ORGANIC LETTERS

2006
Vol. 8, No. 16
3581−3584

# On the Use of Phosphoramidite Ligands in Copper-Catalyzed Asymmetric Transformations with Trialkylaluminum Reagents

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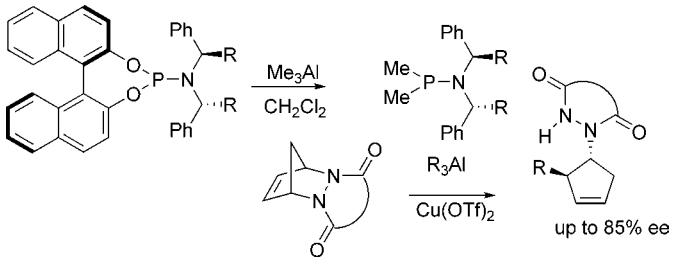
**Received June 15, 2006**

## ABSTRACT




**Phosphoramidites based on BINOL readily react with trimethylaluminum in "noncoordinating" solvents, leading to the corresponding aminophosphine which is the real ligand in copper-catalyzed asymmetric transformations. This artifact explains the experimental differences in the asymmetric ring opening of meso bicyclic hydrazines using dialkylzinc or trialkylaluminum reagents as nucleophiles.**

Phosphoramidites are now well-established ligands for numerous asymmetric transformations such as hydrogenation,[1] 1,4-additions of dialkylzinc[2] and boronic acids,[3] hydrovinylation,[4] hydrosilylation,[5] hydroboration,[6] intramolecular Heck reactions,[7] hydroformylation,[8] or allylic substitutions.[9] More recently, several examples of the use of trialkylaluminum reagents as nucleophiles in copper-catalyzed asymmetric transformations with phosphoramidite ligands have been described.[10] In our ongoing work on asymmetric transformations using bicyclic hydrazines,[11] we were particularly attracted by a recent report on the asymmetric nucleophilic ring opening of these derivatives (Scheme 1).[12]

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(1) (a) Komarov, I. V.; Börner, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 1197. (b) Van den Berg, M.; Minnaard, A. J.; Haak, R. M.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; De Vries, A. H. M.; Maljaars, C. E. P.; Willans, C. E.; Hyett, D.; Boogers, J. A. F.; Henderickx, H. J. W.; De Vries, J. G. *Adv. Synth. Catal.* **2003**, *345*, 308. (c) Hua, Z.; Vassar, V. C.; Choi, H.; Ojima, I. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5411.

(2) (a) Ferringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346. (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221.

(3) Boiteau, J.-G.; Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 681.

(4) (a) Francio, G.; Faraone, F. Leitner, W. *J. Am. Chem. Soc.* **2002**, *124*, 736. (b) Shi, W.-J.; Xie, J.-H.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2005**, *16*, 705.

(5) Jensen, J. F.; Svendsen, B. Y.; La Cour, T. V.; Pedersen, H. L.; Johannsen, M. *J. Am. Chem. Soc.* **2002**, *124*, 4558.

(6) Alexakis, A.; Polet, D.; Bournaud, C.; Bonin, M.; Micouin, L. *Tetrahedron: Asymmetry* **2005**, *16*, 3672.

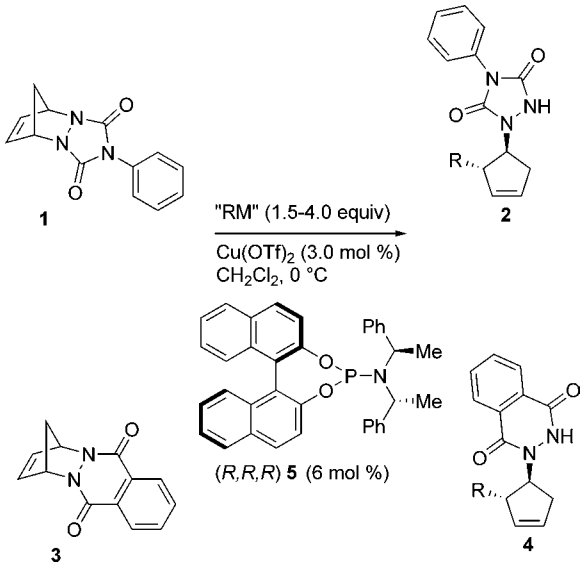
(7) Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 184.

(8) Lambers-Verstappen, M. M. H.; De Vries, J. G. *Adv. Synth. Catal.* **2003**, *345*, 478.

(9) (a) Alexakis, A.; Polet, D. *Org. Lett.* **2005**, *7*, 1621. (b) Leitner, A.; Shu, C.; Hartwig, J. F. *Org. Lett.* **2005**, *7*, 1093. (c) Lipowsky, G.; Miller, N. Helmchen, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4595.

