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Reduction of Tertiary Phosphine Oxides with DIBAL-H

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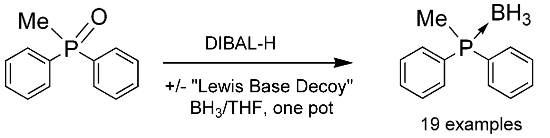
Received November 7, 2007



no Decoy: stalls at 60% conversion
with Decoy: 100% conversion, 98% yield!

The reduction of tertiary phosphine oxides (TPOs) and sulfides with diisobutylaluminum hydride (DIBAL-H) has been studied in detail. An extensive solvent screen has revealed that hindered aliphatic ethers, such as MTBE, are optimum for this reaction at ambient temperature. Many TPOs undergo considerable reduction at ambient temperature and then stall due to inhibition. ^{31}P and ^{13}C NMR studies using isotopically labeled substrates as well as competition studies have revealed that the source of this inhibition is tetraisobutyldialuminoxane (TIBAO), which builds up as the reaction proceeds. TIBAO selectively coordinates the TPO starting material, preventing further reduction. Several strategies have been found to circumvent this inhibition and obtain full conversion with this extremely inexpensive reducing agent for the first time. Practical reduction protocols for these critical targets have been developed.

Introduction

Tertiary phosphines are the single most important compound class for metal ligation, and they are often prepared by reduction of the corresponding tertiary phosphine oxides (TPOs).[1] We have recently developed the use of diisobutylaluminum hydride (DIBAL-H) and triisobutylaluminum (TIBA) for the reduction of *secondary* phosphine oxides (SPOs) and shown that these reductants have superior substrate scope, mildness of conditions, and cost[2d] when compared to other methods.[2] We wished to evaluate tertiary phosphine oxides with these reductants; in addition, the scope and limitations of this reduction had never been determined. Unlike SPOs, the reduction of TPOs with neutral organoaluminums does have some limited precedent in the patent literature, specifically in three patents.[3] In the first, from 1977, the single substrate triphenylphosphine oxide was examined in a total of five solvents. In all cases, the reductions cited did not go to completion. Heptane was chosen as the optimum solvent in that study since the unreacted starting material had the lowest solubility in heptane and could therefore be removed by filtration after quenching.[3a] This is likely the reason that DIBAL-H has not previously been utilized for TPO reductions.

Results and Discussion

We started our research into TPO reductions with a solvent study. Solvents can of course exert a profound effect on reactions and are one of the simplest reaction parameters to systematically

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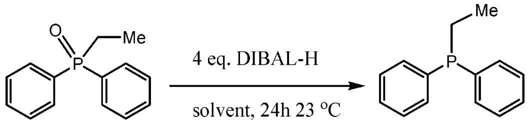
(1) For recent, selected examples, see: Cl_3SiH: (a) Xie, J.-H.; Duan, H.-F.; Fan, B.-M.; Cheng, X.; Wang, L.-X.; Zhou, Q.-L. *Adv. Synth. Catal.* **2004**, *346* (6), 625. (b) RajanBabu, T. V.; Nomura, N.; Jin, J.; Nandi, M.; Park, H.; Sun, X. *J. Org. Chem.* **2003**, *68* (22), 8431. (c) Baillie, C.; Xiao, J. *Tetrahedron* **2004**, *60* (19), 4159. Cl_3SiH/PPh_3: (d) Wu, H.-C.; Yu, J.-Q.; Spencer, J. B. *Org. Lett.* **2004**, *6* (25), 4675. BH_3: (e) Keglevich, G.; Chuluunbaatar, T.; Ludanyi, K.; Toke, L. *Tetrahedron* **1999**, *56* (1), 1. $PhSiH_3$: (f) Botman, P. N. M.; Fraanje, J.; Goubitz, K.; Peschar, R.; Verhoeven, J. W.; van Maarseveen, J. H.; Hiemstra, H. *Adv. Synth. Catal.* **2004**, *346* (7), 743. (g) Pakulski, Z.; Koprowski, M.; Pietrusiewicz, K. M. *Tetrahedron* **2003**, *59* (41), 8219. MeOTf/LAH: (h) Imamoto, T.; Kikuchi, S.-i.; Miura, T.; Wada, Y. *Org. Lett.* **2001**, *3* (1), 87. (i) Guillen, F.; Rivard, M.; Toffano, M.; Legros, J.-Y.; Daran, J.-C.; Fiaud, J.-C. *Tetrahedron* **2002**, *58* (29), 5895. $Ti(O\text{-}i\text{-}Pr)_4/(EtO)_3SiH$: (j) Onodera, G.; Matsumoto, H.; Milton, M. D.; Nishibayashi, Y.; Uemura, S. *Org. Lett.* **2005**, *7* (18), 4029. (k) Allen, A., Jr.; Ma, L.; Lin, W. *Tetrahedron Lett.* **2002**, *43* (20), 3707. (l) Coumbe, T.; Lawrence, N. J.; Muhammad, F. *Tetrahedron Lett.* **1994**, *35* (4), 625. (m) Camps, P.; Colet, G.; Font-Bardia, M.; Munoz-Torrero, V.; Solans, X.; Vazquez, S. *Tetrahedron: Asymmetry* **2002**, *13* (7), 759. $Ti(O\text{-}i\text{-}Pr)_4$/PMHS: (n) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122* (48), 12051. AlH_3: (o) Dandapani, S.; Curran, D. P. *Tetrahedron* **2002**, *58* (20), 3855. (p) Bootle-Wilbraham, A.; Head, S.; Longstaff, J.; Wyatt, P. *Tetrahedron Lett.* **1999**, *40* (28), 5267. K/NH_3: (q) Nycz, J.; Rachon, J. *Phos. Sulf. Sil. Rel. Elem.* **2000**, *161*, 39.

