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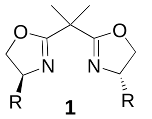
An Insoluble Polymer-Bound Bis-Oxazoline Copper(II) Complex: A Highly Efficient Heterogeneous Catalyst for the Enantioselective Mukaiyama Aldol Reaction**

Simonetta Orlandi, Alessandro Mandoli, Dario Pini, and Piero Salvadori*

In recent years asymmetric catalytic procedures have been emerging as a major option for the preparation of chiral compounds in enantiomerically enriched form, especially when the catalyst system consists of readily available, cheap and nontoxic components.[1] However, the recovery of the catalyst and its reuse is often mandatory for large-scale applications. At present, one of the most promising solutions for this problem seems to be the anchoring of effective soluble systems on an insoluble matrix, ideally without any reduction of catalytic performances with respect to the homogeneous phase.[2, 3] While this strategy is well established in reduction and oxidation processes,[4, 5] few examples have been reported for C–C bond-forming reactions.[6]

In our continuing effort to develop heterogeneously catalyzed asymmetric Mukaiyama aldol reactions,[7] we became interested in bis-oxazoline (box) ligands **1**.[8] In spite of the versatility of this class of chiral auxiliaries, few supported copper box complexes have been reported to date.[9] They rely on ion exchange to anchor them to an organic or inorganic host. The application of these immobilized catalysts to asymmetric cyclopropanation and aziridination led to modest enantioselectivity, which could be related to unfavorable interactions between the metal complex and the support.[10, 11] Better results were recently reported by Evans et al. for a hetero Diels–Alder reaction with Cu^{II}–box in the presence of Florisil, although the use of a poor solvent for the metal complex was required for effective recovery of the catalyst.[12]



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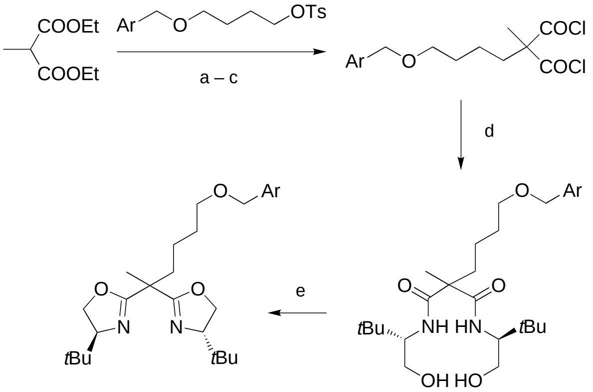
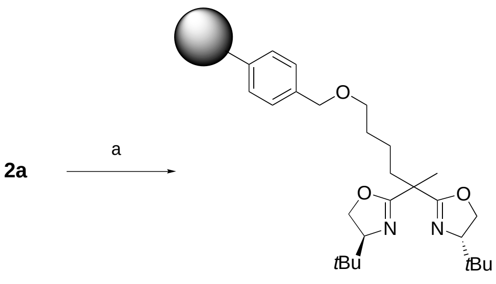
To develop a versatile, reusable, insoluble box ligand equivalent to the homogeneous systems **1**, the preparation of bis-oxazoline covalently bound to an inert polystyrene matrix was designed. The chiral monomer **2a** was synthesized by the route depicted in Scheme 1,[13] together with the soluble model **2b** of the supported ligand.



2a Ar = 4-$CH_2CHC_6H_4$
2b Ar = Ph

Scheme 1. a) NaH, THF, reflux, 24 h, 65–95%; b) 18M KOH, reflux, 3 h, 82–89%; c) $(COCl)_2$, cat. DMF, CH_2Cl_2, RT, 18 h; d) (*S*)-*t*BuCH(NH_2)-CH_2OH (2 equiv), Et_3N, CH_2Cl_2, RT, 35 min; e) TsCl, Et_3N, cat. DMAP, CH_2Cl_2, RT, 27 h, 50–55% over two steps. Ts = *p*-toluenesulfonyl, DMAP = 4-dimethylaminopyridine.

