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Unexpected enhancement of enantioselectivity in copper(II) catalyzed conjugate addition of diethylzinc to cyclic enones with novel TADDOL phosphorus amidite ligands

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Abstract

The copper(II) catalyzed enantioselective 1,4-addition reactions of diethylzinc to cyclic enones in the presence of novel phosphorus amidite ligands, easily prepared from α,α,α′,α′-tetraphenyl-2,2′-dimethyl-1,3-dioxolane-4,5-dimethanol (TADDOL) derivatives, resulted in e.e.s up to 71% for cyclohexenone and up to 62% for cyclopentenone. A remarkable enhancement of enantioselectivity was observed upon the addition of powdered molecular sieves to the reaction mixture.

Conjugate addition reactions of carbon nucleophiles to α,β-unsaturated compounds are among the most widely used methods for carbon–carbon bond formation in organic synthesis.[1] Several chiral catalysts based on Cu(I),[2–7] Ni(II)[8–11] or Co(II)[12] and a variety of chiral ligands have shown encouraging enantioselectivities in 1,4-additions of Grignard, organolithium, or dialkylzinc (R_2Zn) reagents.[13,14] We have introduced chiral phosphorus amidites, based on (*S*)-2,2′-binaphthol (BINOL), as ligands for the $Cu(OTf)_2$-catalyzed addition of dialkyl zincs to both cyclic and acyclic enones with high enantioselectivity.[15] Recently, a novel chiral phosphorus amidite was designed that was effective in the ligand accelerated conjugate addition and tandem conjugate addition–aldol reactions of functionalized organozinc reagents to cyclohexenones with complete stereocontrol.[16] Despite the fact that we could achieve enantioselectivities of >98% with cyclohexenones, the addition of diethylzinc to cyclopentenone gave an almost racemic 1,4-adduct. Pfaltz et al. used chiral BINOL derived phosphites, containing an additional oxazoline moiety, and achieved high enantioselectivity towards cyclopentenone.[17] Alexakis et al. have reported promising results with a number of related phosphorus ligands.[18] In this commu-

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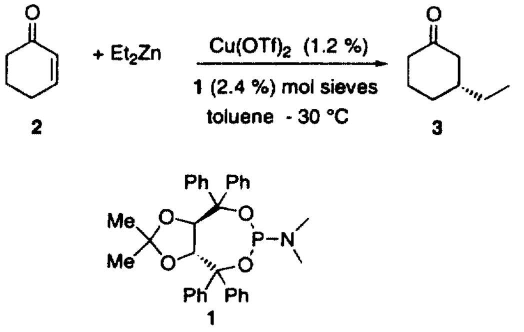
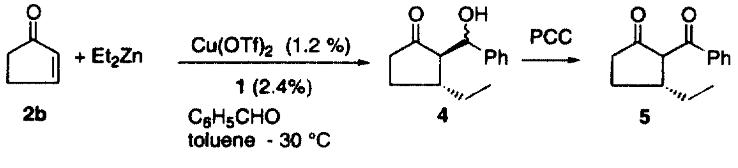
nication we describe the use of novel TADDOL[19,20] derived phosphorus amidites and the unexpected enhancement of enantioselectivity in the conjugate addition of diethylzinc to cyclic enones.

The chiral TADDOL derived phosphorus amidite **1** was readily prepared from the reaction of TADDOL with HMPT in refluxing chloroform. When $Cu(OTf)_2$ (1.2 mol%) and chiral phosphorus amidite **1** (2.4 mol%) was employed in the reaction of diethylzinc with cyclohexenone **2a** at −30°C, the 1,4-adduct (*R*)-**3** was isolated in 90% yield with an e.e. of 54% (Scheme 1).[21] Lowering the reaction temperature or changing the amount of catalyst did not influence the enantioselectivity of the reaction. However, when 1.2 mol% $Cu(OTf)_2$ and 1.2 mol% or 3.6 mol% of **1** were used the e.e.s dropped to 47% and 48%, respectively. Slow addition[3,13] of either the dialkylzinc reagent or the cyclohexenone over 1.5 h resulted in a decrease of the enantioselectivity to 35% and 51%, respectively. Upon addition of powdered molecular sieves (4 Å) to the reaction mixture the enantioselectivity of the conjugate addition increased to 71%. This unexpected rise in e.e. might be caused by the presence of trace amounts of water which could result in the formation of mixed zinc hydroxide intermediates that can play a role in the complex chiral catalyst,[22] or by reaction at the surface of the molecular sieves.[23]



Scheme 1. Enantioselective conjugate addition of diethylzinc

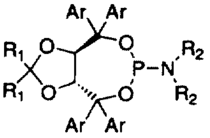
The $Cu(OTf)_2$ catalyzed reaction of diethylzinc with cyclopentenone did also afford the desired 1,4-adduct, however the isolated yield was low because of the reactivity of the intermediate zinc enolate[24] leading to oligomerization even at −30°C and because of the extreme volatility of the product. In order to prevent this undesired oligomerisation, benzaldehyde was added to the reaction mixture for the *in situ* quenching of the zinc enolate formed.[16] Using this protocol, 2,3-disubstituted cyclopentanones are obtained in 80–85% isolated yield as a mixture of trans-*erythro* and trans-*threo* isomers **4** via a tandem conjugate addition–aldol reaction.[16,25,26] PCC oxidation of **4** afforded diketone **5** in 65% yield with an e.e. of 37% (Scheme 2).[27]



Scheme 2. Enantioselective tandem conjugate addition–aldol reaction

The addition of molecular sieves also increased the enantioselectivity in the tandem conjugate addition–aldol reaction yielding **4** with an e.e. of 62%. Although the beneficial effect of molecular sieves has been observed in a number of other catalytic enantioselective reactions[23] the enhancement of e.e.s in R_2Zn reactions is highly remarkable realizing the sensitivity of R_2Zn reagents to hydrolysis. Next, several TADDOL derived phosphorus amidites, obtained by variation of the TADDOL and the amine

