First Synthesis of a Highly Basic Dendrimer and its Catalytic Application in Organic Methodology

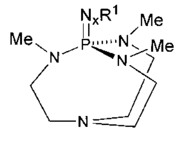
Arunkanti Sarkar, Palanichamy Ilankumaran, Philip Kisanga, John G. Verkade*

Iowa State University, Department of Chemistry, 1275 Gilman Hall, Ames, Iowa 50011, USA
Fax: (+1)-515-294-0105, e-mail:jverkade@iastate.edu

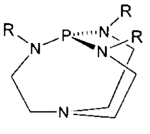
Received: March 19, 2004; Accepted: July 29, 2004

Abstract: Sixteen $OCH_2CH_2N_3P(i\text{-}BuNCH_2CH_2)_3N$ substituents (A) containing the highly basic bicyclic azido-phosphine moiety shown, have been incorporated into the dendrimer $[CH_2CH_2N[(CH_2)_3N[(CH_2)_3NHC(O)\text{-}3,5\text{-bis-}(A)\text{-}C_6H_3]_2]_2]_2$ in five steps from commercially available starting materials with an overall yield of 22.5%. Also presented are examples of Michael additions, nitroaldol reactions and aryl isocyanate trimerizations that are efficiently catalyzed by the dendrimer.

Keywords: catalyst; dendrimers; organic catalysis; phosphine imine; proazaphosphatrane



1a, R^1 = benzyl, x = 3
1b, R^1 = phenyl, x = 1



2a, R = methyl
2b, R = isobutyl

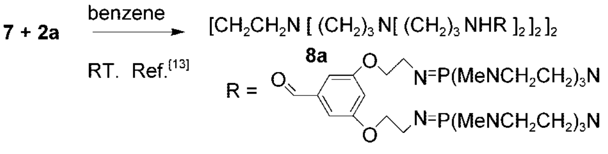
Dendrimer synthesis has fascinated chemists for more than a decade.[1] Phosphorus-containing dendrimers make up an active subarea[2] which have materials, biological and catalysis applications.[3] To our knowledge, however, no reports of catalytic reactions promoted by phosphorus-containing dendrimers have appeared in which the phosphorus-containing moiety itself functions as the active site. We disclose here the first such example and show that it is an efficient catalyst for useful organic transformations such as Michael addition, aldol condensation and isocyanate trimerization. Acyclic phosphine imines $[RN{=}P(NR_2)_3]$ constitute a class of strong nonionic bases[4] wherein $C_6H_5N{=}P(NMe_2)_3$, for example, displays a pK_a of 20.9 in acetonitrile.[5] Such phosphorus imines have been found to be very useful in amino acid synthesis.[6,7] We have found that bicyclic **1a** is a powerful catalyst for acylation,[8] Michael addition[9] and isocyanate trimerization.[10] We were thus attracted to the possibility of grafting such a bicyclic base to a dendrimeric framework. The synthetic approach we report here is based upon a previous study[11] in which we found that **1a** is stable in the azide form[11a] whereas the analogous reaction with phenyl azide gives the iminophosphorane **1b**.[11b]

The strategy we chose for assembling the dendrimeric framework is shown in Scheme 1. In order to realize a substantial number of basic sites in the molecule, we decided to employ the diazido acid **6** to effect branching. Methyl 3,5-dihydroxybenzoate **3** on treatment with dibromoethane in the presence of 18-crown-6 and K_2CO_3 gave the dibromoester **4** in 87% yield.