10.1021/jo7024064 CCC: $40.75

TABLE 1. Ambient Temperature Solvent Screening



1 **2**

entry	solvent	% conv[a]
1	THF-d_8	0
2	1-fluoroheptane	0
3	2,2-dimethyl THF	0
4	*N*-methylimidazole	4
5	DME	12
6	TEA	15
7	ETBE[b]	17
8	anisole	19
9	*n*-Bu_3P	20
10	2,2,5,5-TMTHF[c]	21
11	$CDCl_3$	31
12	2-Me THF	35
13	2,5-dimethyl THF	35
14	tetrachloroethane-d_2	37
15	$PhNMe_2$	40
16	CD_2Cl_2	41
17	1-chloroheptane	44
18	PhF	48
19	$PhCF_3$	49
20	cineole	50
21	DMO OMe[d]	50
22	*p*-dioxane-d_8	51
23	*n*-Bu_2O	51
24	PMP[e]	51
25	thiophene	51
26	tetrahydropyran	51
27	1,4-cineole	52
28	furan-d_4	52
29	PhCl	52
30	*t*-Bu-SMe	52
31	thioanisole	54
32	*t*-amyl OMe	54
33	PhMe-d_8	59
34	C_6D_6	59
35	Et_2O-d_{10}	60
36	none (neat)	61
37	*p*-xylene-d_{10}	62
38	HFE-7100[g]	62
39	(+)-fenchyl OMe	65
40	*i*-Pr_2O	65
41	C_6D_{12}	65
42	isoborneol OMe	72
43	***c*-Pent-OMe**[f]	**72**
44	**MTBE**	**72**

[a] As determined by ^{31}P NMR integration (standard delay time, d1 = 2 s). [b] Ethyl *tert*-butyl ether. [c] Tetramethyl THF. [d] 3,7-Dimethyloctanol methyl ether. [e] Pentamethylpiperidine. [f] Cyclopentyl methyl ether. [g] Perfluorobutyl methyl ethers.

vary.[4a] We chose not to limit ourselves to a few solvents as was earlier done,[3a] but to cast a very wide net in an attempt to gain as much understanding as possible. Our requirements for inclusion into the solvent study were very simple: the material should be a liquid near ambient temperature, and it should not obviously react with DIBAL-H. We chose as our protypical substrate diphenylethylphosphine oxide **1**, and our initial screening conditions were 4 equiv of DIBAL-H at ambient temperature. The results of this completely empirical approach, using a total of 44 solvents, are shown in Table 1. The results are listed in increasing order of percent conversion, as determined by ^{31}P NMR.

Several solvent trends were identified by analysis of the ambient temperature data: (1) aliphatic hydrocarbons give slightly higher conversions than aromatic hydrocarbons, (2) halocarbons generally give poor conversion, (3) chlorocarbons give better conversion than fluorocarbons, (4) hindered aliphatic amines give better conversion than unhindered amines, (5) ethers generally give better conversions than thioethers, (6) aliphatic ethers give better conversion than aromatic ethers, (7) hindered aliphatic ethers give higher conversion than unhindered aliphatic ethers provided there are not *two* α-quaternary centers, and (8) aliphatic ethers hindered on one side and unhindered on the other side give the highest conversions (ca. 70%). MTBE and cyclopentyl methyl ether[4b] fall in the last category. It is interesting to note that performing the reaction *neat in DIBAL-H* (entry 36) does not provide the highest conversion and that THF (entry 1), a very common ethereal solvent, gives no conversion. A typical ^{31}P NMR reaction mixture spectrum (here C_6D_6) is shown in Figure 1. The product phosphine is observed at δ −11 ppm. The resonanace for *free* phosphine oxide **1** is δ 32 ppm, which is *not* observed in the reaction mixture. A cluster of ^{31}P signals around δ 51 ppm are observed in this solvent and similar behavior was seen in all of the solvents screened. When samples such as these are quenched with aqueous NaOH, these multiple downfield signals all convert to one signal for the starting material (δ ∼32 ppm). These resonances are in fact "trapped" starting material, as will be discussed shortly. Two critical observations were made as a result of this solvent screen:

In most cases, no significant reduction occurred after 24 h of reaction time, and in no case could additional conversion be obtained by adding excess DIBAL-H at the 24 h time point. In short, the reductions all stalled and could not be pushed to completion at ambient temperature. The reductions were clearly being inhibited, and the question was how this was occurring.

Our initial working mechanistic model for the reduction of TPO's with DIBAL-H is shown in Scheme 1. It consists of hydroalumination of the P═O bond to generate pentavalent intermediate **3**, followed by loss of H_2 to furnish the product phosphine **4**. This mechanism would require 2 equiv of DIBAL-H and would generate 1 equiv of tetraisobutyldialumi-

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(2) (a) Busacca, C. A.; Lorenz, J. C.; Grinberg, N.; Haddad, N.; Hrapchak, M.; Latli, B.; Lee, H.; Sabila, P.; Saha, A.; Sarvestani, M.; Shen, S.; Varsolona, R.; Wei, X.; Senanayake, C. H. *Org. Lett.* **2005**, *7* (19), 4277. (b) Busacca, C. A.; Lorenz, J. C. U.S. Pat. 7,256,314, 2007. Int. Appl. No. PCT/US05/01526. (c) Busacca, C. A.; Lorenz, J. C.; Sabila, P.; Haddad, N.; Senanayake, C. *Org. Synth.* **2007**, *84*, 242. (d) On a 100 kg scale, the cost of DIBAL-H is ∼$1.50/mol from Albemarle.

(3) (a) GB 1,520,237, Appl. No. 0/18850/77, 1977. (b) Frey, F. W.; Lee, J. Y. U.S. Patent 4,507,503, 1985. (c) Frey, F. W.; Lee, J. Y. U. S. Patent 4,507,504, 1985. (d) See also: Self, M. F.; Sangokoya, S. A.; Pennington, W. T.; Robinson, G. H. *J. Coord. Chem.* **1990**, *21* (4), 301.

(4) (a) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; Wiley-VCH: Weinheim, 2003. (b) Zeon Corporation, www.zeon.co.jp; This solvent is undergoing commercialization. U.S representative: BetaChem, contact: lu.john@beta-chem.com.

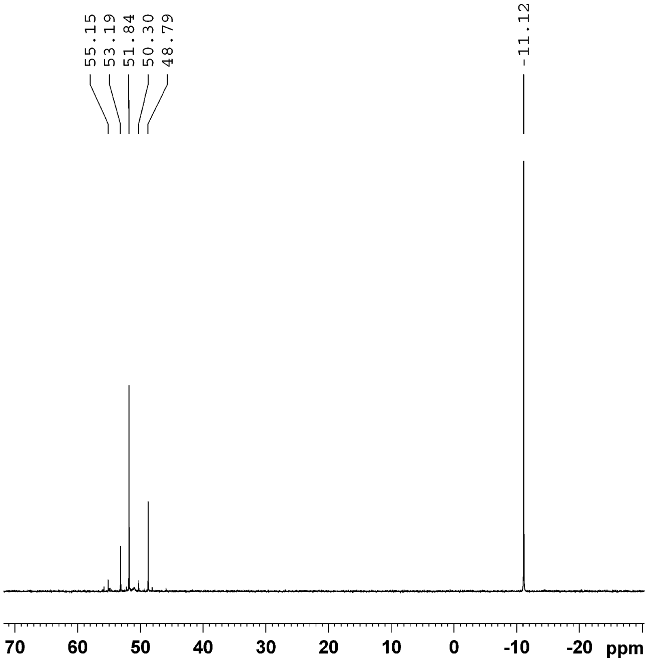
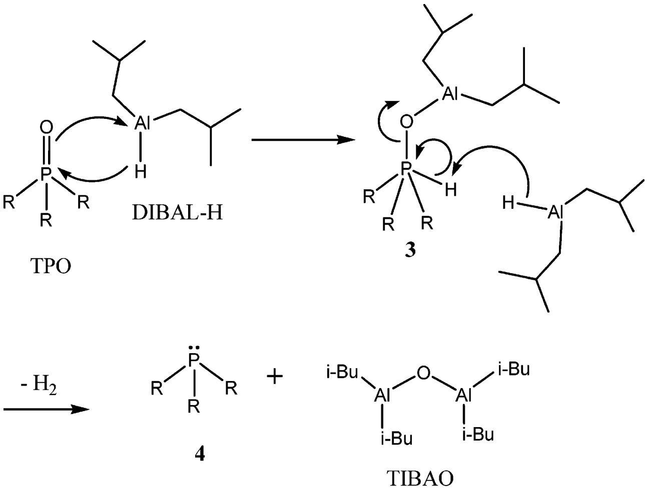