The AIBN-initiated copolymerization of **2a** with styrene and divinylbenzene (DVB), in the presence of toluene as a porogen agent,[14] followed by exhaustive extraction with THF and CH_2Cl_2, afforded **3** (Scheme 2). It was characterized by IR spectroscopy ($\tilde{\nu}_{C=N} = 1655\ cm^{-1}$),[15] and its content of chiral ligand ($0.31\ mmol\,g^{-1}$) was evaluated by nitrogen elemental analysis. A maximum metal uptake of $0.18\ mmol\,g^{-1}$ was determined by equilibrating **3** with an excess of $Cu(OTf)_2$ in THF.



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Scheme 2. a) Styrene, DVB (**2a**:styrene:DVB = 7:42:51), AIBN, toluene (60% v/v), 80 °C, 18 h. AIBN = azobisisobutyronitrile.

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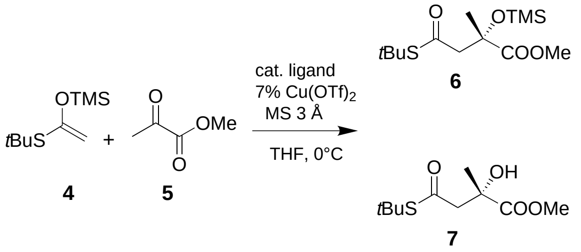
The supported box **3** was next used in the Cu^{II}-catalyzed Mukaiyama aldol addition of ketene thioacetal **4** to methyl pyruvate **5** [Eq. (1); TMS = trimethyl silyl]; for comparative purposes, test runs with the soluble ligand **1** (R = *t*Bu) and the model compound **2b** were also carried out. The reactions were performed under standard conditions[16] with 3 Å molecular sieves (MS) as water scavengers. A slightly higher ligand-to-metal ratio was used in the case of **3** (Table 1) to compensate for the reduced ligand availability (see above). Although the heterogeneous catalyst **3** · Cu(OTf)$_2$ proved less active than the homogeneous catalysts derived from **1** (R = *t*Bu) and **2b** (entries 1 and 2), the silylated aldol **6** and its hydrolysis product **7** were formed after 1 h in high overall yield (entry 3) and with an enantiomeric excess comparable to those obtained with the soluble ligands **1** and **2b**.[17]



(1)

Table 1. Catalytic asymmetric Mukaiyama reaction.

Entry	Recycle	Ligand [mol %]	*t* [min]	**6** + **7** yield [%][a]	(*S*)-**7** *ee* [%][b]
1	–	**1** (R = *t*Bu) (7.7)	15	100	94
2	–	**2b** (7.7)	15	100	92
3	0	**3** (12.4)	60	90	90
4	1	**3**[c] (12.4)	60	85	91
5	2	**3**[c] (12.4)	60	86	89
6	3	**3**[c] (12.4)	60	81	88
7	4	**3**[c] (12.4)	60	52	91
8	5	**3**[c, d] (12.4)	60	96	89
9	6	**3**[d, e] (12.4)	120	97	93
10	7	**3**[d, e] (12.4)	240	97	93

[a] Determined by GLC and ^{1}H NMR spectroscopy with methyl-1-naphthoate as internal standard. [b] Determined by HPLC. Absolute configuration by comparison of the optical rotation and the retention time with those of an authentic sample. [c] Supported ligand from the previous run. [d] Fresh MS were added. [e] Supported copper complex from the previous run.

At the end of the reaction, the polymer-supported catalyst was quantitatively recovered by filtration, together with the MS, washed with CH$_2$Cl$_2$ and dried in vacuum. To assess the recycling effectiveness of the supported ligand, the initial amount of Cu(OTf)$_2$ in THF was added to the recovered material, any excess of metal removed by filtration, and the heterogeneous catalyst employed in a new aldol reaction. In four successive runs by this procedure, almost unchanged *ee* values were obtained together with a moderate reduction in rate (entries 4–7). Most likely this was a consequence of water buildup in the catalyst system,[16] as the simple replacement of the MS with fresh ones effectively restored the activity to the initial value (recycle 5, entry 8). The accumulation of water could also explain the presence in the reaction mixture of the free aldol **7** besides the silylated form **6**: this is probably a consequence of the hydrolysis of Me$_3$SiOTf involved in the catalytic cycle, which is known to effect the in situ conversion of **7** into **6**.[16] Indeed, the relative amount of **6** steadily decreased in the course of the runs, unless fresh MS were added in the fifth recycle (Figure 1).

