ORGANIC
LETTERS

2003
Vol. 5, No. 1
79−80

First Synthesis of a β^2-Homoamino Acid by Enantioselective Catalysis

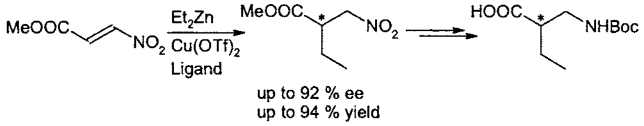
Audrius Rimkus and Norbert Sewald*

*Faculty of Chemistry, University of Bielefeld, PO Box 10 01 31,
D-33501 Bielefeld, Germany*

norbert.sewald@uni-bielefeld.de

Received November 8, 2002

ABSTRACT



The enantioselective conjugate addition of diethylzinc to the activated nitroolefin methyl 3-nitropropenoate is efficiently catalyzed by copper(I) complexes with BINOL-based enantiopure phosphoramidite ligands. The nitroolefin moiety acts as the predominant Michael acceptor, giving rise to the unambiguous formation of 2-alkyl-3-nitro-propanoates. Moderate to excellent enantioselectivities and high chemical yields are obtained. The product can easily be transformed into a β^2-homoamino acid.

The conjugate addition of carbon nucleophiles to α,β-unsaturated compounds belongs to the classical carbon−carbon bond forming strategies.[1] The versatility of this reaction type is due to the wide variety of donors (organometallic reagents, Michael donors, other carbanions) and acceptors (α,β-unsaturated reagents) that can be employed.[2] In particular, the use of dialkylzinc reagents has been extremely successful in the development of highly enantioselective catalytic conjugate additions in recent years.[2b,3]

The addition of nucleophiles to nitroolefins[4] represents a convenient access to nitroalkanes that are versatile intermediates in organic synthesis. The nitro functionality can be easily transformed into an amine, an oxime, a ketone, or a carboxylic acid, etc., providing a wide range of synthetically interesting compounds.[5] Among these, β^2-homoamino acids (side chain at C^α, amino group at C^β) are of special interest, as the corresponding β-peptides adopt novel and unique folding patterns.[6] Syntheses of this class of compounds employing asymmetric catalysis have not yet been described.

In recent years several ligands have been utilized in the enantioselective conjugate addition of diorganozinc compounds to nitroolefins.[7] 3-Nitropropenoates are ideally suited as precursors of β^2-homoamino acids as the side chain R may be introduced by conjugate addition of R_2Zn. Herein we describe an enantioselective conjugate addition of diethylzinc to the activated nitroolefin methyl 3-nitropropenoate[8] **2** catalyzed by BINOL-based enantiopure copper(I)/phosphoramidite complexes (Scheme 1). The synthesis of catalysts of this type and their application in conjugate additions of dialkylzinc compounds to various enones have been first reported by Feringa et al.[9] The influence of the nature of the copper salt on the stereoselectivity of conjugate additions has been recently investigated by us and Alexakis et al.[10]

---

[1] Jung, M. E. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 1−67.

[2] (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171−196.

[3] (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346−353. (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033−8061.

[4] (a) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1−18. (b) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001. (c) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877−1894. (d) Rimkus, A.; Sewald, N. *Org. Lett.* **2002**, *4*, 3289−3291.

[5] (a) Barrett, A. G. M.; Grabowski, G. *Chem. Rev.* **1986**, *86*, 751−762. (b) Kabalka, G. W.; Varma, R. S. *Org. Prep. Proced. Int.* **1987**, *19*, 283−328. (b) Perekalin, V. V.; Lipina, E. S.; Berestovitskaya, V. M.; Efremov, D. A. *Nitroalkenes, Conjugated Nitrocompounds*; John Wiley & Sons: New York, 1994.

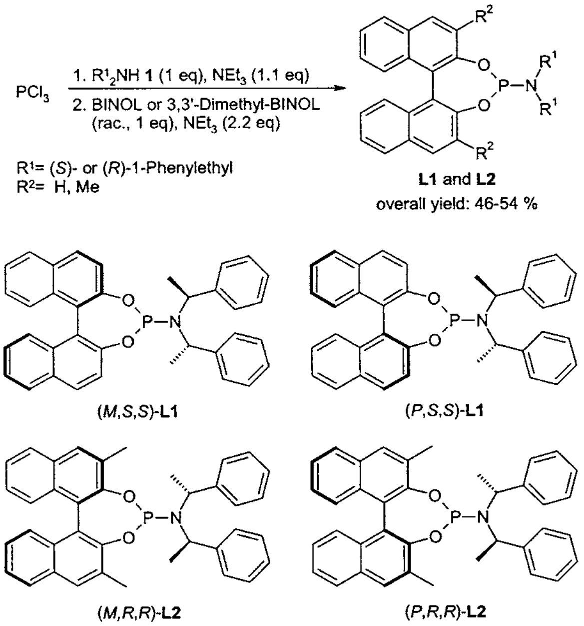
[6] Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219−3232.

[7] (a) Sewald, N.; Wendisch, V. *Tetrahedron: Asymmetry* **1998**, *9*, 1341−1344. (b) Alexakis, A.; Benhaim, C. *Org. Lett.* **2000**, *2*, 2579−2581. (c) Versleijen, J. P. G.; van Leusen, A. M.; Feringa, B. L. *Tetrahedron Lett.* **1999**, *40*, 5803−5806. (d) Ongeri, S.; Piarulli, U.; Jackson, R. F. W.; Gennari, C. *Eur. J. Org. Chem.* **2001**, 803−807. (e) Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192−8193.