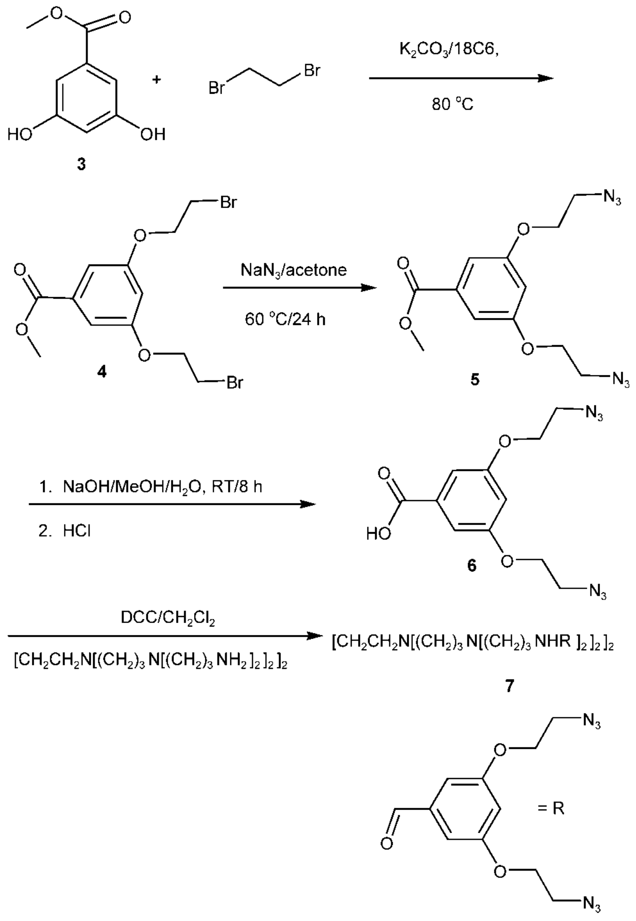
Although a few procedures have been reported[12] for the conversion of a *meta*-dihydroxybenzene (namely, 1-benzyloxy-3,5-dihydroxybenzene) to the corresponding 3,5-bis(2-bromoethyloxy) derivative, none of them afforded the 3,5-bis(2-bromoethyloxy) derivative **4** as a clean product. We therefore developed a modified procedure in which dibromoethane is used as the solvent in the presence of finely powdered K_2CO_3 to give **4**, which was pure by ^1H and ^{13}C NMR spectroscopy. Conversion of **4** to **5** in 93% yield, followed by saponification and acidification gave diazido acid **6** in 90% yield, which was then condensed with DAB-Am-8 dendrimer to afford **7** in 35% yield. The hexadeca-azido dendrimer **7** was found to be pure by NMR spectroscopy, although its polydispersity value ($M_w/M_n = 1.159$ versus a polystyrene standard) obtained by GPC analysis was not ideal (1.00), presumably due to aggregation that occurred in the carrier solvent (THF).[13] Molecular weights estimated by GPC relative to a polystyrene standard depend on the shape and flexibility of the molecules and were considerably lower than calculated values, as was previously experienced with a variety of dendrimers.[14]

Attempts to convert compound **7** to the dendrimeric base **8a** were not successful because combination of solutions of **2a** and azide **7** in benzene [Equation (1)] produced an intractable precipitate. Using an excess of **2a** or changing the solvent to THF did not solve this problem.

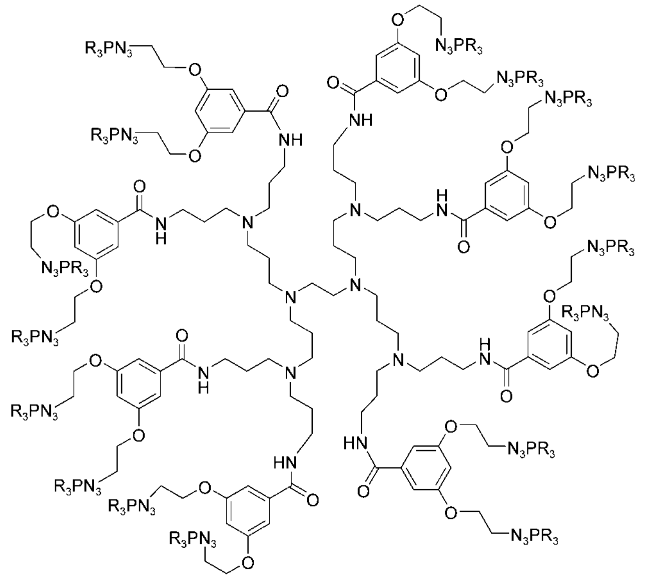
Subsequently we found that compound **2a** is a sufficiently strong base to abstract an N–H proton from aro-



DOI: 10.1002/adsc.200404089



Scheme 1.



