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X-ray crystal structure analysis of $[(Li^+)_2(2^{2-})(OEt_2)_2(thf)_2]$: $C_{44}H_{76}Li_2O_4$, $P\overline{1}$, a = 9.782(1), b = 14.594(1), c = 15.640(1) Å, a = 74.999(2), $\beta = 81.977(2)$, $\gamma = 83.417(2)^\circ$, V = 2128.34 Å³, Z = 2, $\rho_{calcd} = 1.07$ g cm⁻³, $\mu = 0.060$ mm⁻¹, T = 150 K, crystal dimensions ca. $0.25 \times 0.50 \times 0.50$ mm³, 90 frames, 26428 measured (8101 unique) reflections, R = 0.0472 and $R_w = 0.0475$ for 5823 reflections with $I > 6\sigma(I)$, maximum and minimum peak in final Fourier difference synthesis 0.58 and -0.42 e Å⁻³. Unit weights were used in the refinements. The asymmetric unit consists of half of a molecule of $[(Li^+)_2(2^2)(OEt_2)_4]$ and half a molecule $[(Li^+)_2(2^2)(thf)_4]$, each located about an inversion center.

X-ray crystal structure analysis of $[(K^+)_2(2^2-)([18]crown-6)_2]$: $C_{26}H_{88}K_2O_{12}$, $P2_1/n$, $a = 13.959(1), b = 10.403(1), c = 19.733(1) \text{ Å}, \beta = 107.376(1)^{\circ}, V = 2740.31 \text{ Å}^3$ Z = 2, $\rho_{\text{calcd}} = 1.19 \text{ g cm}^{-3}$, $\mu = 0.22 \text{ mm}^{-1}$, T = 150 K, crystal dimensions ca. 0.20×10^{-1} 0.25×0.40 mm³, 90 frames, 29555 measured (6266 unique) reflections, R =0.0422 and $R_w = 0.0464$ for 5403 reflections with $I > 3\sigma(I)$, maximum and minimum peak in final Fourier difference synthesis 0.36 and $-0.23 \text{ e} \text{\AA}^{-3}$. A weighting scheme based on an optimized three-coefficient Chebyshev polynomial was used in the refinements [31]. General crystallographic information: Data were collected on an Enraf-Nonius DIP 2000 image plate diffractometer using graphite-monochromated $Mo_{K\alpha}$ radiation (step of 2° between frames, $\theta_{max} = 26^{\circ}$). Corrections were made for Lorentz and polarization effects [32]. The structures were solved by direct methods using SIR92[33] and refined by using full-matrix least-squares. Hydrogen atoms were fixed in geometrically idealized positions and allowed to ride on their attached carbon atoms. Corrections for the effects of anomalous dispersion and isotropic extinction (through an overall extinction coefficient) [34] but not for absorption, were made in the final stages of refinement. All crystallographic calculations were performed by using the Oxford CRYSTALS system [35] running on a Silicon Graphics Indigo R4000 computer. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100693. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB211EZ, UK (fax: int. code + (1223) 336-033; e-mail: deposit@chemcrys.cam. ac.uk).

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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 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 C₂ 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),



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

Entry	Епопе	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	2 d	3a	4 f	74	>98[d]
5	2e	3a	4h	93	> 98 [d]
6	2a	3b	4d	72	>98[d]
7	2 d	3b	4g	68	>98[d]
8	2a	3c	4e	95	95
9	2a	3 d	4i	95	94
10	2a	3e	4i	53	95
11	2a	3 f	4 k	77	95
12	2a	3g	41	91	97
13	2a	3ที่	4 m	87	93

[a] Reaction conditions as in ref. [5]. [b] Yields of isolated products. [c] Determined by ¹³C 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 R₂Zn 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 alkylzinc 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]	<i>t</i> [min] (<i>T</i> [°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)	6 f/7 f	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 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 $-30^{\circ}C$ 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 1,4addition 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 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 Et₃N/toluene in the second step: chromatography (SiO₂, hexane:CH₂Cl₂ 3:1), yield 40%, $[\alpha]_D = +456.0$ (*c*=0.79, CHCl₃). ¹H NMR: $\delta = 7.98 - 8.08$ (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): $\delta = 150.2$, 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; ³³P NMR: $\delta = 145.3$.

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 1.1 m 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; $[\alpha]_{\rm D} = -50.0 \ (c = 1.52, \text{CH}_2\text{Cl}_2)$; 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, 3 H). ¹³C NMR: $\delta = 214.8$, 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, $[\alpha]_{D} = -23.0$ (c = 1.14, CH₂Cl₂); ¹H NMR (200 MHz, CDCl₃): $\delta = 7.47$ (br.s, 1 H), 7.14–7.37 (m, 3 H), 4.83–4.89 (m, 1 H), 2.61 (dd, J = 7.8 und 4.64 Hz, 1 H), 1.20 – 2.38 (m, 9 H), 0.88 (t, J = 7.8 Hz, 3H); ¹³C NMR: $\delta = 215.0$, 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 CH_2CI_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 (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 (35, 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), 2.35–2.53 (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 $C_{15}H_{17}O_2Br$ 308.0411; found 308.0418.

