



Enantioselective copper(I) catalyzed 1,4-addition of diethylzinc to cyclohexenone: asymmetric induction as an unexpected source of structural information ^{†,‡}

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Abstract: The conjugate addition of diethylzinc to cyclohexenone in the presence of catalytic amounts of homochiral sulfonamides and different copper(I) salts has been examined. The anion of the copper(I) salt significantly influences the topicity of the 1,4-addition. With the same absolute configuration of the chiral catalyst, CuCN favours formation of R-3-ethylcyclohexanone, while the S-configured product predominates for all other copper(I) salts used. This clearly hints towards structural differences between the catalytically active complexes. © 1997 Elsevier Science Ltd

The conjugate addition of organometallics to α,β -unsaturated carbonyl compounds is a well-established preparative method. Many auxiliary-controlled reactions as well as syntheses using stoichiometric amounts of chiral reagents belong to the standard repertoire of synthetic chemistry, while recently more and more catalytic variants have been investigated. Organocuprates,¹ organomagnesium,² organoaluminum³ or organozinc⁴ compounds are applied; asymmetric induction frequently is observed with homochiral Ni^{II}-⁵ or Cu^I-catalysts.⁶ Information on the structure of the reactive intermediate is a prerequisite for the transition from empirical to rational design of homochiral ligands. For example, the structures of organolithium cuprates and, in this context, the role of the cyanide anion in 'higher order' cyanocuprates have been the controversial issue of enthusiastic discussions.⁷

Primary diorganozincs are unreactive in most solvents towards α,β -unsaturated ketones (e.g. cyclohexenone or chalcone).⁸ However, the uncatalyzed conjugate addition of these compounds to acceptor substituted cyclic or acyclic double bond systems is achieved in good yields using N-methylpyrrolidinone (NMP) as a cosolvent.⁹ Diorganozincs smoothly react with enones in the presence of catalytic amounts of Cu^I-salts and further additives (HMPA, TMEDA, etc.).¹⁰ The Cu^I-catalyzed 1,4-addition of diethylzinc to 2-cyclohexenone was described recently to proceed only after addition of catalytic amounts of N-monosubstituted sulfonamides.¹¹ Binaphthol based homochiral phosphoramidite-copper-complexes are reported to catalyze the 1,4-addition of diorganozincs both to cyclic and acyclic α,β -unsaturated ketones with remarkable enantioselectivity.¹²

We examined the Cu^I-catalyzed 1,4-addition of diethylzinc in the presence of the enantiomerically pure sulfonamides **1** and confirmed that both catalysts are necessary for an efficient reaction. No conversion is observed on omission of one of the catalytic components. In contrast, when both a Cu^I-salt and **1** are present (2–10 mol%), complete consumption of the starting material usually is observed within 2 h at 0°C. The product is formed regioselectively, the corresponding 1,2-adduct cannot be detected by GC-MS.

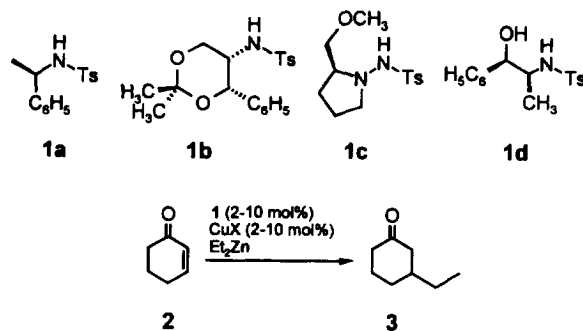
Diethyl ether and toluene are suitable solvents; however, the stereoselectivity is better in the former. In THF only racemic mixtures are obtained in all cases examined. With all homochiral sulfonamides

[†] Dedicated to Prof. Dr Peter Welzel on the occasion of his 60th birthday.

[‡] Key words: catalytic asymmetric synthesis, conjugate addition, diethylzinc, copper(I) salts, sulfonamides.