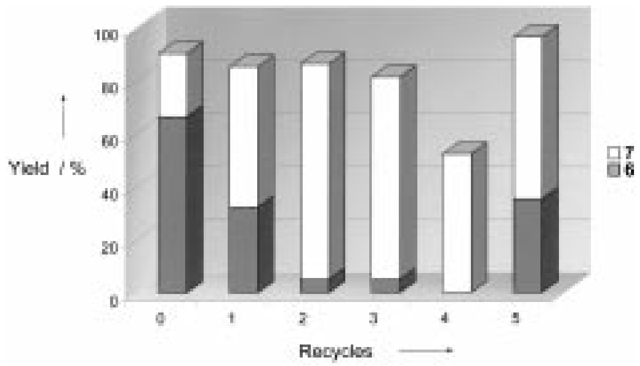
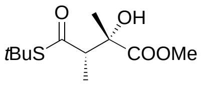


Figure 1. Catalytic activity and product distribution in recycle runs.

The finding that **3** that was recovered after the reactions was green suggested that some copper salt could be retained by the polymer-bound ligand. This prompted us to investigate the possibility of recycling the whole catalyst **3** · Cu(OTf)$_2$ by performing two further runs without the addition of any Cu(OTf)$_2$ (entries 9 and 10). Under these conditions the reaction progressively slowed down. Nevertheless, complete conversion of the substrates could be achieved, albeit at longer times, and a slight increase in the *ee* values was also observed.

Finally, preliminary experiments showed that **3** · Cu(OTf)$_2$ is also active in the catalysis of the Mukaiyama reaction between nucleophilic reagents (2-trimethylsilyloxyfuran) and electrophilic reagents (benzyloxyacetaldehyde) that differ from **4** and **5**. While low *ee* values (10–30 %) were generally obtained, both at 0 and −78 °C, the addition of (*Z*)-1-*tert*-butylthio-1-trimethylsilyloxypropene to methyl pyruvate at 0 °C[16] afforded **8** (*syn*:*anti* = 83:17, *syn* 79 % *ee*) with a stereoselectivity comparable with that obtained with the soluble ligand **1** (R = *t*Bu) under the same conditions (*syn*:*anti* = 85:15, *syn* 81 % *ee*).



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In summary, a convenient route for the preparation of the insoluble polystyrene-supported bis-oxazoline ligand **3** was developed. The use of **3** in the copper(II)-catalyzed aldol addition of silylthioketene acetals to methyl pyruvate led to the first example of a highly enantioselective Mukaiyama reaction involving a heterogeneous catalyst system.[18] Moreover, **3** could be easily recovered by simple filtration and reused several times without any loss of activity and stereoselectivity. Studies are currently underway to extend the scope of the reaction and to develop materials suitable for low-temperature applications.

Experimental Section

General procedure for the Mukaiyama aldol reaction with **3**: in a Schlenk tube provided with a glass frit, **3** (100 mg, 0.031 mmol of supported ligand) and Cu(OTf)$_2$ (0.019 mmol) in dry THF (1 mL) were stirred for 1 h at RT. Activated 3 Å MS (100 mg) were added, and stirring was continued for 1 h.

The mixture was then cooled to $-78\,^{\circ}$C and sequentially treated with methyl pyruvate **5** (0.25 mmol) containing methyl-1-naphthoate (internal standard) and ketene thioacetal **4** (0.30 mmol). After transferring the Schlenk tube into an ice bath, samples were taken at time intervals and filtered through a short (2 cm) silica gel plug,[19] and the conversion and the **6**/**7** ratio were determined by GLC.[16] When conversion was complete, the reaction mixture was filtered under an inert atmosphere, and the filtrate containing **6** and **7** was hydrolyzed as described.[16] Yield and *ee* of **7** were determined by ^{1}H NMR spectroscopy and HPLC (Chiralcel OD-H, 0.5 mL min^{-1}, hexane/2-propanol 99:1), respectively.