FIGURE 1. ^{31}P NMR spectra of TPO **1** reduction.

SCHEME 1. Initial Mechanistic Model of Reduction



noxane (TIBAO) per equivalent of tertiary phosphine produced. Based on this model, the tertiary phosphine product and TIBAO were both possible candidates for the inhibition observed. The reduction of **1** to **2** was therefore carried out in toluene-d_8 in which 2 equiv of the product phosphine **2** were added to **1** prior to addition of DIBAL-H. Quantitative ^{31}P NMR after 24 h showed the same amount of unreacted TPO was observed as was seen in the control experiment without added phosphine. Clearly, phosphine product inhibition was not taking place. We next added 2 and 3 equiv of TIBAO as the commercial toluene solution (0.29 M) to TPO **1** in toluene-d_8, prior to the DIBAL-H charge. The results are shown in Figure 2, in which percent conversion (by ^{31}P NMR) is plotted as a function of time. Reaction inhibition is clearly seen, and 3 equiv of TIBAO profoundly retards the reaction.

It is worth considering the stoichiometry of the reaction mixture at ca. 2/3 conversion (Scheme 2): the *ratio* of TIBAO/TPO at this conversion level would be 2:1, and significant reaction inhibition would be expected.

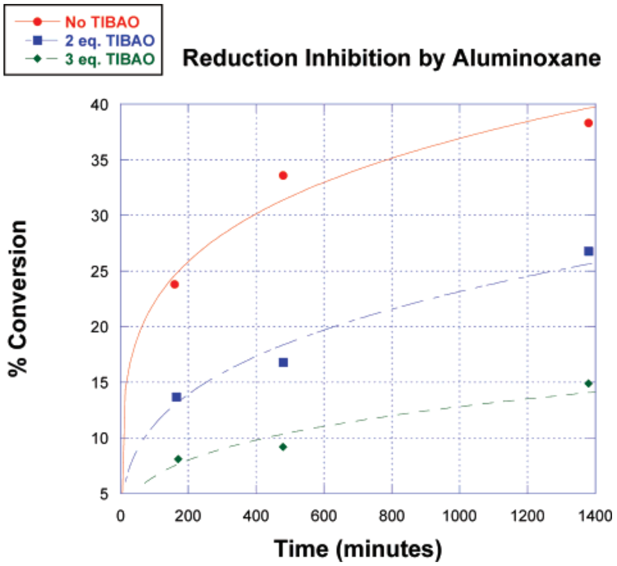
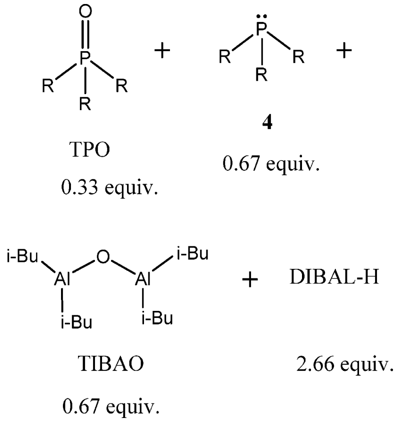


FIGURE 2. Reaction inhibition by aluminoxane.

SCHEME 2. Composition at 67% Conversion



The relative Lewis acidities of a number of organoaluminum compounds toward the Lewis base PhOEt have been studied by ^{1}H NMR.[5] DIBAL-H was found to be a better acid than TIBAO toward this ether. This situation clearly does not extend fully to tertiary phosphine oxides, however, or the buildup of TIBAO in the reaction mixture would be of no consequence and no inhibition would be observed.

Electron-rich aliphatic ether solvents might provide the highest conversion under these conditions because they are capable of displacing the TPO from TIBAO to a significant, though not complete, extent. The preeminence of ethers hindered on one side to positively affect these complexes is a subtlety that we presently have no way of probing directly.

The observed effects with aliphatic ethers suggested a possible strategy for increasing ambient temperature conversion: addition of a "decoy" TPO that was more electron-rich than the TPO substrate undergoing reduction. We originally chose to study this by ^{31}P and ^{13}C NMR using ^{13}C-labeled $Ph_2MeP{=}O$ (**5**) as substrate and commercially available tri-*n*-butylphosphine oxide (TBPO, **6**) as the decoy TPO. However, TBPO is in fact extensively reduced at ambient temperature, as will be discussed later. We therefore examined the reduction of **5** in the presence

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[5] (a) Ushakova, T. M.; Meshkova, I. N.; Markevich, M. A. *Organomet. Chem. USSR* **1988**, *1* (4), 513.

and absence of the more sterically hindered decoy tricyclohexylphosphine oxide (c-Hex$_3$P═O, **7**), which is also commercially available. The proton-decoupled ^{31}P spectrum of **5** (Supporting Information Figure 1A) is a doublet at δ 39.4 ppm, with $^1J_{PC} = 73$ Hz for coupling to ^{13}CH$_3$. The ^{13}C spectrum of the methyl region of **5** shows the methyl signal to be a doublet at δ 16.7 ppm with the same coupling constant. It is well-known that $^1J_{PC}$ is a sensitive probe of phosphorus geometry.[6] $^1J_{PC}$ of tetracoordinate phosphorus compounds like TPOs are generally about 1 order of magnitude larger than $^1J_{PC}$ for tricoordinate phosphorus compounds, such as tertiary phosphines.

