Synthetic Methods

DOI: 10.1002/anie.200501732

Asymmetric Conjugate Addition of Organozinc Compounds to α,β-Unsaturated Aldehydes and Ketones with [2.2]Paracyclophaneketimine Ligands without Added Copper Salts**

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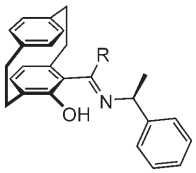
Dedicated to Professor Henri B. Kagan on the occasion of his 75th birthday

Asymmetric catalysis has established itself as a versatile method in modern synthetic chemistry. In particular, many transformations with almost complete enantioselectivity are possible today through the use of chiral ligands. One example is the conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds, especially to ketones.[1] In the presence of copper additives different ligand systems give almost complete stereocontrol. The copper ions influence the electronic properties of the carbonyl group, they determine which alkyl or aryl residues are transferred, and they act as bridging units in the transition state.[2,3] As an extension of the non-enantioselective copper-free 1,4-addition to α,β-unsaturated aldehydes described previously by Knochel et al.,[4] we present here for the first time a highly enantioselective copper-free variant.



(R_p,*S*)-**1a**: R = Me
(R_p,*S*)-**1b**: R = Ph

Over the last few years we have been able to demonstrate that readily accessible, configurationally stable, planar and centrochiral ketimines **1** with a [2.2]paracyclophane framework[5] are highly suitable for the asymmetric addition of alkyl[6] and alkenyl residues[7] to aliphatic aldehydes. In addition, these ligands have proved to be useful in the addition of alkyl[8] and aryl residues[9] to *N*-acylimines.

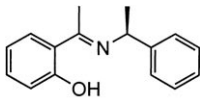
Since the addition to *N*-acylimines is comparable to a conjugate addition, we postulated that α,β-unsaturated aldehydes and ketones could also be suitable as substrates. Therefore different α,β-unsaturated aldehydes were tested under standard reaction conditions (2 mol% ligand **1**, 4 equiv $ZnEt_2$ or 2 equiv diisopropylzinc, −20 °C) (Table 1, entries 1–7). Unlike all previously described ligands,[10] the ketimines **1** also transformed α,β-unsaturated aldehydes **2** into the respective 1,4-addition products **3** in a highly enantioselective manner. This even takes place with a relatively small amount of catalyst, 2 mol%, without the addition[11] of compounds having a soft metal center (copper, nickel, or indium[12]). The 1,2-addition products **4** were also formed in most cases, but with only moderate enantioselectivity. The reason is that with α,β-unsaturated aldehydes, unlike, for example, benzaldehyde,[13] the uncatalyzed reaction also takes place. Other ligands (dimethylaminoethanol, 3-*exo*-(dimethylamino)isoborneol (DAIB)) gave, as described in the literature,[10] only 1,2-addition products **4**.

The ratio between 1,2- and 1,4-addition was temperature dependent: low temperatures increased the proportion of the more thermodynamically favorable 1,4 products. However, the reaction rate dropped to such an extent that a compromise between acceptable reaction rate and selectivity had to be found.

In the addition of diethylzinc to cinnamaldehyde (**2a**, entries 1–3 in Table 1) or its derivatives *o*-methoxycinnamaldehyde (**2b**, entry 5) and *p*-chlorocinnamaldehyde (**2c**, entry 6) and also 3-thiophen-3-yl-propenal (**2d**, entry 7) the yield of the 1,4 product was as high as 52% with enantiomeric excesses of between 96 and 98% *ee*. Better regioselectivity was obtained with 6-methoxy-2,2-dimethyl-2*H*-chromene-3-carbaldehyde (**2e**) after 62 h at 0 °C. Here both (S_p,*S*)-**1a** (Table 1, entry 9) and (R_p,*S*)-**1a** (entry 8) gave the 1,4 product in 78–80% yield and 97 and 96% *ee*, respectively. In both cases the *syn* diastereomers were formed preferentially (74% *de* with (S_p,*S*)-**1a**, 77% *de* with (R_p,*S*)-**1a**), which was confirmed by NOE experiments. The addition of diisopropylzinc to cinnamaldehyde (**2a**) was also successful; the 1,4 product was formed with a yield of 39% at 91% *ee* (entry 4).

