ORGANIC LETTERS

2002
Vol. 4, No. 15
2597−2600

Design and Development of Cyclohexane-Based P,N-Ligands for Transition Metal Catalysis

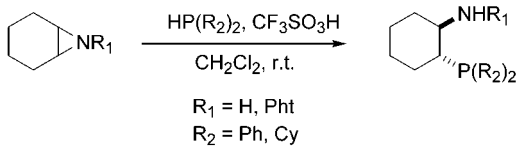
Aldo Caiazzo, Shadi Dalili, and Andrei K. Yudin*

Davenport Research Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario, Canada M5S 3H6

ayudin@chem.utoronto.ca

Received May 28, 2002

ABSTRACT



A new class of cyclohexane-based P,N-ligands is readily obtained through aziridine ring opening with suitable phosphorus nucleophiles under acidic conditions. *trans*-1-Amino-2-diphenylphosphinocyclohexane is resolved with tartaric acid to give the final product in >99% ee. The new ligands show high stability toward oxidation at the phosphorus atom.

Bidentate ligands are ubiquitous components of many transition-metal-based catalysts.[1] Among them, chiral P,N-ligands have found applications in a variety of asymmetric processes ranging from allylic substitution to hydrogenation of ketones.[2,3] From the reactivity standpoint, a P,N-ligand contains a combination of hard (nitrogen) and soft (phosphorus) centers.[2c] Within this environment, metal ions can be stabilized in their low oxidation states by the π-accepting character of the softer phosphorus site. On the other hand, high oxidation states are better stabilized by the harder nitrogen site.[2d,4] This combination of complementary properties of nitrogen and phosphorus has been explored in a number of carbocyclic environments. For instance, in a recent example reported by Jones,[5] the hemilabile character of (dialkylphosphino)-dialkylaminoethane was found to be crucial for the catalytic activity of the derived platinum complexes. The formation of putative five-membered metallacycles in this system was not observed in the presence of chelating diphosphine ligands.

We were puzzled by the absence of examples of P,N-ligands based on the *trans*-1,2-cyclohexane fragment. The cyclohexane template is present in a number of useful chiral ligands for asymmetric catalysis[6] as a result of its ability to rigidify the *trans* configuration of substituents.

We therefore viewed this as an opportunity to explore new catalytic activity. In this paper we describe our efforts toward

(1) For recent developments in bidentate ligands chemistry, see: (a) Pfaltz, A. *Chimia* **2001**, *55*, 708−714. (b) McCarthy, M.; Guiry, P. J. *Tetrahedron* **2001**, *57*, 3809−3844. (c) Van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741−2769. See also: (d) Noyori, R. (ed.) *Asymmetric Catalysis in Organic Synthesis*; J. W. Wiley & Sons: New York, 1994.

(2) For general reviews on P,N-ligands, see: (a) Braunstein, P.; Naud, F. *Angew. Chem., Int. Ed.* **2001**, *40*, 680−699. (b) Gavrilov, K. N.; Polosukhin, A. I. *Russ. Chem. Rev.* **2000**, *69*, 661−682. (c) Slone, C. S.; Weinberger, D. A.; Mirkin, C. A. *Prog. Inorg. Chem.* **1999**, *48*, 233−350. (d) Espinet, P.; Soulantica, K. *Coord. Chem. Rev.* **1999**, *193*−*195*; 499−556.

(3) For allylic substitution, see: (a) Pfaltz A. *Chimia* **2001**, *55*, 708−714. (b) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336−345. (c) Haughton, L.; Williams, J. M. J. *J. Chem. Soc., Perk. Trans. 1* **2000**, 3335−3349. For Heck reaction, see: (d) Loiseleur, O.; Hayashi, M.; Keenan, M.; Schmees, N.; Pfaltz, A. *J. Organomet. Chem.* **1999**, *576*, 16−22. For hydrosilylation, see: (e) Nishiyama, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. I, p 267. For hydroboration, see: (f) Kwong, F. Y.; Yang, Q.; Mak, T. C. W.; Chan, A. S. C.; Chan, K. S. *J. Org. Chem.* **2002**, *67*, 2769−2777 and references therein. For hydroformylation, see: (g) Abu-Gnim, C.; Amer, I. *J. Organomet. Chem.* **1996**, *516*, 235−243. (h) Basoli, C.; Botteghi, C.; Cabras, M. A.; Chelucci, G.; Marchetti, M. *J. Organomet. Chem.* **1995**, *488*, C20−C22. For transfer hydrogenation to ketones, see: (i) Braunstein, P.; Naud, F.; Pfaltz, A.; Rettig, S. J. *Organometallics* **2000**, *19*, 2676−2683. (j) Braunstein, P.; Graiff, C.; Naud, F.; Pfaltz, A.; Tiripicchio, A. *Inorg. Chem.* **2000**, *39*, 4468−4475.

