

Conjugate Addition of Mixed Diorganozinc Compounds and Functionalized Organozinc Cuprates to Nitroolefins

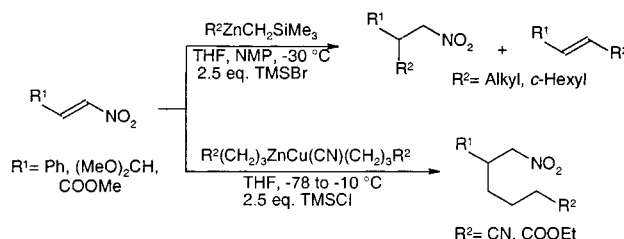
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ABSTRACT



The copper-catalyzed conjugate addition of symmetrical and mixed diorganozinc compounds as well as functionalized diorganozinc cuprates to nitroolefins leads to synthetically versatile nitro compounds in moderate to good yields. Mixed TMSM-organozinc compounds are suitable reagents for conjugate addition, since the TMSM group is not being transferred. Ipso substitution is observed in the absence of a catalytic amount of copper(I) salt. The nitroalkene moiety in 3-nitroacrylates proved to be the predominant Michael acceptor.

The conjugate addition of organometallic compounds to α,β -unsaturated compounds is an important method for the construction of new carbon–carbon bonds.¹ Nitroolefins belong to the most powerful Michael acceptors.² Nitro compounds in general are particularly versatile intermediates since the nitro group may be easily transformed into a wide variety of functionalities.^{2,3} Nitro groups may easily be converted into amino groups. Our interest in amino-substituted carboxylic acids prompted us to embark on a project dealing with the conjugate addition of functionalized and unfunctionalized organozinc reagents to nitroolefins,⁴ which has also been investigated by other groups.^{5,6} The

ligand-accelerated addition of diethyl zinc to nitrostyrene has been described for the first time by Alexakis et al.⁷ Due to the fact that the organozinc compounds display a remarkable functional group tolerance,⁸ a wide range of polyfunctional molecules can be obtained by conjugate addition of functionalized organozinc compounds to Michael acceptors. Functionalized zinc–copper reagents have been added to a series of simple nitroolefins.⁸

Here we report on the addition of symmetrical and mixed diorganozinc compounds as well as functionalized diorganozinc cuprates to aliphatic and aromatic nitroolefins. Mixed diorganozinc reagents composed of one transferable group R together with the nontransferable trimethylsilylmethyl

(1) For a review, see: Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, UK, 1992.

(2) (a) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, 33, 1–18. (b) Barrett, A. G. M. *Chem. Soc. Rev.* **1991**, 20, 95–127. (c) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877–1894.

(3) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833–847.

(4) Wendisch, V.; Sewald, N. *Tetrahedron: Asymmetry* **1998**, 9, 1341–1344.

(5) Versleijen, J. P. G.; van Leusen, A. M.; Feringa, B. L. *Tetrahedron Lett.* **1999**, 40, 5803–5806.

(6) Alexakis, A.; Benhaim, C. *Org. Lett.* **2000**, 2, 2579–2581.

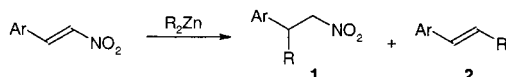
(7) Alexakis, A.; Vastra, J.; Mangeney, P. *Tetrahedron Lett.* **1997**, 38, 7745–7748.

(8) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, 93, 2117–2188 and references therein.

group (TMSMgZnR)^{9,10} are especially useful for this type of conjugate addition, because they avoid the loss of one of the two organic residues R.

Dialkylzinc compounds or mixed diorganozinc compounds TMSMgZnR can be added to nitroolefins and other Michael acceptors in a mixture of THF and the polar cosolvent *N*-methylpyrrolidone (NMP) in the absence of any copper or transition metal catalyst.¹¹ Formation of the ipso-product **2** (Scheme 1) has not been observed under these conditions.

