Communication

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J. Am. Chem. Soc., **2003**, 125 (47), 14260-14261• DOI: 10.1021/ja038291+ • Publication Date (Web): 30 October 2003

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Published on Web 10/30/2003

Asymmetric, Catalytic Synthesis of α-Chiral Amines Using a Novel Bis(phosphine) Monoxide Chiral Ligand

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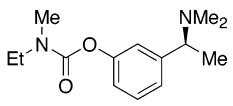
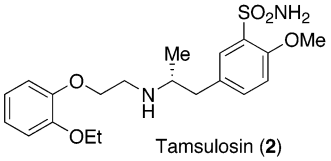
The enantioselective synthesis of α-chiral amines is of primary importance because these chiral synthons are among the most important and commonly found subunits in chiral drugs.[1] Furthermore, these compounds are also useful building blocks for the synthesis of new ligands and natural products. Some relevant examples include rivastigmine (**1**, alzheimer), tamsulosin (**2**, prostate), indanorex (**3**, amphetamine), and repaglinide (**4**, hypoglycemic agent).



Rivastigmine (**1**)



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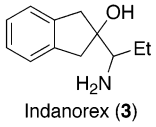
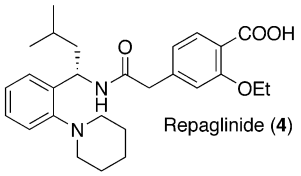
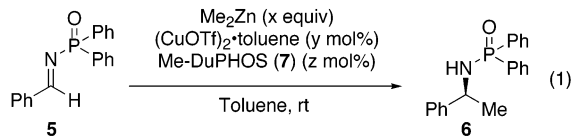


Indanorex (**3**)



Repaglinide (**4**)

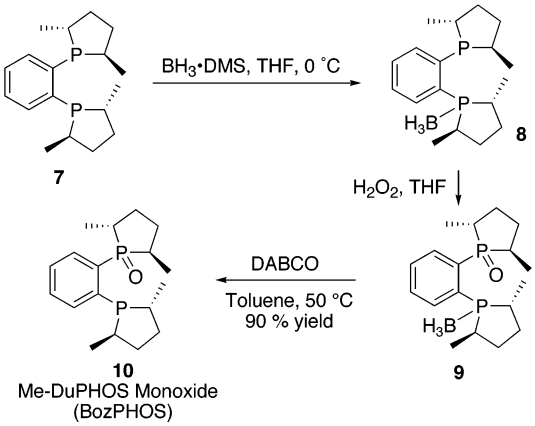
Recently, several methods based on the catalytic, enantioselective addition of diorganozinc reagents to activated aryl-,[2] acyl-,[3] or sulfonylimines[4] have been described. Although these methods are quite effective for the addition of diethylzinc and higher diorganozinc reagents to imines, the efficient addition of dimethylzinc is still problematic. In the most successful systems to date, a large excess (10−15 equiv) of the reagent and higher catalyst loadings are required. Furthermore, modest enantiomeric excesses (84−88%) and conversions are observed. This important drawback has also been observed in our recent report indicating that Me-DuPHOS·$Cu(OTf)_2$ is a superb catalyst for the catalytic asymmetric addition of diorganozinc reagents to *N*-phosphinoylimines.[5,6] Although the addition of diethylzinc proceeds very well, the addition of dimethylzinc requires 10 equiv of the reagent and a much higher catalyst loading (10 mol %) (eq 1). Conversely, very low conversions and enantioselectivities were observed if the number of equivalents was reduced to a practical level.



x = 10; y = 9.5; z = 10	51% yield, 90% ee
x = 10; y = 5; z = 5	35% yield, 73% ee
x = 5; y = 10; z = 5	20% yield, ---

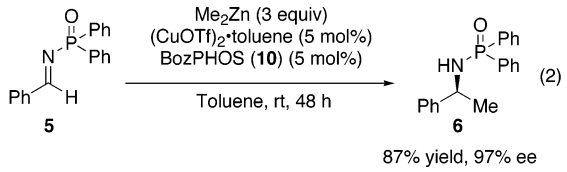
The lack of reactivity of Me_2Zn combined with the importance of the addition products in synthesis convinced us that new and more effective chiral ligands should be developed for this transformation. In this Communication, we report that a novel ligand based on the bis(phosphine) monoxide framework is a valuable ligand for this reaction.

Scheme 1



The rationale for the ligand modication originated from the observation that a significant rate acceleration for this reaction was observed with monodentate phosphines as well as with bidentate ligands bearing one labile group. Furthermore, we observed that the reaction was completely inhibited if ≥2 equiv of Me-DuPHOS (**8**) relative to Cu were used. These results led us to screen a large number of bis(phosphine) monoxide ligands,[7] and we were quite pleased to discover that Me-DuPHOS monoxide (BozPHOS) was a very effective ligand for the copper-catalyzed diorganozinc addition to *N*-phosphinoylimines. This ligand is easily prepared in three steps and 90% overall yield from Me-DuPHOS (Scheme 1).

