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Copper-catalyzed enantioselective conjugate addition of dialkylzinc reagents to enones with new peptidyl phosphane ligands

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Abstract—Copper catalysts based on new peptidyl phosphane ligands have been developed for enantioselective conjugate additions of dialkylzinc reagents to cyclic enones. Enantioselectivities greater than 97% *ee* have been observed.

Copper-mediated and catalyzed conjugate addition of carbon nucleophiles to Michael acceptors is one of the fundamental C/C-bond forming transformations in organic synthesis.[1] In the course of this reaction stereochemistry can be controlled either by the reagent/catalyst or by the substrate.[2] The latter case becomes particularly powerful if substrate bound reagent-directing groups (RDG) are employed, as we have shown recently.[3] In particular *ortho*-diphenylphosphanylbenzoate (*o*-DPPB) has been identified as an ideal RDG.[4] However, a more efficient approach would rely on a non-covalent attachment of the RDG through either hydrogen bonding, Lewis acid base interactions, salt bridges or attractive van der Waals interactions, since this would allow to use substoichiometric amounts of a RDG. Furthermore, if one would add chiral information to such a non-covalent RDG system, a transition from substrate to reagent control and hence, to asymmetric catalysis would be realized (Fig. 1). We envisioned peptidyl-modified *o*-DPPB systems as interesting

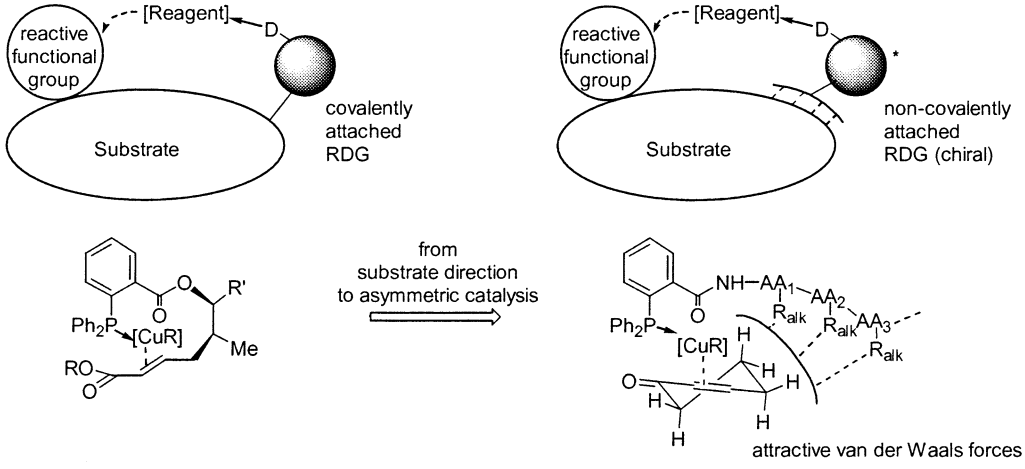

Figure 1. Concept from substrate direction with substrate bound reagent-directing groups (RDG) to asymmetric catalysis with non-covalent bound RDG's for conjugate addition with organocopper reagents.

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candidates for this approach.[5] Dependent on the selected amino acids and their corresponding side chains different sorts of attractive substrate ligand interactions may be initiated.

As a first test reaction, copper-catalyzed conjugate additions of dialkylzinc reagents to cyclic enones were studied.[6] For these type of substrates attractive substrate/ligand interactions may have to rely on van der Waals forces. Thus, we chose valine for the construction of *o*-DPPB-peptidyl ligands. Gennari et al.[7] and Hoveyda et al.[8] have reported a similar class of ligands for conjugate additions to cyclic and acyclic enones.

Ligands **1**–**5** (Fig. 2) were prepared as depicted in Scheme 1. Thus, valine methylester was coupled with *N*-Z-protected valine employing DCC/NEt_3.[9] Deprotection of the Z-group through hydrogenolysis[9] was followed by coupling with the third amino acid or by coupling with the *ortho*-diphenylphosphanyl benzoic acid.[10] The *tert*-butyl-amide ligands **6** and **7** were prepared following similar procedures.

