

New methods in asymmetric catalysis based on new hemi-labile bidentate ligands*

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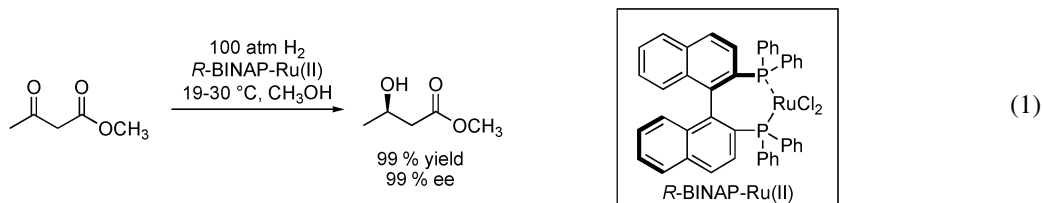
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Abstract: Chiral bidentate hemi-labile bis(phosphine) monoxide ligands were shown to be quite effective in various copper-catalyzed transformations. Among them, the nucleophilic addition to imines, the conjugate addition to α,β -unsaturated nitro derivatives, and the conjugate reduction of α,β -unsaturated sulfones generally gave good to excellent yields and high enantiomeric excesses.

Keywords: bis(phosphine) monoxide; hemi-labile bidentate ligands; organozinc; conjugate addition; chiral amines.

INTRODUCTION

The majority of highly effective asymmetric catalytic reactions involving transition metals employ C_2 -symmetric chiral ligands. One classic example is the asymmetric hydrogenation of β -ketoesters involving BINAP-RuCl₂ (eq. 1) [1]. Extensive mechanistic studies have indicated that the BINAP ligand remains bonded to the ruthenium center throughout the catalytic cycle [2]. One reason for the efficiency of bidentate ligands is their ability to transmit their chirality to the reactive metal center.

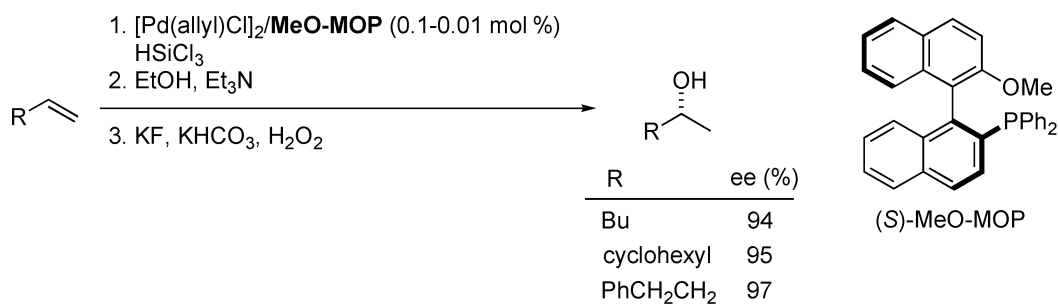


A relatively small number of asymmetric transition-metal-catalyzed transformations employ monodentate chiral ligands. For example, the asymmetric hydrosilylation of alkenes is quite effective with monophosphine ligands derived from binol (Scheme 1) [3]. It has been shown that the methoxy substituent on the chiral ligand is not directly involved in the reaction and can be replaced with a non-chelating group such as a hydrogen.

Our research group has been interested in developing new approaches to generate α -chiral amines from imines [4]. Although several methods are available to generate these compounds, the most effec-

*Paper based on a presentation at the 14th International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-14), 2–6 August 2007, Nara, Japan. Other presentations are published in this issue, pp. 807–1194.

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Scheme 1

tive ones, up until recently, rely on chiral auxiliary-based approaches [5]. While major research efforts of the 1980s and 1990s have been devoted to the catalytic asymmetric nucleophilic addition reactions to carbonyl derivatives, the analogous reactions using imines as electrophiles have emerged only recently [6].

One transformation of particular interest to us was the nucleophilic addition of non-stabilized carbanions to *N*-phosphinoylimines (Fig. 1). We envisioned that diorganozinc reagents would be a suitable class of nucleophiles to initially study this reaction. Indeed, it had been shown that transmetalation from a diorganozinc to copper proceeds smoothly and with high ee in conjugate addition chemistry when a suitable chiral ligand is used [7]. Furthermore, the *N*-phosphinoyl group is quite appealing, since it increases the electrophilicity of the imine relative to *N*-arylimines [8], and the cleavage of the phosphinoyl group, after the addition, can be easily accomplished under mild acidic conditions.

