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Highly Enantioselective Catalytic Conjugate Addition and Tandem Conjugate Addition - Aldol Reactions of Organozinc Reagents**

Ben L. Feringa,* Mauro Pineschi, Leggy A. Arnold, Rosalinde Imbos, and André H. M. de Vries

*Dedicated to Professor D. Seebach
on the occasion of his 60th birthday*

Although efficient catalysts for a number of asymmetric carbon - carbon formations are known to date,^[1] a highly enantioselective catalytic version of the conjugate addition of organometallic reagents to enones is lacking.^[2] Recently chiral catalysts based on Cu^I, Ni^{II}, Zn^{II}, or Co^{II} complexes of a variety of ligands have shown enantioselectivities up to 90 % in 1,4-additions of Grignard, organolithium, or dialkylzinc reagents.^[3] The results so far have not revealed, however, the key elements for realization of complete stereocontrol but do reveal the rather complex nature of some of these chiral catalytic systems.^[4] Previously we have demonstrated that copper complexes of chiral phosphorus amidites show relatively high *ee* values for the 1,4-adducts of R₂Zn reagents and acyclic as well as cyclic enones.^[5]

In this communication both the first catalytic asymmetric 1,4-addition reactions of organometallic reagents with complete

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stereocontrol and highly enantioselective tandem conjugate addition-aldol reactions are reported. In our design of a catalytic asymmetric 1,4-addition the following aspects were considered: a) Can very efficient ligand-accelerated catalysis^[6] be achieved? b) Is it possible to use an enone and an olefin [Eq. (a)] as starting material? c) Are functional groups tolerated?

The remarkable ligand effect of binaphthol-derived phosphorus amidites on the copper-catalyzed 1,4-addition of Et_2Zn to enones^[5] was explored by a modular variation of the binaphthyl and amine moieties in these ligands. Much to our delight the incorporation of two chiral structural units, that is, the sterically demanding (*R,R*)-bis(1-phenylethyl)amine and unsubstituted (*S*)-2,2'-binaphthol (as present in C_2 symmetric ligand **1**), resulted in a *matched* combination^[7] and a highly selective catalyst for the addition of Et_2Zn to cyclohexenone (Scheme 1). Thus the catalyst prepared from $\text{Cu}(\text{OTf})_2$

Scheme 1. Enantioselective 1,4-addition of Et_2Zn to **2**, catalyzed by $\text{Cu}(\text{OTf})_2/\mathbf{1}$. Tf = trifluoromethane sulfonate.

(2 mol %) and **1** (4 mol %) provided (*S*)-**4a** in 94 % yield and an *ee* value greater than 98 %. Excellent yields and enantiomeric excesses ranging from 94 to greater than 98 % are obtained for cyclohexenone and substituted cyclohexenones with a variety of zinc reagents (Table 1).^[8] Having realized complete stereocontrol in the formation of a number of 3-substituted cyclohexanones **4** (Table 1, entries 1, 4 - 7),

Table 1. Enantioselective 1,4-additions of dialkylzinc compounds to enones, catalyzed by $\text{Cu}(\text{OTf})_2/\mathbf{1}$ [a].

Entry	Enone	R_2Zn	1,4-Adduct	Yield [%] [b]	<i>ee</i> [%] [c]
1	2a	3a	4a	94	> 98[d]
2	2b	3a	4b	75	10
3	2c	3a	4c	82	53
4	2d	3a	4f	74	> 98[d]
5	2e	3a	4h	93	> 98[d]
6	2a	3b	4d	72	> 98[d]
7	2d	3b	4g	68	> 98[d]
8	2a	3c	4e	95	95
9	2a	3d	4i	95	94
10	2a	3e	4j	53	95
11	2a	3f	4k	77	95
12	2a	3g	4l	91	97
13	2a	3h	4m	87	93

[a] Reaction conditions as in ref. [5]. [b] Yields of isolated products. [c] Determined by ^{13}C NMR spectroscopy after derivatization with 1,2-diphenyl ethylenediamine [5, 16]. [d] (*S*)-**4** could not be detected.

we examined catalytic 1,4-additions of diheptyl zinc (**3c**) and functionalized dialkylzinc reagents (**3e-3h**).^[9] The R_2Zn reagents were prepared from the corresponding alkenes by hydroboration and subsequent zinc exchange according to Knochel^[10,11] or with the corresponding Grignard reagent (Table 1, entry 9). Again excellent enantioselectivities were achieved (Table 1, entries 8-13). It is particularly noteworthy that the new catalyst tolerates ester and acetal functionalities. So far the catalyst based on $\text{Cu}(\text{OTf})_2/\mathbf{1}$ does not show satisfactory enantioselectivities for five- and seven-membered cyclic enones (Table 1, entries 2,3). For these substrates further ligand tuning is required.