A ^{13}C-labeled substrate was chosen so that ^{31}P resonances associated with the substrate, which would be doublets with J's of ca. 75 Hz, could be readily differentiated from resonances associated with the decoy TPO which was not isotopically labeled and would therefore be present as singlets. In addition, the geometric dependence of $^1J_{PC}$ mentioned above would also provide insight into the structure of reaction intermediates. We first reduced **5** with 4 equiv of DIBAL-H in C_6D_{12} for 4 h. The reaction stalled at ~65% conversion, as expected. The product, Ph$_2$^{13}CH$_3$P (**8**), was observed at δ −24 ppm as a doublet with dramatically reduced $^1J_{PC}$ of 9 Hz, typical of *tricoordinate* phosphorus. No uncomplexed starting material (δ 39 ppm) was observed. We focused on the ^{31}P signals at ~49 ppm, since we knew these were resonances of the "aluminoxane-trapped" starting material, as determined by reaction quenching mentioned above. Two major signals were observed. Examination of the resonances (Supporting Information Figure 2A) instantly showed that both signals were doublets, with $^1J_{PC}$ values of 76 and 74 Hz: these are clearly starting material-derived resonances, since only tetracoordinate phosphorus species will possess these large coupling constants.

The reaction of labeled substrate **5** was then repeated, yet 1 equiv of the decoy c-Hex$_3$P═O was added at the outset, prior to addition of DIBAL-H. The ^{31}P NMR spectrum (Supporting Information Figure 2B) at the same 4 h time point showed the product at δ −25 ppm, a new cluster of intense peaks at ~67 ppm, and the absence of the resonances at ca. 49 ppm. *Close examination of the downfield resonances showed that all of them were singlets*. The signals near 67 ppm are therefore confirmed to be derived from the unlabeled decoy, c-Hex$_3$P═O. The NMR conversion at 4 h was 95%, compared to 65% without the decoy. As expected, NMR thus confirms displacement of the trapped substrate TPO by the superior Lewis base c-Hex$_3$P═O, validating the decoy concept. It should also be noted that no tricyclohexylphosphine was produced under these reaction conditions, and the decoy can be easily recovered and recycled if desired. The ^{31}P NMR spectrum of labeled substrate **5** in the presence of 2 equiv of TIBAO *only* did not show the downfield doublets of the reduction in the absence of decoy. If *both* TIBAO and DIBAL-H were added to **5**, however, a spectrum nearly identical to the nondecoy reduction mixture was generated. It seems possible therefore that the inhibitory complex contains both TIBAO and DIBAL-H. One possible structure for this complex is shown in Figure 3.

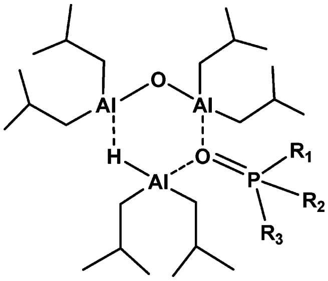
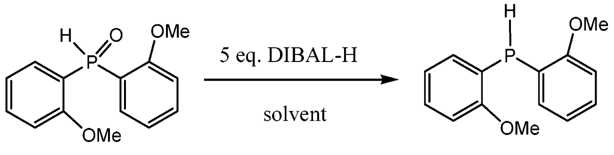


FIGURE 3. Possible structure of inhibitory complex.

SCHEME 3. SPO Solvent Effect



9

10

in THF: 8 hours at 35 °C, 75%
in MTBE: 30 minutes at 23 °C, 78%

We also wanted to examine an alternate method to obtain full conversion in these reductions. Our basic premise was that the TIBAO−TPO complex would be destroyed if β-hydride elimination of the TIBAO component could be induced, likely at elevated temperature. Reduction of **1** in mesitylene-d_{12} was studied first by ^{31}P NMR at temperatures greater than ambient. Following these reactions by NMR allowed us to determine with precision the reaction times and temperatures required to achieve full conversion. The temperature was slowly raised until significant reduction was observed. ^{31}P NMR spectrum of this *crude* reaction mixture after 14 h at 120 °C was remarkably clean (Supporting Information Figure 3), as only a single resonance for the product (**2**) was observed. At 110 °C, the boiling point of toluene, full conversion was not achieved. The curious situation thus exists in that one can obtain 50−60% yield by stirring the reaction overnight at ambient temperature, yet only by overnight reaction at *120 °C* can >90% yield be obtained under purely thermal conditions.

It is known that hydroaluminations of unsaturated systems are fastest in hydrocarbon solvents, where DIBAL-H is "naked" and uncomplexed, while these reactions are far slower in donor solvents.[7] In hydrocarbons such as mesitylene, hydroalumination is probably fast, yet the TIBAO−TPO complex is more stable, and thus high temperatures are required. Conversely, it seems likely that the use of ethers here probably slows down hydroalumination. This effect is apparently more than compensated for, however, by efficient disruption of the TIBAO inhibitory complex, leading to *overall* reduction under milder conditions.

Our previous work with *secondary* phosphine oxides did not include such a broad solvent screen as employed here, since SPOs are readily reduced with DIBAL-H in all organic solvents examined. We did encounter one SPO substrate that reduced slowly, however, due to chelation with DIBAL-H, namely bis(2-methoxyphenyl)phosphine oxide **9**. In THF, 8 h at 35 °C was needed to obtain full conversion to phosphine **10**. Since THF was one of the worst solvents for TPO reductions, we repeated this reduction in MTBE-d_3, the optimum ambient temperature TPO reduction solvent. As shown in Scheme 3, the results were dramatic: the reaction time was reduced from 8 h to 30 min simply by changing the solvent to MTBE.

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[6] (a) Chou, W.-N.; Pomerantz, M. *J. Org. Chem.* **1991**, *56* (8), 2762. (b) Quin, L. D.; Verkade, J. G. *Phosphorus-31 NMR Spectral Properties in Compound Characterization and Structural Analysis*; Wiley-VCH: Hoboken 1994, p197; p 98. (c) Gorenstein, D. G. *Phosphorus-31 NMR*; Academic Press: Orlando, 1984; pp 37−42.

[7] (a) Eisch, J. J.; Fichter, K. C. *J. Am. Chem. Soc.* **1974**, *96* (21), 6815. (b) Eisch, J. J.; Rhee, S.-G. *J. Am. Chem. Soc.* **1974**, *96* (23), 7276. (c) Eisch, J. J.; Foxton, M. W. *J. Org. Chem.* **1971**, *36* (23), 3520.

TABLE 2. Reduction of Ph$_3$P═O

$$\underset{\mathbf{11}}{\mathrm{Ph_3P{=}O}} \xrightarrow{\text{4 DIBAL-H, solvent}} \underset{\mathbf{12}}{\mathrm{Ph_3P}}$$

entry	solvent	T (°C)	time (h)	decoy	% conv[a]
1	C$_6$D$_{12}$	23	14		60
2	MTBE-d_3	23	20		48
3	C$_6$D$_{12}$	23	14	c-Hex$_3$P═O	80
4	C$_6$D$_{12}$	23	14	NMO	73
5	C$_6$D$_{12}$	72	6/20		76/83
6	**C$_6$D$_{12}$**	**72**	**6**	***c*-Hex$_3$P═O**	**100**
7	c-Pent-OMe	90	30		90

[a] Percent conversion by ^{31}P NMR integration.

