Angewandte
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Reaction Mechanisms

Evidence for the Structure of the Enantioactive Ligand in the Phosphine–Copper-Catalyzed Addition of Diorganozinc Reagents to Imines**

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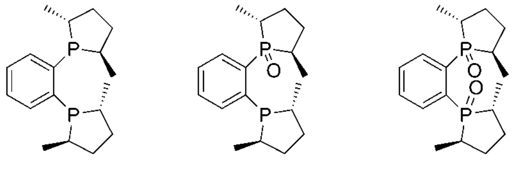
Substantial efforts have been invested recently in the design and development of new chiral ligands for the asymmetric catalytic synthesis of simple chiral building blocks. Among the most effective and popular coordinating groups for chiral ligands are phosphorus-based groups due to their inherent ability to bind strongly but reversibly to several transition metals. However, even though redox processes have been reported between the phosphorus ligand and some transition metals,[1] this potentially harmful process that could lead to important ligand modification has never been highlighted in asymmetric copper-catalyzed reactions. One well-known example is the reduction of Pd^{II} salts into Pd^0 with Ph_3P to produce $Ph_3P{=}O$ as the by-product.[2] It has also been reported that Cu^{II} salts are reduced by 1,2-bis(diphenylphosphino)ethane to produce several phosphine/phosphine oxide ligands.[3] It is surprising to see that even though Cu–phosphine complexes have been used extensively in asymmetric catalysis (conjugate additions and reduction,[4] nucleophilic addition to ketones,[5] enamines[6] and imines[7]) the in situ oxidation of the ligand has never been observed nor highlighted as the key step for high asymmetric induction. In this communication, we demonstrate that the oxidation of Me-duphos (**1**) by Cu^{II} salts to produce the highly effective monoxide ligand **2** (see Figure 1) is a key event for the high asymmetric induction of the Cu-catalyzed addition of di-



1: Me-duphos **2**: bozphos **3**: Me-duphos bisoxide

Figure 1. Phosphine and phosphine oxide ligands derived from Me-duphos.

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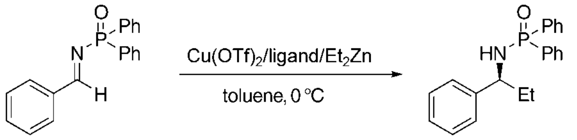
organozinc to *N*-phosphinoylimines. We also report that the efficiency of the oxidation is highly dependent upon the nature of the copper salt and the counterion used in the process.

We recently reported that Cu·**1** is an efficient catalyst for the addition of diorganozinc compounds to imines[8] (Table 1, entry 1). We later disclosed that the replacement of one phospholane group by the hemilabile phosphine oxide (ligand **2**) led to a significant increase of the reaction rate and enantiomeric excesses (Table 1, entry 2).[9]

Table 1: Effect of the order of addition in the Me-duphos-catalyzed reaction.



Entry	Method[a]	Ligand	Conv. [%]	*ee* [%]
1	A	**1**	92	89
2	A	**2**	100	97
3	B	**1**	38	0
4	B	**2**	100	97

[a] Method A: 1) $Cu(OTf)_2$ (6 mol %) and ligand **1** or **2** (3 mol %), 2) addition of Et_2Zn (2 equiv); method B: 1) $Cu(OTf)_2$ (6 mol %) and Et_2Zn (2 equiv), 2) addition of ligand **1** or **2** (3 mol %).