A possible pathway for the 1,4-addition could involve transfer of an alkyl fragment from R_2Zn to the copper complex,^[11] followed by π -complexation of the resulting copper alkyl species to the double bond of the enone^[12] and of the alkyl zinc ion to the enone carbonyl (Scheme 2). Next alkyl transfer to the β -position of the enone generates alkylzinc enolate **5**, which upon protonation provides cyclohexanone **4**.

Scheme 2. Postulated catalytic cycle of the 1,4-addition.

It is anticipated that the zinc enolate **5**, resulting from the conjugate addition, might be trapped by an aldehyde in a subsequent aldol reaction.^[13] The regio- and enantioselective catalytic three-component coupling was indeed achieved with

Table 2. 1,4-Additions of dialkylzinc compounds and subsequent aldol reactions of the zinc enolates **5**.

Entry	Lewis acid[a]	t[min] (T/°C)	Products	<i>erythro:threo</i> 6a-h:7a-h	Yield [%][b]	ee[%][c]
1		10 (-30)	6a/7a	31:69	88	95
2		10 (-30)	6b/7b	38:62	85	93
3	BF ₃ · Et ₂ O	3 (-30)	6b/7b	46:54	78	92
4	ZnCl ₂ · Et ₂ O	3 (-20)	6e/7e	54:46	64	91
5		10 (-20)	6e/7e	38:62	67	91
6	BF ₃ · Et ₂ O	3 (-20)	6f/7f	52:48	82	> 99
7	ZnCl ₂ · Et ₂ O	10 (-30)	6c/7c	32:68[d,e]	88	91
8		10 (-30)	6d/7d	44:56[e]	92	95
9	ZnCl ₂ · Et ₂ O	30 (-30)	6g/7g	65:35[e]	81	97
10	ZnCl ₂ · Et ₂ O	10 (-30)	6h/7h	48:52[d,e]	75	97

[a] 1.0 equiv of Lewis acid added. [b] Yields of isolated, pure aldols. [c] See *Experimental Section* for the determination of the *ee* values. [d] An unseparable mixture of aldols was obtained. [e] The relative configuration (*erythro:threo*) has not been established.

in situ generated enolate (**5**). For example, when enolate **5**, formed from **2** and diethylzinc in the presence of Cu(OTf)₂ (1.2 mol %) and ligand **1** (2.4 mol %), was treated with benzaldehyde at -30°C for 10 min, an approximately 3:7 mixture of *trans,erythro*-**6a** and *trans,threo*-**7a** was obtained in 88% isolated yield (Table 2, No. 1). The aldol products were readily separated by flash chromatography (SiO₂, 30 % ethyl acetate, 70 % hexanes) and oxidized to a single isomer of diketone **8a** with 95 % *ee*. The results shown in Table 2

indicate that other representative aldehydes undergo the tandem 1,4-addition - aldol reactions (in the presence or absence of Lewis acids) affording the corresponding *trans*-2,3-disubstituted cyclohexanones with enantioselectivities always exceeding 90 %. In all cases small amounts of copper catalyst (1.2 mol %) lead to clean zinc enolate formation, fast and regioselective aldol reactions and *trans*-vicinal disubstituted cyclohexanones are exclusively obtained. The relative and absolute stereochemistry of (-)-*trans-erythro*-**6b** was established to be 2*S*,3*S*,1'*S* on the basis of single crystal X-ray analysis.^[14] As far as we know this represents the first catalytic one-pot organozinc conjugate addition - enolate-trapping reaction that proceeds with high enantioselectivity.

The synthetic versatility of the new catalytic enantioselective C-C bond formation is further illustrated by the 1,4-addition of Et₂Zn to highly symmetrical dienone **10** readily obtained by oxidation of hydroquinone **9** (Scheme 3).^[15] In

Scheme 3. Catalytic enantioselective 1,4-addition of Et₂Zn to the dienone **10**.^[15]

view of the potential to use various zinc reagents, the multifunctional nature of **11**, and the short, highly selective, and efficient route from hydroquinone, this new method may allow a versatile entry to a variety of optically active cyclohexenones.