TABLE 3. Reduction of Ph$_2$CH$_3$P═O

$$\underset{\mathbf{13}}{\mathrm{Ph_2CH_3P{=}O}} \xrightarrow{\text{4 DIBAL-H, solvent}} \underset{\mathbf{14}}{\mathrm{Ph_2CH_3P}}$$

entry	solvent	T (°C)	time (h)	decoy	% conv[a]
1	MTBE-d_3	23	8	c-Hex$_3$P═O	36
2	MTBE-d_3	23	16	c-Hex$_3$P═O	76
3	C$_6$D$_6$	23	72	c-Hex$_3$P═O	78
4	C$_6$D$_{12}$	23	60		86
5	**C$_6$D$_{12}$**	**30**	**4/20**	***c*-Hex$_3$P═O**	**90/100**
6	MTBE-d_3	30	4/20	c-Hex$_3$P═O	89/99
7	**C$_6$D$_{12}$**	**72**	**6/20**		**93/100**
8	C$_6$D$_{12}$	72	4/20	c-Hex$_3$P═O	95/99

[a] Percent conversion by ^{31}P NMR integration.

TABLE 4. Reduction of Ph$_2$-*c*-HexP═O

$$\underset{\mathbf{15}}{\mathrm{Ph_2\text{-}\mathit{c}\text{-}HexP{=}O}} \xrightarrow{\text{4 DIBAL-H, solvent}} \underset{\mathbf{16}}{\mathrm{Ph_2\text{-}\mathit{c}\text{-}HexP}}$$

entry	solvent	T (°C)	time (h)	decoy	% conv[a]
1	C$_6$D$_6$	23	14	c-Hex$_3$P═O	38
2	MTBE-d_3	23	14		41
3	C$_6$D$_{12}$	23	14		56
4	C$_6$D$_{12}$	23	14	c-Hex$_3$P═O	76
5	C$_6$D$_{12}$	72	6/20		78/83
6	C$_6$D$_{12}$	23	14	NMO	56
7	C$_6$D$_{12}$	50	4	c-Hex$_3$P═O	85
8	c-Pent-OMe	50	4		66
9	C$_6$D$_{12}$	50	20	c-Hex$_3$P═O	94
10	c-Pent-OMe	50	20		67
11	**C$_6$D$_{12}$**	**72**	**7**	***c*-Hex$_3$P═O**	**100**
12	c-Pent-OMe	100	7		87

[a] Percent conversion by ^{31}P NMR integration.

TABLE 5. Reduction of Ph$_2$-*t*-BuP═O

$$\underset{\mathbf{17}}{\mathrm{Ph_2\text{-}\mathit{t}\text{-}BuP{=}O}} \xrightarrow[\text{solvent}]{\text{4 DIBAL-H}} \underset{\mathbf{18}}{\mathrm{Ph_2\text{-}\mathit{t}\text{-}BuP}}$$

entry	solvent	T (°C)	time (h)	decoy	% conv[a]
1	MTBE-d_3	23	14		0
2	C$_6$D$_6$	23	14		4
3	Et-c-Hex	125	3		53
4	**Et-*c*-Hex**	**125**	**16**		**82**
5	p-xylene-d_{10}	125	3		45
6	p-xylene-d_{10}	125	16		56
7	n-Bu$_2$O	120	2		25
8	IB-OMe[b]	120	5		45
9	IB-OMe[b]	120	14		44
10	IB-OMe[b]	140	4		36
11	C$_6$D$_{12}$	72	7	c-Hex$_3$P═O	52
12	C$_6$D$_{12}$	72	21	c-Hex$_3$P═O	33
13	C$_6$D$_{12}$	72	5	Buchwald(O)[c]	3
14	c-Pent-OMe	100	2		55
15	c-Pent-OMe	100	8		66
16	c-Pent-OMe	100	18		55

[a] Percent conversion by ^{31}P NMR integration. [b] Isoborneol methyl ether. [c] Biphenyl-2-dicyclohexylphospine oxide.

We felt that we had sufficient understanding of the parameters of the reduction at this point to examine a series of TPO substrates and to learn what conditions were required for their successful reduction or where the limitations of this reduction methodology would be found.

We first examined triaryl TPOs, which would be expected to be the most reactive substrate class as they are not electron-rich. The conversion results for the prototypical substrate triphenylphosphine oxide (**11**) are shown in Table 2. Ambient temperature conversion to Ph$_3$P (**12**) in the presence of the decoy was 80% (entry 3) and 100% conversion was achieved in 6 h at 72 °C with the decoy (entry 7). NMO (entry 4) provided slightly higher conversion than the reaction without decoy, though it was less efficient than c-Hex$_3$P═O.

Diphenylmethylphosphine oxide **13** was similarly examined by ^{31}P NMR, as shown in Table 3. Though more electron-rich than the triaryl substrates, it was reduced more easily. Tweny hours at 30 °C (entry 5) and 4 h at 72 °C with c-Hex$_3$P═O gave 100% and 95% conversion respectively for this substrate.

We next examined diphenylcyclohexylphosphine oxide **15** in some detail, and the conversion results are shown in Table 4. In the presence of the decoy TPO, hydrocarbon solvents were found to be superior to ethers. This may be attributable to the formation of a tight decoy TPO−TIBAO complex and thus greater reduction of the freed substrate. High conversions were obtained in 20 h at 50 °C (entry 9) and 7 h at 72 °C (entry 11) with added c-Hex$_3$P═O. The decoy lowers both the reaction temperature and reaction time required to reach completion.

We then examined the more challenging diphenyl-*tert*-butylphosphine oxide substrate **17**, and the results are shown in Table 5. The beneficial effect of added c-Hex$_3$P═O observed with all of the substrates described above was not observed with this substrate. Attempted use of a decoy more sterically hindered than c-Hex$_3$P═O (entry 13) was unsuccessful. In both hydrocarbons and ethers, some product (**18**) decomposition was observed after prolonged reaction times. The best reaction conversion, 82%, was observed after 16 h at 125 °C (entry 4) in ethylcyclohexane.

We next evaluated a series of dialkyl and trialkyl TPOs, and these results are shown in Table 6. Phenyldimethylphosphine oxide **19** was readily reduced (entries 1−6) under a variety of conditions. The more sterically hindered dicyclohexyl substrate **20** was much more resistant. Sixteen hours at 125 °C were required to obtain 95% conversion for this substrate (entry 8). Reduction of the biphenyl-based Buchwald phosphine oxide[8] **21** gave only 17% conversion at 125 °C, as shown in entry 9. Extremely sterically hindered substrates such as these are clearly limitations of this reduction technology. The racemic TPO PhMe-*t*-BuP═O (**22**) was completely reduced in 6 h at 72 °C with decoy (entry 12), yet was untouched at ambient temperature (entry 10). Tri-*n*-butylphosphine oxide **23** was significantly reduced at ambient temperature in the absence of decoy (entry

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(8) Prepared by oxidation of the commercial ligand; see the Experimental Section.