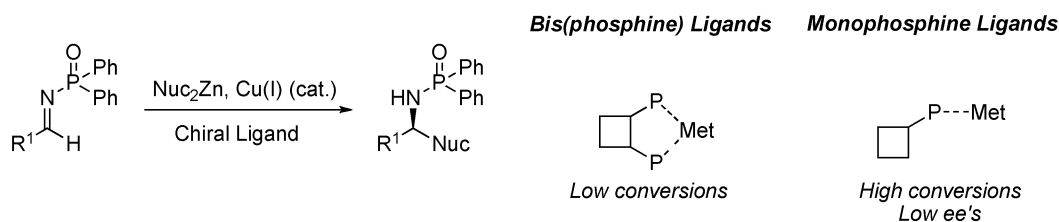


Fig. 1 Bis(phosphine) vs. monophosphine.

A large number of chiral ligands were tested in this reaction in order to learn what type of phosphines can stabilize the various catalytic intermediates. Bis(phosphine) ligands generally produced low yields of the products, whereas monodentate ligands gave high yields but low enantioselectivities. In view of this, we envisioned developing new chiral ligands that would combine the outstanding chirality transmission of bidentate ligands with the high reactivity of metal complexes bearing monodentate ligands.

It was anticipated that the use of a bidentate, hemi-labile chiral ligand would perfectly fit this purpose. We believed that higher turnover numbers could be achieved if one Lewis basic group on the ligand would reversibly bind to the metal center. Generating a free coordination site upon decomplexation may be beneficial in facilitating the transmetalation step and catalyst regeneration in the catalytic cycle.

A readily available class of bidentate, hemi-labile chiral ligands are the bis(phosphine) monoxides. Although the first ligand in this class was prepared in the early 1960s, there are very few highly efficient applications of these ligands in asymmetric catalysis [9]. The phosphine oxide site, known as the hard site, will have a preference to bind to high oxidation-state metals and early transition metals (Fig. 2) [10].

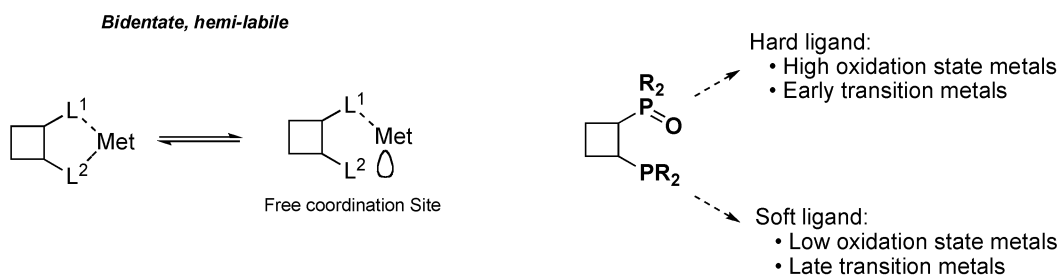
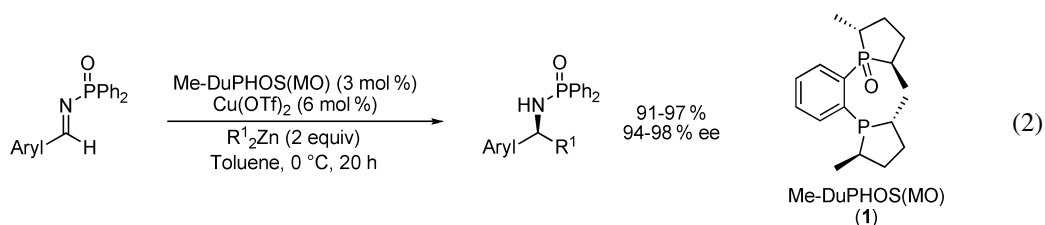