Scheme 1. Conjugate Addition versus Ipso Substitution



Usually ipso-type substitution (vinylic substitution) takes place when nitroolefins bearing an acceptor group are used together with “soft” nucleophiles.¹² However, according to our investigations, the addition of alkyl(trimethylsilylmethyl)-zinc reagents¹³ to nitrostyrene **3a** in a THF/NMP mixture in the absence of copper(I) salts leads to predominant formation of the ipso-substituted products **5** (Table 1, entries 1 and 2).

Table 1. Reaction of Alkyl(trimethylsilylmethyl)zinc Reagents with Nitrostyrene **3a**; Effect of the Copper Salt

$\text{Ph-CH=CH-NO}_2 \xrightarrow[\text{2.5 eq. TMSBr}]{\text{RZnCH}_2\text{SiMe}_3, \text{THF, NMP, -30 } ^\circ\text{C, 12 h}}$				
entry	R	Cu-salt	yield, %	
1	<i>c</i> -hexyl		4a : 5	5a : 28
2	<i>n</i> -heptyl		4b : 15	5b : 43
3	<i>c</i> -hexyl	CuCl	4a : 70	-
4	<i>n</i> -heptyl	Cu(OTf) ₂	4b : 83	-
5 ^a	<i>n</i> -heptyl	Cu(OTf) ₂	4b : 64	-

^a Longer reaction time (24 h).

Upon addition of a catalytic amount of copper(I) salt (ca. 2–4 mol %) or copper(II) triflate, which is reduced to copper(I) under the reaction conditions employed, exclusive formation of the 1,4-adduct is observed in moderate to good yields. Longer reaction time does not lead to the formation

of the ipso product. However, decreasing yields are observed in this case (Table 1, entry 5).

Further results of the copper-catalyzed conjugate addition of TMSMgZnR to nitroolefins **3** are summarized in Table 2.

Table 2. Copper-Catalyzed Conjugate Addition to Nitroolefins

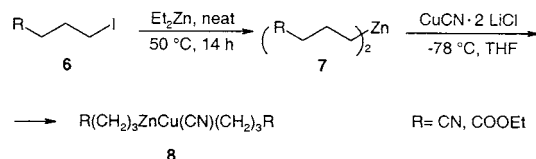
$\text{R}^1\text{-CH=CH-NO}_2 \xrightarrow[\text{2.5 eq. TMSBr, 2-4 mol \% Cu(OTf)}_2]{\text{R}^2\text{ZnCH}_2\text{SiMe}_3, \text{THF, NMP, -30 } ^\circ\text{C}}$				
3a : R ¹ = Ph 3b : R ¹ = (MeO) ₂ CH 3c : R ¹ = COOMe				
entry	nitroolefin	R ²	yield, %	product
1	3a	<i>n</i> -butyl	72	4c
2 ^a	3b	<i>c</i> -hexyl	45	4d
3 ^a	3b	<i>n</i> -heptyl	72	4e
4	3c	<i>n</i> -heptyl	46	4f
5	3c	<i>c</i> -hexyl	69	4g
6	3c	<i>n</i> -hexyl	56	4h

^a TMSCl was used instead of TMSBr.

The addition results show that alkyl(trimethylsilylmethyl)-zinc reagents are suitable for the addition to functionalized nitroolefins. Even in the case of 3-nitropropenoates **3c**, the nitroolefin moiety acts as the Michael acceptor, giving rise to the unambiguous formation of 2-alkyl-3-nitro-propanoates **4f–h**, despite **3c** being a dissonant Michael acceptor (nitroalkene vs acrylate moiety).

Transmetalated diorganozinc compounds RZnCu(CN)R display a significantly higher reactivity and efficiency toward electrophiles compared to the copper–zinc halides RZnCu(CN)X.¹⁴ When nitroolefins are used, useful nitro intermediates can be prepared following this methodology. The functionalized diorganozinc compounds are easily prepared by an iodine–zinc exchange reaction (Scheme 2).¹⁴

Scheme 2. Synthesis of the Functionalized Diorganozinc Compounds



The organozinc cuprates **8**, formed by addition of the THF-soluble salt CuCN·2LiCl,¹⁵ were applied in conjugate additions to nitroolefins **3** to give functionalized nitro compounds **9** in moderate to good yields (Table 3).