Experimental Section

1: The procedure for related phosphorus amidites [5] was followed except that *n*BuLi/THF was used instead of Et₃N/toluene in the second step: chromatography (SiO₂, hexane:CH₂Cl₂ 3:1), yield 40%, [α]_D = +456.0 (*c* = 0.79, CHCl₃). ¹H NMR: δ = 7.98–8.08 (m, 4H), 7.17–7.74 (m, 18H), 4.63 (q, *J* = 7.2 Hz, 2H), 1.85 (d, *J* = 7.2 Hz, 6H); ¹³C NMR (CDCl₃): δ = 150.2, 150.0, 149.6, 142.8, 132.8, 131.4, 130.5, 130.3, 129.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.1, 126.7, 126.0, 124.7, 124.5, 122.4, 52.3, 51.1, 21.8; ³¹P NMR: δ = 145.3.

6b/7b,8b: Typical procedure for the conjugate addition - enolate-trapping reactions with **2**: A solution of Cu(OTf)₂ (0.0045 g, 0.012 mmol) and **1** (0.013 g, 0.024 mmol) in toluene (5.0 mL) was stirred for 1 h at room temperature under nitrogen. The colorless solution was cooled at -30°C and **2** (0.097 g, 1.0 mmol) and ZnEt₂ (1.0 mL of a 1.1M solution in toluene) were added. After 18 h at -30°C *m*-bromobenzaldehyde (0.277 g, 1.5 mmol, freshly distilled) in toluene (1.0 mL) was added, and the reaction mixture was stirred for 10 min, quenched with saturated aqueous NH₄Cl (5.0 mL) and extracted with diethyl ether (2 × 30 mL). The combined organic layers were washed with brine (5.0 mL), dried over Mg(SO₄)₂, filtered, and evaporated to give a crude reaction product that was purified by flash chromatography (SiO₂, mixture of 20% ethyl acetate and 80% hexanes) to afford **6b** and **7b**. Yield of **6b**: 0.10 g, 32 %; solid with m.p. 81.4–82.8°C; [α]_D = -50.0 (*c* = 1.52, CH₂Cl₂); ¹H NMR (200 MHz, CDCl₃): δ 7.35–7.51 (m, 1H), 7.14–7.29 (m, 3H), 5.12 (t, *J* = 6.1 Hz, 1H), 3.31 (d, *J* = 6.3 Hz, 0H), 2.63 (dd, *J* = 6.8 and 4.9 Hz, 1H), 2.31–2.40 (m, 2H), 1.18–1.96 (m, 7H), 0.76 (t, *J* = 7.3 Hz, 3H). ¹³C NMR: δ = 214.8, 145.0, 130.3, 129.7, 129.5, 124.9, 71.9, 60.5, 41.5, 39.3, 27.5, 26.0, 23.0, 10.4. HRMS calcd for C₁₅H₂₀O₂ 232.1463; found 232.1464. Yield of **7b**: 0.164 g, 53%; oil; [α]_D = -23.0 (*c* = 1.14, CH₂Cl₂); ¹H NMR (200 MHz, CDCl₃): δ = 7.47 (br.s, 1H), 7.14–7.37 (m, 3H), 4.83–4.89 (m, 1H), 2.61 (dd, *J* = 7.8 and 4.64 Hz, 1H), 1.20–2.38 (m, 9H), 0.88 (t, *J* = 7.8 Hz, 3H); ¹³C NMR: δ = 215.0, 145.9, 130.1, 129.7, 128.9, 124.3, 71.1, 60.9, 41.8, 41.7, 27.9, 25.5, 25.2, 10.2; HR-MS calcd for C₁₅H₂₀O₂ 232.1463; found 232.1467.

To a mixture of **6b/7b** (0.031 g, 0.1 mmol) in CH₂Cl₂ (2.0 mL) were added molecular sieves (4 Å, 0.10 g) and PCC (0.043 g, 0.2 mmol) at 0°C. After 2 h stirring at room temperature, the reaction mixture was diluted with diethyl ether, filtered over Celite, and evaporated to dryness. Purification by chromatography (SiO₂, mixture of 10% ethyl acetate and 90% hexanes) provided pure **8b** (0.025 g, 81 %). The enantiomeric excess (93% *ee*) was determined by chiral HPLC [Regis (*R*, *R*)-Whelk-01 column, flow rate 0.5 mLmin⁻¹, 5 % *i*PrOH, 95% hexane, *T*_{ret} 34.5 min (3*S*, 2*R*), *T*_{ret} 37.2 min (3*R*, 2*S*)]. HPLC analysis of the recrystallized product (hexane) gave an *ee* value of >98%. M.p. 82.5–83.2°C. [α]_D = -26.4 (*c* = 0.25, CH₂Cl₂). ¹H NMR (200 MHz, CDCl₃): δ 7.98–8.00 (m, 1H), 7.65–7.77 (m, 2H), 7.29–7.37 (m, 1H), 4.09 (d, *J* = 9.5 Hz, 1H), 2.35–2.55 (m, 3H), 2.09–2.14 (m, 2H), 1.22–1.82 (m, 4H), 0.90 (t, *J* = 7.3 Hz, 3H). ¹³C NMR: δ = 208.2, 196.7, 138.9, 135.6, 130.9, 129.9, 126.4, 63.5, 41.9, 41.4, 27.7, 27.0, 23.9, 10.6. HRMS calcd for C₁₅H₁₇O₂Br 308.0411; found 308.0418.