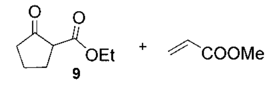
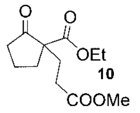
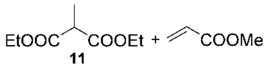
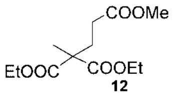
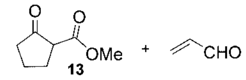
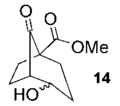
8b $R_3P = P(i\text{-}BuNCH_2CH_2)_3$

matic amide functions in the dendrimer.[15] To circumvent this difficulty, **2b** was employed, hoping that the greater bulk provided by the three *iso*-butyl groups would inhibit penetration of this base to amide functions within the dendrimer molecule, but would still allow **2b** to react with the azide functions on the dendrimer surface. We were successful in this regard, although the product of this reaction is the azidophosphine **8b** which even upon heating in refluxing benzene did not decompose to the corresponding phosphine imine. The NMR spectra (^1H, ^{13}C, ^{31}P), polydispersity value ($M_w/M_n = 1.115$ versus a polystyrene standard) and the elemental analysis of dendrimer **8b** are all consistent with its good purity and proposed formulation.[16] The lack of a peak for **2b** in the ^{31}P NMR spectrum of the dendrimer is consistent with the absence of **2b** trapped within the dendrimer matrix.

The Staudinger reaction is a two-step process involving the initial electrophilic addition of an alkyl or aryl azide to a P(III) center followed by N_2 elimination from the intermediate phosphazide to give the corresponding iminophosphine.[17] Steric hindrance at the P(III) center does not interfere with the electrophilic addition step, but it does suppress decomposition, because steric requirements in the four-membered ring transition state are much more rigorous than those in the addition transition state.[17] Donor character on the part of the P(III) substituents stabilizes azidophosphine intermediates and this factor also apparently operates in **8b** to give it thermal stability. The unusual resistance of **8b** to thermolysis may also be in part due to the rigidity of the cage structure, which by virtue of the planar geometry around the PN_3 cage nitrogens,[18] maintains an *iso*-butyl group in close proximity to the phosphorus-azide moiety.

To our knowledge, **8b** is the first example of a dendrimer bearing highly basic phosphine sites. With this dendrimer in hand, we carried out preliminary studies on its efficacy in catalysis. Michael addition, a highly useful tool in organic synthesis, is efficiently catalyzed by **8b**. Hence the reaction of methyl acrylate with ketoester **9** (Table 1) and with methyl diethyl malonate (**11**) gave the Michael adducts **10** and **12**, respectively, in nearly quantitative yields. A tandem Michael/aldol reaction between ketoester **13** and acrolein were also catalyzed by dendrimer **8b** to give bicyclic **14** in good yield. Dendrimer **8b** catalyzed the aldol reaction of nitromethane with benzaldehyde very efficiently to give **16**. We also investigated **8b** for nucleophilic catalytic properties in the trimerization of isocyanates to isocyanurates.[10] In addition to their use as an additive in nylon-6 manufacture, the polymer industry actively seeks isocyanurate-forming catalysts for the preparation of heat and fire-resistant polymers. Here we find that the azido dendrimer **8b** catalyzes the trimerization of phenyl isocyanate, as well as trimerization of *p*-chlorophenyl isocyanate to the corresponding isocyanurates in 90 and 89% yields, respectively (Table 1). The reactions in Table 1 required only 0.24 mol % of catalyst **8b**, indicating that this dendrimer is a more potent catalyst than **2a** or **1a**, of which 10 mol % and 0.33 mol % were required for Michael[19] and isocyanate trimerization reactions,[9] respectively. The increased potency of **8b** is not entirely unexpected in view of the presence of sixteen catalytic sites per molecule.

Table 1. Reactions catalyzed by dendrimer **8b**.[a]

Reactants	Product	Time [h]	Yield [%]
 **9**	 **10**	25	99
 **11**	 **12**	25	96
 **13**	 **14**	48	79
PhCHO **15** + MeNO$_2$	PhCHOHCH$_2$NO$_2$ **16**	48	95
PhNCO[b] **17**	(PhNCO)$_3$ **18**	23	89
p-Cl-PhNCO[b] **19**	(*p*-Cl-PhNCO)$_3$ **20**	5	99

[a] Reactions were carried out in acetonitrile at room temperature using 0.24 mol % of **8b** unless stated otherwise.
[b] No solvent was used (see Ref.[9]).

