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

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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 R_2Zn 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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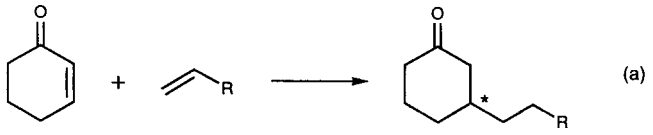
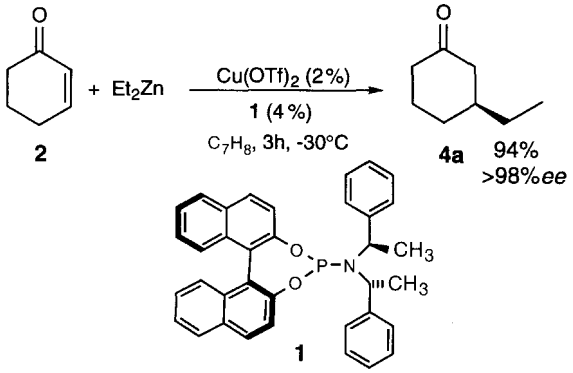
stereocontrol and highly enantioselective tandem conjugate addition-aldol reactions are reported. In our design of a catalytic asymmetric 1,4-addition the following aspects were considered: a) Can very efficient ligand-accelerated catalysis [6] be achieved ? b) Is it possible to use an enone and an olefin [Eq. (a)] as starting material ? c) Are functional groups tolerated ?



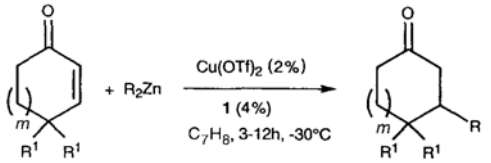
(a)

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 $Cu(OTf)_2$



Scheme 1. Enantioselective 1,4-addition of Et_2Zn to **2**, catalyzed by $Cu(OTf)_2$/**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: R^1=H, *m*=1
2b: R^1=H, *m*=0
2c: R^1=H, *m*=2
2d: R^1=Me, *m*=1
2e: R^1=Ph, *m*=1

3a: R=Et
3b: R=Me
3c: R=Hep
3d: R=*i*Pr
3e: R=$(CH_2)_3$Ph
3f: R=$(CH_2)_5$OAc
3g: R=$(CH_2)_3CH(OEt)_2$
3h: R=$(CH_2)_6$OPiv

4a: R^1=H, R=Et, *m*=1
4b: R^1=H, R=Et, *m*=0
4c: R^1=H, R=Et, *m*=2
4d: R^1=H, R=Me, *m*=1
4e: R^1=H, R=Hep, *m*=1
4f: R^1=Me, R=Et, *m*=1
4g: R^1=Me, R=Me, *m*=1
4h: R^1=Ph, R=Et, *m*=1
4i: R^1=H, R=*i*Pr *m*=1
4j: R^1=H, R=$(CH_2)_3$Ph, *m*=1
4k: R^1=H, R=$(CH_2)_5$OAc, *m*=1
4l: R^1=H, R=$(CH_2)_3CH(OEt)_2$, *m*=1
4m: R^1=H, R=$(CH_2)_6$OPiv, *m*=1

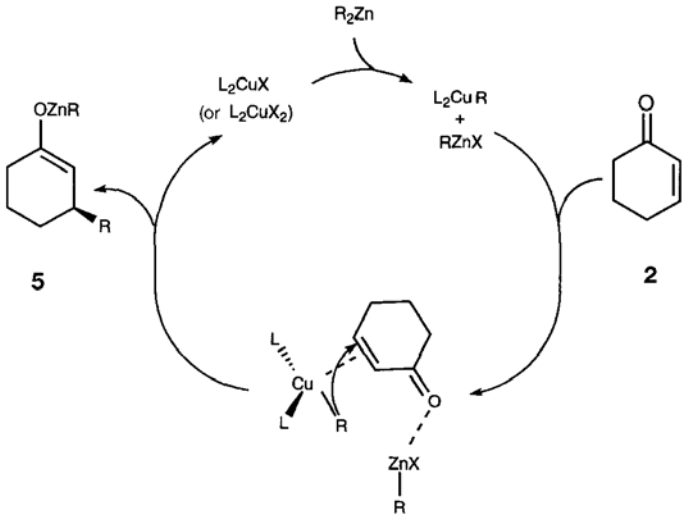
Table 1. Enantioselective 1,4-additions of dialkylzinc compounds to enones, catalyzed by $Cu(OTf)_2$/**1**[a].

