsaturated carbonyls.[8a,18]

The nitroalkane products provide entry to valuable chiral amines that are otherwise not easily accessed. In this respect, reduction of **2** (Pd/C, H_2) serves to exemplify the convenience with which amines can be accessed in high yield [Eq. (3)].[19]

In conclusion, we have developed a novel copper-catalyzed, asymmetric reduction of substituted nitroolefins that

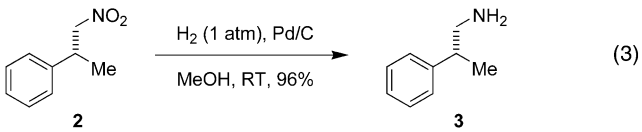


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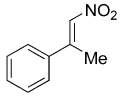
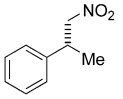
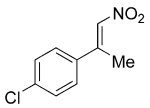
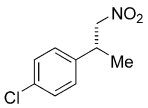
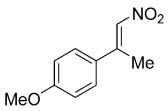
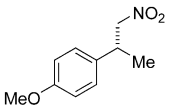
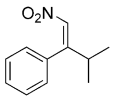
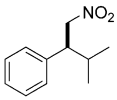
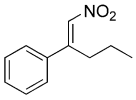
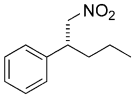
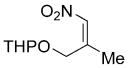
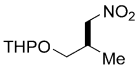
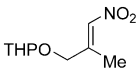
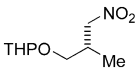
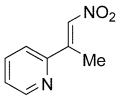
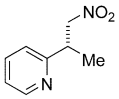
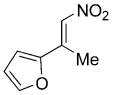
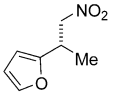
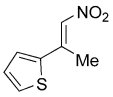
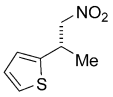
Table 1: Conjugate reduction in the presence of CuO*t*Bu, PMHS, and $PhSiH_3$.

Entry	Substrate	Product	Ligand	Catalyst [mol%]	*t* [h]	Yield [%]	*ee* [%]
1			(*S*)-tol-binap	0.1	24	60	78
			(*S*,*R*)-josiphos	0.1	24	77	88
2			(*S*,*R*)-josiphos	1	5	89	90
			(*S*,*R*)-josiphos	0.1	24	88	90
3			(*S*,*R*)-josiphos	1	5	94	90
4			(*S*,*R*)-josiphos	1	12	83	94
5			(*S*,*R*)-josiphos	1	12	86	92
6			(*S*)-tol-binap	1	5	60	86
			(*S*,*R*)-josiphos	1	5	66	90
			(*S*,*R*)-josiphos	0.3	24	55	86
7			(*S*)-tol-binap	1	5	76	66[b]
			(*S*,*R*)-josiphos	0.1	24	81	86[b]
8			(*S*,*R*)-josiphos	1	5	82	68[b]
			(*S*,*R*)-josiphos	0.1	24	77	66[b]
9			(*S*,*R*)-josiphos	1	12	55	72
10			(*S*,*R*)-josiphos	1	12	72	90
11			(*S*,*R*)-josiphos	1	12	75	84

[a] Reactions were run at 0.2 M of olefin in toluene with $PhSiH_3$ (1.2 equiv), PMHS (0.1 equiv), and water (1.2 equiv) at room temperature. [b] See reference [16].

provides access to optically active β,β-disubstituted nitroalkanes. Importantly, we have documented means by which such reductions can be carried out under operationally convenient conditions with as little as 0.1 mol% of catalyst (CuO*t*Bu, tol-binap, or josiphos). The method described represents the first such report, ultimately providing access to optically active amines. Given the increased importance of copper-catalyzed processes for asymmetric synthesis, of additional significance is the observation that halides can inhibit such catalytic processes. Further work is continuing with the aim of better understanding the mechanism of the reaction and ultimately identifying ligands that lead to further improvement in the selectivity.

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Keywords: asymmetric catalysis · copper · hydrosilylation · nitro compounds · reduction

[1] For the transformation of aliphatic nitro compounds, see: a) V. V. Perekalin, E. S. Lipina, V. M. Berestovitskaya, D. A. Efremov, *Nitroalkenes*, Wiley, Chichester, **1994**; b) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, **2001**.

[2] a) For an excellent review, see: O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877; b) H. Schäfer, D. Seebach, *Tetrahedron* **1995**, *51*, 2305; c) N. Sewald, V. Wendisch, *Tetrahedron: Asymmetry* **1998**, *9*, 1341; d) S. Ongeri, U. Piarulli, R. F. W. Jackson, C. Gennari, *Eur. J. Org. Chem.* **2001**, 803; e) C. Luchaco-Cullis, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 8192; f) A. Alexakis, C. Benhaim, S. Rosset, M. Humam, *J. Am. Chem. Soc.* **2002**, *124*, 5262; g) A. Duursma, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2003**, *125*, 3700.

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[11] The stereochemistry of **2** was assigned by comparison with reference [10b].

[12] Reduction of (*E*)-2-methyl-3-nitro-prop-2-en-1-ol provided (*R*)-2-methyl-3-nitro-propan-1-ol. The absolute stereochemistry of the product was assigned by reduction to the aminoalcohol (Pd/C, H_2) and comparison with R. A. Barrow, T. Hemscheidt, J. Liang, S. Paik, R. E. Moore, M. A. Tius, *J. Am. Chem. Soc.* **1995**, *117*, 2479.

[13] a) D. A. Evans, F. E. Michael, J. S. Tedrow, K. R. Campos, *J. Am. Chem. Soc.* **2003**, *125*, 3534; b) B. Tao, G. C. Fu, *Angew. Chem.* **2002**, *114*, 4048; *Angew. Chem. Int. Ed.* **2002**, *41*, 3892; c) A. Mori, T. Kato, *Synlett* **2002**, *7*, 1167.

[14] For the problem of overreduction of nitroalkenes, see a) H. Shechter, D. E. Ley, E. B. Roberson, Jr., *J. Am. Chem. Soc.* **1956**, *78*, 4984; b) B. C. Ranu, R. Chakraborty, *Tetrahedron*, **1992**, *48*, 5317.

[15] We believe that in the presence of water, the first formed silyl nitronate undergoes protonation faster than it is reduced to the oxime.

[16] Owing to the presence of the THP group, the products of the reduction are diastereomers. The diastereomeric ratio was determined to be 1:1 and the *ee* value for each identical, indicating that the acetal stereocenter has no effect on the stereochemical outcome of the conjugate reduction.

[17] In the synthesis of the nitroalkene starting materials, olefins were obtained as single isomers in most cases (*E* for entries 1, 2, 3, 5, 6, 9, 10, and 11 and *Z* for entry 4).

[18] a) U. Leutenegger, A. Madin, A. Pfaltz, *Angew. Chem.* **1989**, *101*, 61; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 60; b) P. von Matt, A. Pfaltz, *Tetrahedron: Asymmetry* **1991**, *2*, 691; c) M. Misun, A. Pfaltz, *Helv. Chim. Acta* **1996**, *79*, 961; d) T. Yamada, Y. Ohtsuka, T. Ikeno, *Chem. Lett.* **1998**, 1129.

[19] It was shown by analysis of the Mosher amide that no erosion of enantiomeric purity occurred in the course of the reduction.