Experimental Section

Dibromo Ester (4)

A stirred suspension of methyl 3,5-dihydroxybenzoate (10.1 g, 60.0 mmol), finely powdered K_2CO_3 (20.7 g, 150 mmol) and 18-crown-6 (1 g) in 120 mL of 1,2-dibromoethane was heated at 80 °C for 36 h. The reaction mixture was cooled, filtered, washed with methylene chloride (100 mL) and then the filtrate was evaporated under vacuum giving a residue that was purified by column chromatography using silica gel with 20% ethyl acetate in hexanes as eluent to give pure dibromo ester **4**; yield: 14.2 g (87%); ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.22 (d, *J* = 3.0 Hz, 2H), 6.70 (t, *J* = 3.0 Hz, 1H), 4.32 (t, *J* = 6.0 Hz, 4H), 3.91 (s, 3H), 3.64 (t, *J* = 6.0 Hz, 4H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 166.4, 159.2, 132.3, 108.4, 107.2, 68.1, 52.3, 28.9; LR-MS: *m/z* = 382 (M$^+$), 274, 195, 109, 107; HR-MS: calcd. for $C_{12}H_{14}Br_2O_4$: 381.9240; found: 381.9244.

Diazido Ester (5)

A stirred solution of dibromo ester **4** (7.64 g, 20.0 mmol), sodium azide (7.8 g, 120 mmol) and benzyltriethylammonium chloride (200 mg) in 75 mL of acetone was refluxed for 24 h. Acetone was evaporated under vacuum, and then the residue was dissolved in water and extracted twice with 200 mL of ether. The ether layer was dried over Na_2SO_4 and the volatiles were removed under reduced pressure to afford the diazido ester **5**; yield: 5.7 g (93%); ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.23 (d, *J* = 3.0 Hz, 2H), 6.70 (t, *J* = 3.0 Hz, 1H), 4.18 (t, *J* = 6.0 Hz, 4H), 3.91 (s, 3H), 3.61 (t, *J* = 6.0 Hz, 4H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 166.4, 159.2, 132.2, 108.2, 106.8, 67.2, 52.3, 50.0; LR-MS: *m/z* = 324 (M$^+$NH$_4$), 307, 281, 255; HR-MS: calcd. for $C_{12}H_{14}N_6O_4$: 306.1077; found: 306.1080.

Diazido Acid (6)

To a stirred solution of diazido ester **5** (5.7 g, 19 mmol) in MeOH (30 mL) was added NaOH (4.5 g) in water (15 mL). After stirring for 6 h, MeOH was evaporated under reduced pressure, and then water (50 mL) was added. The aqueous layer, on careful acidification with 2 N HCl, precipitated acid 6, which was extracted with dichloromethane (50 × 3 mL). After drying the extract with Na_2SO_4, removal of the volatiles under vacuum afforded diazido acid **6** as a pale yellow solid; yield: 4.9 g (90%); ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.29 (d, *J* = 3.0 Hz, 2H), 6.76 (t, *J* = 3.0 Hz, 1H), 4.20 (t, *J* = 3.0 Hz, 4H), 3.63 (t, *J* = 3.0 Hz, 4H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ = 171.7, 159.3, 131.3, 108.7, 107.9, 67.3, 50.0; LR-MS: *m/z* = 310 (M$^+$NH$_4$), 267, 241, 198; HR-MS: calcd. for $C_{11}H_{12}N_6O_4$: 292.0920; found: 292.0924.

Hexadeca-azido Dendrimer (7)

To a stirred solution of DCC (988.0 mg, 4.80 mmol) and azido acid **6** (1.4 g, 4.8 mmol) in dichloromethane (10 mL) was added DAB-Am-8 Generation 2 polypropyleneimine octamine dendrimer (309.2 mg, 0.400 mmol, Aldrich). After stirring for 24 h, precipitated dicyclohexylurea was filtered and washed with dichloromethane (50 mL) and then the solvent was removed from the filtrate under reduced pressure. The residue was purified by silica gel chromatography by eluting successively with ethyl acetate, a 20:80 mixture of MeOH/ethyl acetate and then a 5:25:70 mixture of triethylamine/MeOH/ethyl acetate to give product **7** as a glassy solid; yield: 419 mg (35%); ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 7.81 (s, 8N-H), 7.0 (d, *J* = 3.0 Hz, 16H), 6.56 (t, *J* = 3.0 Hz, 8H), 4.07 (t, *J* = 3.0 Hz, 32H), 3.44 (t, *J* = 3.0 Hz, 32H) 3.43–3.60 (m, 48H), 2.20–2.60 (m, 36H), 1.24–1.70 (m, 28H); ^{13}C NMR (CDCl$_3$, 75.5 MHz): δ (aromatic carbons only) = 166.9, 159.4, 137.0, 106.1, 104.8; LR-MS (ESI): *m/z* = 2965, 1483 (M^{2+}), 989 (M^{3+}), 741 (M^{4+}).

Azidophosphine Dendrimer (8b)

To azide **7** (41 mg, 0.013 mmol) dissolved in 5 mL of dry benzene was added **2b** (945.0 mg, 0.55 mmol) in 2 mL of dry benzene under argon. The reaction mixture was stirred at room temperature for 36 h and then benzene was evaporated to give a paste. Dry pentane (10 mL) was added and stirring was continued for 1 h to give a slurry. The solvent was removed with a cannula, an additional 10 mL of dry pentane were added and stirring was continued for 30 min. This process was repeated three times after which the solid residue was dried under vacuum to give the product; yield: 91 mg (88%); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 9.27$ (broad s, 8H), 7.75 (s, 16H), 6.96 (s, 8H), 4.57 (broad s, 32H), 4.30 (broad s, 32H), 3.65–3.80 (m, 16H), 2.30–3.0 (m, 340H), 2.20 (septet, 48H), 2.03 (broad s, 8H), 1.76 (broad s, 4H), 1.06 (d, 288H); IR (nujol): $\nu = 3235$, 2923, 1650, 1591, 1541, 1431, 1386, 1332, 1115, 1076, 1025, 861 cm^{-1}; ^{31}P NMR (C_6D_6): $\delta = 36.0$; elemental analysis: calcd. C 59.08, H 9.46, N 20.98; found: C 58.03, H 9.39, N 19.91.

The ^{1}H NMR spectrum of **10** compared favorably with that of an authentic sample. The ^{1}H NMR spectra of **12**,[20] **14**,[21] **16**,[22] **18**[23] and **20**[23] compared favorably with those reported in the cited references.

Acknowledgements

The authors thank the National Science Foundation and also the Donors of the Petroleum Research Fund administered by the American Chemical Society for grant support of this work. They also thank ISU Chemistry Department members Mr. Erik Hagberg in Prof. Valerie Sheares-Ashby's group and Mr. Mike Rodriquez in Prof. Dan Armstrong's group for obtaining the GPC and the mass spectrometric data.

References and Notes

[1] For leading reviews on dendrimers, see: a) G. R. Newkome, C. N. Morrefield, F. Vögtle, *Dendritic Molecules: Concepts Synthesis, Perspectives*; VCH: Weinheim, **1996**; b) M. Fischer, F. Vögtle, *Angew. Chem. Int. Ed.* **1999**, *38*, 884; c) A. M. Bosman, H. M. Janssen, E. W. Meijer, *Chem. Rev.* **1999**, *99*, 1665; d) S. Hecht, J. M. J. Frechet, *Angew. Chem. Int. Ed.* **2001**, *40*, 74; e) S. E. Stiriba, H. Frey, R. Haag, *Angew. Chem. Int. Ed.* **2002**, *41*, 1329 and references cited therein.

[2] a) J. P. Majoral, A. M. Caminade, *Chem. Rev.* **1999**, *99*, 845; b) F. L. Derf, E. Levillain, G. Trippe, A. Gorgues, M. Salle, R. M. Sebastian, A. M. Caminade, J. P. Majoral, *Angew. Chem. Int. Ed.* **2001**, *40*, 224; c) A. Balueva, S. Merino, A. M. Caminade, J. P. Majoral, *J. Organometallic Chem.* **2002**, *112*, 643 and references cited therein; d) J. P. Majoral, A. M. Caminade, V. Maraval, *Chem. Commun.* **2002**, 2929; e) A. M. Caminade, V. Maraval, R. Laurent, C. O. Turrin, P. Sutra, J. Leclaire, L. Griffe, P. Marchand, C. Baudoin-Dehoux, C. Rebout, J. P. Majoral, *Compt. Rend. Chim.* **2003**, *6*, 791, this reference is a review on phosphorus dendrimers and the other reviews in this journal issue are devoted to other aspects of dendrimers.

