First Iminodiazaphospholidines with a Stereogenic Phosphorus Center. Application to Asymmetric Copper-Catalyzed Cyclopropanation

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Iminophosphoranes have been extensively used for the high yield syntheses of a large variety of imines.[1−5] Although triphenylphosphine was usually used because of the stability of the resulting iminophosphorane, the reaction can be performed with a wide variety of phosphines, including trialkylphosphines,[6] mixed alkylarylphosphines,[7] unsaturated phosphines,[8] aminophosphines,[9] tris(dialkylamino)phosphines,[10] cyclic phosphines,[11] or bicyclic phosphines.[12] Nevertheless, although iminophosphoranes of general structure $R_3P{=}N-R'$ possess a donor position at the nitrogen atom capable of metal complexation,[13] few chiral versions have been envisaged and applied in catalytic asymmetric synthesis.[7,14]

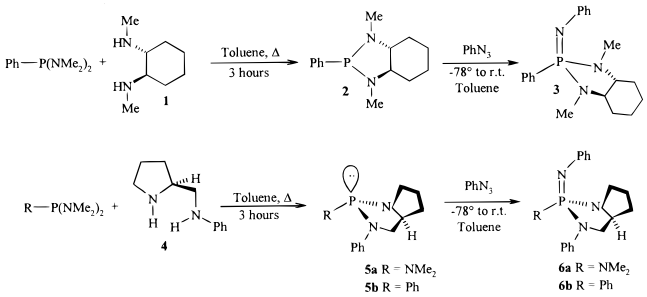
We report here the first diastereoselective synthesis of new chiral iminodiazaphospholidines bearing the chirality at the chain and at the phosphorus atom and their use as ligands in an enantioselective copper-catalyzed cyclopropanation reaction.

Chiral iminophosphorane **3** issued from (*R,R*)-*N,N*′-dimethylcyclohexane-1,2-diamine **1** was synthesized in 63% yield by treatment with phenyl azide in THF at −78 °C of the corresponding phosphine **2** (Scheme 1).

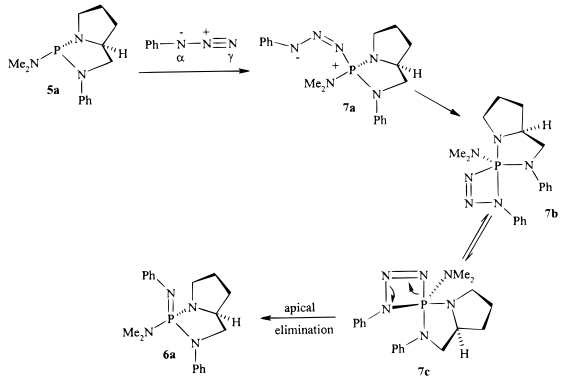
The first chiral iminophosphoranes **6a**,**b** possessing a stereogenic phosphorus center were easily prepared from the corresponding diastereomerically pure phosphines **5a**,**b**[15] according to the procedure described above in 61 and 48% yields, respectively (Scheme 2).

Iminophosphoranes **3**, **6a**, and **6b** are crystalline compounds characterized by standard methods, including ^{31}P NMR spectroscopy (δ 19.09, 14.57, and 14.94, respectively in $CDCl_3$). Moreover, the structure of compound ***anti*-6a** was determined by a single X-ray diffraction study (Figure 1). The $P-N_2$ bond length

Scheme 1. Synthesis of Iminophosphoranes **3**, **6**, and **6b**



Scheme 2. Possible Mechanism for the Stereoselective Formation of Iminophosphorane **6a**



[1.544(3) Å] is within the expected values.[2,16] The P−N−Ph bond angle value is 126.4°, consistent with the proposed sp^2 hybridization of nitrogen. The molecular structure unambiguously showed that the configuration at the phosphorus atom was retained during the nucleophilic attack by the phosphine on the terminal γ-nitrogen of the azide. Indeed, it is clearly established that this reaction proceeds through the formation of a linear phosphazide **7a**, usually not detectable, which then dissociates to iminophosphorane, probably via a four-centered transition state **7b**.[17]

The total retention of absolute configuration at the phosphorus atom may be interpreted through a mechanism involving a trigonal bipyramidal intermediate (TBP). The nucleophilic addition of diazaphospholidine **5a** on phenylazide led to the formation of betain **7a**. In this case, elimination of molecular nitrogen may occur only from TBP intermediates **7b** and **7c** according to the principle of microscopic reversibility.[18] Considering these assumptions, the α-nitrogen atom may attack at one of the adjacent faces of the tetrahedron of **7a**, in line to one of the nitrogen atoms of the diazaphospholane ring leading to **7b** TBP intermediate in which the four- and the five-membered rings adopt an axial−equatorial position. On the other hand, for this TBP intermediate **7b** it is possible to consider a low-energy Berry pseudorotation[19] leading to the formation of **7c** in which the α-nitrogen atom adopts