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(e.g. **1a–1d**) used until now the ee values did not exceed 32%. However, most protocols for Cu^I- or Ni^{II}-catalyzed 1,4-addition of diethylzinc describe an eminent dependence of the enantioselectivity on the substrate (cyclic vs. acyclic enone).¹³



The most remarkable finding, however, is that for the same absolute configuration of the sulfonamide **1a** the topicity of the conjugate addition and the ee values strongly depend on the Cu^I-salt. While with all Cu^I-halogenides, CuOTf, and CuSPh the *si*-face addition predominates in the presence of (**R**)-**1a** (Table 1, Nos 7–13), the *re*-face addition is favoured with all reagents based on (**R**)-**1a** and CuCN (Table 1, Nos 1–6). Such a reversal of the asymmetric induction, depending on the achiral counterion of Cu^I has not yet been observed to this extent. This finding indicates a change in mechanism or in the structure of the reactive species.¹⁴ We conclude from the experimental data, that mixed Cu^I/Zn^{II}-complexes with different structures are involved, depending on the application of CuCN or another Cu^I-salt. Moreover, dimeric or oligomeric complexes are feasible in analogy to the alkylzinc carboxamide RZn[NR'(C=O)R''] chemistry.¹⁵ Presumably, the cyanide ion remains co-ordinated as an additional ligand in the reactive complex. The reversal of the topicity is not limited to ligand **1a**; it is also found with **1b** (Table 1, Nos 14 and 15), but not with the chelating ligand **1c** (Table 1, Nos 16 and 17). (1*R*,2*S*)-*N*-Tosylnorephedrine **1d** catalyzes the diethylzinc addition to cyclohexenone only in the presence of CuCN (Table 1, Nos 18–20).

Feringa et al.¹² assume for their catalytically active complex two phosphoramidite ligands to be co-ordinated to the copper ion. We found for our catalytic system that the yields and enantioselectivities observed do not depend significantly on the ratio CuX: ligand in the range between CuSPh:**1a**=1:3 and CuSPh:**1a**=5:1 (Table 1, Nos 8–10).

Solid state structures of organocuprates with the stoichiometry RCu(CN)M (e.g. M=Li, ZnX, ZnR) are unknown. In analogy to 'lower order' organolithium cuprates,¹⁶ organozinc cuprates are mixed clusters of zinc and copper with the cyanide ion still being co-ordinated to copper. Noyori et al. postulate the analogous CuX¹⁷/*N*-benzyl benzenesulfonamide catalyzed 1,4-addition of ZnR₂ to proceed via a mixed metal complex RZn(NR*SO₂Ar)CuR, where the sulfonamide connects both metal centres as a bridging ligand (N,O) and Cu is co-ordinated by the sulfonyl oxygen. This hypothesis seems to be plausible but has to be modified for the cuprous cyanide case. This active complex (catalytic conditions: excess diethylzinc) can be described in structural analogy to the 'higher order' organolithium cuprates^{7a,g,h} as an organozinc cuprate with the stoichiometry RZn(NR*SO₂Ar)CuR(CN)(ZnR).¹⁸

No conversion is observed on stoichiometric application of CuX:**1a** (Et₂Zn:CuCN:**1a**:**2**=1:1:1:1; Table 2, No. 1). The species EtZnL (LH=**1a**) is obviously not capable of transferring the remaining ethyl group to the cuprous ion or the substrate. With the ratio Et₂Zn:CuCN:**1a**:**2**=2:1:1:1 the reaction is slowed down considerably compared to the catalytic protocol (Table 1, No. 6; Table 2, No. 2). Only low conversion is obtained for a ratio Et₂Zn:CuCN:**1a**:**2**=3:1:2:1 with negligible selectivity (Table 2, No. 3). Similar results are obtained with CuSPh (Table 2, Nos 4 and 5).