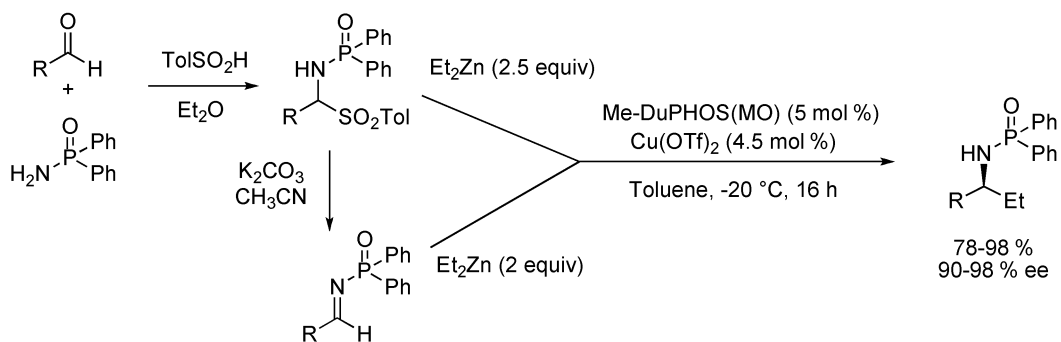
Fig. 2 Different reactivities of hemi-labile ligands.

Conversely, the phosphine site will bind preferentially to low oxidation-state metals and late transition metals. It is believed that this combination will be optimal for the copper-catalyzed reaction involving diorganozinc reagents.

Screening of bis(phosphine) monoxide ligands led to the discovery that ligand **1**, derived from Me-DuPHOS, was extremely efficient for the copper-catalyzed nucleophilic addition to *N*-phosphenoylimines derived from aryl-substituted aldehydes (eq. 2) [11].

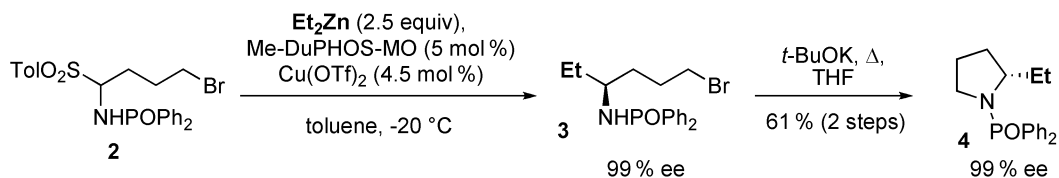


The *N*-phosphenoylimines derived from alkyl-substituted aldehydes were also quite effective electrophiles in this reaction. However, due to their relative sensitivity, it was best to prepare the starting materials in situ from their *p*-toluenesulfonic acid adducts using an extra equivalent of the diorganozinc reagent (Scheme 2) [12]. Although the *p*-toluenesulfonic acid adduct is very stable in the solid state, it is in equilibrium with the imine when dissolved in dimethyl sulfoxide. If an expensive nucleophile is used, it is best to convert the starting *p*-toluenesulfonic acid adduct into the *N*-phosphenoylimine with potassium carbonate in acetonitrile. Filtration and concentration of this solution led to the corresponding imine; however, unlike its aryl-substituted counterpart, this imine could not be stored for more than several weeks without undergoing significant decomposition.



