J|A|C|S
COMMUNICATIONS

Published on Web 01/21/2003

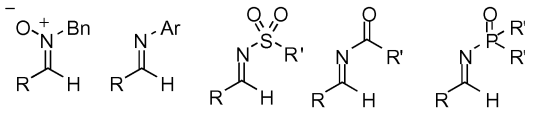
Catalytic Enantioselective Addition of Dialkylzinc to *N*-Diphenylphosphinoylimines. A Practical Synthesis of α-Chiral Amines

Alessandro A. Boezio and André B. Charette*

Département de Chimie, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal, Québec, Canada H3C 3J7

Received July 12, 2002; E-mail: andre.charette@umontreal.ca

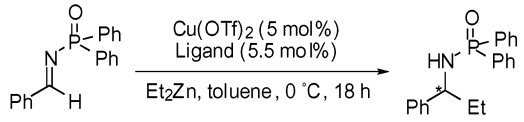
The catalytic, enantioselective addition of nucleophiles to imines is a very important process[1] due to the predominant role that α-chiral amines play in biologically important systems. Efficient catalysts have been developed for amine synthesis, but the nature of the starting imine plays a prominent role for the success of these reactions. Alkynylzinc reagents have been added to nitrones **1**,[2] whereas dialkylzinc reagents have been added to *N*-arylimines **2**,[3] *N*-sulfonylimines **3**,[4] and *N*-acylimines **4**[5] in the presence of the appropriate chiral catalyst or ligand. Although these methods are highly enantioselective, harsh conditions are sometimes required to reveal the amine functionality. A very attractive precursor to chiral, nonracemic amines is the *N*-phosphinoylimine **5**; however, its lower electrophilicity has resulted in the observation that significant amounts of ligands (0.5−1 equiv) were necessary for obtaining high enantioselectivities.[6] Conversely, the main advantage of this approach is that the resulting α-chiral amine is readily revealed under mild conditions, making this method very attractive relative to those requiring oxidizing, reducing, or acidic conditions for the cleavage. In this communication, we report that the enantioselective addition of dialkylzinc reagents to *N*-diphenylphosphinoylimines is efficiently catalyzed by a copper(II) triflate/diphosphine complex.[7] The lower electrophilicity of the imine is overcome by an increased nucleophilicity of the reagent imparted by the strong donating ability of the ligand.



1 **2** **3** **4** **5**

The copper-catalyzed addition of dialkylzinc reagents to electrophiles, which presumably proceeds via an organocopper intermediate, is a well-established process. This exchange has been successfully used in a number of asymmetric processes such as in conjugate addition[8,9] and in nucleophilic addition reactions.[4] Our interest in the development of new stereoselective methods for the nucleophilic addition to C=N[10] led us to explore new chiral copper•phosphine complexes in the nucleophilic addition to *N*-phosphinoylimines. Our initial efforts focused on the identification of the optimal copper(II) catalyst in terms of both conversions and enantiomeric ratios. Numerous mono- and bidentate phosphines were screened, and a small sample of these results is highlighted in Table 1. The first important conclusion was that the conversions to the protected amine were very good in most cases. The exceptions were with weaker donating phosphines (entries 1 and 2) and with sterically hindered ligands (entries 8 and 9). It appears that the catalysts based on $Cu(OTf)_2$ and a dialkylarylphosphine or a diarylalkylphosphine are more reactive that those involving a triarylphosphine. More importantly, the observed enantiomeric ratios

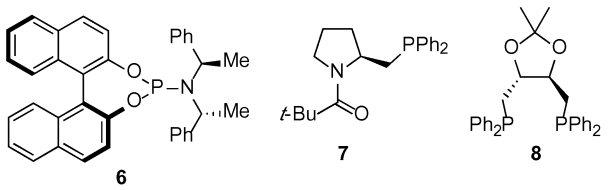
Table 1. $Cu(OTf)_2$•L_2 Catalyzed Addition of Et_2Zn to *N*-Diphenylphosphinoylimines



