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A Superior Method for the Reduction of Secondary Phosphine Oxides

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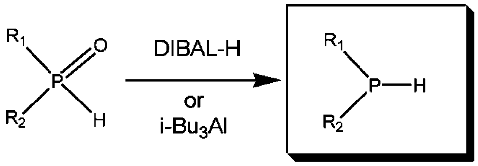
ABSTRACT



R_1, R_2 = aryl, 1°, 2°, 3° alkyl
21 examples, 72- 92% yield

Diisobutylaluminum hydride (DIBAL-H) and triisobutylaluminum have been found to be outstanding reductants for secondary phosphine oxides (SPOs). All classes of SPOs can be readily reduced, including diaryl, arylalkyl, and dialkyl members. Many SPOs can now be reduced at cryogenic temperatures, and conditions for preservation of reducible functional groups have been found. Even the most electron-rich and sterically hindered phosphine oxides can be reduced in a few hours at 50–70 °C. This new reduction has distinct advantages over existing technologies.

Secondary phosphine oxides (SPOs) are crucial building blocks for the construction of phosphine ligands and have also been used as ligands themselves with both actinide metals[1] and transition metals in organic synthesis.[2] Secondary phosphines are also used in S_NAr, S_N2, Michael addition, hydrophosphination, and cross-coupling syntheses of tertiary phosphines.[3] We have recently patented the BIPI ligands[4] (Figure 1) as electronically tunable scaffolds for asymmetric catalysis, and these ligands have now been utilized in a variety of asymmetric transformations.[5] Retrosynthetically, the BIPI ligands are prepared from secondary phosphines, and we sought acceptable methods for larger scale syntheses of this class of compounds. A survey of the literature showed a number of possible methods, yet none were found to be satisfactory: SPOs can be converted to chlorophosphines and then reduced,[6] yet distillation of the intermediate chloro-

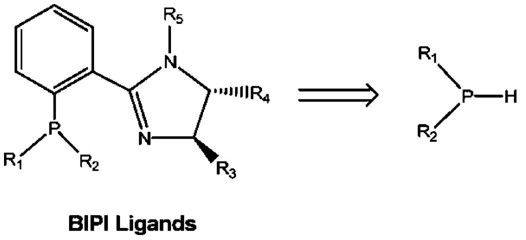


Figure 1. BIPI ligand retrosynthesis.

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[1] For examples, see: (a) Grim, S. O.; Satek, L. C. *J. Inorg. Nucl. Chem.* **1977**, *39*, 499. (b) Gatrone, R. C.; Dietz, M. L.; Horwitz, E. P. *Solv. Extr. Ion Exch.* **1993**, *11* (3), 411.

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phosphines is required for optimum results. The high vacuum needed to accomplish this is simply not available in a typical pilot plant. In addition, LAH is often used for the reduction, and this is a hazardous substance to handle on large scale. We also wanted to avoid a two-step procedure for the transformation. The reduction has been performed with neutral silanes such as diphenylsilane,[7] yet temperatures in excess of 200 °C are often used. This is beyond the upper working temperature (∼150 °C) of most types of plant reactor systems. SPOs have been reduced with electron-deficient silanes such as trichlorosilane, usually in refluxing toluene or xylene, with added amines.[8] Trichlorosilane has both a low flash point (−13 °C) and low boiling point (31 °C) and is used at temperatures far above its boiling point. This approach was therefore rejected on safety grounds. Mechanistically, trichlorosilane is the electrophilic partner in a nucleophilic attack by the SPO oxygen. This type of reduction is therefore known to be quite difficult in the case of electron-deficient phosphine oxides,[9] and we were particularly interested in the reduction of these substrates. LAH alone has also been used for this reduction,[10] yet it presents handling difficulties, is nonchemoselective, and most importantly, can lead to primary phosphine impurities through aryl C−P bond cleavage.[11] The reduction of SPOs has also been achieved with borane, in a significant advance recently made by Pietrusiewicz.[12] However, a recent severe industrial accident with borane has been reported,[13] reducing the enthusiasm for large-scale use of this reagent which is used in considerable excess in the reported procedure. The latter method can also lead to significant amounts of the borane adduct of the phosphinous acid tautomer as an impurity.

