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Stereospecific Deoxygenation of Phosphine Oxides with Retention of Configuration Using Triphenylphosphine or Triethyl Phosphite as an Oxygen Acceptor

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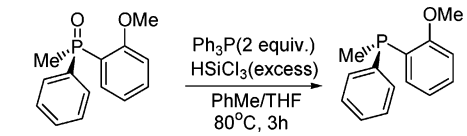
ABSTRACT



(*R*)-PAMPO, 99.5% e.e. (*S*)-PAMP, 95%, 99% e.e.

A new protocol for deoxygenation of various phosphine oxides with retention of configuration is described. The advantage of the new method includes milder conditions and considerably shortened reaction times. Mechanistic studies about the oxygen transfer between the starting phosphine oxide and the sacrificial triphenylphosphine are also presented.

Development of efficient synthetic routes for tertiary phosphines, as an important class of ligands in transition-metal-mediated reactions, continues to be an important area of research.[1] The synthesis of 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) has received the most attention due to its spectacular performance in catalytic asymmetric induction.[2] Despite the development of various synthetic routes,[3] the conventional method of coupling an aryl Grignard with a phosphinyl chloride or phosphinate to give the triarylphosphine oxide precursor is still the most reliable choice. This route provides wider substrate scope and also benefits from the fact that triarylphosphine oxides can be efficiently resolved into optical antipodes using readily available optically active acids. However, the deoxygenation step with the commonly used reducing reagents $HSiCl_3/Et_3N$ or SmI_2/THF requires long reaction times and is often problematic with sterically hindered or electron-deficient phosphine oxides.[4] Herein we report an improved method using Ph_3P or $(EtO)_3P$ as an oxygen acceptor that can reduce a wide range of substrates with much shortened reaction times including the most challenging electron-deficient triarylphosphine oxides. This provides convenient synthetic access to electron-deficient phosphine ligands.

Rationalization of electronic effects in transition-metal-mediated catalytic reactions is critically important for the design of new ligands.[5] The BINAP system is an ideal model to investigate and rationalize the electronic effect in asymmetric catalysis because of its wide scope of substrates and reaction types. Since electron-rich BINAP ligands are readily

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(1) Crepy, K. V. L.; Imamoto, T. *Top. Curr. Chem.* **2003**, *229*, 1 and references therein.

(2) (a) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley: New York, 1994.

(3) Cai, D. W.; Payack, J. F.; Bender, D. R.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 7180.

(4) (a) Hayashi, T.; Hirate, S.; Kitayama, K.; Tsuji, H.; Torii, A.; Uozumi, Y. *J. Org. Chem.* **2001**, *66*, 1441. (b) Imamoto, T.; Kikuchi, S.; Miura, T.; Wada, Y. *Org. Lett.* **2001**, *3*, 87. (c) Coumbe, T.; Lawrence, N. J.; Muhammad, F. *Tetrahedron Lett.* **1994**, *35*, 625. (d) Pietrusiewicz, K. M.; Zablocka, M. *Chem. Rev.* **1994**, *94*, 1375.

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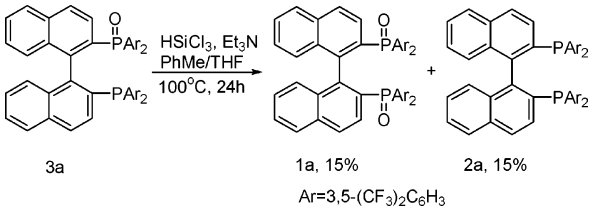
available and comprehensively screened, we set out to prepare electron-deficient BINAP ligands containing CF_3 groups attached to the phenyl rings. To take advantage of the facile chiral resolution of the BINAP(O)$_2$ system (2,2′-bis(diphenylphospinyl)-1,1′-binaphthyl), we prepared the electron-deficient BINAP(O)$_2$ **1a** by quantitatively oxidizing **2a** which was prepared by coupling diarylbromophosphine with binaphthylmagnesium bromide in 70% isolated yield.[6]

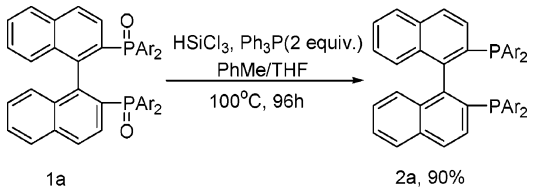
Considerable difficulties were met in the reduction of the electron-deficient BINAP(O)$_2$ compound (**1a**) involving the most commonly used reagent $HSiCl_3/Et_3N$. After several failed attempts with other reduction methods [$LiAlH_4$/$NaBH_4$/$CeCl_3$, MeOTf/$LiAlH_4$/DME, SmI_2/THF, and $(EtO)_3SiH$/$Ti(O^iPr)_4$],[4] the $HSiCl_3/Et_3N$ system was investigated in great detail. The monoxide (**3a**) was the only product isolated (40%) along with the starting material (50%) under various conditions. When pure monoxide **3a** was further subjected to the reducing reagent under anerobic conditions a mixture of dioxide (**1a**) and BINAP (**2a**) was obtained with 70% of monoxide (**3a**) being recovered (Scheme 1).