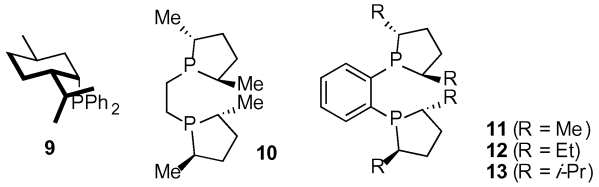
entry	ligand[a]	conversion (%)[b]	ee[c]
1	(*R*)-BINAP	75	39 (*R*)
2	**6**[d]	61	5 (*S*)
3	**7**	95	23 (*R*)
4	(*S*,*S*)-DIOP (**8**)	81	13 (*S*)
5	**9**[d]	>95	5 (*R*)
6	**10**	63	36 (*R*)
7	**11**	96	93 (*S*)
8	**12**	44	38 (*S*)
9	**13**	<10	nd

[a] Unless otherwise noted, 5.5 mol % of the ligand was used. [b] Conversions were determined by ^1H NMR. [c] Enantiomeric excesses (ee) were determined by SFC and/or HPLC on chiral stationary phases. The absolute stereochemistry was established by comparison with literature data. [d] 11 mol % of the ligand was used.

were significant in many cases, indicating that the ligand is involved in the addition step. Gratifyingly, (*R*,*R*)-Me-DuPHOS (**11**) gave an outstanding enantiomeric excess for the addition of diethylzinc to the *N*-diphenylphosphinoylimine derived from benzaldehyde. Quite interestingly, the rate of the reaction and the observed enantiomeric excess decreased dramatically with more sterically demanding ligands (compare entry 7 with 8 and 9).



6 **7** **8**



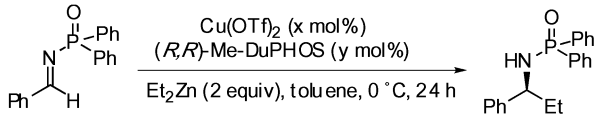
9 **10**

11 (R = Me)
12 (R = Et)
13 (R = *i*-Pr)

(*R*,*R*)-Me-DuPHOS (**11**) was chosen as the best chiral ligand for further optimization, and the results are shown in Table 2. An increase in catalyst loading from 5.0 to 8.0 mol % led to an improved enantiomeric excess (entry 1 vs 2). It is apparent in these reactions that the copper(II) catalyst is initially reduced to a copper(I) species by Et_2Zn because CuOTf is also a suitable catalyst precursor. However, the enantiomeric excess is lower under these

10.1021/ja027673x CCC: $25.00

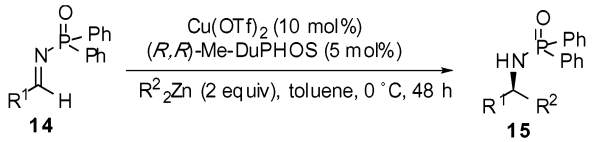
Table 2. Optimization of the Reaction Conditions



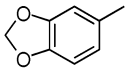
entry	*x*	*y*	conversion (%)[a]	ee[b]
1	5.0	5.5	96	93
2	8.0	8.5	96	96
3	2.5[c]	5.5	85	86
4[d]	5.0	5.5	86	96
5	10.0	5.0	95	96
6[e]	10.0	5.0	88	96
7	6.0	3.0	95	93
8	10.0	3.0	93	95

[a] Conversions were determined by ^{1}H NMR. [b] Enantiomeric excesses were determined by HPLC on chiral stationary phase. See the Supporting Information for details. [c] $(CuOTf)_2 \cdot C_6H_5CH_3$ was used. [d] $Zn(OTf)_2$ (5 mol %) was used as an additive. [e] Reaction was carried out at −15 °C.