We screened a series of commercially available reducing agents with diphenylphosphine oxide and quickly found that diisobutylaluminum hydride (DIBAL-H) effected clean reduction to diphenylphosphine in minutes at ambient temperature. This reducing agent has never been reported for the reduction of SPOs,[14] although it was reported more than 25 years ago for the reduction of triphenylphosphine oxide.[15]

DIBAL-H is an inexpensive aluminum alkyl which is available in bulk in “process friendly” solvents such as toluene, heptane, and THF. This is due to its central role in the polymer industry for the production of polyethylene and polybutadiene under Ziegler−Natta catalysis.[16] We therefore screened a series of diaryl SPOs with DIBAL-H, as shown in Table 1. Our screening conditions used 3 equiv of DIBAL-H/THF at ambient temperature, and all initial substrates (entries 1−10) were reduced within the time required to reach the spectrometer (∼10 min). The extremely electron-rich[17a] *p*-NMe$_2$ derivative (**12**, $\sigma_P = -0.83$) as well as the methoxy-substituted SPOs **13** and **14**, however, all required 5 equiv of DIBAL-H to reach completion at 25−35 °C. It seems likely that 2 equiv of reducing agent are chelated unproductively to the heteroatoms in these species.

We next evaluated lower reaction temperatures and reduced DIBAL-H charges. Many of the diaryl substrates could actually be reduced between −78 and −20 °C. The DIBAL-H charge could also be reduced to ∼1.5 equiv in many cases, although this was ultimately found to depend on the hydration state of the SPOs. A few of the phosphine oxides crystallized as hydrates. We have found that both coulometric and volumetric Karl Fisher water determinations on SPOs are very treacherous—we routinely oberved “false positives” for these species and subsequently found that only TGA-IR in conjunction with DSC and elemental analysis could reveal the true hydration state of these substrates. As expected, the hydrates require additional DIBAL-H to effect the reduction. We next focused on arylalkyl and dialkyl SPOs. Phenylisopropylphosphine oxide **15** was reduced in ca. 10 min at ambient temperature, yet phenyl-*tert*-butylphosphine oxide **16** showed no reduction after several hours at 25 °C. This substrate was cleanly reduced in 4 h at 50

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(3) For selected examples, see the following. S$_N$Ar: (a) Williams, J. M. J.; Coote, S. J.; Dawson, G. J.; Frost, C. G. *Synlett* **1993**, 509. S$_N$2: (b) Sakai, T.; Kodama, T.; Fujimoto, T.; Ohta, K.; Yamamoto, I.; Kakehi, A. *J. Org. Chem.* **1994**, *59* (23), 7144 (c) Heidel, H.; Huttner, G.; Helmchen, G. *Z. Naturforsch. B* **1993**, *48* (11), 1681. (d) Imamoto, T.; Oshiki, T.; Onozawa, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112* (13), 5244. Michael: (e) Blinn, D. A.; Button, R. S.; Farazi, V.; Neeb, M. K.; Tapley, C. L. *J. Organomet. Chem.* **1990**, *393* (1), 143. (f) Lavenot, L.; Bortoletto, M. H.; Roucoux, A.; Larpent, C.; Patin, H. *J. Organomet. Chem.* **1996**, *509* (1), 9. Hydrophosphination: (g) Shulyupin, M. O.; Kazankova, M. A.; Beletskaya, I. P. *Org. Lett.* **2002**, *4* (5), 761. (h) Kawaoka, A. M.; Marks, T. J. *J. Am. Chem. Soc.* **2004**, *126* (40), 12764. Cross-coupling: (i) Herd, O.; Hessler, A.; Hingst, M.; Tepper, M.; Stelzer, O. *J. Organomet. Chem.* **1996**, *522*, 69. (j) Cai, D.; Payack, J. F.; Bender, D. R.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59* (23), 7180. (k) Kraatz, H.-B.; Pletsch, A. *Tetrahedron: Asymmetry* **2000**, *11*, 1617. (l) Hillhouse, J. H. U. S. Pat. 5,550,295, 1996.

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(11) Treatment of (3,5-F$_2$-C$_6$H$_3$)$_2$POH with LAH from 0 to 25 °C leads to a mixture of the desired secondary phosphine and 3,5-difluorophenylphosphine, ^{31}P NMR δ −121 ppm, t, $^1J_{P-H} = 203$ Hz.