(4) Schnyder, A.; Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 931−933.

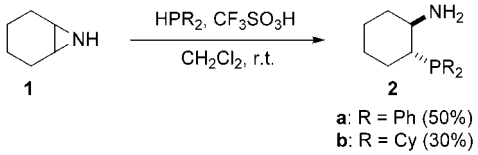
(5) Müller, C.; Lachicotte, R. J.; Jones, D. W. *Organometallics* **2002**, *21*, 1118−1123.

10.1021/ol026249y CCC: $22.00
Published on Web 07/02/2002

preparation of a new family of P,N-ligands based on aziridine ring opening chemistry.[7]

Our recent interest in the synthesis and applications of functionalized aziridines[8] prompted us to investigate their ring opening with phosphine nucleophiles. Readily available 7-azabicyclo[4.1.0]heptane (**1**)[7a] was subjected to nucleophilic ring opening with diphenylphosphine according to Scheme 1, yielding *trans*-1-amino-2-diphenylphosphino cyclohexane (**2a**) in 50% yield. The use of trifluoromethanesulfonic (triflic) acid was crucial in order to activate the aziridine ring toward opening. When trifluoroacetic acid was utilized in place of triflic acid, rapid oxidation of the phosphorus center was observed.[9]

Scheme 1



Analogously, the opening of aziridine **1** by using dicyclohexylphosphine as a nucleophile led to the formation of *trans*-1-amino-2-dicyclohexylphosphino-cyclohexane (**2b**) as a white solid in 30% yield (Scheme 1). This opens up to the possibility of synthesizing a wide variety of P,N-ligands with different kinds of disubstituted phosphines.

The *trans*-stereochemistry of **2a** and its coordinating ability were confirmed by X-ray analysis (Figure 1) of the bis(*trans*-1-amino-2-diphenylphosphino cyclohexane) nickel(II) di(tetrafluoroborate) (**3**). This complex was formed in 50% yield during the reaction between 2 equiv of **2a** and $NiCl_2 \cdot 6H_2O$ in the presence of lithium tetrafluoroborate. The geometry of **3** is square planar, with a bite angle [P(1A)−Ni(1A)−N(1A)] in the 84.6(3)°−85.1(3)° range.[10]

The homochiral complex, which contains a C_2 axis, was the only observed product. The preferred formation of the *cis* complex as opposed to the *trans* isomer can be attributed to the higher *trans* influence of the PPh_2 group with respect to the NH_2 group.[11]

The results obtained in parent aziridine ring opening led us to investigate other derivatives of cyclohexene aziridine, such as 2-(7-azabicyclo[4.1.0]hept-7-yl)-1*H*-isoindole-1,3-(2*H*)-dione (**4**), which became readily available using electrosynthesis recently developed in our lab.[8] We subjected aziridine **4** to ring opening with diphenylphosphine under the same conditions as for **1**. Accordingly, 2-{[2-(diphenylphosphino)cyclohexyl]amino}-1*H*-isoindole-1,3(2*H*)-dione (**5**) was obtained in 65% yield (Scheme 2).

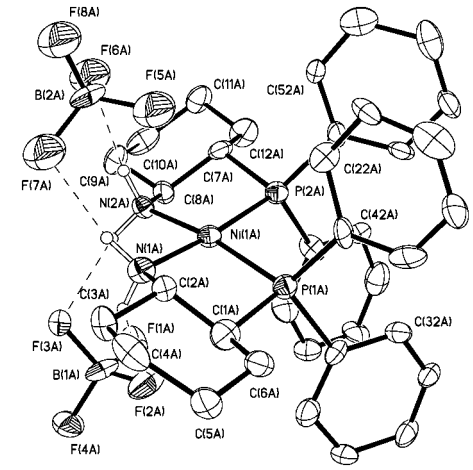
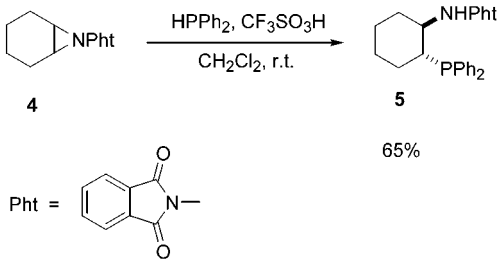


Figure 1. Thermal ellipsoid plot of complex **3**. Selected distances [Å] and bond angles [deg]: Ni−N1 1.930(9), Ni−N2 1.928(9), Ni−P1 2.197(3), Ni−P2 2.196(3), N1−Ni−P1 84.6(3), N2−Ni−P2 85.1(3), N1−Ni−P2 175.3(3), N2−Ni−P1 172.1(3).