10.1021/ol061471e CCC: $33.50 
**Published on Web 07/13/2006**

**Scheme 1.** Desymmetrization of Polycyclic Hydrazines with Organometallic Reagents Reported by Pineschi et al.[12]




Although this transformation proved to be particularly efficient, several points, outlined by the authors, were intriguing. First, very different results were obtained using $Et_2Zn$ or $Et_3Al$ as a nucleophile (Table 1, entries 1 and 2),

**Table 1.** Desymmetrization of Polycyclic Hydrazines with Organometallic Reagents Reported by Pineschi et al.[12]

| entry | substrate | RM | yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | **1** | $Et_2Zn$ | 38[a] | 3 |
| 2 | **1** | $Et_3Al$ | 80 | 66 (+) |
| 3 | **3** | $Me_3Al$ | 90 | 86 (+) |
| 4[b] | **3** | $Me_3Al$ | >98[c] | 64 (−) |

[a] Conversion after 24 h. [b] Reaction carried out with diastereomeric ligand (*R,S,S*)-**5**. [c] Conversion after 4 h.

although organometallics are supposed to be mainly alkyl donors for the in situ generation of the reactive organocopper species. Second, the sense of chirality of the amine part of the ligand proved to exert a major influence on the stereochemical outcome of the reaction (Table 1, entries 3 and 4), with an almost complete reversal of absolute configuration, a result in strong contrast with the normal trend in which the BINOL part controls the enantioselectivity in conjugate additions. All these troublesome observations prompted us to investigate more details of this transformation.

We first decided to follow the reaction by phosphorus NMR in methylene chloride. As depicted in Figure 1, we observed a complete disappearance of the characteristic signal of ligand **5** as soon as a solution of $AlMe_3$ was added in the NMR tube, leading to a new species with a single signal at 35 ppm. Workup and chromatographic purification led to the isolation of two compounds. The less polar one proved to be BINOL, and the phosphoramide **6** was isolated as the more polar compound, with a signal at 43 ppm. The formation of this compound could result from the oxidation of the corresponding aminophosphine **7** during isolation. An authentic sample of **7** was then prepared (see below), but this ligand gave a signal at 13 ppm. However, in the presence of an $AlMe_3$ solution, a single signal at 35 ppm was again observed, indicating that the species formed by mixing phosphoramidite **5** and an $AlMe_3$ solution is probably a complex between **7** and $AlMe_3$.

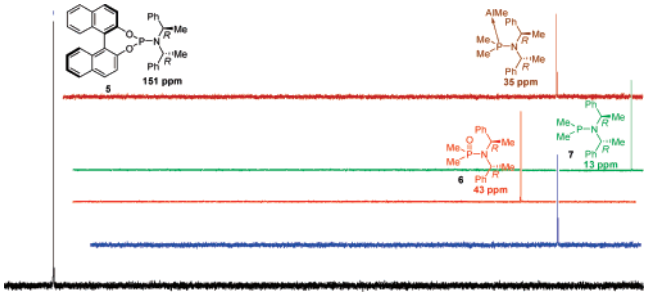



**Figure 1.** Phosphorus NMR of ligands in $CH_2Cl_2$. (a) Black: ligand **5** in $CH_2Cl_2$. (b) Blue: ligand **5** in the presence of an excess of $AlMe_3$. (c) Red: compound **6** isolated after methanolic quenching and chromatography. (d) Green: dimethylaminophosphine in $CH_2Cl_2$. (f) Brown: dimethylaminophosphine in the presence of an excess of $AlMe_3$.

The same transformation was observed when running NMR studies in toluene, whereas *no modification of the phosphoramidite signal could be observed in THF or diethyl ether*.

The in situ formation of **7** can be tentatively explained by the cleavage of the BINOL moiety by the organoaluminic reagent, triggered by a precoordination of this species (Scheme 2).[13] This reaction does not occur (or is much slower) in more coordinating solvents such as THF or with the less-oxophilic organozinc reagents.