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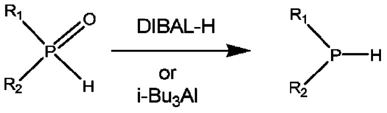
Table 1. Reduction of Secondary Phosphineoxides by DIBAL-H and *i*-Bu_3Al



1-21 **22-42**

entry	R_1	SPO	R_2	time/*T* (°C)	Al species[a]	R_1R_2PH	yield (%)
1	C_6H_5	**1**	C_6H_5	10 min/25	D	**22**	86
2	4-F-C_6H_4	**2**	4-F-C_6H_4	10 min/25	D	**23**	90
3	4-Cl-C_6H_4	**3**	4-Cl-C_6H_4	10 min/25	D	**24**	83
4	4-Me-C_6H_4	**4**	4-Me-C_6H_4	10 min/25	D	**25**	80[b]
5	3-F-C_6H_4	**5**	3-F-C_6H_4	10 min/25	D	**26**	89
6	3-Cl-C_6H_4	**6**	3-Cl-C_6H_4	10 min/25	D	**27**	81
7	3-F, 5-Me-C_6H_3	**7**	3-F, 5-Me-C_6H_3	10 min/25	D	**28**	82
8	3,5-F_2, 4-OMe-C_6H_2	**8**	3,5-F_2, 4-OMe-C_6H_2	10 min/25	D	**29**	90
9	3,5-Cl_2-C_6H_3	**9**	3,5-Cl_2-C_6H_3	1 h/−20	D	**30**	90
10	3,5-F_2-C_6H_3	**10**	3,5-F_2-C_6H_3	1 h/−20	D	**31**	80
11	2-Me-C_6H_4	**11**	2-Me-C_6H_4	8 h/25	D	**32**	80
12	4-NMe_2-C_6H_4	**12**	4-NMe_2-C_6H_4	45 min/25[c]	D	**33**	92
13	4-OMe-C_6H_4	**13**	4-OMe-C_6H_4	40 min/25[c]	D	**34**	91
14	2-OMe-C_6H_4	**14**	2-OMe-C_6H_4	8 h/35[c]	D	**35**	75
15	C_6H_5	**15**	*i*-Pr	10 min/25	D	**36**	90
16	C_6H_5	**16**	*t*-Bu	4 h/50	D	**37**	86
17	*n*-Bu	**17**	*n*-Bu	1 h/25	D	**38**	85
18	C_6H_{11}	**18**	C_6H_{11}	4 h/50	D	**39**	88
19	*t*-Bu	**19**	*t*-Bu	4 h/50	D	**40**	87
20	3,5-$(CF_3)_2$-C_6H_3	**20**	3,5-$(CF_3)_2$-C_6H_3	15 min/25	D	**41**	72
21	3-F, 5-Me-C_6H_3 + PhI[d]	**7**	3-F, 5-Me-C_6H_3 + PhI[d]	30 min/25	T	**28**	82
22	3-F, 5-Me-C_6H_3 + $PhCONMe_2$[d]	**7**	3-F, 5-Me-C_6H_3 + $PhCONMe_2$[d]	30 min/25	T	**28**	81
23	2,4,6-Me_3-C_6H_2	**21**	2,4,6-Me_3-C_6H_2	24 h/70[e]	T	**42**	75

[a] D = DIBAL-H; T = *i*-Bu_3Al. [b] Yield of phosphine borane complex. [c] 5 equiv of DIBAL-H was used. [d] Competition experiment. [e] 8 equiv of *i*-Bu_3Al was used.

°C, however. The result underscores the role of sterics in the DIBAL-H reduction. Di-*n*-butylphosphine oxide and dicyclohexylphosphine oxide (entries 17 and 18) were readily reduced at 25 and 50 °C, respectively. We next examined di-*tert*-butylphosphine oxide **19**, certainly one of the most electron-rich and sterically hindered SPOs known. In 4 h at 50 °C, complete reduction to the secondary phosphine was observed. The substrate scope of this new reduction is clearly quite broad.

The reduction of 3,5-bis-CF_3-substituted SPO **20** requires special comment. When this reduction was attempted with DIBAL-H in THF, long reaction times at −78 °C were required to minimize formation of the primary phosphine,[17b] which arose by aryl C−P cleavage. This substrate is the most electron deficient[17a] ($2\sigma_M = +0.86$) of the entire series and the only substrate where primary phosphine impurities were ever observed. A remarkable solvent effect was subsequently uncovered, however; DIBAL-H *in hydrocarbons* gave rapid reduction at 23 °C with no primary phosphine formation.