Scheme 1. $HSiCl_3$-Mediated Oxygen Transfer between Phosphines



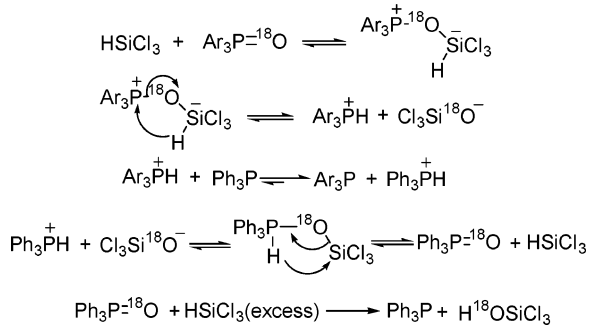
A control experiment in the absence of $HSiCl_3$ was also carried out, and no formation of the dioxide was observed. These combined results are consistent with a proposal that oxygen transfer takes place between the phosphine oxide and phosphine under the influence of $HSiCl_3$. This observation suggested that if a sacrificial phosphine was added to the reaction mixture it could alter the equilibrium to afford a better yield of the reduced ligand. Therefore, triphenylphosphine was introduced into the reaction, and interestingly, the dioxide **1a** was reduced to a mixture of **2a** (30%) and **3a** (60%). Two well-documented mechanisms could explain this reactivity: either an intramolecular hydride transfer in the absence of Et_3N leading to retention of configuration or an intermolecular hydride transfer promoted by Et_3N with inversion of configuration.[7] Since an oxygen transfer pathway can be conceived within the framework of the intramolecular hydride transfer mechanism (Scheme 3), we carried out the reduction reaction using $HSiCl_3/PPh_3$ (2 equiv) in the absence of Et_3N. To our delight the dioxide **1a** was reduced to the desired product **2a** in 90% yield to achieve the first practical preparation of this type of electron-withdrawing BINAP ligands (Scheme 2).

Scheme 2



An ^{18}O labeling study was carried out to investigate in detail the oxygen transfer mechanism. ^{18}O-labeled BINAP(O)$_2$ was prepared via coupling Grignard reagent with ^{18}O-diarylphosphinyl chloride which was obtained from using $^{18}O_2$. The reduction reaction was then performed using the ^{18}O-labeled substrate and triphenylphosphine as the oxygen acceptor. The reaction was stopped after 2 days since at the end of the reaction virtually all of the triphenylphosphine oxide generated was reduced under these conditions by the excess silane. In fact, this probably helps to drive the oxygen transfer to completion by pulling the equilibrium over in favor of the formation of sacrificial triphenylphosphine oxide. Consistent with the proposed oxygen transfer mechanism, the ^{18}O-labeled triphenylphosphine oxide was isolated and characterized by mass spectrometry. To the best of our knowledge, this is the first observation of an oxygen transfer reaction between phosphorus atoms mediated by silane (Scheme 3).[8]

Scheme 3. Proposed Mechanism for $HSiCl_3$-Mediated Oxygen-Transfer Reaction



Electron-deficient triarylphosphine $[C_6H_3(CF_3)_2]_3P$ was also tested as an oxygen acceptor but was found to be much

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(6) The coupling of aryl Grignard with the commonly used phosphinyl chloride gave poor yields under the optimized conditions.

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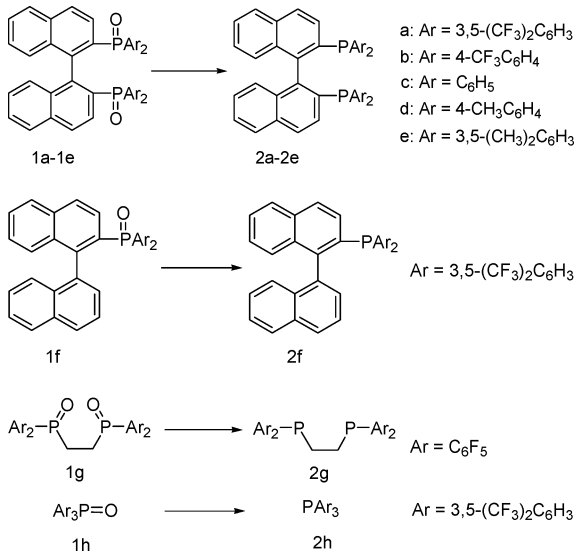
(8) An interesting example of intramolecular oxygen transfer reaction between phosphine and arsine was reported previously: Cook, V. C.; Willis, A. C.; Zank, J.; Wild, S. B. *Inorg. Chem.* **2002**, *41*, 1897. For examples of oxygen transfer from epoxide to triphenyl phosphine−iodine complex, see: Paryzek, Z.; Wydra, R. *Tetrahedron Lett.* **1984**, *25*, 2601. Sonnet, P. E. *Synthesis* **1980**, 828.