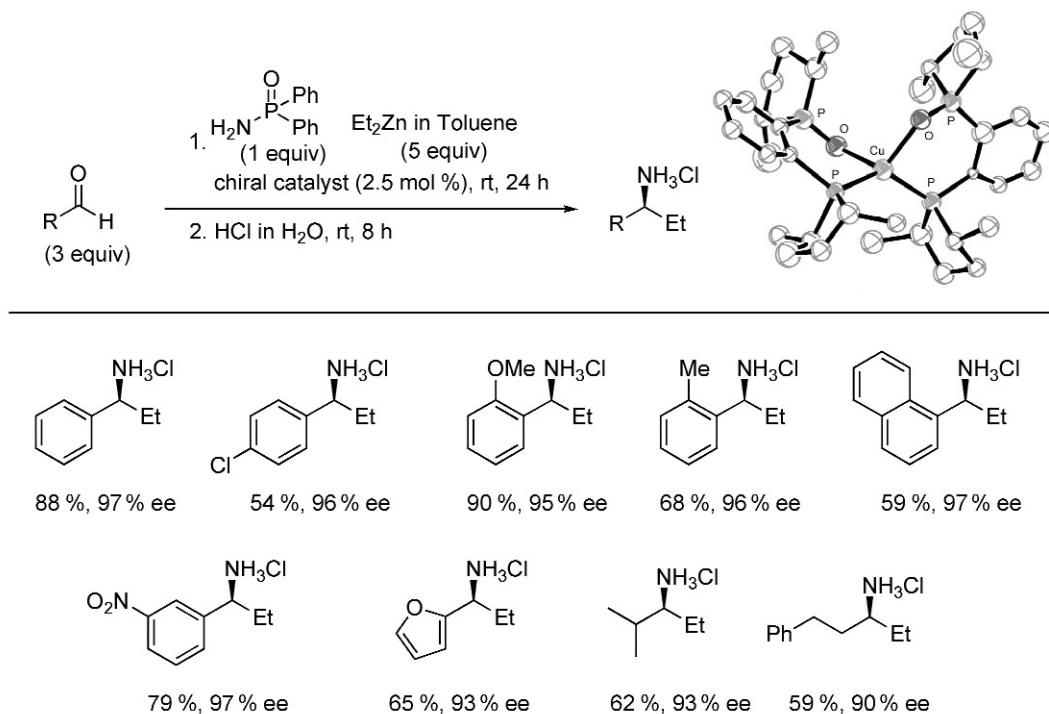
Scheme 2

One advantage of using diorganozinc reagents is their functional group compatibilities. An application of this reaction is shown in Scheme 3. It is possible to generate the *p*-toluenesulfonic acid adduct of the *N*-phosphinoylimine derived from γ -bromobutyraldehyde. Adduct **2**, when treated with diethylzinc in the presence of a catalytic amount of Cu(II) triflate and Me-DuPHOS(MO), generated the protected amine **3** in 97 % ee. A subsequent ring closure under basic conditions led to the 2-substituted pyrrolidine **4** in good yield and high ee.



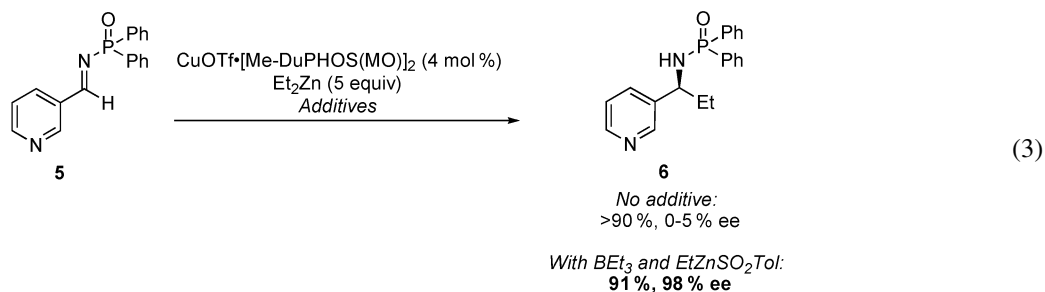
Scheme 3

To facilitate the preparation of α -chiral amines, we developed a one-pot multicomponent procedure from commercially available starting materials [13]. The reaction involves mixing an aldehyde, diphenylphosphinic amide, a dialkylzinc and an air-stable Cu(I)-[Me-DuPHOS(MO)]₂ complex in toluene for 24 h at room temperature. A subsequent acidic work-up led to the corresponding hydrochloride salts of α -chiral amines in good yields and high ee. It is worth mentioning that the air-stable precatalyst is easily prepared from Cu(I) triflate and 2 equiv of Me-DuPHOS(MO). This complex is so stable that it can be chromatographed without taking any precautions to remove oxygen. An X-ray crystal structure of the complex is shown below (Scheme 4). We believe that this complex is a precatalyst for the reaction that needs to lose one ligand before transmetalation with the dialkylzinc can occur.