Scheme 2



Using these methods, functionalized hydrazines were easily prepared and subsequently served as precursors to more complex ligands.[12] For instance, the deprotection of the phthalimide group was achieved using an excess of *n*-butylamine in refluxing ethanol. This reaction resulted in the formation of 1-[2-(diphenylphosphino)cyclohexyl]-hydrazine (**6**) (Scheme 3).

The resulting hydrazine **6** was directly subjected to reaction with 2,4-pentanedione to give the pyrazole-based P,N-ligand *trans*-1-[2-(diphenylphosphino)cyclohexyl]-3,5-dimethyl-1*H*-pyrazole (**7**) in 70% overall yield over two steps (Scheme 3).

The complexation of **7** with bis(benzonitrile)palladium-(II) dichloride (1:1 ratio) in dichloromethane provided {*trans*-

(6) (a) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421−431. (b) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968−5976. (c) Ito, Y. N.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 603−619.

(7) (a) Christoffers, J.; Schulze, Y.; Pickardt, J. *Tetrahedron* **2001**, *57*, 1765−1769. (b) Katagiri, T.; Takahashi, M.; Fujiwara, Y.; Ihara, H.; Uneyama, K. *J. Org. Chem.* **1999**, *64*, 7323−7329.

(8) Siu, T.; Yudin, A. K. *J. Am. Chem. Soc.* **2002**, *35*, 2723−2727.

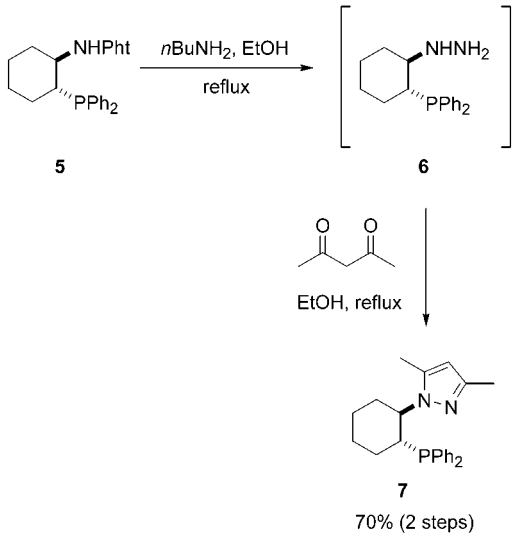
(9) For cyclohexene oxide ring opening with diphenylphosphine, see: Muller, G.; Sainz, D. *J. Organomet. Chem.* **1995**, *495*, 103−111.

(10) Suzuki, T.; Morikawa, A.; Kashibawara, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2539−2548.

(11) Suzuki, T.; Rude, M.; Simonsen, K. P.; Morooka, M.; Tanaka, H.; Ohba, S.; Galsbøl, F.; Fujita, *J. Bull. Chem. Soc. Jpn.* **1994**, *67*, 1013−1023.

(12) (a) Barz, M.; Rauch, M. U.; Thiel, W. R. *J. Chem. Soc., Dalton Trans.* **1997**, 2155−2161. (b) Barz, M.; Herdtweck, E.; Thiel, W. R. *Angew. Chem., Int. Ed.* **1998**, *37*, 2262−2265.

Scheme 3



1-[2-(diphenylphosphino) cyclohexyl]-3,5-dimethyl-1*H*-pyrazole} palladium(II) dichloride (**8**) in 80% yield as a yellow solid. The X-ray analysis of **8** shows that the complex has a square planar geometry, with a bite angle [N(1)−Pd(1)−P(1)] of 83.03(11)°. The Pd−Cl bond *trans* to the phosphorus atom is longer than the one *trans* to the nitrogen atom [Pd−Cl1 = 2.3743(13) Å vs Pd−Cl2 = 2.2902(12) Å, Figure 2].

