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Published in:
Angewandte Chemie-International Edition in English

DOI:
[10.1002/anie.199726201](https://doi.org/10.1002/anie.199726201)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
1997

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Feringa, B. L., Pineschi, M., Arnold, L. A., Imbos, R., & de Vries, A. H. M. (1997). Highly enantioselective catalytic conjugate addition and tandem conjugate addition - Aldol reactions of organozinc reagents. *Angewandte Chemie-International Edition in English*, 36(23), 2620 - 2623. DOI: 10.1002/anie.199726201

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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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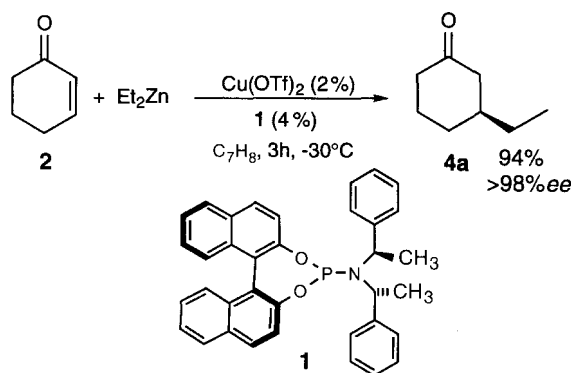
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[**] We are grateful to Prof. Dr. P. Knochel, University of Marburg, for valuable discussions and suggestions on the preparation of organozinc reagents and to Dr. J. van Esch for the creation of the artwork. Financial support (TMR postdoctoral fellow for M. P.) from the European Community (EU contract no.: ERBFMBICT961635) is gratefully acknowledged.

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?

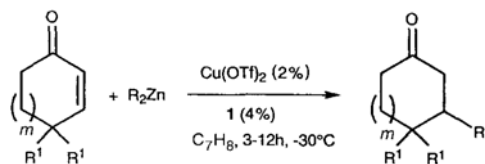


The remarkable ligand effect of binaphthol-derived phosphorus amidites on the copper-catalyzed 1,4-addition of Et_2Zn to enones^[5] was explored by a modular variation of the binaphthyl and amine moieties in these ligands. Much to our delight the incorporation of two chiral structural units, that is, 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),



2a: $\text{R}^1=\text{H}$, $m=1$	3a: $\text{R}=\text{Et}$	4a: $\text{R}^1=\text{H}$, $\text{R}=\text{Et}$, $m=1$
2b: $\text{R}^1=\text{H}$, $m=0$	3b: $\text{R}=\text{Me}$	4b: $\text{R}^1=\text{H}$, $\text{R}=\text{Et}$, $m=0$
2c: $\text{R}^1=\text{H}$, $m=2$	3c: $\text{R}=\text{Hep}$	4c: $\text{R}^1=\text{H}$, $\text{R}=\text{Et}$, $m=2$
2d: $\text{R}^1=\text{Me}$, $m=1$	3d: $\text{R}=\text{iPr}$	4d: $\text{R}^1=\text{H}$, $\text{R}=\text{Me}$, $m=1$
2e: $\text{R}^1=\text{Ph}$, $m=1$	3e: $\text{R}=(\text{CH}_2)_3\text{Ph}$	4e: $\text{R}^1=\text{H}$, $\text{R}=\text{Hep}$, $m=1$
	3f: $\text{R}=(\text{CH}_2)_5\text{OAc}$	4f: $\text{R}^1=\text{Me}$, $\text{R}=\text{Et}$, $m=1$
	3g: $\text{R}=(\text{CH}_2)_3\text{CH}(\text{OEt})_2$	4g: $\text{R}^1=\text{Me}$, $\text{R}=\text{Me}$, $m=1$
	3h: $\text{R}=(\text{CH}_2)_6\text{OPiv}$	4h: $\text{R}^1=\text{Ph}$, $\text{R}=\text{Et}$, $m=1$
		4i: $\text{R}^1=\text{H}$, $\text{R}=\text{iPr}$, $m=1$
		4j: $\text{R}^1=\text{H}$, $\text{R}=(\text{CH}_2)_3\text{Ph}$, $m=1$
		4k: $\text{R}^1=\text{H}$, $\text{R}=(\text{CH}_2)_5\text{OAc}$, $m=1$
		4l: $\text{R}^1=\text{H}$, $\text{R}=(\text{CH}_2)_3\text{CH}(\text{OEt})_2$, $m=1$
		4m: $\text{R}^1=\text{H}$, $\text{R}=(\text{CH}_2)_6\text{OPiv}$, $m=1$

