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# Convenient Catalytic, Enantioselective Conjugate Reduction of Nitroalkenes Using $CuF_2$

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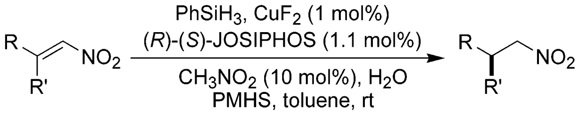
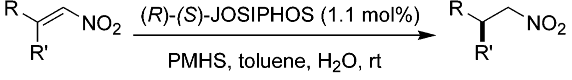
## ABSTRACT



**We document the use of a new catalyst system for the enantioselective conjugate reduction of nitroalkenes utilizing commercially available $CuF_2$ and the bis-phosphine JOSIPHOS as a ligand. This new protocol not only facilitates ready access to a variety of optically active nitroalkanes, but the results provide also new insight into copper-catalyzed reactions.**

Optically active nitroalkanes are valuable building blocks in organic synthesis. They can be processed to other useful chiral intermediates in fine-chemical synthesis such as amines, aldehydes, or acids and can be employed as precursors to nitrile oxides in dipolar cycloaddition reactions.[1] There have been recent reports of highly enantioselective addition reactions of various C-nucleophiles to nitroalkenes.[2] We have documented a novel conjugate reduction of $\beta,\beta$-disubstituted nitroalkenes employing a catalyst prepared from $CuO^tBu$ and the chiral bis-phosphine JOSIPHOS.[3,4] Use of this catalyst system can effect the preparation of optically active $\beta,\beta$-disubstituted nitroalkanes with catalyst loadings as low as 0.1 mol %. The use of $CuO^tBu$ can be a drawback to the broad application of this process, because it is sensitive to oxygen and moisture. Thus, we have been interested in evaluating an alternative catalyst system for enantioselective reduction of nitroalkenes employing inexpensive, commercially available copper salts that are conveniently handled. In this communication, we report such a system in which the combination of a chiral bis-phosphine ligand and $CuF_2$ can be employed (eq 1).[4] The ability to use $CuF_2$ was rather unexpected, as we have previously shown that halides inhibit this process. Additionally, we disclose an unusual observation wherein nitromethane is used as an additive and activator for the enantioselective reduction of more electron-rich nitroalkene substrates.



(1)

In our initial investigations of the enantioselective reduction of nitroalkenes, we had observed the inhibition of the

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(1) (a) *The Nitro Group in Organic Synthesis*; Ono, N.; Wiley-VCH: New York, 2001. (b) *Nitroalkenes*; Perekalin, V. V.; Lipina, E. S.; Berestovitskaya, V. M.; Efremov, D. A. John Wiley & Sons: Chichester, 1994. (c) *Nitro Compounds—Recent Advances in Synthesis and Chemistry: Organic Nitro Chemistry Series*; Feuer, H., Nielsen, A. T., Eds.; VCH: Weinheim, 1990. (d) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1−18. For the concept of polarity control and umpolung, see: (e) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239−258. (f) *Polarity Control for Synthesis*; Ho, T.-L.; John Wiley & Sons: New York, 1991.

(2) (a) For a review, see: Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877−1894. (b) Schäfer, H.; Seebach, D. *Tetrahedron* **1995**, *51*, 2305−2324. (c) Sewald, N.; Wendisch, V. *Tetrahedron: Asymmetry* **1998**, *9*, 1341−1344. (d) Ongeri, S.; Piarulli, U.; Jackson, R. F. W.; Gennari, C. *Eur. J. Org. Chem.* **2001**, 803−807. (e) Luchaco-Cullis, C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192−8193. (f) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262−5263. (g) Mampreian, D. M.; Hoveyda, A. H. *Org. Lett.* **2004**, *6*, 2829−2832. (h) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700−3701. (i) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906−9907. (j) Choi, H.; Hua, Z.; Ojima, I. *Org. Lett.* **2004**, *6*, 2689−2691. (k) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558−9559.

(3) Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4793−4795; *Angew. Chem.* **2003**, *115*, 4941−4943.