The reactivity difference between Me-DuPHOS (**7**) and BozPHOS (**10**) is quite striking for the addition of dimethylzinc to the *N*-phosphinoylimine derived from benzaldehyde (eq 2). A lower catalyst loading led to a high yield and enantiomeric excess for the reduction of **5** to **6**.



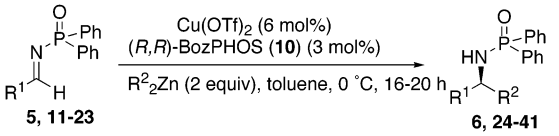
87% yield, 97% ee

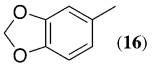
Conversely, the yield was only 48% and the product was 92% ee when the reaction was carried out with Me-DuPHOS under the same conditions.

This rate acceleration and increase in the enantiomeric excess of the product with this ligand are also observed in the addition of other diorganozinc reagents to *N*-phosphinoylimines. As the data summarized in Table 1 illustrate, the BozPHOS·Cu-catalyzed

10.1021/ja038291+ CCC: $25.00

Table 1. **10**·Cu-Catalyzed Addition of Diorganozinc to Imines

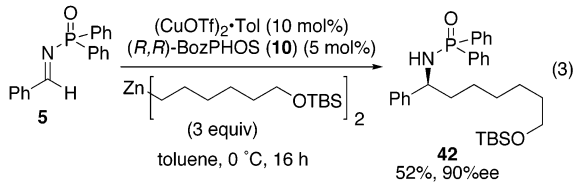


Entry	R^1	R^2	yield (%)	ee [a,b]
1	Ph (**5**)	Et	96 (**24**)	98 (96)
2	4-MeC_6H_4 (**11**)	Et	94 (**25**)	98 (95)
3	3-MeC_6H_4 (**12**)	Et	96 (**26**)	97 (94)
4	4-ClC_6H_4 (**13**)	Et	97 (**27**)	97 (90)
5	4-BrC_6H_4 (**14**)	Et	97 (**28**)	97 (92)
6	4-MeOC_6H_4 (**15**)	Et	91 (**29**)	98 (95)
7	 (**16**)	Et	93 (**30**)	98 (95)
8	1-naphthyl (**17**)	Et	93 (**31**)	97 (92)
9	2-naphthyl (**18**)	Et	96 (**32**)	97 (93)
10[c]	2-furyl (**19**)	Et	97 (**33**)	96 (89)
11	cyclopropyl (**20**)	Et	95 (**34**)	94 (85)
12	2-MeOC_6H_4 (**21**)	Et	98 (**35**)	98
13	2-ClC_6H_4 (**22**)	Et	96 (**36**)	92
14	2-MeC_6H_4 (**23**)	Et	97 (**37**)	99
15[d]	Ph (**5**)	Me	87 (**6**)	97 (90)
16[d]	3-MeC_6H_4 (**12**)	Me	80 (**38**)	92
17[e]	2-furyl (**19**)	Me	90 (**39**)	89
18[f]	Ph (**5**)	*n*-Bu	92 (**40**)	96 (91)
19[g]	Ph (**5**)	*i*-Pr	84 (**41**)	95

[a] Enantiomeric excesses were determined by HPLC on chiral stationary phase. [b] The ee's in parentheses are those obtained with Me-DuPHOS (ref 5). [c] 2.8 mol % of $Cu(OTf)_2$ and 3 mol % of **10** were used. [d] 5 mol % of $(CuOTf)_2$·toluene, 5 mol % of **10**, and 3 equiv of Me_2Zn were used (room temperature, 48 h). [e] 2.5 mol % of $(CuOTf)_2$·toluene, 5 mol % of **10**, and 3 equiv of Me_2Zn were used (room temperature, 48 h). [f] 5 mol % of $(CuOTf)_2$·toluene, 5 mol % of **10**, and 2 equiv of Bu_2Zn were used (0 °C, 20 h). [g] 10 mol % of $Cu(OTf)_2$, 5 mol % of **10**, and 3 equiv of *i*-Pr_2Zn were used (0 °C, 16 h).