In a first screening we looked at the copper-catalyzed conjugate addition of diethylzinc to cyclohexenone, which is a well-studied prototype for this class of reactions (Table 1).[6] The first experiments were done with the monopeptide ligand L-**1** and with $(CuOTf)_2$·PhMe as the copper(I) source. Good yields and a promising *ee* of 83% were observed (Table 1, entry 1). Changing the copper salt to CuTC, which was reported recently as a superior copper(I) source for these type of reactions,[11] increased reactivity and enantioselectivity of the catalyst to 88% *ee* (Table 1, entries 2 and 3). However, the best results were observed when $CuBr{\cdot}SMe_2$ was employed in diethyl ether at −30°C to give the (*R*)-configured conjugate adduct in quantitative yields and an *ee* of 93% (Table 1, entries 6 and 7).[12] Even better results were found when going to the dipeptide ligand L,L-**2**. Thus, under identical conditions (compare entries 7 and 12, Table 1) the reaction was faster (2 h at −30°C) and gave the (*R*)-configured conjugate adduct in quantitative yield and an *ee* of >97%. To explore the role of the second amino acid, the test reaction with ligand D,L-**4** was studied. As expected the (*S*)-configured adduct was obtained with an *ee* of 89%. Hence, the amino acid, coupled to the *o*-DPPB unit directly, is most important for the enantiodiscriminating step, and its absolute configuration determines the absolute configuration of the new stereogenic center of the product. However, the second amino acid provides a fine tuning, which can either lead to an increase [matched case for L,L-**2**] or decrease [mismatched case D,L-**4**] of enantioinduction. In order to study the effect of a third amino acid ligands L,L,L-**3** and D,D,L-**5** were examined. The copper catalysts derived from these ligands showed significantly reduced *ee*'s, with 70 and 74%, respectively (Table 1, entries 14

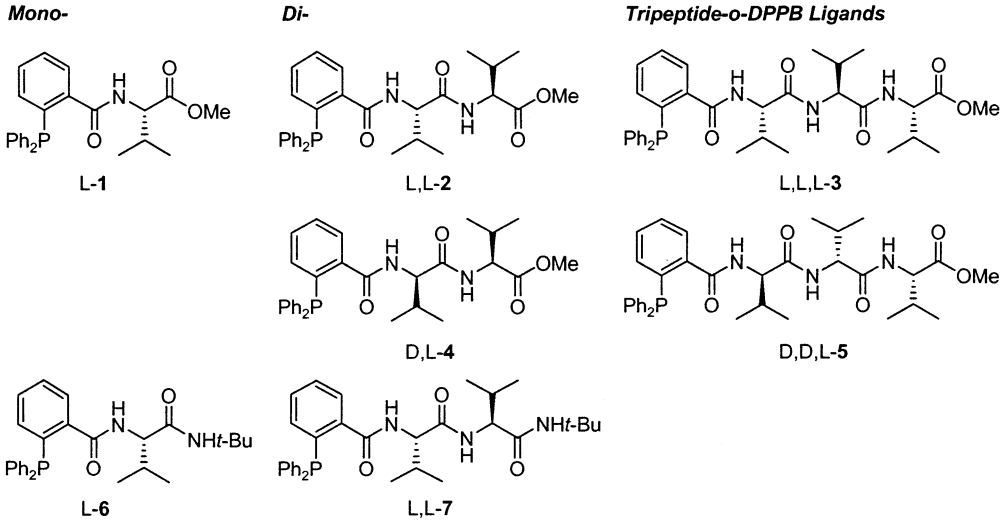
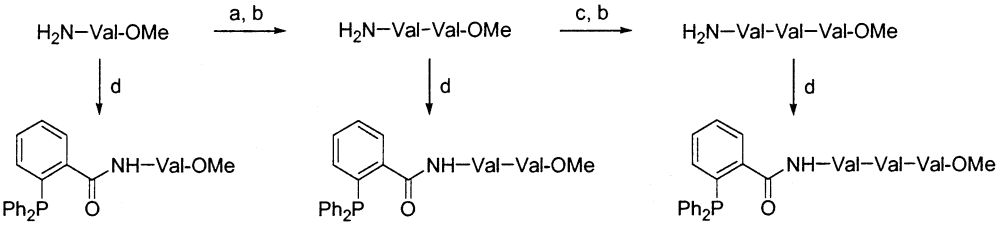
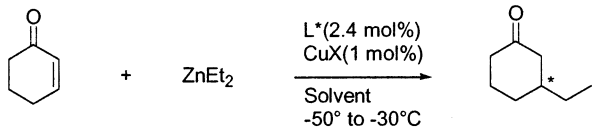


Figure 2. New chiral peptidyl-*o*-DPPB ligands synthesized and examined in this study.



