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TETRAHEDRON: *ASYMMETRY*

Enantioselective copper(I) catalyzed 1,4-addition of diethylzinc to nitroolefins

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Abstract

The asymmetric 1,4-addition of diethylzinc to nitroolefins is efficiently catalyzed by copper(I) complexes with BINOL based phosphoramidite ligands.

Many attempts have been undertaken to achieve an asymmetric 1,4-addition to α,β-unsaturated carbonyl compounds. Organocuprates,[1,2] organomagnesium,[3–6] organoaluminum[7,8] or organozinc[9] compounds have been investigated. The conjugate addition of dialkylzinc compounds to enones is a well-established preparative method. Primary diorganozincs are unreactive in most solvents towards α,β-unsaturated ketones (e.g. cyclohexenone or chalcone),[10] but react smoothly in the presence of catalytic amounts of Cu(I) salts and further additives [HMPA, TMEDA, $P(OR)_3$].[11–15] Asymmetric induction is frequently observed with homochiral Ni(II)[16–21] or Cu(I) catalysts.[22–27] However, in most cases satisfactory enantioselectivities with respect to a broader range of substrates have not been achieved. While some catalytic systems are successful mainly for cyclic enones, others are more successful in acyclic systems.[16–27]

We recently reported on the asymmetric Cu(I) catalyzed 1,4-addition of diethylzinc to 2-cyclohexenone in the presence of chiral sulfonamides.[28] The anion of the copper(I) salt significantly influences the topicity of the 1,4-addition. Such a reversal of the asymmetric induction, depending on the achiral counterion of Cu(I), has also been observed in a similar case[29] and hints towards structural differences between the catalytically active complexes. However, the enantioselectivity of this catalytic system still remains insufficiently high.

Binaphthol based homochiral phosphoramidite–copper complexes have recently been reported by Feringa et al.[30,31] and Pfaltz et al.[32] to catalyze the 1,4-addition of diorganozincs both to cyclic and acyclic α,β-unsaturated ketones with remarkable enantioselectivity. Two phosphoramidite ligands are assumed to be co-ordinated to the copper(I) ion in the catalytically active complex.[31]

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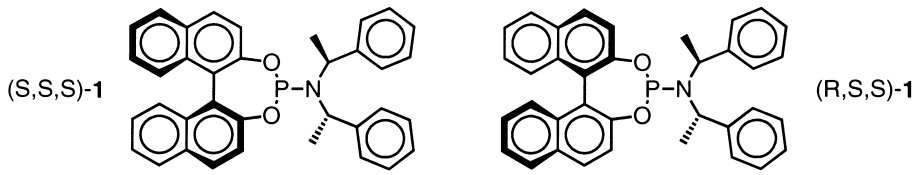
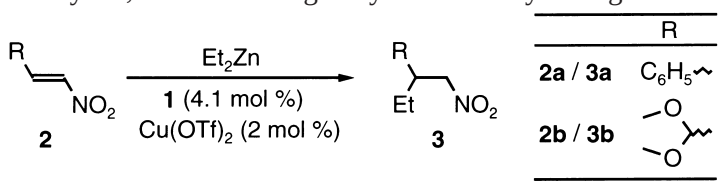


Nitroolefins are powerful Michael acceptors and are readily available, e.g. by the Henry nitroaldol reaction.[33] Nitrostyrene smoothly reacts with diethylzinc in the presence of Cu(I) salts and phosphites.[15] A highly enantioselective 1,4-addition of dialkylzinc compounds to nitrostyrene derivatives in the presence of 1.2 equivalents of a titanium TADDOLate as a chiral Lewis acid has been described by Seebach et al.[34] We investigated[†] the Cu(I) catalyzed addition of diethylzinc to nitroolefins in the presence of the chiral catalyst **1**, which was originally described by Feringa et al.[30]



The copper(I) species is conveniently prepared in situ from $Cu(OTf)_2$. We found that the addition proceeds in some cases with acceptable to excellent enantioselectivity (up to 86%) and yields (up to 84% isolated yield). The reaction is both temperature and solvent dependent. The best results for substrate **2b** have been obtained in toluene at −30°C. The catalyst (*R,S,S*)-**1** containing *R*-BINOL and (*S,S*)-bis(1-phenylethyl)amine represents the matched pair for additions to **2b** (Table 1, entries 6–9 versus 15–17).