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- [1] a) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, Weinheim, **1993**; b) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**; c) H.-U. Blaser, B. Pugin, F. Spindler in *Applied Homogeneous Catalysis with Organometallic Compounds, Vol. 2* (Eds.: B. Cornils, W. A. Herrmann), VCH, Weinheim, **1996**, p. 992.
- [2] Recent review: B. L. Feringa, A. H. M. de Vries in *Advances in Catalytic Processes, Vol. 1* (Ed: M. D. Doyle), JAI, CT, USA, **1995**, p. 151.
- [3] a) Q.-L. Zhou, A. Pfaltz, *Tetrahedron* **1994**, *50*, 4467; b) M. van Klaveren, F. Lambert, D. J. F. M. Eijkelkamp, D. M. Grove, G. van Koten, *Tetrahedron Lett.* **1994**, *35*, 6135; c) M. Spescha, G. Rihs, *Helv. Chim. Acta* **1993**, *76*, 1219; d) M. Kanai, K. Tomioka, *Tetrahedron Lett.* **1995**, *36*, 4275; e) K. Soai, T. Hayasaka, S. Ugajin, S. Yokoyama, *Chem. Lett.* **1988**, 1571; f) C. Bolm, M. Ewald, *Tetrahedron Lett.* **1990**, *31*, 5011; g) A. H. M. de Vries, J. F. G. A. Jansen, B. L. Feringa, *Tetrahedron* **1994**, *50*, 4479; h) A. H. M. de Vries, B. L. Feringa, *Tetrahedron: Asymmetry* **1997**, *8*, 1377.
- [4] An excellent review on recent progress in organocopper chemistry: N. Krause, A. Gerold, *Angew. Chem.* **1997**, *109*, 194; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 187.
- [5] a) A. H. M. de Vries, A. Meetsma, B. L. Feringa, *Angew. Chem.* **1996**, *108*, 2526; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2374; b) one other example of an enantioselective copper-catalyzed addition of Et₂Zn to cyclohexenone (*ee* 30%) has been reported: A. Alexakis, J. Frutos, P. Mangeney, *Tetrahedron: Asymmetry* **1993**, *4*, 2427.
- [6] D.J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem.* **1995**, *107*, 1159; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059.
- [7] a) Mismatched ligand *S,S,S*-**1** afforded **4a** with 82 % yield and 75 % *ee*; b) the introduction of substituents at the 3,3'-positions of the binaphthol moiety only marginally affected the enantioselectivities.
- [8] The spectral and analytical data for all new compounds were in agreement with the indicated structures.
- [9] Cu^I-catalyzed addition of functionalized organozinc reagents; B. H. Lipshutz, M. R. Wood, R. Tirado, *J. Am. Chem. Soc.* **1995**, *117*, 6126.
- [10] F. Langer, A. Devasagayaram, P.-Y. Chavant, P. Knochel, *Synlett* **1994**, 410.
- [11] P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117.
- [12] a) C. Ullenius, B. Christenson, *Pure Appl. Chem.* **1988**, *60*, 57; b) E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* **1985**, *26*, 6015; c) N. Krause, R. Wagner, A. Gerold, *J. Am. Chem. Soc.* **1994**, *116*, 381; d) J. P. Snyder, *Angew. Chem.* **1995**, *107*, 80; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 80.
- [13] a) For a catalytic asymmetric tandem Michael - aldol reaction, see T. Arai, H. Sasai, K. Aoe, K. Okamura, T. Date, M. Shibasaki, *Angew. Chem.* **1996**, *108*, 103; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 104; b) M. Kitamura, T. Miki, K. Nakano, R. Noyori, *Tetrahedron Lett.* **1996**, *37*, 5141.
- [14] The X-ray structural analysis of compound **6b** was performed by Dr. A. L. Spek (Utrecht University). Details will be reported separately.
- [15] Synthesis of **10**: G. L. Buchanan, R. A. Raphael, R. Taylor *J. Chem. Soc. Perkin I* **1972**, 373, and references therein.
- [16] A. Alexakis, J. C. Frutos, P. Mangeney, *Tetrahedron: Asymmetry* **1993**, *4*, 2431.