Although these two reactions appear to differ simply by the selection of the ligand, we were puzzled by the observation that the level of enantiocontrol was greatly dependant upon the order of addition to the reagents. For example, a high level of stereocontrol was observed with both ligands if $Cu(OTf)_2$ was mixed with Me-duphos or bozphos prior to the addition of Et_2Zn. In sharp contrast, no enantioselection was observed with Me-duphos if the Cu^{II} salt was initially reduced with Et_2Zn (to generate EtCu) followed by the addition of the chiral ligand (Table 1, entry 3). Conversely, the order of addition did not affect the *ee* value of the product if bozphos was used (Table 1, entry 4). One explanation for this behavior is that the Cu·**1** complex is only a precatalyst for the reaction, and it needs to undergo phosphine oxidation to generate the more reactive and selective Cu·**2** complex. To demonstrate whether Me-duphos oxidation is a viable pathway under the reaction conditions, we undertook a systematic spectroscopic investigation of the reaction to identify whether **2** or **3** is formed upon treatment with Cu salts. Unfortunately, the reaction could not be followed by in situ NMR methods due to the presence of paramagnetic Cu^{II}/Cu^0 species and the rapid equilibration and disproportionation between various complexes.

To overcome this problem, we removed the residual Cu salts from the crude reaction mixture by treatment with aqueous KCN under deoxygenated conditions. This is a nice alternative to the use of dithiocatechol dilithium salts, which have been used to scavenge and recover phosphine ligands.[10] Each ligand (**1**–**3**) was submitted to $Cu(OTf)_2/Et_2Zn$ by the normal or reverse-addition protocol. After a standard KCN workup, the crude mixture was analyzed by ^{31}P NMR spectroscopy (Table 2). The first striking observation is that significant oxidation (up to 20 %) of one of the free phosphine of Me-duphos was observed when the ligand was initally premixed with $Cu(OTf)_2$ (Table 2, entry 2). Conversely, inverting the order of addition almost completely suppressed the oxidation of the phosphine (only 3 % of bozphos was formed; Table 2, entry 1). The same series of experiments carried with bozphos (**2**) indicated that very little oxidation to give **3** (2–6 %) was observed regardless of the order of addition. This is not too surprising since the monoxide should be less prone to oxidation than Me-duphos. The relatively low level of oxidation with procedure A could be attributed to the background oxidation during the workup under a noninert atmosphere and not to a formal oxidation of phosphorus by the in situ formed EtCu.

Table 2: Oxidation of ligands **1**–**3** by $Cu(OTf)_2$.

$$\mathbf{1}, \mathbf{2}, \text{or } \mathbf{3} \xrightarrow[\text{(2 equiv)}]{Cu(OTf)_2^{[a]}} \text{mixture of } \mathbf{1}, \mathbf{2}, \text{and } \mathbf{3}$$

Entry	Starting ligand	Method[b]	Prod. ratio[c] **1**:**2**:**3**
1	**1**	A	96:3:1
2	**1**	B	76:20:4
3	**2**	A	0:98:2
4	**2**	B	0:94:6
5	**3**	A	0:0:100
6	**3**	B	0:0:100

[a] $Cu(OTf)_2$ was purchased from Strem Chemical Inc. [b] Method A: 1) $Cu(OTf)_2$ (2 equiv) and Et_2Zn (10 equiv), 2) addition of ligand **1**, **2**, or **3** (1 equiv); method B: 1) $Cu(OTf)_2$ (2 equiv) and ligand **1**, **2**, or **3** (1 equiv), 2) addition of Et_2Zn (10 equiv). [c] The ratios were determined by quantitative ^{31}P NMR spectroscopy, and the mass recovery was >70 %. See the Supporting Information for details.

The next step was to establish whether other species present in the reaction mixture could potentially oxidize Me-duphos to give bozphos (Table 3). CuOTf also led to significant oxidation of Me-duphos (up to 39 %; Table 3, entry 2). Conversely, both CuCl and CuOAc led to lower levels of phosphine oxidation, indicating that the nature of the counterion is also important. Since the level of oxidation appeared to be somewhat dependant upon the source of the copper salt used, we began to suspect that the presence of water could accelerate the oxidation process. Indeed, a much higher amount of oxidized product **2** was observed if a

Table 3: Oxidation of **1** with various copper salts.

$$\mathbf{1} \xrightarrow[\text{(2 equiv)}]{CuX} \mathbf{1}+\mathbf{2}+\mathbf{3}$$