Scheme 1. Preparation of peptidyl-*o*-DPPB phosphanes. *Reagents and conditions*: (a) *N*-Z-Valine, DCC, NEt_3, CH_2Cl_2, rt (62–91%); (b) H_2 (1 atm) Pd/C, MeOH, rt (95–99%); (c) *N*-Z-valine, DCC, DMAP, CH_2Cl_2, rt (28–66%); (d) *o*-DPPBA, DCC, DMAP, CH_2Cl_2, rt (29–85%).

Table 1. Enantioselective copper-L* catalyzed conjugate addition of diethylzinc to cyclohexenone. Screening for optimal reaction parameters



Entry	Ligand	Cu-salt	Solvent	T (°C)	t (h)	Conversion (%)[a]	Yield (%)[b]	*ee* (%)[c]
1	L-**1**	$(CuOTf)_2$·PhMe	Toluene	−30	6	100	94	83 (*R*)
2	L-**1**	CuTC	Toluene	−30	2	99	95	88 (*R*)
3	L-**1**	CuTC	Ether	−30	5	100	96	84 (*R*)
4	L-**1**	CuTC	THF	−30	19	97	85	62 (*R*)
5	L-**1**	CuBr·SMe_2	Ether	−50 to −30	5	99	95	85 (*R*)
6	L-**1**	CuBr·SMe_2	Toluene	−50 to −30	3	100	92	89 (*R*)
7	**L-1**	**CuBr·SMe_2**	**Ether**	**−30**	**4**	**100**	**97**	**93 (*R*)**
8	L,L-**2**	$(CuOTf)_2$·PhMe	Toluene	−50 to −30	6	100	95	84 (*R*)
9	L,L-**2**	CuTC	Toluene	−50 to −30	5	100	95	82 (*R*)
10	L,L-**2**	CuBr·SMe_2	Toluene	−50 to −30	4	100	89	93 (*R*)
11	L,L-**2**	CuBr·SMe_2	Ether	−50 to −30	4	100	95	95 (*R*)
12	**L,L-2**	**CuBr·SMe_2**	**Ether**	**−30**	**2**	**100**	**98**	**>97 (*R*)**
13	D,L-**4**	CuBr·SMe_2	Ether	−30	2	98	89	89 (*S*)
14	L,L,L-**3**	CuBr·SMe_2	Ether	−30	20	98	97	70 (*R*)
15	D,D,L-**5**	CuBr·SMe_2	Ether	−30	21	99	82	74 (*S*)
16	L-**6**	CuBr·SMe_2	Ether	−30	3	96	94	72 (*R*)
17	L,L-**7**	CuBr·SMe_2	Ether	−30	<20	100	96	76 (*R*)

[a] Determined by GC analysis.
[b] Isolated yield after chromatographic work-up.
[c] Determined by chiral GC (GT-A).

and 15). Thus, attachment of a third amino acid, irrespective of its configuration, is inferior for the ligands ability to induce enantioselectivity. In a final stage of ligand investigation, we examined the role of the ester termination of the peptide chain. For this reason, ligands L-**6** and L,L-**7** which possess a secondary amide chain termination were explored. Interestingly, the catalysts derived from these ligands gave significantly lower stereoinduction (Table 1, entries 16 and 17). Hence, the ester chain termination plays, for yet unknown reasons, an important role for enantioinduction.

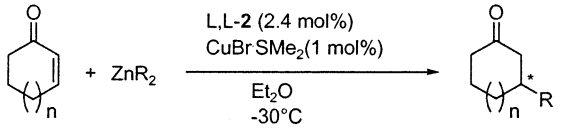
Having identified the copper complex derived from dipeptide ligand L,L-**1** as the best catalyst, a small survey of this catalysts' scope with respect to substrate structure and organozinc reagents was undertaken (Table 2).

Thus, addition of the dibutyl zinc reagent to cyclohexenone occurred with similar efficiency as observed for diethyl zinc (see Table 2, entries 1 and 2). However, addition of dimethyl zinc to cyclohexenone proved to be problematic in both ether and toluene as the solvent (Table 2, entries 3 and 4). When going from cyclohexenone to cycloheptenone the *ee* dropped to 82% (entry 5) for diethylzinc addition. However, for the cylcopentenone system, which is generally regarded as a difficult case for these reactions,[8c] good enantioselection of 91% *ee* was detected (entry 6).

In summary, starting with the idea of changing the covalent connection of an RDG based on the *o*-DPPB system to a non-covalent attractive interaction, has led us to peptidyl-*o*-DPPB esters, which by nature are chiral and hence, represent attractive ligands for asymmetric catalysis.

This study has shown that for conjugate addition of dialkylzinc reagents to enones the peptidyl-*o*-DPPB systems provide efficient catalysts, which combine high reactivity with high enantioselectivity. Furthermore, these systems should offer a much broader potential,

Table 2. Enantioselective copper-catalyzed conjugate addition of dialkylzinc to cycloalkenones with L,L-**2**



Entry	n	R	t (h)	Conv.[a]	Yield[b]	*ee* (%)[c]
1	1	Et	2	100	98	>97 (*R*)
2	1	*n*-Bu	2.5	100	96	94 (*R*)
3	1	Me	23	91	n.d.	31 (*R*)
4[d]	1	Me	23	95	n.d.	49 (*R*)
5	2	Et	4	76	75	82 (*R*)
6	0	Et	1.5	100	77	91 (*R*)[e]

[a] Determined by GC analysis.
[b] Isolated yield after chromatographic work-up.
[c] Determined by chiral GC (GT-A).
[d] Reaction was performed in toluene at −30°C.
[e] Determined by chiral HPLC (*Chiralcel* OB-H).

since their modular construction in combination with the possibilities of solid phase peptide synthesis should allow the adjustment of the ligands architecture and the nature of its attractive interactions to the substrate by changing the nature of the peptide side chain. Hence, the peptidyl-*o*-DPPB systems have a great potential as interesting ligands for many transition metal catalyzed processes.

Acknowledgements

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To a solution of L-valyl-L-valine methylester (0.900 g, 3.91 mmol), 2-(diphenylphosphino)-benzoic acid (1.33 g, 4.34 mmol) and DMAP (0.480 g, 3.93 mmol) in anhydrous dichloromethane (20 ml) was added at room temperature DCC (0.910 g, 4.41 mmol). The resultant yellow, chalky mixture was stirred at room temperature for further 20 h. The mixture was filtered through a 2-cm pad of Celite (wetted with dichloromethane), and the filter cake was washed with dichloromethane (2×20 ml). After concentration in vacuo, the residue was chromatographed on silica gel (petrolether/ethyl acetate, 2:1) to give ligand L,L-**2** as a glass foam (1.74 g, 85%, R_f 0.49). Mp 65–67°C; $[\alpha]_D^{26} = -22.6$ (*c* 0.975, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.84$ (d, $J = 6.9$ Hz, 3H), 0.87–0.97 (3d, $J = 7.3$ Hz, $J = 7.1$ Hz, $J = 7.0$ Hz, 9H), 2.05–2.22 (m, 2H), 3.73 (s, 3H), 4.38 (dd, $J = 8.2$, 6.3 Hz, 1H), 4.52 (dd, $J = 8.6$, 5.0 Hz, 1H), 6.46 (bd, $J = 8.5$ Hz, 1H), 6.54 (bd, $J = 8.2$ Hz, 1H), 6.96–7.02 (m, 1H), 7.21–7.44 (m, 12H), 7.60–7.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 18.1, 18.2, 19.1, 19.2, 30.9, 31.2, 57.5, 59.4, 60.5, 127.9, 128.7 (d, $J = 5.8$ Hz, 4C), 128.8, 128.9 (d, $J = 5.8$ Hz, 2C), 129.0, 130.6, 132.1 (d, $J = 10.2$ Hz), 132.4 (d, $J = 8.7$ Hz), 132.6, 133.7 (d, $J = 20.3$ Hz, 2C), 133.9 (d, $J = 20.3$ Hz, 2C), 134.6, 169.0, 170.9, 172.0; ^{31}P NMR (121 MHz, $CDCl_3$): $\delta = -10.3$. Anal. calcd for $C_{30}H_{35}N_2O_4P$: C, 69.48; H, 6.80; N, 5.40. Found: C, 69.22; H, 6.67; N, 5.14.
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12. **General procedure for the catalytic conjugate addition of dialkylzinc to enones**:
A solution of $CuBr{\cdot}SMe_2$ (2.1 mg, 0.01 mmol) and chiral ligand L,L-**2** (12.5 mg, 0.024 mmol) in diethyl ether (1.5 ml) was stirred for 30 min. The pale green solution was cooled to −30°C and dialkylzinc reagent (3.0 equiv.) was added followed by addition of a solution of enone (1.0 equiv.) in diethyl ether (0.5 ml) after 1 h at −30°C. The reaction was monitored by TLC and quenched with 1N aqueous HCl. The crude product was filtered and dried over silica gel/$MgSO_4$ to give the 1,4-addition products.