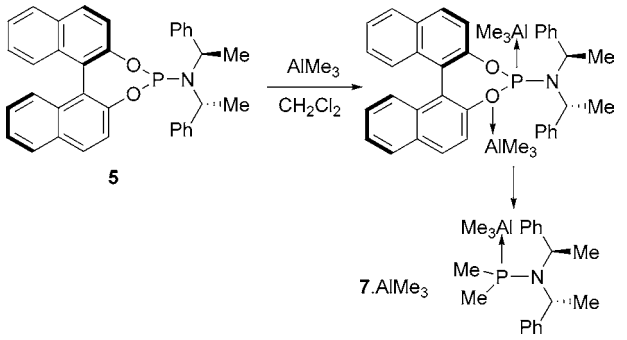
(10) Reactions in THF or $Et_2O$: (a) Alexakis, A.; Albrow, V.; Biswas, K.; d'Augustin, M.; Prieto, O.; Woodward, S. *Chem. Commun.* **2005**, 2843. (b) Polet, D.; Alexakis, A. *Tetrahedron: Asymmetry* **2005**, *46*, 1529. (c) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376. Reactions in toluene or $CH_2Cl_2$: (d) Pineschi, M.; Del Moro, F.; Di Bussolo, V.; Macchia, F. *Adv. Synth. Catal.* **2006**, *348*, 301. (e) Pineschi, M.; Del Moro, F.; Gini, F.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2004**, 1244. (f) Equey, O.; Alexakis, A. *Tetrahedron: Asymmetry* **2004**, *15*, 1531. (g) Eilitz, U.; Lessmann, F.; Seidelmann, O.; Wendisch, V. *Tetrahedron: Asymmetry* **2003**, *14*, 3095.

(11) (a) Pérez Luna, A.; Ceschi, M.-A.; Bonin, M.; Micouin, L.; Husson, H.-P.; Gougeon, S.; Estenne-Bouhtou, G.; Marabout, B.; Sevrin, M.; George, P. *J. Org. Chem.* **2002**, *67*, 3522. (b) Pérez Luna, A.; Bonin, M.; Micouin, L.; Husson, H.-P. *J. Am. Chem. Soc.* **2002**, *124*, 12098. (c) Pérez Luna, A.; Cesario, M.; Bonin, M.; Micouin, L. *Org. Lett.* **2003**, *5*, 4771. (d) Bunlaksananusorn, T.; Pérez Luna, A.; Bonin, M.; Micouin, L.; Knochel, P. *Synlett* **2003**, 2240. (e) Bournaud, C.; Robic, D.; Bonin, M.; Micouin, L. *J. Org. Chem.* **2005**, *70*, 3316 and ref 6.

(12) (a) Pineschi, M.; Del Moro, F.; Crotti, P.; Macchia, F. *Org. Lett.* **2005**, *7*, 3605. See also: (b) Pineschi, M.; Del Moro, F.; Crotti, P.; Macchia, F. *Pure Appl. Chem.* **2006**, *78*, 463.

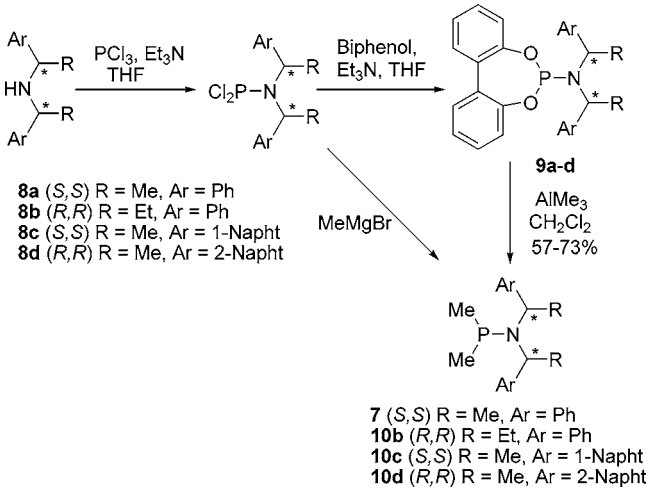
(13) For a closely related reactivity of the P−O bond in phosphine−borane complexes, see: Jugé, S.; Stephan, M.; Merdes, R.; Genet, J.-P.; Halut-Desportes, S. *J. Chem. Soc., Chem. Commun.* **1993**, *6*, 531.

**Scheme 2.** In-Situ Reaction of **5** with Trimethylaluminum




We then prepared several dimethylaminophosphines to evaluate their role as ligands in the asymmetric ring opening of hydrazines **1** and **3** (Scheme 3).