Diorganozinc reagents R₂Zn are less readily available compared to organozinc halides RZnX. However, they

(9) For synthesis of TMSMgZnR, see: Berger, S.; Langer, F.; Lutz, C.; Knochel, P.; Mobley, T. A.; Reddy, C. K. *Angew. Chem., Int. Ed.* **1997**, *36*, 1496–1498.

(10) TMSM group as a nontransferrable ligand: Bertz, S. H.; Eriksson, S. H.; Miao, G.; Snyder, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 10906–10907.

(11) (a) Reddy, C. K.; Davaagayaraj, A.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 4495–4498. (b) Jones, P.; Knochel, P. *J. Chem. Soc., Perkin. Trans. 1* **1997**, 3117–3118. (c) Jones, P.; Reddy, C. K.; Knochel, P. *Tetrahedron* **1998**, *54*, 1471–1490.

(12) (a) Rappoport, Z.; Gazit, A. *J. Org. Chem.* **1985**, *50*, 3184–3194. (b) Jubert, C.; Knochel, P. *J. Org. Chem.* **1994**, *59*, 1053–1057 and literature cited therein.

(13) Synthesized from trimethylsilylmethylolithium (TMSMLi) and the corresponding iodide. See also footnote 4.

(14) Rozema, M. J.; Sidduri, A.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956–1958.

(15) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. J. *J. Org. Chem.* **1988**, *53*, 2390–2392.

Table 3. Conjugate Addition of Functionalized Diorganozinc Compounds

3a: R¹ = Ph
3c: R¹ = COOMe

entry	nitroolefin	R ²	yield, %	product
1	3a	CN	67	9a
2	3c	CN	66	9b
3	3c	COOEt	53	9c

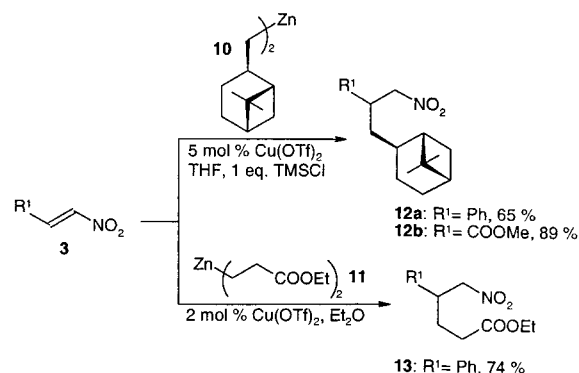
display a higher reactivity toward many electrophiles. It has been reported earlier that a wide variety of functionalized diorganozinc compounds can be easily prepared via boron–zinc transmetalation.^{8,16} Diorganozinc compounds such as dimyrtanylzinc **10** or bis[2-(ethoxycarbonyl)ethyl]zinc **11**¹⁷ can be efficiently added to nitroolefins in a copper-catalyzed conjugate addition reaction (Scheme 3), providing access to more complex molecules **12** and **13**.

In summary, we have shown that alkyl(trimethylsilyl)zinc compounds (TMSMZnR) can be successfully added to aliphatic and aromatic nitroolefins affording the corresponding nitro compounds in moderate to good yields. A catalytic amount of copper(I) salt in the reaction medium prevents the formation of ipso-substituted product.

(16) Langer, F.; Schwink, L.; Devasagayaram, A.; Chavant, P.-Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229–8243.

(17) For synthesis of 1-trimethylsilyloxy-1-ethoxycyclopropane, see: Rühlmann, K. *Synthesis* **1971**, *5*, 236–253.

Scheme 3. Conjugate Addition of Diorganozinc Compounds



Synthetically versatile functionalized nitro compounds have been synthesized by conjugate addition of functionalized diorganozinc cuprates ($RZnCu(CN)R$) and diorganozinc compounds (R_2Zn) to nitroolefins.

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Supporting Information Available: Full experimental procedures, yields, and the physical and spectroscopic data of the synthesized compounds (¹H NMR, ¹³C NMR, MS, IR, microanalyses). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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