TABLE 6. Reduction of Dialkyl and Trialkyl TPOs

$$\underset{\mathbf{19\text{-}24}}{R_1R_2R_3P{=}O} \xrightarrow{\text{4 DIBAL-H, solvent}} \underset{\mathbf{25\text{-}30}}{R_1R_2R_3P}$$

entry	TPO	R_1	R_2	R_3	solvent	*T* (°C)	time (h)	decoy	% conv[a]
1	**19**	phenyl	Me	Me	MTBE-d_3	50	16		54
2	**19**	phenyl	Me	Me	MTBE-d_3	50	20	*c*-Hex$_3$P=O	100
3	**19**	phenyl	Me	Me	*c*-PentOMe	100	16		87
4	**19**	phenyl	Me	Me	MTBE-d_3	23	16	*c*-Hex$_3$P=O	26
5	**19**	phenyl	Me	Me	C_6D_{12}	72	6/20		93/100
6	**19**	phenyl	Me	Me	C_6D_{12}	72	6	*c*-Hex$_3$P=O	100
7	**20**	phenyl	*c*-Hex	*c*-Hex	Et-*c*-Hex	125	4		79
8	**20**	phenyl	*c*-Hex	*c*-Hex	Et-*c*-Hex	125	16		95
9	**21**	2-biphenyl	*c*-Hex	*c*-Hex	Et-*c*-Hex	125	4		17
10	**22**	phenyl	Me	*t*-Bu	MTBE-d_3	23	16	*c*-Hex$_3$P=O	0
11	**22**	phenyl	Me	*t*-Bu	MTBE-d_3	50	20	*c*-Hex$_3$P=O	25
12	**22**	phenyl	Me	*t*-Bu	C_6D_{12}	72	6	*c*-Hex$_3$P=O	100
13	**23**	*n*-Bu	*n*-Bu	*n*-Bu	C_6D_{12}	23	14		68
14	**23**	*n*-Bu	*n*-Bu	*n*-Bu	C_6D_{12}	23	14	*c*-Hex$_3$P=O	94
15	**24**	Me	Me	Me	C_6D_{12}	23	15		100

[a] Percent conversion by ^{31}P NMR integration.

TABLE 7. One-Gram-Scale Reductions of TPOs

entry	TPO	R_1	R_2	R_3	solvent	*T* (°C)	time (h)	decoy TPO	TP	yield[a] (%)
1	**11**	C_6H_5	C_6H_5	C_6H_5	C_6H_{12}	72	7	*c*-Hex$_3$P=O	**12**	91
2	**11**	C_6H_5	C_6H_5	C_6H_5	C_6H_{12}	72	7	*c*-Hex$_3$P=O	**12**	99[b]
3	**31**	4-$CF_3C_6H_4$	4-$CF_3C_6H_4$	4-$CF_3C_6H_4$	C_6H_{12}	72	7	*c*-Hex$_3$P=O	**36**	93
4	**32**	4-ClC_6H_4	4-ClC_6H_4	4−ClC_6H_4	C_6H_{12}	72	7	*c*-Hex$_3$P=O	**37**	98
5	**13**	C_6H_5	C_6H_5	CH_3	C_6H_{12}	72	8		**14**	98[b]
6	**1**	C_6H_5	C_6H_5	C_2H_5	C_6H_{12}	72	14		**2**	91[b]
7	**15**	C_6H_5	C_6H_5	*c*-Hex	C_6H_{12}	72	16	*c*-Hex$_3$P=O	**16**	90[b]
8	**41**	C_6H_5	3,5-$F_2C_6H_3$	CH_3	C_6H_{12}	72	7	*c*-Hex$_3$P=O	**42**	98
9	**22**	C_6H_5	CH_3	*t*-Bu	C_6H_{12}	72	7		**28**	89
10	**19**	C_6H_5	CH_3	CH_3	C_6H_{12}	72	4		25	97[b]
11	**20**	C_6H_5	*c*-Hex	*c*-Hex	Et-*c*-Hex	125	15		**26**	90[b]
12	**23**	*n*-Bu	*n*-Bu	*n*-Bu	C_6H_{12}	72	4		**29**	97[b]
13	**24**	CH_3	CH_3	CH_3	C_6H_{12}	23	15		**30**	99[b]

[a] Isolated yield of pure material on ca. 1 g scale. [b] Yield of phosphine borane adduct.

13), and 94% conversion was achieved for this substrate under the same conditions with decoy present (entry 14). The most sterically accessible TPO possible, Me$_3$P=O (**24**), was trivially reduced at ambient temperature without decoy, as shown in entry 15.

Having established the requirements for reduction of the various substrate classes, we then carried out gram-scale experiments (Table 7) so that isolated yields for these processes could be obtained. Triphenylphosphine oxide **11** was reduced in 91% isolated yield (entry 1) after 7 h reaction time, and in situ conversion of the product to its phosphine borane[9] adduct gave the desired product in 99% isolated yield. The reaction mixtures were quenched at ~0 °C with aqueous NaOH, giving two clear phases, as previously described for the reduction of secondary phosphine oxides.[2] The aqueous/organic partition can thus be carried out under non-inert conditions, which is a significant operational advantage. Standard silica gel chromatography then furnished the pure phosphine boranes, generally in very high yield.

The triaryl substrates (entries 1−4), as well as the diphenylalkylphosphine oxides (entries 5−7), were all reduced in >90% isolated yield. Two racemic targets (entries 8−9) were produced in 98% and 89% isolated yield, respectively, under the standard conditions.

Two pairs of dialkyl- and trialkylphosphine oxides were then similarly reduced (entries 10−13), in high yield, and all were isolated as the phosphine borane adducts.