In addition to diisobutylaluminum hydride, several other organoaluminums were found to be capable of effecting the reduction of SPOs (Figure 2). Triisobutylaluminum and triisobutyldialuminoxane are both competent reductants in the range of 25−70 °C, and tetraisobutyldialuminoxane can also be used at somewhat elevated temperatures. Entries 21−23 of Table 1 show reductions with *i*-Bu_3Al (TIBA).

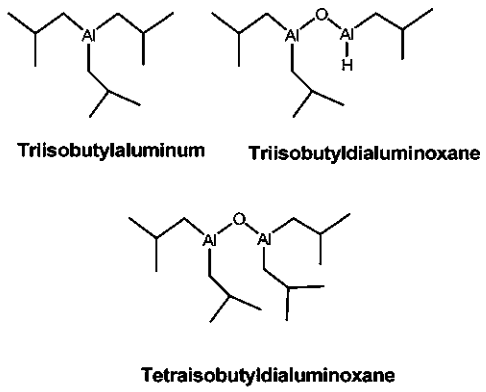


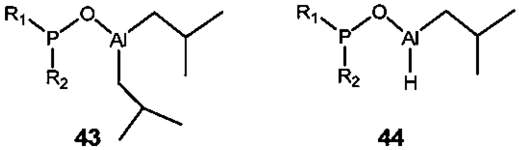
Figure 2. Additional organoaluminum reductants.

Two competition experiments (21,22) showed that both amide and aryl iodide functionality are preserved during the SPO reductions with *i*-Bu_3Al. In addition, entries 13 and 14 have established that ethers are similarly unaffected by

DIBAL-H at ambient temperature, despite the susceptibility of ethers to this reductant at elevated temperatures.[18] Entry 23 is significant, as the exceedingly hindered mesityl SPO **21** was reduced in toluene in 24 h at 70 °C. A solvent study revealed an aceleleration of the SPO reduction rate by *i*-Bu_3-Al when toluene was used, rather than THF. It is noteworthy that the very hindered phosphines **40** and **42** have not been synthesized previously by direct reduction of their oxides.

Secondary phosphines are extremely air-sensitive compounds, and the electron-rich varieties oxidize very rapidly when exposed to air. For this reason, we developed several interlocking strategies for reaction workup to minimize inadvertent oxidation of the products. First, a water-immiscible solvent, such as MTBE (methyl *tert*-butyl ether) is added and the cooled reaction mixture then quenched with aqueous NaOH while sparging with argon. This results in two clear phases free of any solids or gels, as the aluminum hydroxide byproduct is solubilized by base. For small-scale reactions, the phase separation could conveniently be performed in the body of a 50 mL syringe using a ~15 cm long needle. The organic phase was then transferred to an inerted Airfree[18] filter containing $MgSO_4$, connected to a recovery flask.[19] For larger scale reactions, we used a jacketed flask with a bottom drain valve. At still greater scale, the organic phase was dried by azeotropic distillation. In this way, dry solutions of secondary phosphines ready for further transformation were conveniently obtained. Many solvents in addition to THF can be used for the SPO reduction including toluene, heptane, cyclohexane, methyl-THF, and CH_2Cl_2.

The mechanism of the DIBAL-H reduction of SPOs is not yet clear. The "expected" acid−base reaction between the two components would generate H_2 and intermediate **43**, as shown in Figure 3. A gas is indeed evolved when the two reagents are combined. However, GC analysis of this gas shows it contains *both* H_2 and *isobutane*, suggesting the potential intermediacy of species **44** (Figure 3). The mechanism of this reduction is under intense scrutiny and will be reported elsewhere shortly along with full calorimetric analyses.



43 **44**

Figure 3. Possible reaction intermediates.

In summary, a new reduction of secondary phosphine oxides using neutral organoaluminums has been discovered. The reaction is extremely broad in scope, can be performed at moderate temperatures, is operationally simple, and provides secondary phosphines in high yields and purities.

Supporting Information Available: Synthetic details, characterization of all species, and digital photographs of glassware setups are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Chemglass Catal. No. AF-0542-22; AF-0542-25.

(19) Photographs of the glassware are found in the Supporting Information.