However, the complexity of the reaction and the possibility of intermediary equilibria between monomeric, dimeric, and higher aggregated species do not allow to draw a conclusive structure of the catalytic species based on the present data. Further investigations are in progress.

Table 1. Selected experimental data of the catalytic reaction [standard reaction time 2 h, diethyl ether]

No.	1	CuX	mol % CuX	CuX:1	T [°C]	Yield [%]	ee [%]
1.	1a	CuCN	5.8	1:1	-15	53	25 R
2.	1a	CuCN	6.6	1:1	-5	58	20 R
3.	1a	CuCN	5.6	1:1	0	80	30 R
4.	1a	CuCN	9.3	1:1	+5	64	19 R
5.	1a	CuCN	3.6	1:1	+20	66	17 R
6.	1a	CuCN	8.7	1:1	0	81	30 R
7.	1a	CuOTf	9.3	1:1	0	77	16 S
8.	1a	CuSPh	3.1	1:3	0	68	18 S
9.	1a	CuSPh	9.3	1:1	0	84	22 S
10.	1a	CuSPh	1.9	5:1	0	82	21 S
11.	1a	CuI	5.2	1:1	0	28	12 S
12.	1a	CuCl	5.9	1:1	0	6	6 S
13.	1a	CuCl/ LiCl	5.9	1:1	0	63	13 S
14.	1b	CuCN	8.5	1:1	0	47	12 S
15.	1b	CuOTf	2.8	1:2	0	20	15 R
16.	1c	CuCN	10.6	1:1	0	54	25 R
17.	1c	CuSPh	13.0	1:1	0	80	24 R
18.	1d	CuCN	7.2	1:1	0	26	31 R
19.	1d	CuSPh	9.3	1:1	0	1	-
20.	1d	CuSPh	9.3	1:3	0	0	-

Table 2. Selected experimental data of the stoichiometric reaction [ligand 1a, the concentrations of 1a are comparable to the catalytic protocol: 0.005 M (Nos 2 and 3), 0.006 M (Nos 4 and 5), diethyl ether]

No.	CuX	mol % CuX	t [min]	Et ₂ Zn:CuX:1a:2	Yield [%]	ee [%]
1.	CuCN	100	45	1:1:1:1	0	-
2.	CuCN	100	120	2:1:1:1	26	32 R
3.	CuCN	100	120	3:1:2:1	1	rac
4.	CuSPh	100	120	2:1:1:1	31	12 S
5.	CuSPh	100	120	3:1:2:1	27	rac

Experimental

Illustrative procedure for the catalytic conjugate addition: Cu^I-salt (0.06–0.3 mmol) and ligand 1 (0.06–0.3 mmol) are stirred at r.t. under argon atmosphere in 40 ml abs. diethyl ether for 1 h. Diethylzinc (4.0 mmol, 1.0 M solution in hexane) is added at 0°C, after stirring for 1 h at 0°C cyclohexenone (3.0 mmol) is added. After 2 h at 0°C the reaction is quenched with 5 ml satd. ammonium chloride solution. All reactions were performed under standard conditions (reaction time) to safeguard comparable results. Relatively poor yields in some cases are mainly the consequence of incomplete conversion. Chemical yields and ee values were determined by GC (Shimadzu GC-8A, Macherey–Nagel chiral column Lipodex E, 50 m, isothermic, 110°C) with internal standard (dodecane). The absolute configuration was verified after derivatization with homochiral 1,2-diphenylethylenediamine by ¹³C-NMR-spectroscopy.¹⁹

Acknowledgements

This project was funded by Deutsche Forschungsgemeinschaft (grants Se 609/2–4, 2–5), BASF AG (PhD fellowship to V.W.), and Fonds der Chemischen Industrie which is gratefully acknowledged.

The gas chromatograph (Shimadzu GC-8A) used for chiral GC analysis was a gift from Bayerisches Landeskriminalamt.

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(Received in UK 6 February 1997)