Until this point, no optically active phosphine oxides had been examined in the reduction. We were able to prepare optically enriched (+)-**41** by chiral preparative chromatography (Chiralcel AD). We then subjected (+)-**41** thus isolated to DIBAL-H reduction, in the presence and absence of *c*-Hex$_3$P=O, and then oxidized the phosphine products back to the oxide. As shown in Scheme 4, starting with (+)-**41** of 79% ee led to regenerated (+)-**41** of only 10% ee in each case. Phosphine oxidation with H_2O_2 is known to proceed with retention of configuration.[10] In at least some cases, the DIBAL-H reduction of tertiary phosphine oxides thus proceeds with retention of configuration, yet very low stereoselectivity, probably due to pseudorotation of

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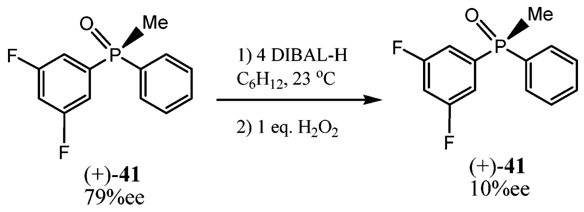
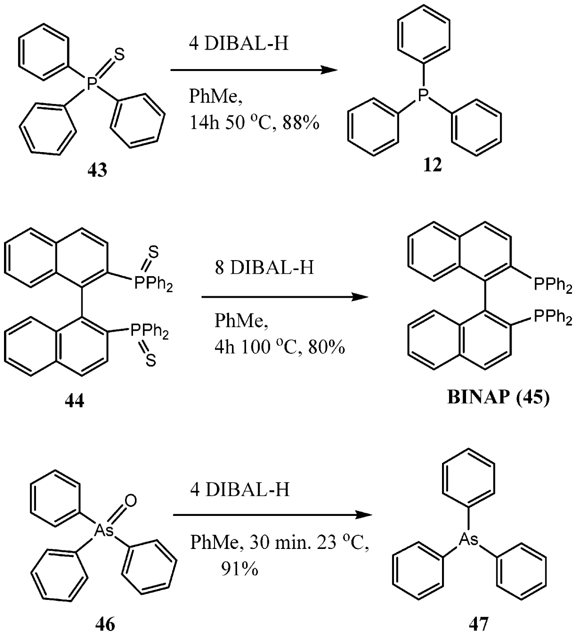
[9] For reviews, see: (a) Imamoto, T.; *Pure Appl. Chem.* **1993**, *65*(4), 655−660. (b) Ohff, M.; Holz, J.; Quirmbach, M.; Boerner, A. *Synthesis* **1998**, *10*, 1391−1415. (c) Brunel, J. M.; Faure, B.; Maffei, M. *Coord. Chem. Rev.* **1998**, 178−180 (Part 1), 665−698. (d) Carboni, B.; Monnier, L. *Tetrahedron* **1999**, *55* (5), 1197−1248.

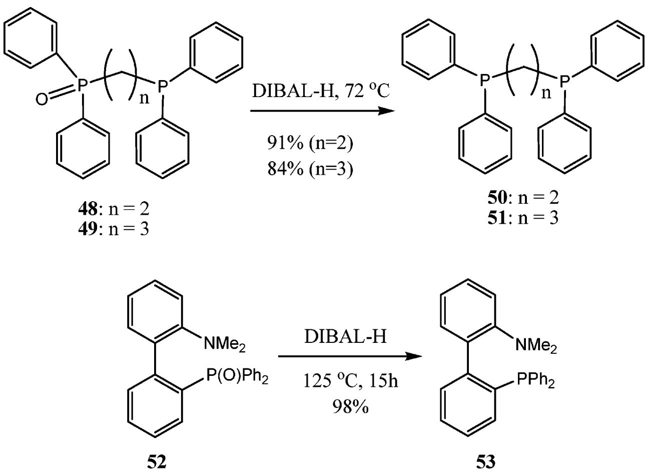
SCHEME 4. Reduction of Optically Active TPO



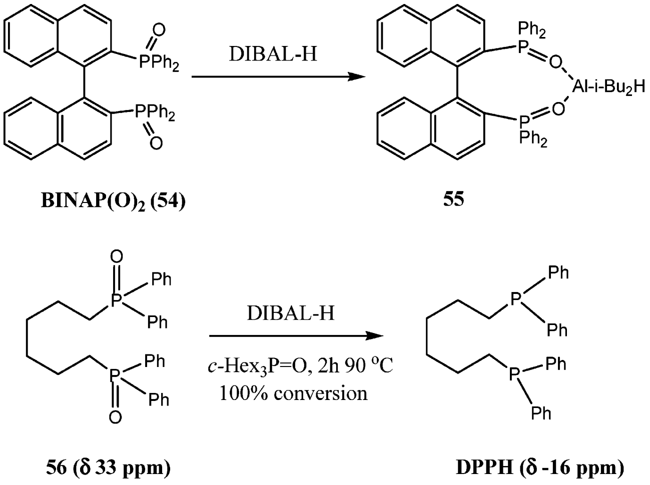
SCHEME 5. Reduction of Phosphine Sulfides and Arsine Oxides



SCHEME 6. Reduction of Difunctional TPOs



SCHEME 7. Reactions of Bis-phosphineoxides



the pentacoordinate phosphorus intermediate (**3** in Scheme 1).[11] Pseudorotation is a low-energy process in which axial and equatorial substituents are exchanged, pairwise, from a trigonal bipyramidal structure. The existence of a pentacoordinate intermediate does not *guarantee* racemization, although multiple successive pseudorotations will cause racemization of an organophosphorus compound.

We concluded our determination of the scope and limitations of these reductions by examining phosphine sulfides, arsine oxides, bis-phosphine oxides, and related substrates with a potentially chelating second heteroatom. Triphenyl phosphine sulfide (**43**) and BINAP-bis-sulfide **44**[12] were easily reduced at 50−100 °C, as shown in Scheme 5. It is known that phosphine sulfides are easier to reduce than the analogous oxides with other reducing agents,[10,13] and the same holds true with DIBAL-H. When triphenylphosphine sulfide was allowed to react with 2 equiv of TIBAO prior to the DIBAL-H charge, no inhibition of the reduction was observed. It seems that the thiophilicity of aluminum is far weaker than its oxophilicity. Triphenylarsine oxide **46** was also trivially reduced, in 91% yield, at ambient temperature to furnish arsine **47**.

We then evaluated a series of potentially chelating substrates including bis-phosphine monooxides (BPMOs)[14] and amino phosphineoxides. The monooxides of dppe and dppp were readily reduced under conditions established for the analogous TPOs as shown in Scheme 6. Amino-TPO **52** was also readily converted to the desired aminophosphine **53** in excellent yield, yet 15 h reaction time at 125 °C was required for full conversion.

The bis-oxide of BINAP[15] (**54**) was treated with DIBAL-H in a variety of solvents and studied by ^{31}P NMR. ^{31}P NMR quickly established that this bisoxide forms an extremely stable bidentate chelate with DIBAL-H (**55**, Scheme 7), as well as other organoaluminum reagents such as triisobutylaluminum (TIBA) and diisobutylaluminum chloride (DIBAL-Cl). The complexes all resonate about 10 ppm downfield of the bisoxide starting material. Clearly, both oxygens are required for this inhibition, since the bisphosphine monooxides described above are reduced without incident. Even at elevated temperature, no

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[10] (a) Naumann, K.; Zon, G.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91* (10), 2788. (b) Luckenbach, R. *Tetrahedron Lett.* **1976**, *24*, 2017. See also ref 13a, p 300.

[11] a) Holmes, R. H. *Pentacoordinate Phosphorus, V.I*; American Chemical Society: Washington 1980; pp 281−287. (b) Holmes, R. H. *Pentacoordinate Phosphorus, V.II*; American Chemical Society: Washington 1980; pp 100−109, pp 154−155. For closely related results with boron-based reductants, see: (c) Stankevic, M.; Pietrusiewicz, M. *Synlett* **2003**, *7*, 1012.

[12] Chapman, C. J.; Frost, C. G.; Gill-Carey, M. P.; Kociok-Kohn, G.; Mahon, M. F.; Weller, A. S.; Willis, M. C. *Tetrahedron: Asymmetry* **2003**, *14* (6), 705.

[13] (a) Quin, L. D.; Quin, G. S. *A Guide to Organophosphorus Chemistry*; Wiley: New York, 2000; pp 116−117. (b) Yang, C.; Goldstein, E.; Breffle, S.; Jin, S. *THEOCHEM* **1992**, *91*, 345−368.

[14] Grushin, V. V. *Organometallics* **2001**, *20* (18), 3950.

[15] (a) Shimada, T.; Kurushima, H.; Cho, Y.-H.; Hayashi, T. *J. Org. Chem.* **2001**, *66* (26), 8854. For the reduction of dppe(O_2) at elevated temperature, see: (b) Self, M. F.; Sangokoya, S. A.; Pennington, W. T.; Robinson, G. H. *J. Coord. Chem.* **1990**, *21* (4), 301.

production of BINAP was observed. BINAP-bisoxide aluminum complexes such as these have not been previously reported. Although their potential use as chiral Lewis acids is intriguing, they currently represent a limitation of this reductive methodology. We were curious whether a bis-phosphine oxide with sufficiently large bite angle might be successfully reduced. As shown in Scheme 7, DIBAL-H in the presence of $c\text{-Hex}_3\text{P}{=}\text{O}$ gave 100% conversion of DPPH(O_2), **56**, to DPPH in 2 h at 90 °C (Supporting Information Figure 4). Thus, if bidentate chelation to aluminum becomes untenable, as in this six-carbon spacer example, reduction of bis-phosphine oxides to bis-phosphines can again be readily achieved.

In summary, the reduction of tertiary phosphine oxides by DIBAL-H has been studied in detail for the first time. Significant solvent effects have been found, and hindered aliphatic ethers such as MTBE provide the best ambient temperature conversions, while some common ethereal solvents such as THF are ineffective. The origin of the inhibition of these reductions has been uncovered, namely the aluminoxane that forms as a byproduct of the reaction. More importantly, two different strategies have been found to overcome this inhibition and obtain full conversions in this transformation for the first time. A study of the major structural classes of tertiary phosphine oxides has been carried out, and in this way, the scope and limitations of the reduction technology have been determined. Sterics, rather than electronics, are the most important parameter for the DIBAL-H reduction of tertiary phosphine oxides. Practical experimental procedures, critically including the in situ conversion of the tertiary phosphines to phosphine boranes, have been developed which allow for the one-pot synthesis of these important targets in high yield.

Experimental Section

NMR Reactions. A 5 mm × 7 in. screw-cap NMR tube with PTFE septum (Wilmad 535-TR-7) was charged with 46 mg of diphenylethylphosphine oxide **1** (0.20 mmol, 1 equiv) and 0.80 mL of solvent. The NMR tube was then agitated on a vortex mixer for ~2 min, generally giving a suspension. To this was then added by syringe 0.14 mL of neat DIBAL-H (CAUTION: Pyrophoric!, 0.80 mmol, 4 equiv). This mixture was then agitated for a full 5 min on the vortex mixer, generally giving a clear, colorless solution, with evolution of gas. The tube was then aged at ambient temperature with an Ar line through the tube septum. The ^{31}P spectrum were then acquired with proton decoupling and a d1 delay of 5−10 s, and the signals were integrated to determine percent conversion.

General Reduction Procedure. Diphenylcyclohexylphosphine Borane 16. A 100 mL three-necked flask equipped with a thermocouple and addition funnel was charged with 0.50 g of phosphine oxide **15** (1.8 mmol, 1 equiv) and 0.52 g of $c\text{-Hex}_3\text{P}{=}\text{O}$ (1.8 mmol, 1 equiv). The flask was then evacuated/Ar filled (2×), and 7.2 mL of 1 M DIBAL-H/C_6H_{12} (7.2 mmol, 4 equiv) was added via syringe. The reaction mixture was then placed in a pre-equilibrated 72 °C oil bath under Ar. After 16 h, the mixture was cooled to ambient temperature, and then 2.3 mL of 1 M BH_3/THF (2.3 mmol, 1.5 equiv) was added via syringe. The resultant mixture was then stirred for 1 h at 23 °C, at which time ^{31}P NMR showed complete conversion to the phosphine borane. MTBE (14 mL) was then added via syringe. After 5 min, the reaction mixture was cooled to 0 °C, and then 11 mL of 6 N NaOH was slowly added (CAUTION!:Vigorous reaction! Gas evolution!) via addition funnel. The bath was then removed and the reaction mixture allowed to warm to 23 °C. After 15 min, it was transferred to a separatory funnel, and the phases were separated. The aqueous phase was reextracted with MTBE (1 × 15 mL). The combined organics were then dried ($MgSO_4$) and filtered. The filtrate (unconcentrated) was then passed through a pad of silica gel eluting with ~100 mL of MTBE. The solvents were then removed in vacuo, and the residue was chromatographed on silica gel eluting with 4:1 Hex:CH_2Cl_2 to give 0.447 g of phosphine borane **16** (90%) as a colorless solid: mp 93−94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79−7.72 (m, 4H), 7.51−7.41 (m, 6H), 2.41 (q, $J = 13$ Hz, 1H), 1.86−1.77 (m, 2H), 1.76−1.63 (m, 3H), 1.56−1.42 (m, 2H), 1.35−1.21 (m, 4H), 0.97 (q, 3H, $^1J_{HB} = 89$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 132.66 (d, $J_{CP} = 8.4$ Hz), 130.97 (d, $J_{CP} = 2.3$ Hz), 128.65 (d, $J_{CP} = 9.6$ Hz), 128.23 (s), 33.76 (d, $^1J_{CP} = 36$ Hz), 26.72 (t, $J_{CP} = 12$ Hz), 26.53 (t), 25.81 (t, $J_{CP} = 1.2$ Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 20.93; HRMS $(M - BH_3 + H)^+$ $C_{18}H_{22}P$ calcd 269.1453, obsd 269.1463, difference = 3.4713 ppm. Anal. Calcd for $C_{18}H_{24}BP$: C, 76.62; H, 8.57. Found: C, 76.50; H, 8.77.

Supporting Information Available: Experimental procedures and characterization data for all new and known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7024064