Conjugate addition of diethylzinc to α,β-unsaturated lactones catalyzed by copper–phosphite complexes

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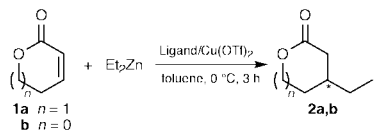
Highly enantioselective conjugate addition of diethylzinc to α,β-unsaturated lactones was achieved by using chiral diphosphite–copper catalysts; the structure of a chiral diphosphite–copper(I) catalyst was determined by single crystal X-ray diffraction.

The enantioselective conjugate addition of organometallic reagents to α,β-unsaturated ketones and esters provides an efficient method for asymmetric carbon–carbon bond formation in organic synthesis.[1] In recent years copper complexes of various chiral phosphorus ligands have been used as efficient catalysts for the conjugate addition of organozinc reagents to enones,[2] but there are no reports concerning the asymmetric conjugate addition of organozinc reagents to α,β-unsaturated lactones. Tomioka reported the enantioselective conjugate addition of Grignard reagents to 5,6-dihydro-2*H*-pyran-2-one catalyzed by a chiral phosphine–copper iodide catalyst with good enantioselectivity. However, a high loading of chiral ligand (32 mol%) was necessary to achieve high enantioselectivity.[3] Recently we found chiral aryl diphosphites to be efficient ligands for the copper-catalyzed conjugate addition of diethylzinc to cyclic enones.[4,5] Here we report the enantioselective conjugate addition of diethylzinc to α,β-unsaturated lactones with chiral diphosphite–copper catalysts. A cationic chiral diphosphite–copper(I) catalyst was isolated and its structure was determined by single crystal X-ray diffraction.

Table 1 Conjugate addition of diethylzinc to α,β-unsaturated lactones catalyzed by copper–phosphorus complexes[a]