**Scheme 3.** Synthesis of Aminophosphines **7** and **10b**−**d**

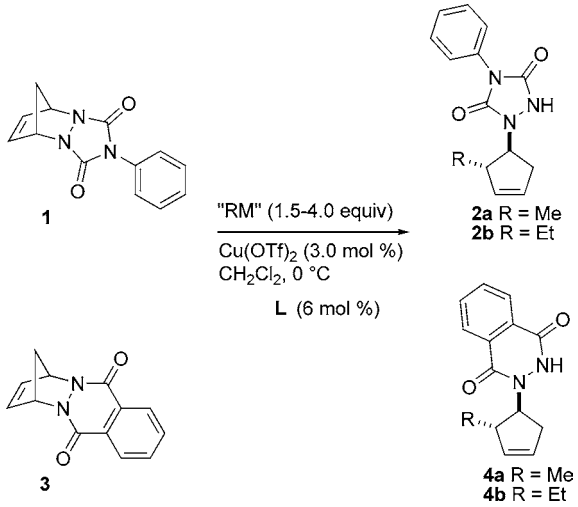



Although the reaction between dichlorophosphoramines and methylmagnesium bromide seemed to be the simplest access to these ligands, this route proved to be problematic, leading to ligands **7** and **10b**−**d** contaminated by traces of amines **8a**−**d**. We therefore developed a more convenient three-step route, leading to the expected aminophosphines after a simple filtration.[14] These rather air-sensitive ligands were rapidly used after isolation.

Desymmetrization of polycyclic hydrazines was then investigated (Scheme 4 and Table 2). Compound **4** could be obtained with the same enantioselectivity using either **5** or **7** as the ligand under similar experimental conditions, confirming that **7** is the operating ligand in this transformation (entries 1 and 2). The chemical yield was improved using ligand **7**. No reaction occurred in the absence of copper salt,

(14) Phosphoramidites **5** and **9a**−**d** were prepared according to reported procedures: (a) Alexakis, A.; Rosset, S.; Allamand, J.; March, S.; Guillen, F.; Benhaim, C. *Synlett* **2001**, *9*, 1375. (b) Alexakis, A.; Polet, D.; Benhaim, C.; Rosset, S. *Tetrahedron*: *Asymmetry* **2004**, *15*, 2199. (c) Monti, C.; Gennari, C.; Piarulli, U. *Tetrahedron. Lett.* **2004**, *45*, 6859.

**Scheme 4.** Desymmetrization of Polycyclic Hydrazines with Organometallic Reagents with Aminophosphines or Phosphoramidites




whereas the use of the free amine **8a** led to the substituted cyclopentene **4** with 51% ee (entry 3). Structural variations of the amine part of the ligands led to a strong effect on the enantioselectivity (entries 4−7), delivering compound **2** with an ee from 72% with ligand **7** to 85% with ligand **10d**.[15] Introduction of the ethyl group could also be performed (entries 8 and 9) but with lower enantioselectivities and conversion than those with ligand **5**.

**Table 2.** Desymmetrization of Polycyclic Hydrazines with Organometallic Reagents with Aminophosphines or Phosphoramidites

| entry | substrate | ligand | RM | yield (%) | ee (%)[a] |
|---|---|---|---|---|---|
| 1 | **3** | **5** (*S*,*S*,*S*) | $Me_3Al$ | 75 | 77 (−) |
| 2 | **3** | **7** (*S*,*S*) | $Me_3Al$ | 94 | 79 (−) |
| 3 | **3** | **8a** (*S*,*S*) | $Me_3Al$ | 47 | 51 (−) |
| 4 | **1** | **7** (*S*,*S*) | $Me_3Al$ | 86 | 67 (−) |
| 5 | **1** | **10b** (*R*,*R*) | $Me_3Al$ | 74 | 72 (+) |
| 6 | **1** | **10c** (*S*,*S*) | $Me_3Al$ | 92 | 46 (−) |
| 7 | **1** | **10d** (*R*,*R*) | $Me_3Al$ | 85 | 85 (+) |
| 8 | **3** | **7** (*S*,*S*) | $Et_3Al$ | 6 | 55[b] |
| 9 | **1** | **7** (*S*,*S*) | $Et_3Al$ | 56 | 48[b] |

[a] Determined by chiral SFC chromatography. Absolute configuration was established by comparison with configurations described in ref 12. [b] Absolute configuration was not determined.

In conclusion, we have shown that binol- or biphenol-based phosphoramidites react readily in noncoordinating solvents with trimethylaluminum, leading to the corresponding dimethylaminophosphines. These species appeared to be the real ligands in the copper-catalyzed nucleophilic ring

(15) In our hands, enantiomeric excess slightly differed from the ones reported in ref 12. This could be explained by the fact that the authors in some cases measured the ee after crystallization (see Supporting Information of ref 12a), leading to uncontrolled enantiomeric enrichment.

opening of bicyclic hydrazines. This study shows that extreme care is required when using phosphoramidite ligands in conjunction with organometallic nucleophiles and that the selectivities observed could result from an experimental artifact.

**Acknowledgment.** C.B. thanks the MRT for a grant. We thank the CNRS for financial support. This work was supported by a French−Swiss "Germaine de Staels" program.

**Supporting Information Available:** Analytical data for all new compounds and NMR spectra of all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061471E