10.1021/ol048035h CCC: $27.50

reaction by chloride; this prompted us to use CuO$^t$Bu.[3] Our subsequent interest in developing a more convenient protocol led us to examine the use of copper fluoride salts, as these have been demonstrated to function in a variety of catalytic processes.[5] A particularly attractive feature of $CuF_2$ is its stability, allowing it to be conveniently handled. Of additional importance, despite our observations with halides, we anticipated that the fluorides would be compatible with the process, because this halide would be sequestered from the reaction mixture through its reaction with the silanes to form compounds with strong Si−F bonds (ca. 135 kcal/mol).

When commercially available $CuF_2$ and JOSIPHOS in toluene along with phenylsilane, PMHS, and water were utilized in the conjugate reduction of 2-phenyl-1-nitropropene, the formation of the desired nitroalkane was observed, but the reaction did not go to completion (61% conversion). Recent observations by Riant in the context of copper fluoride bis-phosphine complexes as catalysts for ketone hydrosilylation compelled us to examine purposefully exposing our system to oxygen; however, the presence of oxygen led to significant inhibition of the conjugate reduction.[6] Optimization studies revealed that best results were obtained when 1.5 equiv of phenylsilane were added portionwise in two batches of 0.5 equiv and an additional 1.0 equiv after 12 h, respectively. Under these conditions, full conversion was observed. Applying this optimized procedure, we investigated the reduction of differently substituted nitroalkenes. In all cases, use of 1 mol % catalyst provided the nitroalkane products in useful yields and selectivity (eq 1, Table 1).[7]

Although the protocol described above was effective for a series of nitroalkenes, some substrates that had proven to be successful in the earlier procedure involving CuO$^t$Bu now failed to undergo reduction. In particular, the more electron-rich substrates such as *p*-methoxyphenyl- or furanyl-substituted nitroalkenes (Scheme 1) proved to be inert under these conditions, and only traces of products were formed.

**Scheme 1.** Reduction of Nitroalkenes by Addition of Nitromethane

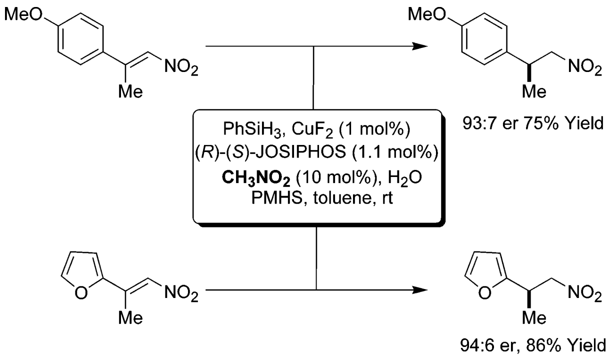
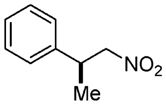
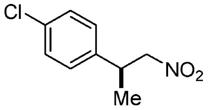
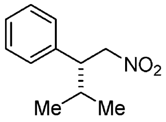
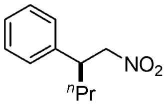
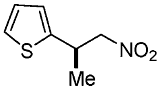
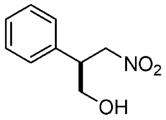


**Table 1.** Conjugate Reduction of Nitroalkenes Using a Complex Prepared from $CuF_2$[a]

| entry | product | yield | er |
|---|---|---|---|
| 1 |  | 76% | 96:4 |
| 2 |  | 88% | 95:5 |
| 3 |  | 74% | 98:2 |
| 4 |  | 76% | 96:4 |
| 5 |  | 88% | 91:9 |
| 6 |  | 52% | 95:5 |

[a] Reaction conditions: $PhSiH_3$ (1.5 equiv), PMHS (0.1 equiv), $CuF_2$ (1 mol %), JOSIPHOS (1.1 mol %), $H_2O$ (1.0 equiv), toluene, 16 h at room temperature.