Whereas in the 1,4-addition to aldehydes temperatures of −20 °C (or 0 °C) are of advantage for selectivity reasons, 1,4-additions to ketones such as benzylideneacetone (**2f**) and 3-octen-2-one (**2g**) can be carried out at room temperature (Table 1, entries 10–12). The 1,2-addition products were never formed as by-products, only the corresponding aldol addition products. However, in the case of benzylideneacetone their fraction could be reduced from 15 to 5% by increasing the amount of ligand from 2 to 4 mol% (Table 1, entries 10 and 11). The enantioselectivities varied between 73 and 90% *ee* for the ketones. Ketones were also successfully reacted with diisopropylzinc (see the Supporting Information).

The diastereomeric ketimine ligands (S_p,*S*)-**1a** and (R_p,*S*)-**1a** led in each case to the complementary main enantiomers of the 1,4- and 1,2-addition products. This pivotal influence of the planar chirality on product configuration confirms previous investigations on 1,2-additions to saturated aldehydes, which also indicated the strongly dominating effect of the planar chirality as opposed to the centrochirality of the ligands.[14]



(*S*)-**5**

The nonplanar analogue **5** of the paracyclophaneketimine ligand **1** also catalyzed conjugate addition, albeit

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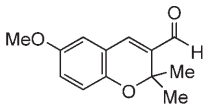
[**] This research was supported by the Fonds der Chemischen Industrie. We thank Alexander Tung-Qiang Wong and Jens Adler for their contributions to the experimental work.

Supporting information for this article is available on the web under http://www.angewandte.com or from the author.

Table 1: Asymmetric conjugate addition of diethylzinc and diisopropylzinc to aldehydes and ketones.

2a–e → **3a–e** (1.4-Addition) + **4a–e** (1.2-Addition)

a: R^1 = Ph; R^2 = H
b: R^1 = *o*-$MeOC_6H_4$; R^2 = H
c: R^1 = *p*-ClC_6H_4; R^2 = H
d: R^1 = 3-C_4H_3S; R^2 = H



2e

Entry	Substr.	Variant[a]	R	*T* [°C]	Ligand	1,4 Product		1,2 Product	
						Yield [%][b]	*ee* [%][c]	Yield [%][b]	*ee* [%][c]
1	**2a**	B[f]	Et	−20	(R_p,*S*)-**1a**	43	98(*S*)	23	69
2	**2a**	B[f]	Et	−20	(S_p,*S*)-**1a**	36	99(*R*)	37	58
3	**2a**	B[f]	Et	−20	(S_p,*S*)-**1b**	46	97(*R*)	38	53
4	**2a**	D[f]	*i*Pr	−20	(S_p,*S*)-**1a**	39	91	22	n.d.[d]
5	**2b**	B[f]	Et	−20	(S_p,*S*)-**1a**	52	97	13	n.s.[e]
6	**2c**	A[f]	Et	−20	(S_p,*S*)-**1a**	42	96	34	57
7	**2d**	A[f]	Et	−20	(R_p,*S*)-**1a**	45	99	31	50
8	**2e**	C	Et	0	(R_p,*S*)-**1a**	80	96	4	n.d.[d]
9	**2e**	C	Et	0	(S_p,*S*)-**1a**	78	97	12	n.d.[d]
10	**2f**	E[g]	Et	RT	(S_p,*S*)-**1a**	85	87(*R*)	–	–
11	**2f**	E[g,h]	Et	RT	(S_p,*S*)-**1a**	95	90(*R*)	–	–
12	**2g**	E[g]	Et	RT	(S_p,*S*)-**1a**	88	73	–	–