The recovered complex **3** · Cu(OTf)$_2$ was washed with dry CH$_2$Cl$_2$ and dried under vacuum. The MS could be mechanically removed at this stage. Recycle runs were carried out according to the general procedure, beginning with the addition of the initial amount of Cu(OTf)$_2$ (entries 4–8) or skipping this step (entries 9–10).

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[17] Control experiments showed that the enantioselectivities for the formation of **6** and **7** were identical within the experimental uncertainty. Therefore the *ee* values were routinely determined after the conversion of **6** to **7** (see *Experimental Section*).

[18] The heterogeneous nature of the catalytic system was demonstrated by the fact that removing **3** · Cu(OTf)$_2$ by filtration at 30 % conversion completely stopped the reaction.

[19] This treatment did not cause desilylation of **6**.

Self-Assembly of Pyramidal Tetrapalladium Complexes with a Halide at the Apex[**]

Camino Bartolomé, Raquel de Blas, Pablo Espinet,* José M. Martín-Álvarez, and Fernando Villafañe

Compared to the ubiquitous presence of μ_1-X and μ_2-X ligands (X = halide), and the frequent μ_3-X coordination (often involved in cubane-like structures), higher coordination numbers for halide ligands in discrete molecules are much less common.[1] A coordination number four (μ_4-X) is rare. Apart from a few scattered cases found in polynuclear V, Mn, Zn, or Sb compounds,[2] the examples known seem to concentrate on d^{10} Cu$^{\mathrm{I}}$,[3] Ag$^{\mathrm{I}}$, or Hg$^{\mathrm{II}}$ complexes.

The group of Hawthorne[4] has reported a number of such structures based on [12]mercuracarborand-4 macrocycles containing four Hg atoms defining a square plane. These electrophilic Hg atoms can bind one halide in an almost square-planar (for X = Cl) or square-pyramidal (for X = I) fashion, depending on the size of the halide. Removal of the halide guest regenerates the free host. On the other hand, the group of Puddephatt has reported the inclusion of halides in electrophilic bowl-shaped calix(4)arene complexes of Cu$^{\mathrm{I}}$ or Ag$^{\mathrm{I}}$, where the geometry imposed by the calixarene host can stabilize either μ_3- or μ_4-binding modes of the halide, depending on the size of the latter.[5] The mercury macrocycles cited above, as well as other similar ones containing three or five mercury atoms, can even take a second halide to give bipyramidal structures with one halide at each apex.[6] In all these cases the hosting electrophilic metal centers are d^{10} ions which are involved in a macrocyclic structure which exists independently of the presence of the μ_4-binding halide. We present here a case of self-assembly of d^8 metal centers and halides around a pyramidal halide to give tetrapalladium complexes. Unlike the cases reported by Hawthorne and Puddephat, in our case the metallamacrocycle owes its formation to the halide acting as a template.

The reaction of precursors of "Pd(Fmes)" (Fmes = 2,4,6-tris(trifluoromethyl)phenyl) such as **1** or **2** (Scheme 1)[7] with halides QX (the overall ratio of Pd:X is 4:5) in CH$_2$Cl$_2$ affords high yields of the tetrametallic species Q[Pd$_4$(Fmes)$_4$X$_5$] (**3**) (X = Cl, Br, I; Q = PPh$_4$ or PPN (bis(diphenylphosphane)-iminium)).[8] The formation of compounds **3** involves the displacement of MeCN and becomes easier in the order I > Br > Cl; thus, only for X = I is compound **3** readily formed starting from the MeCN-rich complex **2**.

Figure 1 shows the crystal structure of the anion in (PPN)[Pd$_4$(Fmes)$_4$Cl$_5$]. The four Pd atoms display a square-

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