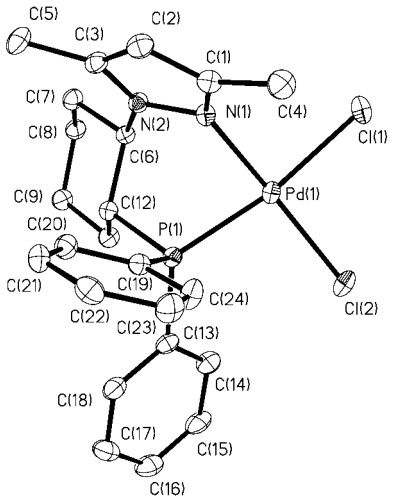
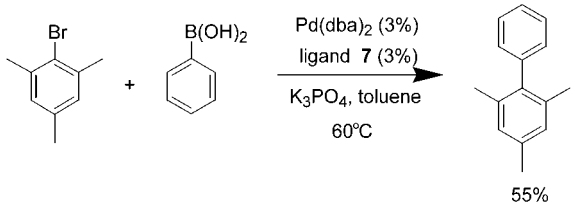


Figure 2. Thermal ellipsoid plot of complex **8**. Selected distances [Å] and bond angles [deg]: Pd−Cl1 2.3743(13), Pd−Cl2 2.2902(12), Pd−N1 2.0480(4), Pd−P1 2.2389(12), Cl2−Pd−Cl1 92.94(5), N1−Pd−P1 83.0(11), N1−Pd−Cl2 95.2(5), Cl1−Pd−P1 168.7(5), N1−Pd−Cl2 167.6(11).

An equimolar mixture of ligand **7** and $Pd(dba)_2$ was found to catalyze the Suzuki coupling between sterically hindered 2-bromomesitylene and phenylboronic acid in 55% yield and 98% selectivity (Scheme 4), indicating that these new P,N-ligands are precursors to active catalysts. The conversion/time study revealed that the Suzuki coupling was complete after 8 h.

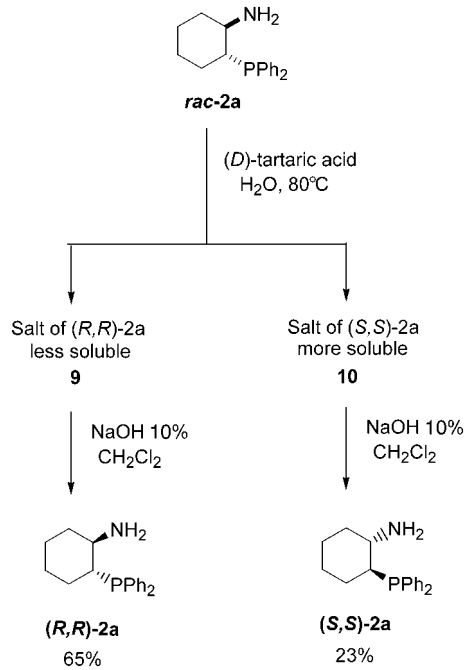
Scheme 4



The ligand **2a** was successfully resolved using D-tartaric acid via the formation of the tartrate salt, which was filtered and recrystallized from water. X-ray analysis carried out on crystals grown in 95% aqueous ethanol showed that the enantiomer separated from the racemic mixture had (*R*,*R*) absolute configuration.

The enantiomerically pure P,N-ligand was then recovered by dissolving the tartrate salt in 10% sodium hydroxide solution and extracting the mixture with dichloromethane (Scheme 5). The enantiomeric excess of the recovered ligand

Scheme 5



(> 99%, 65% yield) was analyzed by converting it into Mosher acid amide.[13] Throughout these manipulations, the P,N-derivatives showed considerable stability toward air oxidation. When a solution of **2a** in $CDCl_3$ was stirred under air for 16 h, less than 4% oxidation was observed.

In summary, cyclohexane-based P,N-ligands can be prepared in enantiomerically pure form from readily available

(13) Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165−7166.

aziridines and are precursors to active catalysts. Straightforward manipulation of the substituents on nitrogen renders these ligands applicable in asymmetric catalysis. A particularly useful property of these ligands is significant oxidative stability of the phosphorus center. The choice of phosphine during the ring opening step allows one to manipulate electronic properties of the system. These and related studies are in progress and will be reported in due course.

Acknowledgment. We thank the National Science and Engineering Research Council (NSERC), Canada Foundation for Innovation, ORDCF, and the University of Toronto for financial support. Prof. Andrei Yudin is a Cottrell Scholar of Research Corporation. We also thank Dr. Alan Lough for his contribution to X-ray analyses and Ms. Katherine Groom for the help given in the resolution of compound **2a**.

Supporting Information Available: Experimental procedures, characterization data and spectra for compounds **1**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026249Y