Entry	CuX	Source	Prod. ratio[a] **1**:**2**:**3**
1	$(CuOTf)_2$·benzene	freshly prepared	75:20:5
2	$(CuOTf)_2$·toluene	commercial	55:39:6
3	CuOAc	commercial	90:8:2
4	CuCl	commercial	96:3:1
5	$Cu(OTf)_2\cdot 2.3\,H_2O$	freshly prepared[b]	52:42:6

[a] The ratios were determined by quantitative ^{31}P NMR spectroscopy. [b] Hydration of commercial $Cu(OTf)_2$ and analyzed by elemental analysis.

partially hydrated form of $Cu(OTf)_2$ was used (Table 3, entry 5). We also noticed that the nature of the phosphine is also very important since the replacement of Me-duphos by PPh_3 under the conditions given in Table 3, entry 2 led to about 5 % of $Ph_3P{=}O$.

Plots of the course of the reaction with (Table 1, entries 3 and 4) with different ligands ligand using the reverse-addition procedure are shown in Figure 2. The data strongly suggest that the ligand **2** is responsible for the highly enantioselective pathway. One striking feature is the difference in the reactivity between complex Cu^I·**1** and Cu^I·**2** in the reaction. This accounts for the observation that high enantioselectivities are obtained even when both complexes are present (Table 1, entry 1). The excellent catalytic activity of bis(phosphine) monoxide complexes has been observed in several reactions.[11–13] Further evidence for the structure of the active catalyst resides in the demonstration that the reaction displays first-order kinetics in catalyst (1:1 stoichiometry ligand:Cu; Figure 3).

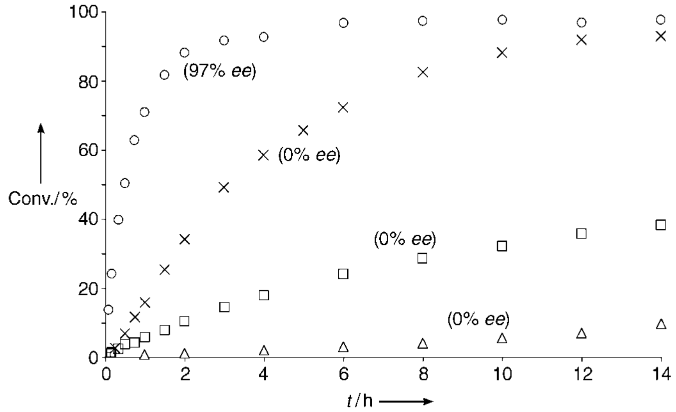


Figure 2. Plot of the course of the reaction with ligands **1**–**3** (3 mol% ligand/6 mol% $Cu(OTf)_2$). □ = Me-duphos (**1**), ○ = bozphos (**2**), △ = bozphos (**2**) without Cu, × = Me-duphos bisoxide (**3**).

In conclusion, this paper highlights the very important observation that this copper–phosphine-catalyzed process involve an initial phosphine oxidation, leading to a more reactive and selective metal complex.

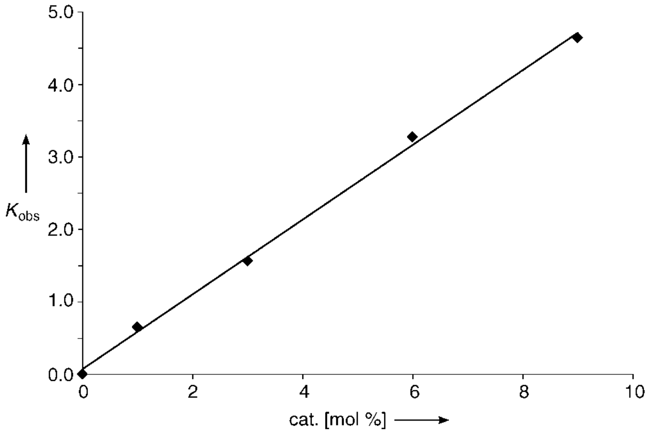


Figure 3. Plot showing that the reaction is first order in catalyst. Ratio bozphos/$Cu(OTf)_2$ = 1:1.

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