[8] For synthesis of nitroolefins, see also: (a) Shin, C.; Yamaura, M.; Inui, E.; Ishida, Y.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2618−2621. (b) Shechter, H.; Conrad, F. *J. Am. Chem. Soc.* **1953**, *75*, 5610−5613. (c) Piet, J. C.; Le Hetet, G.; Cailleux, P.; Benhaoua, H.; Carrié, R. *Bull. Soc. Chim. Belg.* **1996**, *105*, 33−44.

10.1021/ol027252k CCC: $25.00

Scheme 1. Synthesis of Phosphoramidites **L1** and **L2**

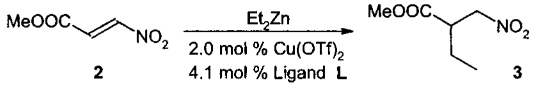


We used copper(II) triflate as the source of copper(I), because it is easy to handle and reduced in situ by diethyl zinc.

The synthesis of phosphoramidites **L1** and **L2** was performed following a modified procedure originally described by Feringa et al. Starting from phosphorus trichloride, enantiomerically pure bis(phenylethyl)amine **1** and racemic BINOL or its 3,3′-dimethyl derivative (Scheme 1) are reacted, followed by chromatographic resolution of the diastereomeric phosphoramidites.[11] Alternatively, enantiomerically pure BINOL may be employed. The 3,3′-dimethyl derivative of BINOL was synthesized according to Woodward's method.[12]

We found that the copper(I)-catalyzed conjugate addition of diethylzinc to methyl 3-nitropropenoate **2** proceeds with varying enantioselectivity, depending on ligand, solvent, and reaction conditions employed. Substrate and catalyst concentrations also influence the enantioselectivity.[7b] The best results are obtained with ligand (*P*,*R*,*R*)-**L2** in diethyl ether at −78 °C, which provides **3** in 94% yield and 92% ee (Table 1, entry 11). Enantioselectivity drops to 15% ee when the diastereomeric ligand (*M*,*R*,*R*)-**L2** is used under these reaction conditions (Table 1, entry 12). Even less than 0.5 mol % of copper(II) and 1.0 mol % of chiral phosphoramidite **L** are sufficient for very fast and clean reaction at −78 °C.

Table 1. Enantioselective Copper(I)-Catalyzed Conjugate Addition of Diethylzinc to Methyl 3-Nitropropenoate **2**[a]

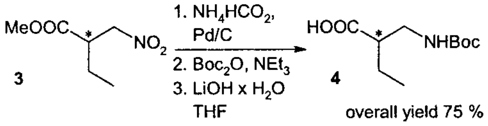


entry	ligand	solvent	*T*, °C	ee, %	isomer
1	(*M*,*S*,*S*)-**L1**	toluene	−50	10	(+)
2	(*M*,*S*,*S*)-**L1**	toluene	−30	28	(+)
3	(*P*,*S*,*S*)-**L1**	toluene	−30	12	(−)
4	(*M*,*S*,*S*)-**L1**	ether	−30	68	(+)
5	(*M*,*S*,*S*)-**L1**	ether	−78	77	(+)
6	(*M*,*S*,*S*)-**L1**	THF	−30	16	(−)
7	(*P*,*R*,*R*)-**L2**	toluene	−30	67	(+)
8	(*M*,*R*,*R*)-**L2**	toluene	−30	52	(+)
9	(*P*,*R*,*R*)-**L2**	ether	−30	73	(+)
10	(*M*,*R*,*R*)-**L2**	ether	−30	12	(−)
11[b]	(*P*,*R*,*R*)-**L2**	ether	−78	92	(+)
12[b]	(*M*,*R*,*R*)-**L2**	ether	−78	15	(+)

[a] Isolated yields of **3** range from 70% to 94%. [b] 0.5 mol % $Cu(OTf)_2$ and 1.0 mol % ligand.

The *β*-nitroester **3** can easily be reduced by catalytic transfer hydrogenation using ammonium formate, protected by the *tert.*-butyloxycarbonyl group (Boc), and subsequently saponified to give the β^2-homoamino acid **4** (Scheme 2).

Scheme 2. Synthesis of the Boc-Protected β^2-Homoamino Acid **4**



In conclusion, we found that diethylzinc can be efficiently added to the activated nitroolefin methyl 3-nitropropenoate **2**. The reaction is catalyzed by BINOL-based enantiopure phosphoramidite/copper complexes and provides nitro precursors of β^2-homoamino acids. Enantioselectivities up to 92% ee and chemical yields up to 94% have been obtained. The nitroolefin moiety acts as the predominant Michael acceptor, giving rise to the unambiguous formation of 2-alkyl-3-nitro-propanoate **3**. These experiments clearly show that 3-nitropropenoate **2** is ideally suited as a valuable precursor in the catalytic asymmetric synthesis of β^2-homoamino acids. Different side chains may be introduced via conjugate addition of organozinc reagents.

Acknowledgment. The authors gratefully acknowledge support from Konrad Adenauer Foundation and University of Bielefeld (Ph.D. grants to A.R.) and Fonds der Chemischen Industrie.

Supporting Information Available: Experimental procedures and listings of physical and spectroscopic data of the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL027252K

---

(9) (a) de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374−2376. (b) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620−2623.

(10) (a) Wendisch, V.; Sewald, N. *Tetrahedron: Asymmetry* **1997**, *8*, 1253−1257. (b) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262−5263.

(11) See Supporting Information for details.

(12) Dennis, M. R.; Woodward, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1081−1085.