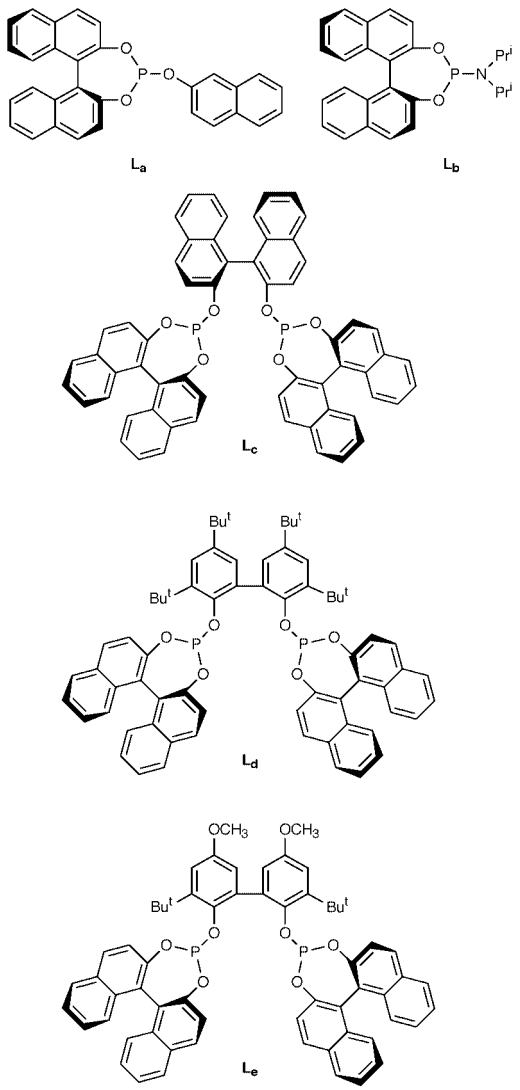
1a $n = 1$
b $n = 0$ — **2a,b**

Entry	Ligand	Substrate	Conversion (%)[b]	Ee (%)[b]
1	—	**1a**	—	—
2	PPh_3	**1a**	14.3	—
3	$P(OPh)_3$	**1a**	10	—
4	$P(OEt)_3$	**1a**	17	—
5	$\mathbf{L_a}$	**1a**	68.4	10
6	$\mathbf{L_b}$	**1a**	66.9	16.8
7	$\mathbf{L_c}$	**1a**	100	73
8	$\mathbf{L_c}$	**1b**	85.2	38.5
9	$\mathbf{L_d}$	**1a**	100	92
10[c]	$\mathbf{L_d}$	**1a**	100	91.1
11[d]	$\mathbf{L_d}$	**1a**	100	86.7
12[e]	$\mathbf{L_d}$	**1a**	93	88.3
13	$\mathbf{L_d}$	**1b**	77	56.0
14	$\mathbf{L_e}$	**1a**	94.6	89.5
15	$\mathbf{L_e}$	**1b**	100	38.6

[a] The reactions were carried out in toluene at 0 °C for 3 h (copper : ligand : substrate : Et_2Zn = 0.01 : 0.02 : 1 : 1.5). [b] The data on conversion and the ee values of **2a** and **2b** were determined by GC with a Chiraldex A-TA column (30 m × 0.25 mm). [c] $[Cu(OTf)]_2$·benzene was used as the source of copper ($\mathbf{L_d}$/Cu = 2). [d] $[Cu(OTf)]_2$·benzene was used as the source of copper ($\mathbf{L_d}$/Cu = 1). [e] Isolated $[Cu\mathbf{L_d}(MeCN)_2]^+$ $CF_3SO_3^-$ was used as the catalyst.

The conjugate addition of diethylzinc to 5,6-dihydro-2*H*-pyran-2-one **1a** was selected as a model reaction. Typically the reaction was carried out in toluene at 0 °C for 3 h, using 1 mol% $Cu(OTf)_2$ and phosphorus ligands (4 mol% monodentate phosphorus ligands or 2 mol% bidentate phosphorus ligands) as the catalysts, and the results are summarized in Table 1.

$Cu(OTf)_2$ did not show catalytic activity activity in the absence of phosphorus ligands (entry 1). The $Cu(OTf)_2$ complexes of PPh_3, $P(OPh)_3$ and $P(OEt)_3$ showed low catalytic activity (entries 2–4).[6] Chiral phosphite $\mathbf{L_a}$ and phosphorus amidite $\mathbf{L_b}$ provided higher acceleration effects, but the enantioselectivities were rather poor (entries 5 and 6).[7,8] When aryl diphosphite $\mathbf{L_c}$ and $\mathbf{L_d}$ were examined in the reaction, high catalytic activity was achieved (entries 7 and 9). In addition excellent enantioselectivity was obtained when $Cu(OTf)_2$–$\mathbf{L_d}$



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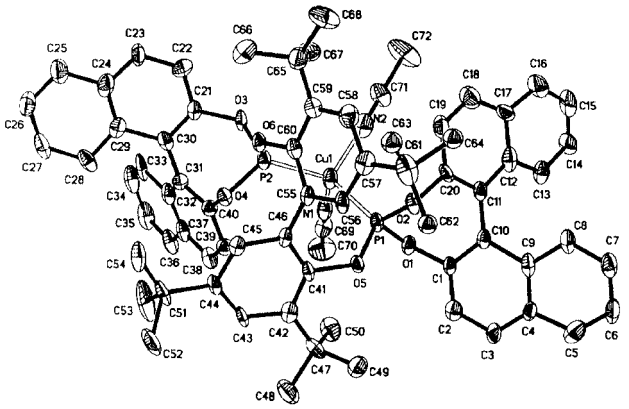