(1) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.
(2) For reviews dealing with Staudinger reaction, see: (a) Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437. (b) Johnson, A. W. *Ylides and Imines of Phosphorus, Iminophosphoranes and Related Compounds*; John Wiley & Sons: New York, 1993.
(3) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353.
(4) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 298.
(5) For recent applications, see: (a) Molina, P.; Aller, E.; Lorenzo, A. *Synthesis* **1998**, 283. (b) Okawa, T.; Kawase, M.; Eguchi, S. *Synthesis* **1998**, 1185. (c) Takahashi, M.; Suga, D. *Synthesis* **1998**, 986.
(6) (a) Birkofer, L.; Kim, S. M. *Chem. Ber.* **1964**, *97*, 2100. (b) Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **1986**, *27*, 4623.
(7) Wilson, S. R.; Pasternak, A. *Synlett* **1990**, 199.
(8) Baechler, R. D.; Blohm, M.; Rocco, K. *Tetrahedron Lett.* **1988**, *29*, 5353.
(9) (a) Vetter, H. J.; Noth, H. *Chem. Ber.* **1963**, *96*, 1308. (b) Wilburn, J. C.; Nielson, R. H. *Inorg. Chem.* **1977**, *16*, 2519.
(10) Schwesinger, R. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1164.
(11) Baccolini, G.; Todesco, P. E.; Bartoli, G. *Phosphorus Sulfur* **1981**, *10*, 387.
(12) Quin, L. D.; Keglevich, G.; Caster, K. C. *Phosphorus Sulfur* **1987**, *31*, 133.
(13) (a) Abel, E. W.; Muckle, J. *Inorg. Chim. Acta* **1979**, *37*, 107. (b) Imhoff, P.; Elsevier, C. J.; Stam, C. H. *Inorg. Chim. Acta* **1990**, *175*, 209. (c) Reed, R. W.; Santasierso, B.; Cavell, R. G. *Inorg. Chem.* **1996**, *35*, 4292. (d) Apppel, R.; Volz, P. *Z. Anorg. Allg. Chem.* **1975**, *413*, 45. (e) Crociani, L.; Tisato, F.; Refosco, F.; Bandoli, G.; Corain, B.; Venanzi, L. M. *J. Am. Chem. Soc.* **1998**, *120*, 2973.
(14) Reetz, M. T.; Bohres, E.; Goddard, R. *Chem. Commun.* **1998**, 935.
(15) (a) Brunel, J. M.; Chiodi, O.; Faure, B.; Fotiadu, F.; Buono, G. *J. Organomet. Chem.* **1997**, *529*, 285. (b) Legrand, O.; Brunel, J. M.; Constantieux, T.; Buono, G. *Chem.—Eur. J.* **1998**, *4*, 1061.

(16) Two nitrogen atoms N_3 and N_5 display different P−N bonds length against $P-N_4$ ($P-N_3$ 1.686 Å, $P-N_5$ 1.633 Å, and $P-N_4$ 1.655 Å, respectively). Moreover, nitrogen atoms N_3 and N_5 are essentially coplanar (sum of angles around nitrogen atoms respectively, 358.1 and 359.5°) while the nitrogen N_4 has a pyramidal configuration (sum of angles around N_4 = 346.7°). This is likely to be a consequence of the location of N_4 at a bridgehead position between the two five-membered rings.
(17) Bock, H.; Schnoller, M. *Angew. Chem.* **1968**, *7*, 636. Bock and Schnoller demonstrated using ^{15}N-labeled azide that the α-nitrogen of the original azide is the one present in the imine product, the β- and γ-nitrogen atoms being evolved as molecular nitrogen.
(18) (a) Westheimer, F. *Acc. Chem. Res.* **1968**, *1*, 70. (b) Mislow, K. *Acc. Chem. Res.* **1970**, *3*, 321. (c) Luckenbach, R. *Dynamic Stereochemistry of Pentacoordinated Phosphorus and Related Elements*; Georg Thieme Verlag: Stuttgart, 1973; pp 99−107.