In 1998, we investigated and documented the behavior of different Cu(I) and Cu(II) catalysts in the enantioselective addition of silyl dienolates to aldehydes.[8] In this process, a number of observations are consistent with a catalytically active Cu(I) species: the isolation of dimeric dienolate products that were the product of oxidative dimerization of the starting enolate and the fact that CuO$^t$Bu was shown to be an effective catalyst. In our model for the enantioselective conjugate reduction of nitroalkenes, we have worked under the assumption that Cu(I) is also the active species. However, in contrast to the dienolate chemistry, we had hypothesized that it was the silane that effects the requisite reduction (Cu(II) → Cu(I)). The inability to observe reduction of the more electron-rich nitroalkenes led us to question this

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(4) JOSIPHOS = 1-[2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine; PMHS = Poly(methylhydrosiloxane).

(5) (a) Suto, Y.; Kumagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3147−3150. (b) Oisaki, K.; Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5644−5645. (c) Agnelli, F.; Sulikowski, G. A. *Tetrahedron Lett.* **1998**, *39*, 8807−8810.

(6) (a) Sirol, S.; Courmarcel, J.; Mostefai, N.; Riant, O. *Org. Lett.* **2001**, *3*, 4111−4113. (b) Courmarcel, J.; Mostefaï, N.; Sirol, S.; Choppin, S.; Riant, O. *Isr. J. Chem.* **2001**, *41*, 231−240.

(7) For the assignment of absolute stereochemistry, see ref 3.

(8) (a) Pagenkopf, B. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3124−3126. (b) Krüger, J.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 7013−7016. (c) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837−838. (d) For the preparation of CuO$^t$Bu, see: Tsuda, T.; Hashimoto, T.; Saegusa, T. *J. Am. Chem. Soc.* **1972**, *94*, 658−659.

hypothesis. Our experience with dienolates prompted us to consider that the generation of a nitronate in the reaction and its subsequent oxidative dimerization could be responsible for the generation of the active Cu(I) species. The difference in acidity between the various nitroalkenes would account for the absence of reaction with electron-rich nitroolefins, as the active catalyst would never be generated.

To examine this new working hypothesis, an experiment was designed in which the active catalyst generated from the reduction of a reactive nitroalkene was subsequently exposed to a more electron-rich nitroalkene. In the experiment, a reaction mixture was set up incorporating the requisite components for the catalytic reduction ($CuF_2$, ligand, phenylsilane, PMHS, and water) and 2-phenyl-1-nitro-propene as a substrate. After stirring for 30 min, the starting material had been consumed; subsequently, a 10-fold excess of the previously unreactive 2-(*p*-methoxyphenyl)-1-nitro-propene was added. This substrate now underwent reduction at a good rate.

To simplify the reaction protocol and generate a process that was more amenable, we tested a procedure in which nitromethane is added at the outset of the reaction mixture. Indeed, a solution of the catalyst (1 mol %) and nitromethane (10 mol %) under otherwise identical conditions effected the enantioselective reduction of previously unreactive substrates (Scheme 1). With this simplified, convenient protocol, the products are isolated in useful yields and selectivity.

The results we have described imply at least two mechanistically different explanations. In the first of these, in the presence of nitromethane or 2-phenyl-1-nitro-propane a new catalytically active species is generated that exhibits increased reactivity such that more electron-rich substrates can be effectively reduced. These nitrocompounds would need to act as modifying ligands in the catalyst complex. In the second possibility, the difference between the two classes of nitroalkenes is related to the ability of these to undergo deprotonation and oxidative coupling. Importantly, in neither scenario is the silane the active agent that provides initial access to the active catalyst. Both modes of action would be mechanistically interesting for the application of copper fluoride complexes in further studies.

In summary, we document the use of a new catalyst system for the enantioselective conjugate reduction of nitroalkenes utilizing commercially available $CuF_2$ and a bis-phosphine ligand. Fundamentally, the results we document disclose the unique features of $CuF_2$ in a process that is otherwise inhibited by halides and reveal the unusual effect of adding nitromethane for initial catalyst activation. From a more practical perspective, this new protocol allows for ready access to a variety of optically active nitroalkanes. The possibility to start from a commercially available, bench-stable copper(II) salt and to generate a catalytically active species in situ by addition of nitromethane facilitates the reaction setup. Furthermore, this new protocol may find additional application in other copper-catalyzed processes in large-scale as well as in fine-chemical synthesis.

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**Supporting Information Available:** Characterization data and representative experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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