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Palladium-Catalyzed Cross-Coupling of Organozinc Bromides with Aryl Iodides in Perfluorinated Solvents**

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The formation of new carbon – carbon bonds by palladiumcatalyzed cross-coupling has experienced a spectacular development over the past ten years.^[1] Most of these reactions require relatively large quantities of a costly palladium catalyst $(1-5 \text{ mol }\%)^{[2]}$ and removal of traces of palladium compounds from the reaction products; this has hampered

[*] Prof. Dr. P. Knochel, Dipl.-Chem. B. Betzemeier Fachbereich Chemie der Universität Hans-Meerwein-Strasse, D-35032 Marburg (Germany) Fax: Int. code + (6421)282-189 e-mail: knochel@ps1515.chemie.uni-marburg.de applications of this methodology to large-scale syntheses. Recently we showed that perfluorinated solvents are a convenient medium for transition metal catalyzed oxidations with a perfluorinated metal complex as the catalyst.^[3,4] At high temperatures (ca. 60°C) many organic solvents and reagents are soluble in perfluorinated solvents, but at room temperature organic compounds are insoluble; this leads to a two-phase system at room temperature. Fluorous biphasic catalysis, popularized by Horvárth,^[5] has the advantage of easy phase separation and avoids pollution of the reaction product with the transition metal catalyst, which is only soluble in the fluorous phase and can be reused several times after simple phase separation. Here we report that palladium(0)-catalyzed cross-coupling^[6] between arylzinc bromides (Ar¹ZnBr, 1) and aryl iodides (Ar²I, 2) proceeds smoothly in the presence of the perfluorinated phosphane 3 (0.6 mol%) and bis(dibenzylideneacetone)palladium(0) ([Pd(dba)₂], 0.15 mol %)^[7] with 1-bromoperfluorooctane $(C_8F_{17}Br)$ and toluene as the solvent system to provide polyfunctional biphenyls of type 4 in high yields (Table 1).

Table 1. Palladium-catalyzed cross-coupling between arylzinc bromides 1 and aryl iodides 2 in a toluene/1-bromoperfluorooctane biphasic system.

	Ar ¹ ZnBr + Ar ²	$\frac{\left(F_{13}C_{6} \swarrow\right)}{\left[Pd(dba)_{2}\right](0.15)}$	(3 , 0.6 mol%)	Ar ¹ —Ar ²	
	1 2	toluene / C ₈ F ₁₇ Bi 60 °C, 0.2-0.5 h	r	4	
Entry	Ar ¹	Ar ²	Product 4	Yield[%][a]	
1	Ph	4-AcOC ₆ H ₄		93	
2	4-ClC ₆ H ₄	$4-NO_2C_6H_4$	4b	93	
3	4-ClC ₆ H ₄	3-EtO ₂ CC ₆ H ₄	4c	97	
4	3-CF ₃ C ₆ H ₄	4-MeOC ₆ H ₄	4d	89	
5	3-CF ₃ C ₆ H ₄	$4-BrC_6H_4$	4e	92	
6	2-thienyl	3-MeOC ₆ H ₄	4f	98	
7	2-thienyl	$4-NO_2C_6H_4$	4g	87	
8	4-TIPS-OC ₆ H₄[b]	3-EtO ₂ CC ₆ H ₄	4h	97	
9	4-TIPS-OC ₆ H ₄	$4-BrC_6H_4$	4i	99	

[a] Yield of isolated product. [b] $TIPS = iPr_3Si$.

Arylzinc bromides 1 were prepared from the corresponding aryl bromides by bromine-lithium exchange followed by lithium-zinc transmetalation with zinc bromide.^[8] 2-Thienyllithium used to prepare 2-thienylzinc bromide was obtained by deprotonation of thiophene with *n*-butyllithium.^[9] The use of triarylphosphane 3, which bears long perfluorinated chains, is essential for the success of the reaction. No activity of the palladium catalyst was observed with the previously known $(C_6F_{13}C_2H_4)_3P^{[5,10]}$ The new phosphane 3 was prepared in three steps from 4-iodoaniline. Treatment of 3 with copper and $C_6F_{13}I$ in DMSO (120 °C, 2 h) gave the substituted aniline 5 in 86% yield.^[11] Sandmeyer reaction of 5 [a) NaNO₂, HBr; b) CuBr] provided the corresponding aryl bromide 6 in 76% yield. Bromine-lithium exchange with nBuLi in THF followed by addition of PCl₃ afforded the phosphane-borane complex 7 in 37% yield after protection with borane (Scheme 1). After 7 was purified, the borane protecting group was removed with diethylamine.^[12]

The free phosphane **3** was treated with $[Pd(dba)_2]$ in $C_8F_{17}Br$ to afford an orange solution of $[Pd\{P(C_6H_4-C_6F_{13})_3\}_4]$ (8). With this catalyst (0.15 mol%), the reaction between an arylzinc bromide and an aryl iodide is complete within 0.5 h at 60°C. At this temperature, the reaction mixture is homogeneous and a two-phase system is again obtained upon cooling to room temperature. The cross-coupling product **4** is easily

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