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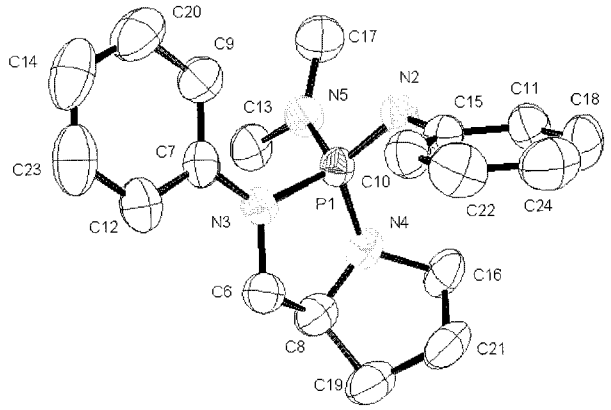


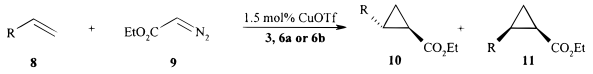
Figure 1. Structure of ***anti*-6a**, showing labeling scheme. Selected bond distances (Å): P1−N2, 1.544(3); P1−N3, 1.686(3); P1−N4, 1.655(3); P1−N5, 1.633(3); N2−C15, 1.406(4) N3−C7, 1.409(5). Selected bond angles (deg): N2−P1−N3, 122.2(2); N2−P1−N4, 117.7(2); N2−P1−N5, 106.0(2); N4−P1−N3, 92.8(2); N4−P1−N5, 109.9(2); N3−P1−N5, 107.4(2); P1−N2−C15, 126.1(3); P1−N3−C7, 125.4(3); P1−N5−C13, 119.4(3); P1−N4−C8, 114.9(3); P1−N3−C6, 113.6(3); P1−N5−C17, 124.1(3); P1−N4−C16, 122.1(3); C6−N3−C7, 119.1(2); C8−N4−C16, 109.7(3); C13−N5−C17, 116.0(3).

a favored apical position, allowing apical departure of molecular nitrogen.[20]

The catalytic asymmetric cyclopropanation of olefins with various diazoacetates in the presence of chiral copper and rhodium catalysts has been carefully optimized.[21] The methods developed by Evans,[22a] Pfaltz,[22b] Musamune,[22c] and Doyle[22d] are exemplifying. Although these chiral catalysts can provide substituted cyclopropanes with a high level of enantioselectivity, these reactions are not highly diastereoselective, and a mixture of trans and cis adducts **10** and **11** is obtained.[23] Due to their metal complexation properties,[13] iminophosphoranes **3**, **6a**, and **6b** have been successfully used as ligands in an asymmetric copper-catalyzed cyclopropanation of olefins **8** by ethyl diazoacetate **9** (see Table 1). The best results were obtained with copper(I) triflate.[24,25]

The expected adducts **10** and **11** were formed in chemical yields varying from 60 to 85% using 1.5 mol % of the complex **6a**−CuOTf. In the case of vinyl aryl substrates, the catalyst exhibits high enantiocontrol especially for the thermodynamically more stable trans isomer **10** which was preferentially formed (the trans/cis ratio varying from 76/24 to 100/0 depending on the experimental conditions and the nature of the considered olefin). Using styrene as substrate test, dichloromethane appeared to be the best solvent with respect to enantiomeric excesses (ee) and diastereoselectivity (entries 5, 94 and 90% ee, respectively, for *trans*-**10** and *cis*-**11** isomers (ratio 98/2)) while THF led to poor enantioselectivities (entry 3, 52 and 43% ee, respectively for *trans*-**10** and *cis*-**11** isomers (ratio 80/20)). Furthermore, it clearly appears that the rate of addition of ethyl diazoacetate is important to ensure a high enantiomeric excess reproducibility (entries 4 and 5). Under the best experimental conditions (entry 5), the use of iminophosphoranes **6b** and **3** led to similar results in terms of conversion and enantioselectivities (entries 8 and 9).[26] Performing the reaction on various olefins led in all cases to high ratio diastereoselectivities varying from 83/17 to 100/0 (entries 10−13). The best result was obtained using 1-vinylnaphthalene which led to a total diastereoselectivity in *trans*-**10** with 95% ee (entry 11). On the other hand, when R = $PhCH_2$ and $PhOCH_2$, we noticed a significant decrease of the enantioselectivity (entries 12 and 13).