The target molecules **3** are highly versatile intermediates. The nitro group can, for instance, easily be reduced to an amino group, e.g. by transfer hydrogenation.[35] Consequently, this protocol is part of a projected new modular synthetic route towards a catalytic asymmetric synthesis of β^2-homoamino acids[36] or the corresponding aldehydes. As organozinc reagents tolerate a broad variety of functional groups (e.g. esters, acetals, etc.), multifunctional derivatives can be obtained.

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[†] Illustrative procedure for the catalytic conjugate addition: A solution of 0.02 equiv. $Cu(OTf)_2$ and 0.041 equiv. **1**[30,31] in 25 ml of the solvent given in Table 1 is stirred for 1 h under argon atmosphere. The solution is cooled to the reaction temperature given in Table 1 and 1.5 equiv. diethylzinc and a solution of 1.0 equiv. of the nitroolefin **2** in 5 ml solvent are added consecutively. The reaction mixture is stirred for 3 h at the reaction temperature given in Table 1 and is subsequently quenched by addition of 10 ml saturated NH_4Cl solution. The organic layer is separated after warming to room temperature, the aqueous layer is extracted twice, and the organic layers are pooled and dried. Conversion and enantiomeric purity are analyzed by GC–MS (HP5-MS) and GC (Macherey–Nagel, Lipodex E, 50 m), respectively. Analytically pure **3b** was obtained after Kugelrohr distillation (bp 100°C, 0.2 torr). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.91 (t, J 7.2, 3H); 1.20–1.68 (m, 2H); 2.41 (m, 1H); 3.32 (s, 3H); 3.34 (s, 3H); 4.24 (d, J 5.4, 1H); 4.24 (dd, J 13.0, 7.4, 1H); 4.48 (dd, J 13.0, 5.8, 1H).

Table 1
Asymmetric Cu(I) catalyzed addition of diethylzinc to nitroolefins **2**

Entry	Ligand	Nitroolefin	Solvent	T [°C]	Conversion [%]	ee [%]	Isomer
1.	(*R,S,S*)-**1**	**2a**	Toluene	-78	90	48	S ‡
2.	(*S,S,S*)-**1**	**2a**	Ether	-15	80	32	S ‡
3.	(*S,S,S*)-**1**	**2a**	Ether	-78	80	39	S ‡
4.	(*R,S,S*)-**1**	**2b**	Ether	-78	50	68	(-)
5.	(*R,S,S*)-**1**	**2b**	Ether	-15	90	31	(-)
6.	(*R,S,S*)-**1**	**2b**	Toluene	-78	95	80	(-)
7.	(*R,S,S*)-**1**	**2b**	Toluene	-30	100	86	(-)
8.	(*R,S,S*)-**1**	**2b**	Toluene	-15	95	78	(-)
9.	(*R,S,S*)-**1**	**2b**	Toluene	0	100	64	(-)
10.	(*S,S,S*)-**1**	**2b**	Pet. ether	-78	90	16	(-)
11.	(*S,S,S*)-**1**	**2b**	THF	-78	85	35	(-)
12.	(*S,S,S*)-**1**	**2b**	Ether	-78	60	50	(-)
13.	(*S,S,S*)-**1**	**2b**	Ether	-15	85	11	(+)
14.	(*S,S,S*)-**1**	**2b**	Ether	0	80	26	(+)
15.	(*S,S,S*)-**1**	**2b**	Toluene	-78	50	6	(-)
16.	(*S,S,S*)-**1**	**2b**	Toluene	-15	100	16	(-)
17.	(*S,S,S*)-**1**	**2b**	Toluene	0	100	13	(-)

‡ Assignment of the absolute configuration by comparison of the retention behaviour in the gas chromatographic resolution on a Macherey-Nagel Lipodex E column with data given in ref. [34].

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