Entry	Enone	R_2Zn	1,4-Adduct	Yield [%] [b]	*ee*[%] [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 particular noteworthy that the new catalyst tolerates ester and acetal functionalities. So far the catalyst based on $Cu(OTf)_2$/ligand **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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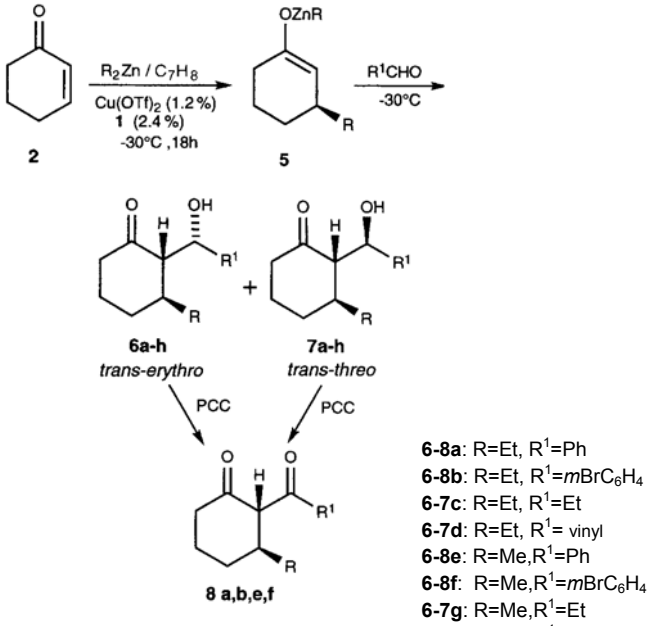
Table 2. 1,4-Additions of dialkylzinc compounds and subsequent aldol reactions of the zinc enolates **5**.

Entry	Lewis acid[a]	*t*[min] (*T*[°C])	Products	*erythro*:*threo* **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	$BF_3 \cdot Et_2O$	3 (-30)	**6b/7b**	46:54	78	92
4	$ZnCl_2 \cdot Et_2O$	3 (-20)	**6e/7e**	54:46	64	91
5		10 (-20)	**6e/7e**	38:62	67	91
6	$BF_3 \cdot Et_2O$	3 (-20)	**6f/7f**	52:48	82	> 99
7	$ZnCl_2 \cdot Et_2O$	10 (-30)	**6c/7c**	32:68[d,e]	88	91
8		10 (-30)	**6d/7d**	44:56[e]	92	95
9	$ZnCl_2 \cdot Et_2O$	30 (-30)	**6g/7g**	65:35[e]	81	97
10	$ZnCl_2 \cdot Et_2O$	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 eonfiguration (*erythro*:*threo*) has not been established.

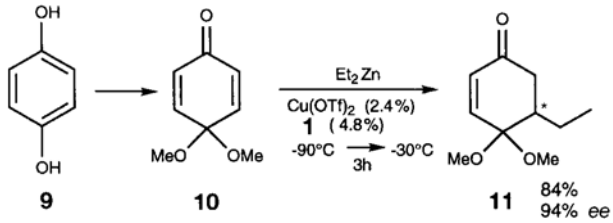
in situ generated enolate (Table 2). For example, when enolate **5**, formed from **2** and diethylzinc in the presence of $Cu(OTf)_2$ (1.2 mol %) and ligand **1** (2.4 mol %), was treated with benzaldehyde at -30°C for 10 min, an approximately 3:7 mixture of *trans*,*erythro*-**6a** and *trans,threo*-**7a** was obtained in 88% isolated yield (Table 2, No. 1). The aldol products were readily separated by flash chromatography (SiO_2, 30 % ethyl acetate, 70 % hexanes) and oxidized to a single isomer of diketone **8a** with 95 % ee. The results shown in Table 2



6-8a: R=Et, R^1=Ph
6-8b: R=Et, R^1=*m*BrC_6H_4
6-7c: R=Et, R^1=Et
6-7d: R=Et, R^1= vinyl
6-8e: R=Me,R^1=Ph
6-8f: R=Me,R^1=*m*BrC_6H_4
6-7g: R=Me,R^1=Et
6-7h: R=Me,R^1= vinyl

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 Et_2Zn to highly symmetrical dienone **10** readily obtained by oxidation of hydroquinone **9** (Scheme 3).[15] In



Scheme 3. Catalytic enantioselective 1,4-addition of Et_2Zn 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 Et_3N/toluene in the second step: chromatography (SiO_2, hexane:CH_2Cl_2 3:1), yield 40%, $[\alpha]_D$ =+456.0 (*c* = 0.79, $CHCl_3$). ^{1}H 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); ^{13}C NMR ($CDCl_3$): 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; ^{31}P 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. Thc colorless solution was cooled at –30°C and **2** (0.097 g, 1.0 mmol) and $ZnEt_2$ (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 NH_4Cl (5.0 mL) and extracted with diethyl ether (2 × 30 mL). The combined organic layers were washed with brine (5.0 mL), dried over $Mg(SO_4)_2$, filtered, and evaporated to give a crude reaction product that was purified by flash chromatography (SiO_2, 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; $[\alpha]_D$ =-50.0 (*c* = 1.52, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) 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). ^{13}C 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 $C_{15}H_{20}O_2$ 232.1463; found 232.1464. Yield of **7b**: 0.164g, 53%; oil, $[\alpha]_D$ =-23.0 (*c*=1.14, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.47 (br.s, 1H), 7.14-7.37 (m, 3H), 4.83-4.89 (m, 1H), 2.61 (dd, *J*=7.8 und 4.64 Hz, 1H), 1.20-2.38 (m, 9H), 0.88 (t, *J*=7.8 Hz, 3H); ^{13}C 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 $C_{15}H_{20}O_2$ 232.1463; found 232.1467.

To a mixture of **6b**/**7b** (0.031 g, 0.1 mmol) in CH_2Cl_2 (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 (SiO_2, 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. $[\alpha]_D$ =-26.4 (*c*=0.25, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): 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). ^{13}C 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 $C_{15}H_{17}O_2Br$ 308.0411; found 308.0418.

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