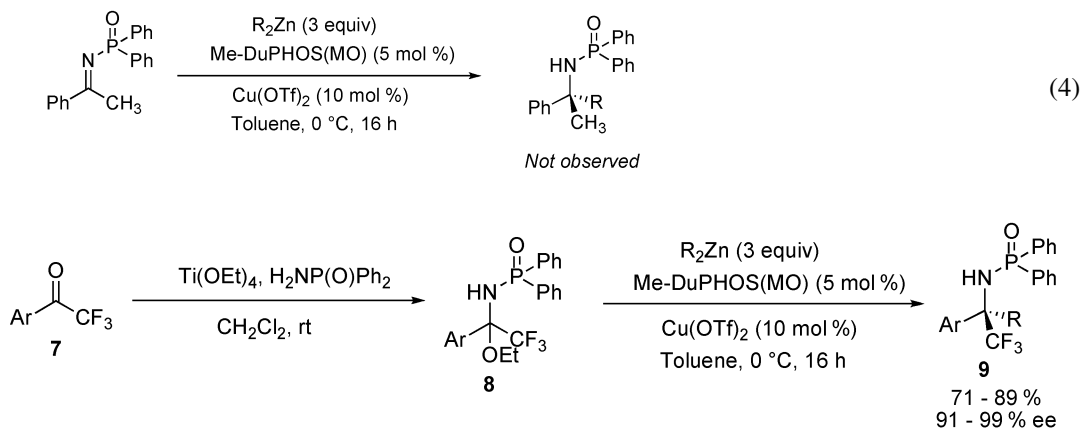
Scheme 4

It is not possible to use these conditions to generate α -chiral amines bearing heterocycles containing basic nitrogen atoms (eq. 3). For example, racemic protected amine **6** was obtained when imine **5** was treated under the standard conditions.



In order to achieve a highly enantioselective addition, a Lewis acidic additive must be added to temporarily protect the basic nitrogen. After extensive screening of Lewis acids, it was found that pre-complexing imine **5** with a stoichiometric mixture of triethylborane and ethylzinc *p*-toluenesulfonate led to a very efficient addition reaction that produced the protected α -chiral amine **6** in high yield and high enantioselectivity. These conditions were effective with a large number of imines bearing a heterocycle containing a Lewis basic atom.

The enantioselective addition to *N*-phosphinoylketimines bearing α -acidic protons was not successful (eq. 4). Presumably, proton abstraction was the major side reaction with these substrates. The only successful examples are with imines derived from aryl trifluoromethyl ketones (Scheme 5) [14]. When aryl trifluoromethyl ketones **7** were treated with diphenylphosphinic amide in the presence of titanium tetraethoxide, the ethanol adducts **8** were obtained in good yields. The reaction proceeds well with aryl groups bearing electron-donating as well as electron-withdrawing substituents. It should be pointed out that this adduct is not very stable and it fragments under mild conditions to the required electrophilic imine. A subsequent addition reaction using excess nucleophile led to the addition products **9** in high yields and ee.



Scheme 5

The working model for the asymmetric induction is shown in Fig. 3. We believe that the phosphine ligand binds to the ethylcopper species, and the phosphine oxide preferentially binds to ethylzinc triflate. Our working model is that this helps speed up the transmetalation process to regenerate the catalyst. It is unclear whether or not chirality is required on both ligands.