Fig. 1 ORTEP drawing of the molecular structure of [Cu$\mathbf{L_d}$(MeCN)$_2$]$^+$OTf$^-$. The triflate and hydrogen atoms have been omitted for clarity. The *tert*-butyl group (C47–C50) is disordered and only one of the disordered sets of atoms is shown. The P1–Cu–P2 angle is 119.1°. The bond lengths of P1–Cu and P2–Cu are 2.242 and 2.214 Å, respectively. The dihedral angles of the two binaphthyl units are 57.4 and 55.7°. The bridging 3,3′,5,5′-tetra-*tert*-butylbiphenol unit has a dihedral angle 61.5°.

complex was used as the catalyst (entry 9). To the best of our knowledge, this is the first example of the highly enantioselective conjugate addition of an organozinc reagent to an α,β-unsaturated lactone. The reaction was found to be highly regioselective and no 1,2-addition product was observed by GC analysis. When [Cu(OTf)]$_2$·benzene–$\mathbf{L_d}$ was tested as the catalyst in the conjugate addition of diethylzinc to **1a**, similar enantioselectivity was observed as that from using Cu(OTf)$_2$–$\mathbf{L_d}$ complex (entry 10 *vs.* entry 9). The $\mathbf{L_c}$–Cu(OTf)$_2$ and $\mathbf{L_d}$–Cu(OTf)$_2$ complexes were also tested in the addition of diethylzinc to 5*H*-furan-2-one **1b** and 38.5 and 56.0% ee were obtained respectively (entries 8 and 13).

A catalytic cycle for copper-catalyzed conjugate addition of diethylzinc to cyclic enones had been proposed by Fergina.[2a] A copper(I) species was proposed to be the catalyst in the reaction and direct evidence to support this hypothesis is desirable. To this end we carefully chose crystallization conditions and obtained colorless crystals from an MeCN solution of $\mathbf{L_d}$ and [Cu(OTf)]$_2$·benzene. A single crystal X-ray diffraction study of this species revealed a Cu$^{\mathrm{I}}$ complex with the molecular formula [Cu$\mathbf{L_d}$(MeCN)$_2$]$^+$ OTf$^-$ which took a twist tetrahedron geometry (Fig. 1).† The *tert*-butyl group (C47–C50) is disordered.

As expected the isolated [Cu$\mathbf{L_d}$(MeCN)$_2$]$^+$OTf$^-$ crystals were also found to be an efficient catalyst in the conjugate addition of diethylzinc to **1a** (entry 12) and the enantioselectivity was similar to that obtained using the [Cu(OTf)]$_2$·benzene–$\mathbf{L_d}$ catalyst prepared *in situ* ($\mathbf{L_d}$/Cu = 1. entry 11). The X-ray crystallography of the [Cu$\mathbf{L_d}$(MeCN)$_2$]$^+$OTf$^-$ complex showed that the two terminal binaphthyl units form a good chiral pocket around the copper atom. In addition the four *tert*-butyl groups in the bridging biphenyl unit effectively fix the conformation of the complex and shield the space above the copper atom. In order to assess the importance of the *tert*-butyl groups at the 5,5′-positions of the bridging biphenyl unit, ligand $\mathbf{L_e}$ was prepared and tested for the reaction. The Cu(OTf)$_2$–$\mathbf{L_e}$ complex also gave good enantioselectivity in the conjugate addition of diethylzinc to **1a** (entry 14).

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Notes and references

† *Crystal data* for [CuL$_\mathbf{d}$(MeCN)$_2$]OTf: $C_{72}H_{70}N_2O_6P_2Cu{\cdot}CF_3SO_3$, M = 1333.85, orthorhombic, a = 17.518(4), b = 17.524(4), c = 27.033(5) A, T = 293(2) K, space group $P2_12_12_1$, Z = 8299(3) Å^3, μ = 0.381 mm^{-1}, 18368 (R_{int} = 0.1071) independent reflections, refinement converged at a final R = 0.0623, wR = 0.1684. CCDC 182/1492. See http://www.rsc.org/suppdata/cc/a9/a908467c/ for crystallographic data in .cif format.

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