Table 1
Effect of modular modifications on the TADDOL phosphorus amidite ligands on the tandem conjugate–aldol reaction



Entry	Ligand	R_1	R_2	Ar	*Erythro/threo* ratio	e.e.	Absolute configuration
1	**1**	CH_3	CH_3	C_6H_5	33:67	62	R,R
2	**6**	CH_3	iPr	C_6H_5	34:66	4 [a]	S,S
3	**7**	CH_3	Bn	C_6H_5	42:58	17	R,R
4	**8**	CH_3	$-(CH_2)_5-$	C_6H_5	35:65	24 [a]	R,R
5	**9**	$-(CH_2)_4$	CH_3	C_6H_5	31:69	48	R,R
6	**10**	CH_3	CH_3	$o-CH_3C_6H_4$	45:55	0	-

[a] No molecular sieves were added.

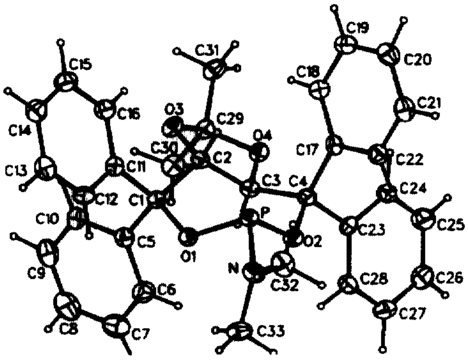


Fig. 1. ORTEP drawing of the molecular structure of **1**

moieties in these ligands, were examined.[28] The results are outlined for the tandem conjugate addition reaction to cyclopentenone in Table 1.

Omission of sieves (entry 2) or introduction of additional steric bulk on the amine part (**6**–**8**) of the ligand resulted in a drastic drop in enantioselectivity (entries 3–4). Modification of the acetal part of the phosphorus amidite (**9**) also effected the enantioselectivity (entry 5). To our surprise, racemic product was isolated when a phosphorus amidite derived from α,α,α′,α′-tetra-orthomethyl-phenyl-2,2′-dimethyl-1,3-dioxolane-4,5-dimethanol **10** was used (entry 6). When the BINOL derived phosphorus amidites[15,16] and the TADDOL derived analogs are compared, it is remarkable that whereas in the first case enhanced steric hindrance at the amine part increases the enantioselectivity to a large extent, in the latter case the opposite effect is observed. The negative influence of the sterically more demanding amine part of the ligands can be explained by the fact that one of the alkyl groups at the planar nitrogen is pointing in the same direction as the lone pair of the phosphorus, as can be seen in the molecular structure of **1** (Fig. 1).[29] Furthermore, hindered rotation of the aromatic groups in tetra-*o*-methyl substituted ligand **10** presumably prevents the preferential formation of a single well defined complex in solution (entry 6).

In conclusion, novel phosphorus amidites derived from TADDOL have been developed that show strongly improved enantioselectivities in the $Cu(OTf)_2$ catalyzed ligand accelerated conjugate addition of diethylzinc to cyclopentenone compared to the BINOL derived analogs. An unexpected enhancement of enantioselectivity was observed upon the addition of molecular sieves. Further modifications of the TADDOL derived phosphorus amidite ligands and the elucidation of the 'molecular sieves effect' is currently in progress.

Acknowledgements

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21. The e.e. of **3** was determined by GC analysis on a chiral stationary phase (CHIRALPAK G-TA, 50 m×0.25 mm, 100°C, t_r=23.6 (*R*)/24.8 (*S*).
22. Much to our surprise, addition of a small amount of water to the reaction mixture of the addition of diethyl zinc to cyclopentenone also increased the enantioselectivity, Keller, E., Imbos, R., Feringa, B. L. unpublished results.
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27. The e.e. of **5** was determined by HPLC analysis on a chiral stationary phase (DAICEL CHIRALPAK OJ, *i*PrOH:hexane 1:19, 1.0 ml/min, RT, t_r=15.0 (*R*,*R*) t_r=21.7 (*S*,*S*).
28. The procedure for related phosphorus amidites was followed (Ref. 15) and purification by column chromatography (SiO_2 hexanes:diethylether) or crystallization. All spectroscopic and analytical data are in accordance with the proposed structures.

29. Crystal data for **1** were recorded on an Enraf–Nonius CAD-4F^2 diffractometer, interfaced to an INDY (Silicon Graphics) UNIX computer (Mo tube, 50 kV, 40 mA, monochromated Mo-Kα radiation, $\Delta\omega=0.80+0.34$ tg θ). ($C_{33}H_{34}NO_4P$), colorless transparent parallelepiped crystal of approximate crystal dimensions 12×0.15×0.22 mm, $M=539.61$, triclinic, space group $P1$, $a=9.130(1)$ Å, $b=9.181(1)$ Å, $c=9.732(1)$ Å, $\alpha=80.174(5)°$, $\beta=72.356(5)°$, $\chi=62.913(5)°$, $V=619.61(13)$ Å^3, $Z=1$, $D_x=1.296$ g cm^{-3}, (Mo-Kα)=0.71073 Å, $\mu=1.39$ cm^{-1}, $F(000)=286$, $T=130$ K, $wR(F^2)=0.0759$ for 2877 reflections with $F_o{}^2\geq 0$ and 488 parameters and $R(F)=0.0338$ for 2607 reflections obeying the $F_o>4.0\sigma(F_o)$ criterion of observability. Atomic coordinates, thermal parameters, bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre.