CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.200((will be filled in by the editorial staff))

Cleavage of P=O in the Presence of P-N: Aminophosphine Oxide Reduction with *in situ* boronation of the P(III) product

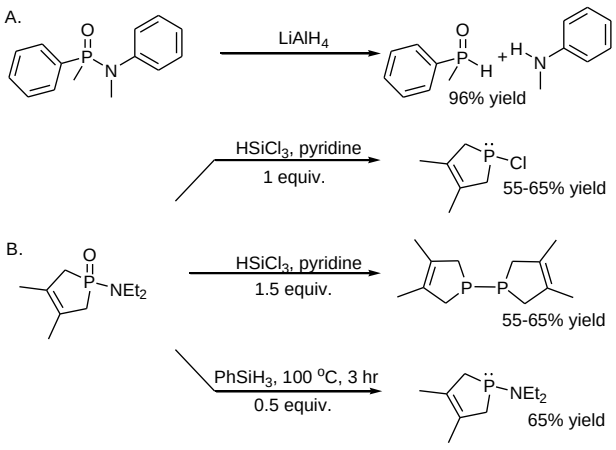
Niall P. Kenny, Kamalraj V. Rajendran, Elizabeth V. Jennings and Declan G. Gilheany*[a]

Abstract: In contrast to tertiary phosphine oxides, the deoxygenation of aminophosphine oxides is effectively impossible due to the need to break the immensely strong and inert P=O bond in the presence of a relatively weak and more reactive P-N bond. This long-standing problem in organophosphorus synthesis is solved by use of oxalyl chloride, which chemoselectively cleaves the P=O bond forming a chlorophosphonium salt (CPS), leaving the P-N bond(s) intact. Subsequent reduction of the CPS with sodium borohydride forms the P(III) aminophosphine borane adduct. This simple one-pot procedure was applied with good yields for a wide range of P-N containing phosphoryl compounds. The borane product can be easily deprotected to produce the free P(III) aminophosphine. Along with no observed P-N bond cleavage, the use of sodium borohydride also permits the presence of ester functional groups in the substrate. The availability of this methodology opens up previously unavailable synthetic options in organophosphorus chemistry, two of which are exemplified.

Keywords: aminophosphine oxide • reduction • phosphinamide • *in situ* protection • chemoselective

Introduction

The P=O bond is one of the strongest of those commonly encountered.[1] As such, the large amount of energy released during its formation can be of great benefit, acting as the driving force for many important transformations in organic chemistry; the Wittig, Appel and Mitsunobu reactions being classic examples.[2] Conversely, this same bond strength leads to substantial difficulties in the deoxgenation of P=O containing species; the conversion being highly desirable, permitting access to the, often very valuable, P(III) analogue.[3,4] The challenge is two-fold – how to avoid scission of other bonds to phosphorus and how to avoid reduction of other sensitive groups that may be present. Due to the inert nature of P-C bonds, options do exist for the reduction of most tertiary phosphine oxides,[5,6,7,8] which are successfully deoxygenated with both metal hydride[7] and silane reagents,[4d,8] in reasonable time and with good yields. However, the harsh conditions characteristic of these reagents renders them useless for deoxygenation of most other P=O containing compounds such as phosphonates, phosphinates, phosphinamides and phosphinamidates, which react with cleavage of the phosphorus-heteroatom (P-N and/or P-O) bond.[9, 10] Similarly, phosphine oxides containing other reducible groups (e.g. esters, amides) are vulnerable to concomitant reduction, although excellent progress in this regard was achieved by Beller and co-workers.[8j, k]



Scheme 1. Previous attempts of aminophosphine oxide reduction.

For the case of aminophosphine oxides – those compounds containing at least one, direct phosphorus to nitrogen bond,[11] the difficulties are exemplified in Scheme 1. As shown by Henson *et al*,[9a] the P-N bond is generally cleaved on deoxygenation with LAH (Scheme 1A), with only one reported exception for the case of a cyclic phosphinamide.[12] Reduction with silanes was studied by Quin and Szewczyk[10b] (Scheme 1B); using chlorosilane, they

[a] Mr. N. P. Kenny, Dr. K. V. Rajendran, Miss E. V. Jennings and Prof. D. G. Gilheany
Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology,
University College Dublin,
Belfield, Dublin 4, Ireland.
Fax: (+353)-1-7162127
E-mail: declan.gilheany@ucd.ie

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

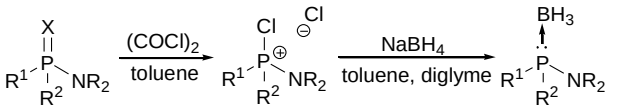
showed that, once again, loss of the P-N bond occurs but with formation of chlorophosphines or diphosphines, both of synthetic use in their own right.[13] More noteworthy was that, with phenyl silane, they did find cases, again mostly cyclic, of successful deoxygenation with retention of the P-N bond (Scheme 1B).[10b]

However the relatively moderate yields combined with the restricted scope, long reaction times and the need for careful control of stoichiometry limit the usefulness of this method.

Results and Discussion

Herein, we present a new methodology for the reduction of aminophosphine oxides (Table 1). The reaction is a reliable, one-pot, high yielding transformation; the final product being obtained as the aminophosphine borane adduct. The scope of the method is shown in Table 1, where it can be seen that it is applicable to both aryl and alkyl phosphinamides as well as examples of phosphonamide, phosphoramide and thiophosphinamide.

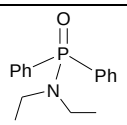
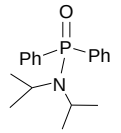
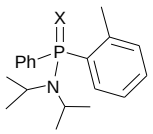
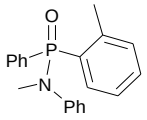
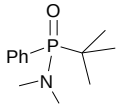
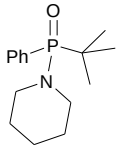
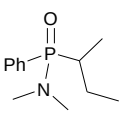
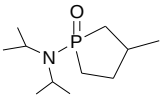
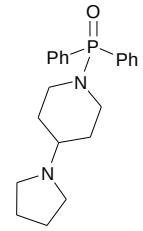
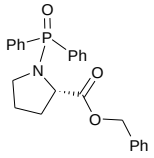
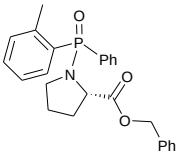
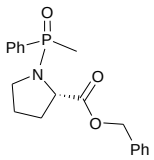
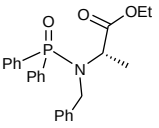
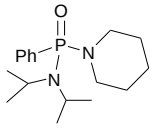
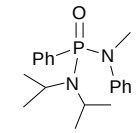
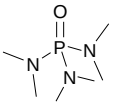
Table 1 Aminophosphine oxides reduced[a] with ^{31}P NMR data for substrates, CPS intermediates and borane products.



X = O, S
R^n = C, N

CPS

>95% conversion

Entry	Substrate	Yield %	^{31}P NMR shifts (ppm) PX[b]	CPS[c]	PB[d]
1		86	30.4	70.8	67.5
2[e]		87	29.8	68.4	62.1
3[e]		86	X=O 34.1 X=S 61.1	69.8	64.2
4		84	32.3	64.5	68.1
5[e]		80	47.9	96.7	85.4
6[e]		83	44.8	91.9	83.0
7[f]		72	45.1 45.4	93.6	74.4
8[f]		90	68.3 67.8	105.2	79.8
9[g]		83	28.8	69.3	67.4
10		84	26.6	64.4	60.4
11[f]		88	30.3 30.5	66	59.6
12[f,h]		75	32.3 33.1	72.9	55.1
13		84	31.9	73.5	73.0
14[e]		85	26.2	58.4	85.1
15[e]		86	23.3	58.3	88.1
16[e]		82	24.2	53.9	103.4

[a] Procedure available in ESI, isolated yields. [b] PX: phosphine oxide or sulfide. [c] CPS: shift assigned as chlorophosphonium salt, not isolated. [d] PB: phosphine borane, usually as broad quartets. [e] initial coversion to CPS required heating to 70 °C. [f] starting oxide was a mixture of two diastereomers. [g] reduction product has second borane moiety bound to trialkyl amino group. [h] in the presence of Et_3N.

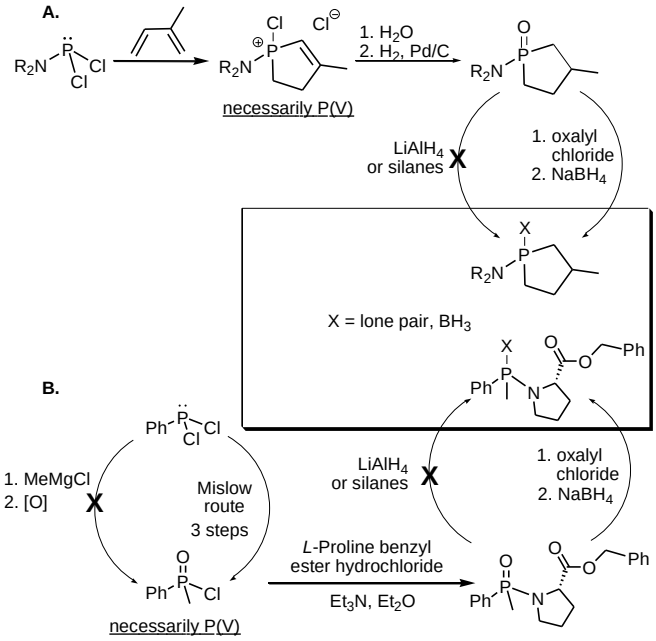
The method depends for its success on the generation *in situ* of an intermediate chlorophosphonium salt (CPS), which is then subsequently reduced/boronated with sodium borohydride. The conversion of tertiary phosphine oxide to chlorophosphonium salt with oxalyl chloride was first described by Masaki and Fukui[14] some time ago and the transformation has been used to good effect by several groups.[4g, 6, 7h] We ourselves recently published a related reduction of secondary and tertiary phosphine oxides and sulfides.[15] However its use for phosphorus amides had never previously been considered. It occurred to us that, if it would work, the way would then be open to have chloride act as the leaving group while allowing nitrogen to remain and were gratified to find that the whole conversion can indeed be performed irrespective of the number of P-N bonds present, and that each bond is fully

retained in the product. The irreversible formation of the chlorophosphonium salt[16] (CO_2 and CO by-products) allows it to act as a convenient intermediate, effectively breaking the thermodynamic profile of the reaction down from one very large step into two more energetically feasible steps. The specificity of the oxalyl chloride reaction combined with the lowering of energy required at any one time permits the observed chemoselectivity, and retention of the susceptible P-N bond. Also significant is that other reducible groups can be present such as esters (Table 1, entries 10-13).

The reaction procedure is relatively straightforward. For certain examples, particularly those featuring small substituents on the phosphorus centre, reaction with oxalyl chloride occurs almost immediately, with obvious evolution of the gaseous by-products. In contrast, bulky and strongly electron-donating groups close to the site of reaction significantly reduce the rate of reactions; these compounds typically require heating for complete conversion to CPS. The CPS can be observed and monitored by NMR, but is relatively unstable and so once formed should be promptly reduced/boronated by the addition of sodium borohydride in diglyme (2.1 equivalents).

It is also favourable that the final product is the phosphine borane adduct as these have long been used for convenient handling and storage, owing to enhanced oxygen and moisture stability. The borane can be easily displaced, with stereocontrol, by a number of methods,[17] demonstrated for entries 6 and 11 (Table 1) using DABCO (5 equiv., 80 ˚C) yielding the free aminophosphine with 100% conversion (see ESI for procedure and characterisation). In aminophosphines it is to be expected[18] that the phosphorus rather than the nitrogen is boronated and this was confirmed by X-ray crystallography in selected cases (entries 9, 10 and 14). It is also notable that, where there is a free amino group, this was also boronated giving a bis-borane adduct (entry 9). This is caused by the need for two equivalents of sodium borohydride, leading to two equivalents of borane as by-product.

While being a good general method for aminophosphine oxide reduction, this new reaction also lifts a significant limitation in organophosphorus synthesis methodology: until now it was not possible to construct a P(III) aminophosphine by a route that involved attachment of the nitrogen substituent to a P(V) centre. Since many important organophosphorus methods necessarily generate such centres, this was a major restriction. Its lifting is illustrated by two of the examples in Table 1 (entries 8 and 12). McCormack cycloaddition[19] (Scheme 2A) is a most useful method for forming P-containing five-membered rings. However, the methodology always yields a P(V) species, initially a chlorophosphonium salt which upon hydrolysis becomes a phosphine oxide, therefore the aminophosphine product of entry 8 could not previously have been made easily. Another example concerns the phenylmethyl substitution motif, which is very difficult to construct in the P(III) series due to uncontrollable multiple substitutions. For instance the aminophosphine with a ester-protected amino acid substituent in Scheme 2B cannot be made by sequential addition of the groups to a P(III) precursor without either significant contamination of double addition products, if methyl Grignard is added first, or attack at the carbonyl if the organometallic is added second. For this reason, the motif seen is normally accessed from methylphenylphosphinic chloride, produced via a sequence of steps developed by Mislow. [20] This method can also be applied for other non-bulky aminophosphines. Furthermore, one of the main advantages of being able to work with P(V) compounds, the increased stability, early on in the synthesis, with subsequent reduction to a P(III) product, if desired, is now a possibility for a myriad of novel compounds. Finally, since the amino substituent can act as a dummy group for other heteroatom substituents,[21] the synthesis of phosphorous, phosphonous and phosphinous acid derivatives is now, in principle, much easier.



Scheme 2. Examples of aminophosphine boranes difficult to synthesise by other means

Conclusion

In summary, we present an unprecedented high-yielding aminophosphine oxide deoxygenation, with no phosphorus-nitrogen bond cleavage. Furthermore the product is the protected borane adduct, allowing easy manipulation. The methodology breaks the transformation down into two steps, first breaking the very strong phosphoryl bond, replacing the oxygen with the better leaving group, chloride. This facilitates subsequent reduction with safe and cheap sodium borohydride, allowing the presence of e.g. ester functional groups. We believe that this new methodology opens up completely new synthetic strategies in organophosphorus chemistry because nitrogen (and oxygen by proxy) substitents can now be attached to P(V) centres and be retained on conversion to P(III).

Experimental Section

General procedure for deoxygenation of amino phosphine oxides and sulfides: To a stirred solution of aminophosphine oxide or sulfide (1.0 mmol) in toluene (2 mL) was added oxalyl chloride (1.0 mmol) dissolved in toluene (2 mL) dropwise at room temperature under a nitrogen atmosphere. The formation of chlorophosphonium salt (CPS) at this point was normally evident by vigorous gas evolution and was confirmed by ^{31}P-NMR of the reaction mixture. In some cases noted in the ESI, where the gas evolution was less pronounced, the mixture had to be heated to 70 ^{o}C (approx. b.pt of oxalyl chloride) for one hour to effect complete conversion to CPS. Alternatively in those cases, the reaction could be left at room temperature overnight. After formation of CPS (typically 30 min), sodium borohydride (2.1 mmol) dissolved in diglyme (~3 mL) was added dropwise to the reaction mixture and heated to 70 ^{o}C for one hour, after which ^{31}P-NMR shows full completion of CPS to phosphine borane (as indicated by characteristic quartet splitting). The reaction mixture was washed with deionised water

(2 x 5 mL) and the isolated organic layer was dried over anhydrous $MgSO_4$. The drying agent was removed by filtration, and the toluene was removed in vacuo to give a colourless solution, which was eluted through a silica plug first with cyclohexane to remove the high boiling diglyme then with 50:50 cyclohexane/ ethyl acetate to isolate the aminophosphine borane product. Solvent removal in vacuo yielded the pure aminophosphine borane.

Acknowledgements

We thank sincerely Science Foundation Ireland (SFI) for funding this chemistry under Grant 09/IN.1/B2627. We are also grateful to UCD Centre for Synthesis and Chemical Biology (CSCB) and the UCD School of Chemistry and Chemical Biology for access to their extensive analysis facilities and Helge Müller Bunz for X-ray analysis. We also thank the EU COST Network PhosSciNet. DGG also thanks University College Dublin for a President's Research Fellowship, held partly in Stanford University in the Laboratory of Professor James Collman.

[1] a) C. L. Chernick, H. A. Skinner, *J. Chem. Soc.* **1956**, 1401; b) D. G. Gilheany, *Chem. Rev*. **1994**, *94*, 1339.

[2] a) J. I. G. Cadogan, in *Organophosphorus Reagents in Organic Synthesis*, (Eds: J. I. G. Cadogan), Academic Press, New York, **1979**; b) *Organophosphorus Reagents* (Ed.: P. J. Murphy), Oxford University Press: Oxford, **2004**; c) P. A. Byrne, D. G. Gilheany, *Chem. Soc. Rev*. **2013**, DOI: 10.1039/C3CS60105F.

[3] For the use of phosphines in metal-based catalysis, see: a) *Comprehensive Asymmetric Catalysis*, Vol. I-III (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**; b) *Catalytic Asymmetric Synthesis*, (Ed.: I. Ojima), 3rd Edn, Wiley, New York, **2010**; c) S. Lühr, J. Holz, A. Börner, *ChemCatChem*, **2011**, *3*, 1708; d) *Privileged Chiral Ligands and Catalysts* (Ed.: Q.-L. Zhou), Wiley-VCH, Weinheim, **2011**.

[4] For the use of phosphines as organocatalysts, see: a) J. G. Verkade, *Top. Curr. Chem*. **2003**, *223*, 1; b) J. A. MacKay, E. Vedejs, *J. Org. Chem.* **2005**, *71*, 498; c) L. Ye, J. Zhou, Y. Tang, *Chem. Soc. Rev*. **2008**, *37*, 1140; d) C. J. O'Brien, J. L. Tellez, Z. S. Nixon, L. J. Kang, A. L. Carter, S. R. Kunkel, K. C. Przeworski, G. A. Chass, *Angew. Chem. Int. Ed*. **2009**, *48*, 6836; e) M. Zablocka, A. Hameau, A. M. Caminade, J. P. Majoral, *Adv. Synth. Catal*. **2010**, *352*, 2341; f) S. E. Denmark, D. Kalyani, W. R. Collins, *J. Am. Chem. Soc*. **2010**, *132*, 15752; g) R. M. Denton, J. An, B. Adeniran, A. J. Blake, W. Lewis, A. M. Poulton, *J. Org. Chem.* **2011**, *76*, 6749.

[5] a) L. Maier, in *Organic Phosphorus Compounds*, Vol. 1, (Eds.: L. Maier, G. M. Kosolapoff), Wiley-Interscience, New York, **1972**, Ch 1, pp. 1-226; b) P. Beck, in *Organic Phosphorus Compounds* Vol. 2, (Eds.: L. Maier, G. M. Kosolapoff), Wiley-Interscience, New York, **1972**, Ch. 4, pp. 189-508. c) D. G. Gilheany, C. M. Mitchell, in *The Chemistry of Organophosphorus Compounds*, Vol 1, (Ed.: F. R. Hartley), Wiley-Interscience, Chicester, **1990**, Ch. 7, pp. 151-190; d) M. J. Gallagher, in *The Chemistry of Organophosphorus Compounds*, Vol 2, (Ed.: F. R. Hartley), Wiley-Interscience: Chicester, **1992**, Ch. 2, pp. 53-76.

[6] Electrochemical reduction: T. Yano, M. Hoshino, M. Kuroboshi, H. Tanaka, *Synlett* **2010**, *5*, 801.

[7] Metal hydride reductants: a) T. Imamoto, T. Oshiki, T. Onozawa, T. Kusumoto, K. Sato, *J. Am. Chem. Soc*. **1990**, *112*, 5244; b) S. Griffin, L. Heath, P. Wyatt, *Tetrahedron Lett.* **1998**, *39*, 4405; c) T. Imamoto, S. Kikuchi, T. Miura, Y. Wada, *Org. Lett.* **2001**, *3*, 87; d) G. Keglevich, M. Fekete, T. Chuluunbaatar, A. Dobó, V. Harmatc, L. Toke, *J. Chem. Soc. Perkin Trans. 1* **2000**, 4451; e) Y. Wang, X. Li, K. Ding, *Tetrahedron: Asymmetry* **2002**, *13*, 1291; f) M. Stankevic, K. M. Pietrusiewicz, *Synlett* **2003**, 1012; g) C. A. Busacca, R. Raju, N. Grinberg, N. Haddad, P. James-Jones, H. Lee, J. C. Lorenz, A. Saha, C. H. Senanayake, *J. Org. Chem.* **2008**, *73*, 1524; h) P. A. Byrne, K. V. Rajendran, J. Muldoon, D. G. Gilheany, *Org. Biomol. Chem*. **2012**, *10*, 3531.

[8] Silane reductants: a) K. Naumann, G. Zon, K. Mislow, *J. Am. Chem. Soc*. **1969**, *91*, 7012; e) K. L. Marsi, *J. Org. Chem.* **1974**, *39*, 265; f) T. Coumbe, N. J. Lawrence, F. Muhammad, *Tetrahedron Lett.* **1994,** *35*, 625; g) H.-C. Wu, J.-Q. Yu, J. B. Spencer, *Org. Lett.* **2004**, *6*, 4675; h) C. Petit, A. Favre-Reguillon, B. Albela, L. Bonneviot, G. Mignani, M. Lemaire, *Organometallics* **2009**, *28*, 6379; j) Y. Li, S. Das, S. Zhou, K. Junge, M. Beller, *J. Am. Chem. Soc*. **2012**, *134*, 9727; k) Y. Li, L-Q Lu, S. Das, S. Pisiewicz, K. Junge, M. Beller, *J. Am. Chem. Soc*. **2012,** *134*, 18325.

[9] a) P. D. Henson, S. B. Ockrymiek, J. Raymond, E. Markham, *J. Org. Chem.* **1974**, *39*, 2296; b) E. P. Kyba, S.-T. Liu, R. L. Harris, *Organometallics* **1983**, *2*, 1877.

[10] a) H. Fritzsche, U. Hasserodt, F. Korte, *Chem. Ber.* **1965**, *98*, 1681; b) L. D. Quin, J. Szewczyk, *Phos. Sulf.* **1984**, *21*, 161.

[11] Encompassing phosphinamides, phosphonamides and phosphoramides.

[12] I. G. M. Campbell, J. K. Way, *J. Chem. Soc.* **1960**, 5034. In this specific case, the phosphinamide is part of a six-membered ring system, which may explain its stability.

[13] a) L. D. Quin, G. Keglevich, *J. Chem. Soc., Perkin Trans. 2* **1986**, *7*, 1029; b) J. Szewczyk, L. D. Quin, *J. Org. Chem.* **1987**, *52*, 1190; c) L. D. Quin, G. Keglevich, K. C. Caster, *Phos. Sulf.* **1987**, *31*, 133; d) G. Keglevich, A. Kovacs, L. Toke, K. Ujszaszy, G. Argay, M. Czugler, A. Kalman, *Heteroatom Chem.* **1993**, *4*, 329.

[14] M. Masaki, K. Fukui, *Chem. Lett*. **1977**, 151.

[15] a) D. G. Gilheany, J. S. Kudavalli, A. D. Molloy, K. Nikitin, K. V. Rajendran, WO 2012113889 A1 201220830, 2012; b) K. V. Rajendran, D. G. Gilheany, *Chem. Commun*. **2012**, *48*, 817.

[16] a) S. M. Godfrey, C. A. McAuliffe, R. G. Pritchard, J. M. Sheffield, *Chem. Commun*. **1996**, 2521; b) S. M. Godfrey, C. A. McAuliffe, R. G. Pritchard, J. M. Sheffield, *Chem. Commun*. **1998**, 921; c) N. C. Gonnella, C. Busacca, S. Campbell, M. Eriksson, N. Grinberg, T. Bartholomeyzik, S. Ma, D. L. Norwood, *Mag. Res. Chem*. **2009**, *47*, 461.

[17] For borane use and displacement, see: a) H. Yang, N. Lugan, R. Mathieu, *Organometallics* **1997**, *16*, 2089; b) L. McKinstry, T. Livinghouse, *Tetrahedron Lett*. **1994**, *35*, 9319; c) J. Uziel, C. Darcel, D. Moulin, C. Baudin, S. Juge, *Tetrahedron Asymmetry* **2001**, *12*, 1441; d) M. V. Overschelde, E. Vervecken, S. G. Modha, S. Cogen, E. V. D. Eycken, J. V. D. Eycken, *Tetrahedron* **2009**, *65*, 6410; e) A. Staubitz, A. P. M. Robertson, M. E. Sloan, I. Manners, *Chem. Rev*. **2010**, *110*, 4023.

[18] R. K. Kanjolia, D. K. Srivastava, C. L. Watkins, L. K. Krannich, *Inorg. Chem*. **1989**, *28*, 3341.

[19] a) W. B. McCormack, *Org Synth*. **1963**, *5*, 787; b) C. K. Soohoo, S. G. Baxter, *J. Am. Chem. Soc.* **1983**, *105*, 7443; c) A. H. Cowley, R. A. Kemp, J. G. Lasch, N. C. Norman, C. A. Stewart, *J. Am. Chem. Soc*. **1983**, *105*, 7444.

[20] For instance, in the preparation of the ligand DiPAMP and its analogues: a) B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc*. **1977**, *99*, 5946; b) O. Korpiun, R. A. Lewis, J. Chickos, K. Mislow, *J. Am. Chem. Soc*. **1968**, *90*, 4842.

[21] M. J. P. Harger, *J. Chem. Soc. Perkin Trans. 1*, **1977**, 18, 2057.