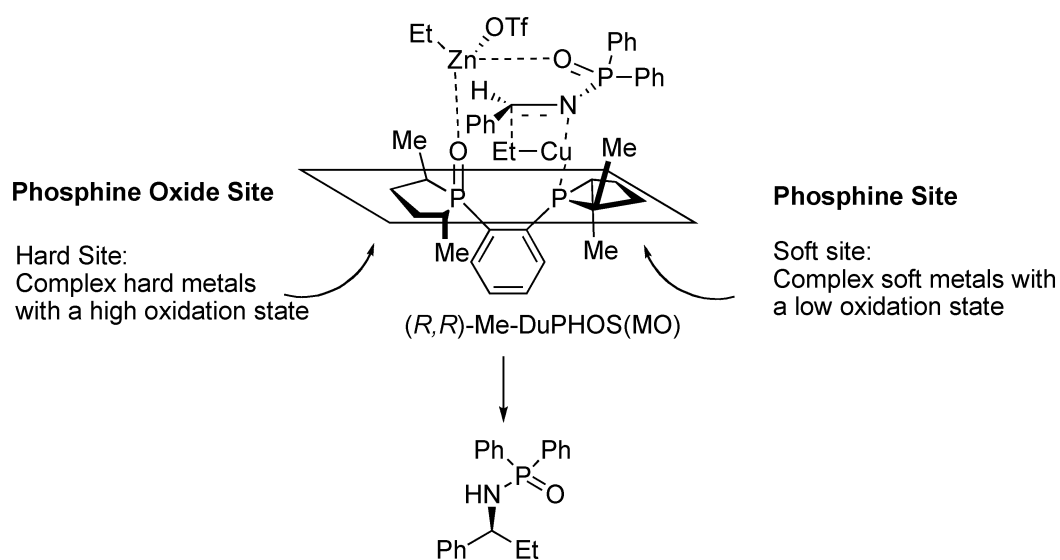
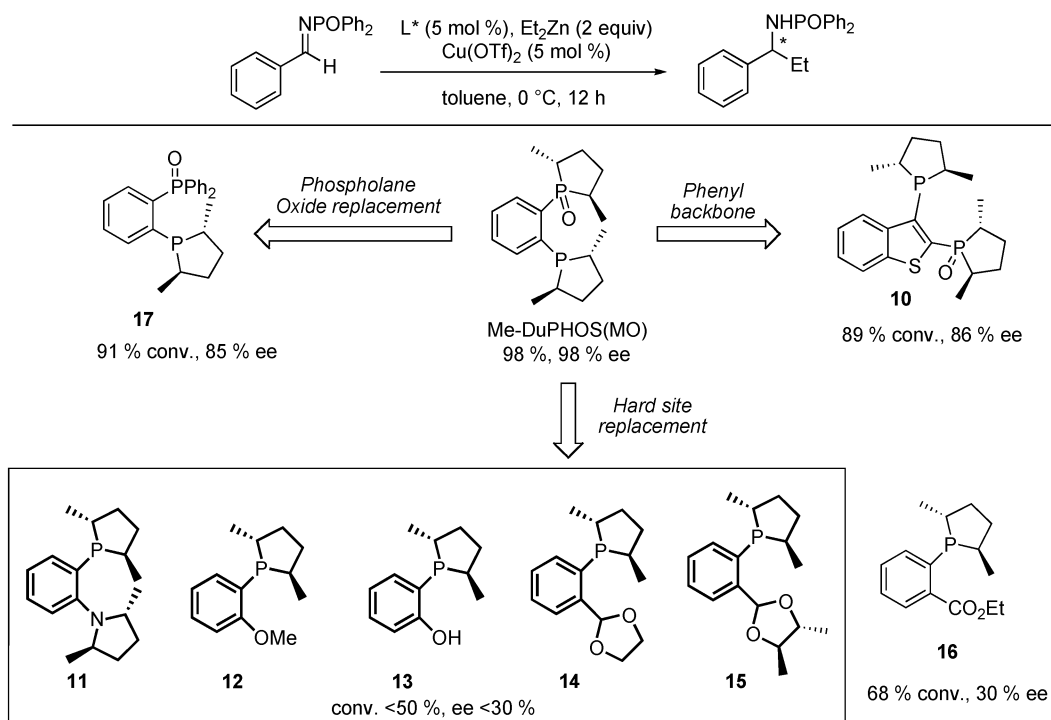


Fig. 3 Asymmetric induction of Me-DuPHOS(MO).

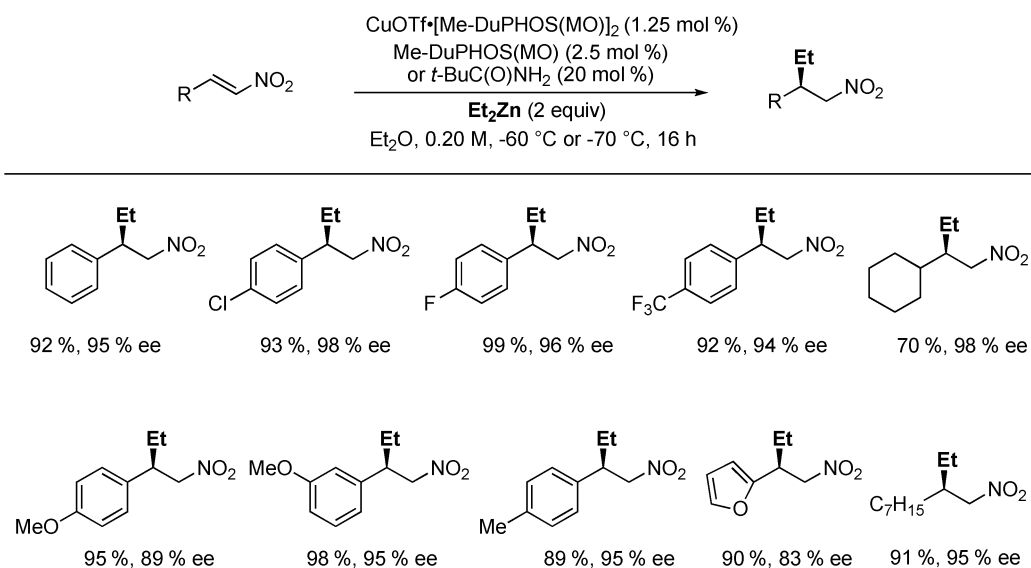
In order to gain more insight into the nature of the stereochemical induction in these reactions, we varied the structure of the ligand to evaluate the importance of both Lewis basic ligands (Scheme 6). When the phenyl linker was replaced by a benzothiophenyl group (ligand **10**), good enantioselectivities were observed. Conversely, when the phosphine oxide Lewis basic group was replaced by several other