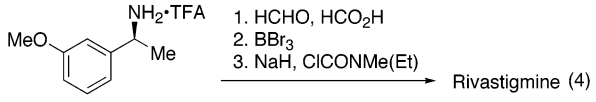
addition of dialkylzinc reagents to *N*-phosphinoylimines is quite general, the main limitation being the availability of the *N*-phosphinoylimine precursor. In all cases tested, significant increases in product ee's were observed when compared to the related MeDuPHOS-catalyzed addition (entries 1−11). The most striking examples are the imine derived from 2-furaldehyde (entry 10) and from cyclopropane carboxyaldehyde (entry 11), which gave the corresponding α-chiral amine in much higher enantiomeric excess. Furthermore, the reaction was shown to be very effective with imines bearing 2-substituted aryl groups (entries 12−14). Several other diorganozinc reagents (Me_2Zn, *n*-Bu_2Zn, and *i*-Pr_2Zn) were also added with high enantiocontrol (entries 16−19).

The reaction is also compatible with the use of functionalized diorganozinc reagents (eq 3).[8] It is usually preferable to use copper(I) triflate when valuable dialkylzinc reagents or Me_2Zn are used.



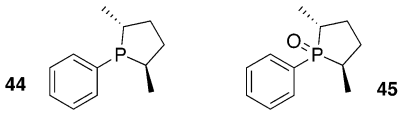
The rivastigmine precursor **43** is readily available in 88% yield and 92% ee when dimethylzinc is added to the suitable imine precursor. The enantiomeric excess of the product could be increased to 99% after a single recrystallization (67% yield). A simple deprotection/methylation/carbamoylation sequence led to rivastigmine in high overall yield.[9]

The bidentate ligand **10** containing a hemilabile ligand behaves in a unique manner in this reaction, and the cooperative effect of



43
88% yield, 92% ee
67% yield, 99% ee (1 recryst.)

both donor groups is essential to reach high enantioselectivities. The use of borane adduct **8** as a ligand which is ineffective in this reaction (<10% conversion) supports this hypohesis. High conversions to racemic product **24** were observed with phosphine **44** or phosphine oxide **45**. Furthermore, an equimolar mixture of **44** and **45** led to good catalytic activity, but no enantioinduction for the addition of diethylzinc to imine **5** was observed. These observations are consistent with the conclusion that both groups possessing different binding properties are instrumental for high chiral induction.



In conclusion, we have shown that Me-DuPHOS monoxide is a very effective ligand in the copper-catalyzed addition of dialkylzinc to *N*-phosphinoylimines. The major advantages of this process are high yields and enantioselectivities as well as the mild conditions for the deprotection of the *N*-protecting group.[10] The study of further applications of bis(phosphine) monoxide ligands in asymmetric catalysis is in progress.

Acknowledgment. This work was supported by NSERC, Merck Frosst Canada, Boehringer Ingelheim (Canada), and the University de Montréal. A.A.B. is grateful to NSERC (PGF B) and F.C.A.R. (B2) for postgraduate fellowships.

Supporting Information Available: Experimental procedures and data for each reaction (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Reviews: (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094.:
(2) (a) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984−985. (b) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409−10410. (c) Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2003**, *5*, ASAP.
(3) (a) Dahmen, S.; Bräse, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940−5941. (b) Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692−3694.
(4) (a) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055−12056. (b) Nagai, K.; Fujihara, H.; Kuriyama, M.; Yamada, K.; Tomioka, K. *Chem. Lett.* **2002**, 8−9. (c) Hayashi, T.; Ishigedani, M. *Tetrahedron* **2001**, *57*, 2589−2595. (d) Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976−977.
(5) Boezio, A. A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 1692−1693.
(6) For examples of stoichiometric ligands, see: (a) Jimeno, C.; Reddy, K. S.; Sola, L.; Moyano, A.; Pericas, M. A.; Riera, A. *Org. Lett.* **2000**, *2*, 3157−3159. (b) Sato, I.; Kodaka, R.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2912−2914. (c) Pinho, P.; Andersson, P. G. *Tetrahedron* **2001**, *57*, 1615−1618. (d) Zhang, H. L.; Zhang, X. M.; Gong, L. Z.; Mi, A. Q.; Cui, X.; Jiang, Y. Z.; Choi, M. C. K.; Chan, A. S. C. *Org. Lett.* **2002**, *4*, 1399−1402.
(7) Only a few chiral BPMO ligands have been reported thus far: (a) Marshall, W. J.; Grushin, V. V. *Organometallics* **2003**, *22*, 555−562. (b) Grushin, V. V. *Organometallics* **2001**, *20*, 3950−3961. (c) Grushin, V. V. *J. Am. Chem. Soc.* **1999**, *121*, 5831−5832. (d) Coye, R. J.; Slovokhotov, Y. L.; Antipin, M. Y.; Grushin, V. V. *Polyhedron* **1998**, *17*, 3059−3070.
(8) Knochel, P. Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React.* **2001**, *58*, 417−731.
(9) Amstutz, R.; Enz, A.; Marzi, M.; Boelsterli, J.; Walkinshaw, M. *Helv. Chim. Acta* **1990**, *73*, 739−753.
(10) (a) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634−5635. (b) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712−4713.

JA038291+