Table 3. Addition of Et_2Zn to *N*-Diphenylphosphinoylimines



14 **15**

Entry	R^1	R^2	yield (%)	ee [a]
1	Ph (**14a**)	Et	94 (**15a**)	96
2	4-MeC_6H_4 (**14b**)	Et	91 (**15b**)	95
3	3-MeC_6H_4 (**14c**)	Et	98 (**15c**)	94
4	4-ClC_6H_4 (**14d**)	Et	95 (**15d**)	90
5	4-BrC_6H_4 (**14e**)	Et	96 (**15e**)	92
6	4-$MeOC_6H_4$ (**14f**)	Et	74 (**15f**)	95
7	 (**14g**)	Et	81 (**15g**)	95
8	1-naphthyl (**14h**)	Et	93 (**15h**)	92
9	2-naphthyl (**14i**)	Et	94 (**15i**)	93
10	2-furyl (**14j**)	Et	97 (**15j**)	89
11	cyclopropyl (**14k**)	Et	82 (**15k**)	85[b]
12	Ph (**14a**)	Me[c]	51 (**15l**)	90
13	Ph (**14a**)	Bu	71 (**15m**)	91

[a] Enantiomeric excesses were determined by HPLC on chiral stationary phase. The absolute stereochemistry was established by comparison with the authentic sample, except in entries 4 and 5, which were tentatively assigned on the basis of HPLC retention times. See the Supporting Information for details. [b] Absolute stereochemistry has not been established. [c] $(CuOTf)_2 \cdot C_6H_5CH_3$ was used in this case.

reactions conditions presumably due to the greater sensitivity of the catalyst precursor (entry 3). Because the enantiomeric excesses dropped significantly with lower catalyst loadings, several additives were tested to improve the enantioselectivities. We found that the addition of 5 mol % of $Zn(OTf)_2$ played a significant role at lower loadings (entry 4). We reasoned that the increase in concentration of EtZnOTf (through the Schlenk equilibrium between Et_2Zn and $Zn(OTf)_2$) improved the catalytic turnovers and the regeneration of the active copper catalyst (entry 4).[9] We later found that it was more convenient to simply use a slight excess of $Cu(OTf)_2$ relative to the chiral ligand (entry 5−8). The ligand loading could be decreased to 3 mol % without any erosion of the enantiomeric excesses (entry 8).[11]

These reaction conditions were then tested on other *N*-phosphinoylimines derived from aryl-, furyl-, and cyclopropyl aldehydes, and the results are presented in Table 3. The reaction proceeded extremely well with a wide range of *N*-phosphinoylimines derived from aldehydes containing nonenolizable protons. The enantiomeric excesses are excellent, and the efficiency of the reaction is not jeopardized by the presence of electron-donating or electron-withdrawing substituents on the aromatic ring. However, the presence of electron-donating substituents on the aromatic ring decreases the rate of the reaction, but slightly higher enantiomeric excesses were observed. The presence of an ortho- or a meta-substituent on the ring is also compatible with these reaction conditions. Other dialkylzinc reagents can also be used, providing α-chiral amines with excellent enantiomeric excesses (entries 12 and 13).

In conclusion, we have reported the first practical new catalytic system for the addition of dialkylzinc reagents to *N*-diphenylphosphinoylimines.[12] Both antipodes of Me-DuPHOS are commercially available, and the reaction conditions are quite mild. Further applications of this methodology will be reported in due course.

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

Supporting Information Available: Experimental procedure and conditions for the separation of enantiomers for analytical purposes (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Reviews: (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069−1094.
(2) Frantz, D. E.; Fassler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373−381.
(3) (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) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638−5639.
(4) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055−12056.
(5) Dahmen, S.; Brase, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940−5941.
(6) (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) For recent examples of Cu•phosphine catalysts: (a) Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 2892−2893. (b) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J.; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67−77.
(8) (a) Alexakis, A.; Mutti, S.; Normant, J. F. *J. Am. Chem. Soc.* **1991**, *113*, 6332−6334. (b) Alexakis, A.; Burton, J.; Vastra, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1997**, *8*, 3987−3990.
(9) (a) deVries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374−2376. (b) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620−2623.
(10) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829−11830.
(11) The ligand loading could be decreased down to 1 mol % under these conditions when the reaction is carried out on larger scale.
(12) **15a** is cleaved in 95% yield and no racemization with 2 M HCl/MeOH (room temperature, 4 h).

JA027673X