less effective with a mixture of products isolated (**2a**, 30%; **3a**, 40%). In this case, the sacrificial triarylphosphine oxide is not readily reduced by the silane resulting in all the phosphine oxide species being in equilibrium with one another, which may account for the observed product distribution. In addition the formation of $[C_6H_3(CF_3)_2]_3PH^+$ is not favored compared to $(C_6H_5)_3PH^+$ due to its weaker basicity. *The involvement of $(C_6H_5)_3PH^+$ as the key intermediates was also supported by the complete loss of reactivity in the presence of a sterically bulky base 2, 6-di-tert-butylpyridine.* It is interesting to note that triethylamine also retards the reaction, although reduction can still take place to give the monoxide **3a**, which presumably results from the Mislow pathway by forming the triethylamine−trichlorosilane complex.[7b]

The substrate scope of this new protocol was evaluated with other phosphine oxides. Triaryl phosphine oxides **1a**−**h** were efficiently deoxygenated to give phosphine ligands in excellent yields (Table 1). Of note is the significantly milder conditions used for the deoxygenation employing PPh_3/$HSiCl_3$ (100 °C), compared to the Et_3N/$HSiCl_3$ protocol (120−140 °C). This is particularly important in the reduction of the electron-deficient phosphine oxides since they decompose at high temperature. The advantage of using this method to reduce phosphine oxides other than electron deficient ones is also clear, as the reaction time may be drastically reduced (Table 1). For example, the reduction of **1f** (entry 6) using PPh_3/$HSiCl_3$ afforded 88% yield of **2f** after 20 h. In contrast, the Et_3N/$HSiCl_3$ protocol gave 72% yield of **2f** with reaction time of 5 days.[4a] The utility of this new protocol for deoxygenation was also exemplified with substrates bearing a *P*-chiral center. The efficient reduction of (*R*)-(2-methoxyphenyl)methylphenyl phosphine oxide [(*R*)-PAMP] with retention of configuration furnished a complimentary protocol to the $HSiCl_3$/Et_3N system that normally leads to an inversion (Scheme 4).[7b]

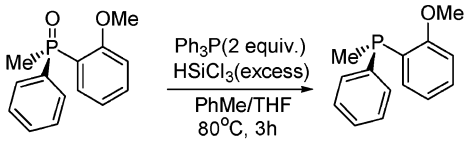
Table 1. Deoxygenation of Phosphine Oxides Using Ph_3P[a] as a Sacrificial Reagent



entry[b]	phosphine oxides	reduced products	time (h)	yield[c] (%)
1	**1a**	**2a**	96	90
2	**1b**	**2b**	18	88
3	**1c**	**2c**	3	95
4	(*R*)-**1d**	(*R*)-**2d**	2	92
5	**1e**	**2e**	2	96
6	**1f**	**2f**	20	88
7	**1g**	**2g**	4	90
8	**1h**	**2h**	15	93

[a] 2 equiv. [b] All reactions were carried out in the mixture of toluene−THF (1:1) at 100 °C using excess $HSiCl_3$ as reducing reagent. [c] Isolated yield.

Scheme 4. Stereospecific Deoxygenation of Phosphine Oxide



(*R*)-PAMPO, 99.5% e.e. (*S*)-PAMP, 95%, 99% e.e.

Although Ph_3P serves as a very efficient oxygen acceptor in the deoxygenation reaction, difficulties were encountered separating it from some of the triarylphosphine products. To try to simplify the workup, other compounds were investigated as suitable oxygen acceptors. $(EtO)_3P$ was previously reported to deoxygenate triphenylarsine oxide to triphenylarsine[9] and has the benefit of being easily separated from phosphines. We found that $(EtO)_3P$ to be just as competent an oxygen acceptor as PPh_3 with all the substrates used previously and could be readily separated from the triarylphosphine products by a short pad of silica gel to give good isolated yields (Table 2). Slightly faster reaction times were also achieved since a large excess (10 equiv) of $(EtO)_3P$ could be used in the reactions as it was simpler to remove

Table 2. Deoxygenation of Phosphine Oxides Using $(EtO)_3P$[a] as a Sacrificial Reagent

entry[b]	phosphine oxides	reduced products	time (h)	yield[c] (%)
1	**1a**	**2a**	88	90
2	**1b**	**2b**	16	90
3	**1c**	**2c**	3	95
4	(*R*)-**1d**	(*R*)-**2d**	2	92
5	**1e**	**2e**	2	96
6	**1f**	**2f**	18	88
7	**1g**	**2g**	3.5	90
8	**1h**	**2h**	12	92

[a] 10 equiv. [b] All reactions were carried out in the mixture of toluene−THF (1:1) at 100 °C using excess $HSiCl_3$ as reducing reagent. [c] Isolated yield.

than PPh_3. Therefore, using $(EtO)_3P$ as an oxygen acceptor is practically a more useful method for the deoxygenation of phosphine oxides.

In conclusion, we have observed a novel $HSiCl_3$-mediated oxygen transfer reaction between phosphorus atoms. An efficient and general protocol for the reduction of triarylphosphine oxides has been developed. This has allowed the convenient synthesis of electron-deficient chiral phosphine ligands such as BINAP derivatives **2a** and **2b** for the first time.

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Supporting Information Available: General experimental procedure details and characterization data for all products. The crystal structures of **1a**, **1b**, **2a**, and **2b** are available in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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