Scheme 6

groups such as amines (**11**), ethers (**12**), zinc alkoxides (**13**), and acetals (**14–15**), low enantioselectivities were observed. The replacement of the phosphine oxide ligand by an ester group (**16**) led to modest enantioselectivities. Finally, the substitution of the chiral phospholane oxide by a diphenylphosphine oxide (ligand **17**) led to good enantioselectivities. This last example seems to indicate that chirality on the hemi-labile ligand is not mandatory in order to obtain high enantioselectivities; however, having a phosphine oxide appears to be necessary.

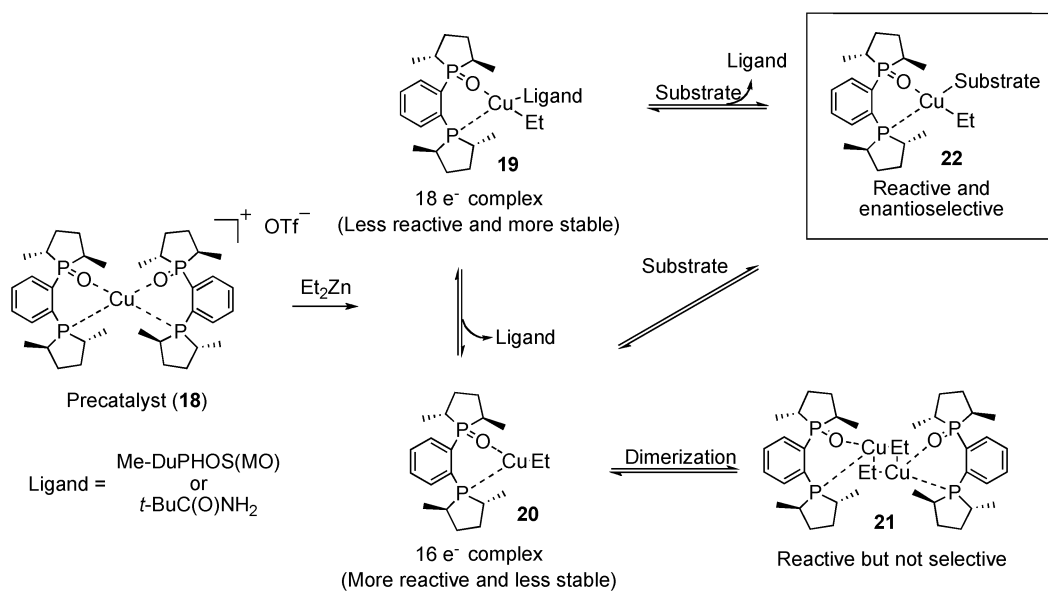
Our next efforts were directed at further exploring the synthetic utility of these hemi-labile, bidentate ligands. Me-DuPHOS monoxide was shown to be a very effective ligand in the asymmetric copper-catalyzed addition of dialkylzinc reagents to α,β -unsaturated nitro derivatives providing access to chiral nitroalkanes [15]. The scope of the reaction is shown in Scheme 7. The reaction is quite efficient, producing high yields and high enantioselectivities. The addition was successful with β -aryl- and β -alkyl-substituted nitroalkenes. One striking difference, however, is that an excess of a Lewis basic ligand (chiral or achiral) is required in this reaction for obtaining high enantioselectivities. In the absence of such a ligand, high yields of the products are obtained but with low enantioinduction. We believe that the role of the Lewis basic ligand is to ensure that the reactive alkylcopper species remains monomeric (such as **19** in Scheme 8). In the absence of a Lewis basic ligand, we believe that the ethylcopper species **20** forms reactive aggregates (such as **21**) that lead to a less enantioselective transformation. The products obtained from these reactions are quite synthetically useful. They can be reduced to amines or converted into nitriles or aldehydes [16].