[a] See Experimental Section for details. [b] Determination by GC on an achiral stationary phase (HP1). [c] Determination by GC on a chiral stationary phase (CP-Chirasil-Dex for entries 1–8 and 11; Lipodex E for entries 9 and 10). [d] n.d. = not determined. [e] n.s. = no separation of enantiomers on chiral stationary phase. [f] The condensation product of the 1,2 product was also identified by GC-MS. [g] The aldol products were formed as by-products. [h] Amount of catalyst used: 4 mol%.

with a poorer ratio of 1,2- to 1,4-addition products and lower enantioselectivities. The reaction of cinnamaldehyde (**2a**) at −20 °C gave the 1,2 and 1,4 products in a ratio 2.3:1 (with 17% *ee* for the 1,4 product and 4% *ee* for the 1,2 product).

Here the first copper-free[11] asymmetric 1,4-addition of diethylzinc or diisopropylzinc to α,β-unsaturated aldehydes and ketones has been described. This methodology supplements the spectrum of synthetic methods for β-chiral aldehydes and ketones.[15] The application to the synthesis of biologically active compounds and the extension of the substrate spectrum represents further objectives of our investigations.

Experimental section

Variant A: The ligand (0.01 mmol) and the aldehyde (0.5 mmol) were placed in a 10-mL flask. The reaction vessel was purged with argon and cooled to −20 °C before a solution of diethylzinc (1M in toluene or hexane; 1 mL, 1 mmol) was added. The reaction mixture was stirred for 24 h at this temperature before more diethylzinc solution (1 mL) was added. The reaction mixture was then stirred at −20 °C for 38 h, warmed to room temperature, and stirred for a further 24 h. The reaction was quenched by the addition of semisaturated ammonium chloride solution (3 mL). The reaction mixture was treated with diethyl ether, filtered, and separated in a separating funnel. The organic phase was washed three times with deionized water and dried over magnesium sulfate. GC chromatograms were recorded for these solutions. The solution was then concentrated under reduced pressure, and the regioisomers were separated by column chromatography on silica 60 (eluent: cyclohexane/ethyl acetate).

Variant B: The same as variant A but the twice the quantities were used.

Variant C: The same as variant A, but the reaction was carried out at 0 °C (62 h) and not warmed to room temperature.

Variant D: The ligand (S_p,*S*)-**1a** (0.01 mmol) and cinnamaldehyde (0.5 mmol) were mixed. The reaction vessel was purged with argon and cooled to −20 °C before a solution of diisopropylzinc (1M in toluene; 1 mL, 1 mmol) was added. The reaction mixture was then stirred for 62 h at −20 °C before the reaction was quenched by the addition of semisaturated ammonium chloride solution (3 mL) and worked up as in variant A.

Variant E: (S_p,*S*)-**1a** (0.01 mmol) and the ketone (0.5 mmol) were placed in a 10-mL flask. The reaction vessel was purged with argon before diethylzinc or diisopropylzinc solution was added (1M in hexane or toluene; 1 mL, 1 mmol). After 62 h stirring at room temperature the reaction was quenched by the addition of semisaturated ammonium chloride solution (3 mL) and worked up as in variant A.

Received: May 19, 2005
Revised: August 17, 2005
Published online: November 17, 2005

Keywords: aldehydes · asymmetric catalysis · conjugate additions · cyclophanes · zinc

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[11] According to ICPMS measurements the copper content of the commercial diethylzinc solutions used is (50 ± 5) μM or less. This gives a ligand/copper ratio of at least 100:1 and a zinc/copper ratio of at least 20000:1. We assume that these copper ions do not play any role in the catalyst cycle since other catalysts show no cuprate-like behavior. We thank Dr. Zsolt Berner, Institut für Mineralogie und Geochemie der Universität Karlsruhe (TH), for carrying out these measurements.
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