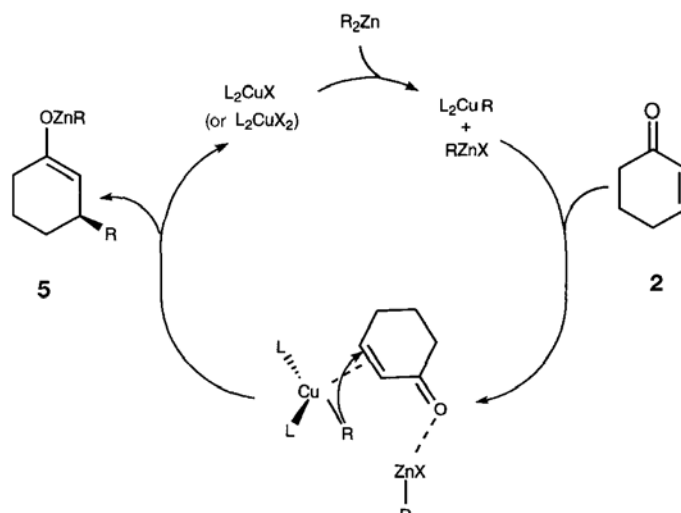
Table 1. Enantioselective 1,4-additions of dialkylzinc compounds to enones, catalyzed by $\text{Cu}(\text{OTf})_2/\mathbf{1}$ [a].

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 ethyl-enediamine [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 $\text{Cu}(\text{OTf})_2/\text{ligand } \mathbf{1}$ 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

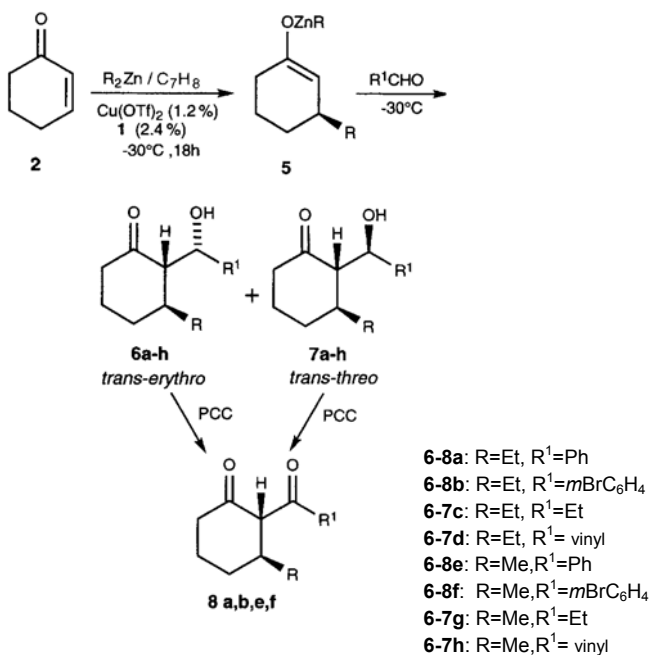
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Table 2. 1,4-Additions of dialkylzinc compounds and subsequent aldol reactions of the zinc enolates **5**.

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

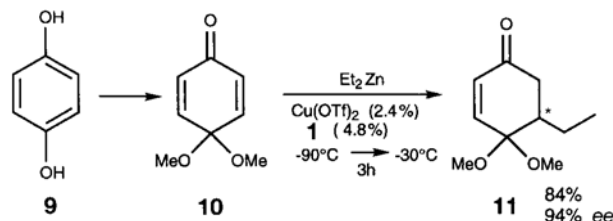
[a] 1.0 equiv of Lewis acid added. [b] Yields of isolated, pure aldols. [c] See *Experimental Section* for the determination of the *ee* values. [d] An inseparable mixture of aldols was obtained. [e] The relative configuration (*erythro:threo*) has not been established.

in situ generated enolate (Table 2). 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, 127.2, 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, OH), 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 mL·min⁻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.

Received: August 1, 1997 [Z10770IE]
 German version: *Angew. Chem.* **1997**, *109*, 2733–2736

Keywords: 1,4-additions · aldol reactions · asymmetric synthesis · C-C coupling · homogeneous catalysis · zinc

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