Scheme 7

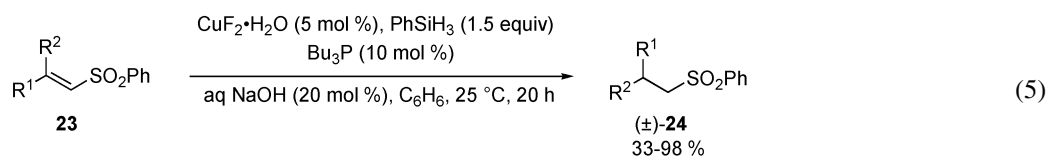
The effectiveness of this ligand in copper-catalyzed processes led us to explore its use in other reactions such as in the copper hydride reduction of β,β -disubstituted alkenes bearing an electron-withdrawing group.

The copper-catalyzed hydrosilylation of prochiral unsaturated derivatives bearing electron-withdrawing substituents has been very versatile. β,β -disubstituted- α,β -unsaturated carbonyls, nitroalkenes, imines, ketones, and nitriles have been reduced in high yields under these conditions [17]. Quite surprisingly, there were no reports on the conjugate reduction of α,β -unsaturated sulfone derivatives **23** [18].



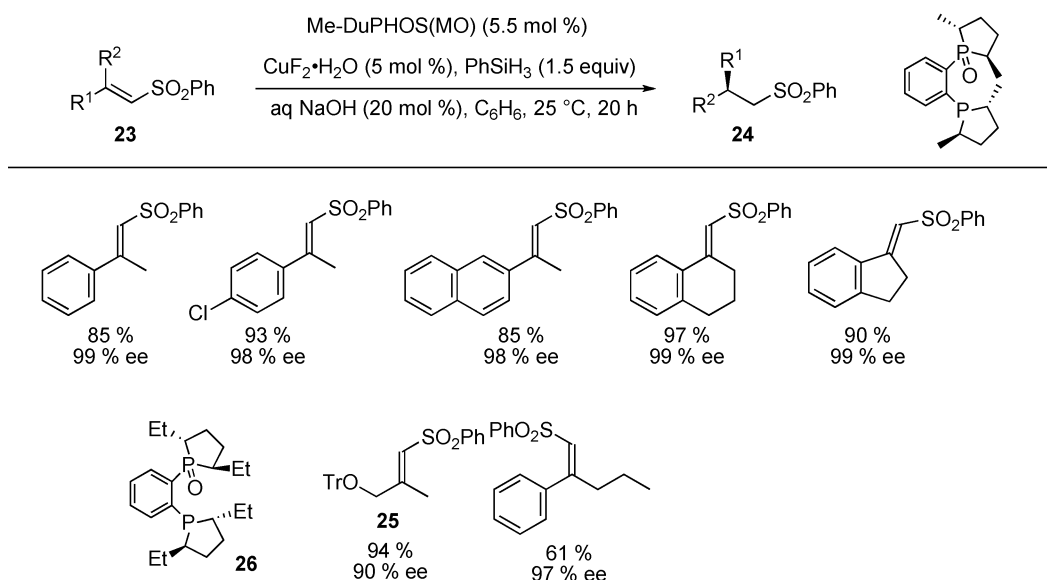
Scheme 8

Our initial efforts were focused on determining whether achiral phosphines could be used as ligands in the copper-catalyzed silane reduction. After considerable optimization, it was found that treatment of sulfones **23** with phenylsilane in the presence of catalytic Cu(II) fluoride, tributylphosphine, and aqueous sodium hydroxide led to the reduced products in high yields (eq. 5).



Gratifyingly, replacement of tributylphosphine by Me-DuPHOS monoxide led to a very efficient and highly enantioselective reaction (Scheme 9) [19]. One exception is for the reduction of sulfone **25** for which Me-DuPHOS(MO) led to the reduced product in 70 % ee. However, replacement of Me-DuPHOS(MO) with the Et-DuPHOS analog **26** led to a highly selective reaction.

In conclusion, we have shown that hemi-labile bidentate ligands derived from bis(phosphine) are quite useful in asymmetric catalysis. Further work is in progress to exploit these ligands in other asymmetric transformations.



Scheme 9

ACKNOWLEDGMENTS

This work was supported by NSERC, Merck Frosst Canada, Boehringer Ingelheim (Canada), the Canada Research Chairs Program, the Canadian Foundation for Innovation, and the Université de Montréal. A.C. is grateful to NSERC (ES D) and to TD Bank Financial Group for postgraduate fellowships. J.-N.D. is grateful to NSERC (CGS D) and to TD Bank Financial Group for postgraduate fellowships. I.B. is grateful to the Université de Montréal for postgraduate fellowship. We also thank Solvias AG for generously providing us with the *R,R*-butiphane used in these studies.

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