[3] a) I. Cuadrado, M. Moran, C. M. Casado, B. Alomso, J. Losada, *Coord. Chem. Rev.* **1999**, *193*, 395; b) C. Kollner, B. Pugin, A. Togni, *J. Am. Chem. Soc.* **1998**, *120*, 10274; c) V. Maraval, R. Laurent, A. M. Caminade, J. P. Majoral, *Organometallics* **2000**, *19*, 4025.

[4] a) R. Schwesinger, *Chimia*, **1985**, *39*, 296; b) R. Schwesinger, *Nachr. Chem. Tech. Lab.* **1990**, *38*, 1214.

[5] T. Rodina, V. Maemets, I. Koppel, *J. Chem. Soc. Perkin Trans. 1*, **2000**, 2637.

[6] M. J. O'Donnell, C. Zhow, W. L. Scott, *J. Am. Chem. Soc.* **1996**, *118*, 6070.

[7] E. Dominguez, M. J. O'Donnell, W. L. Scott, *Tetrahedron Lett.* **1998**, *39*, 2167.

[8] P. Ilankumaran, J. G. Verkade, *J. Org. Chem.* **1999**, *64*, 9063.

[9] J. Tang, T. Mohan, J. G. Verkade, *J. Org. Chem.* **1994**, *59*, 4931.

[10] J. Tang, J. G. Verkade, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 896.

[11] a) B. F. Fetterly, J. G. Verkade, in preparation; b) J. Tang, J. Dopke, J. G. Verkade, *J. Am. Chem. Soc.* **1993**, *115*, 5015.

[12] H. F. Chow, Z. Y. Wang, Y. F. Lau, *Tetrahedron* **1998**, *54*, 13813.

[13] a) M. J. Laufersweiler, J. M. Rohde, J. L. Chaumette, D. Sarazin, J. R. Parquette, *J. Org. Chem.* **2001**, *66*, 6440; b) I. S. Stupp, R. E. Zubarev, *J. Am. Chem. Soc.* **2002**, *124*, 5763.

[14] E. R. Zubarev, S. I. Stupp, *J. Am. Chem. Soc.* **2002**, *124*, 5762.

[15] While a ^{1}H NMR spectrum of *N*-methylbenzamide shows a doublet for the CH_3 protons due to coupling with the *N-H* proton, a 1:1 mixture of *N*-methylbenzamide and **2a** shows a singlet for the CH_3 protons. A ^{31}P NMR spectrum of this mixture displays a single peak for **2a**H$^+$.

[16] Although success was attained in obtaining the molecular weight of **7** by ESI-mass spectrometry, this was not the case for **8b** despite exhaustive attempts with MALDI and ESI experiments using a variety of conditions and matrices.

[17] a) Y. G. Gololobov, I. N. Zhmurova, L. F. Kasukhin, *Tetrahedron* **1981**, *37*, 437 and references cited therein; b) Y. G. Gololobov, L. F. Kasukhin, *Tetrahedron*, **1992**, *48*, 1353 and references cited therein; c) C. Widauer, H. Grutzmacher, I. Shevchenko, V. Gramlich, *Eur. J. Inorg. Chem.* **1999**, #38#1659.

[18] The postulate of virtual planarity around the PN_3 nitrogens in **8b** is supported by the near planarity of the PN_3 nitrogens observed in the structures (determined by X-ray means) of the isoelectronic compounds $O{=}P(MeNCH_2CH_2)_3N$: J.-S. Tang, T. Mohan, J. G. Verkade, *J. Org. Chem.*, **1994**, *59*, 4931; and $S{=}P(MeNCH_2CH_2)_3N$: S.-K. Xi, C. Lensink, J. G. Verkade, *Inorg. Chem.* **1990**, *29*, 2214.

[19] P. B. Kisanga, P. Ilankumaran, B. M. Fetterly, J. G. Verkade, *J. Org. Chem.* **2002**, *67*, 3555.

[20] L. S. Hegedus, W. H. Darlington, *J. Am. Chem. Soc.* **1980**, *102*, 4980.

[21] M. Filippini, R. Faure, J. Rodriguez, *J. Org. Chem.* **1995**, *60*, 6872.

[22] S. Kiyooka, T. Tsutsui, H. Maeda, Y. Kaneko, K. Isobe, *Tetrahedron Lett.* **1995**, *36*, 6531.

[23] See first citation in Ref.[18]