Table 1. Catalytic Asymmetric Cyclopropanation of Olefins **8** by Ethyl Diazoacetate **9**



entry	L*	R	solvent	yield (%)[g]	ratio **10**:**11**[h]	ee (%) **10**:**11**
1[a,i]	**6a**[c,d]	Ph	THF	68	95	17
					5	0
2[a,i]	**6a**[c,e]	Ph	THF	61	92	34
					8	12
3[a,i]	**6a**[e,f]	Ph	THF	67	80	52
					20	43
4[a,i]	**6a**[d,f]	Ph	CH_2Cl_2	60	76	63
					24	20
5[a,i]	**6a**[e,f]	Ph	CH_2Cl_2	80	98	94
					2	90
6[a,i]	**6a**[e,f]	Ph	$ClCH_2CH_2Cl$	85	95	93
					5	91
7[a,i]	**6a**[e,f]	Ph	$CHCl_3$	78	97	92
					3	91
8[a,i]	**6b**[e,f]	Ph	CH_2Cl_2	83	95	87
					5	76
9[a,i]	**3**[e,f]	Ph	CH_2Cl_2	78	82	84
					18	76
10[a,i]	**6a**[e,f]	1-Naphthyl	CH_2Cl_2	89	90	50
					10	35
11[b,i]	**6a**[e,f]	1-Naphthyl	CH_2Cl_2	76	100	95
					0	
12[b,j]	**6a**[e,f]	$PhCH_2$–	CH_2Cl_2	71	98	12
					2	0
13[b,j]	**6a**[e,f]	$PhOCH_2$–	CH_2Cl_2	78	83	34
					17	23

[a] Reactions performed on 1 mmol scale at −20 °C during 72 h. [b] Reactions performed on 1 mmol scale at −78 °C during 72 h. [c] Reaction performed using 1 equiv of L* with respect to CuOTf. [d] Rapid addition of N_2CH_2COOEt in 1 min. [e] Addition of N_2CH_2COOEt using a pump syringe over a period of 10 h. [f] Reaction performed using 2 equiv of L* with respect to CuOTf. [g] Isolated yield. [h] Ratio **10**:**11** determined by capillary GC. [i] ee determined by HPLC analysis. [j] ee determined by GC analysis using a LIPODEX E column.

Additional studies dealing with the use of such ligands in various asymmetric catalyzed reactions as well as mechanistic features are under current investigations.

Acknowledgment. We thank Dr. M. Giorgi for his kind assistance with X-ray analysis of compound **6a**. This paper is dedicated to Pr. H. B. Kagan on the occasion of his 69th birthday.

Supporting Information Available: Experimental procedures for the synthesis of phosphines **2**, **5a**,**b** and iminophosphoranes **3**, **6a**,**b** as well as for catalytic asymmetric copper cyclopropanation reaction (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Berry, R. S. *J. Chem. Phys.* **1960**, *32*, 933. Nevertheless, in any case Turnstile rotation must be taken into consideration as a mechanistic alternative: (a) Gillepsie, P.; Hoffmann, P.; Klusacek, H.; Marquading, D.; Pfohl, S.; Ramirez, F.; Tsolis, E. A.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1971**, *83*, 691. (b) Ramirez, F. *Bull. Soc. Chim. Fr.* **1970**, 3491.

(20) The inversion of configuration at the phosphorus atom is energetically unfavored since it would involve the epimerization of the phosphorus P(V) atom implying high-energy intermediates in which the two rings will be forced to adopt a constrained diequatorial position.[18]

(21) For recent reviews dealing with copper cyclopropanation reaction, see: (a) Singh, V. K.; DattaGupta, A.; Sekar, G. *Synthesis* **1997**, 137. (b) Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, *54*, 7919. (c) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911.

(22) (a) Evans, D. A.; Woerpel, K. A.; Hinnan, M. M.; Feud, M. M. *J. Am. Chem. Soc*. **1991**, *113*, 726. (b) Pfaltz, A. *Acc. Chem. Res*. **1993**, *26*, 339. (c) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005. (d) Doyle, M. P.; Dratkin, A. B.; Protopopova, M. N.; Yang, C. I.; Miertschin, C. S.; Winchester, W. R.; Simonsen, S. H.; Lynch, V.; Chosh, R. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 163.

(23) For high trans diastereoselectivity of the reaction, see: Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K. L. *J. Am. Chem. Soc.* **1990**, *112*, 1906.

(24) Solomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 3300.

(25) Copper(II) triflate complexes do not catalyze the reaction unless they are heated to 65 °C. Other Cu(I) and Cu(II) salts (for example, halide, cyanide, acetate, and perchlorate) show little or no catalytic activity, and the observed enantioselectivity is markedly inferior to that obtained for the triflate−ligand complexes.

(26) It is interesting to note that compounds **3**, **6a**, and **6b** do not function as imido donor groups for the aziridination of styrene catalyzed by CuOTf. On the other hand, the corresponding ligands **2**, **5a**, **5b** do not lead to the formation with high level of enantioselectivity to the cyclopropane adducts **10** and **11** (enantioselectivity up to 7% ee).