Heteroatom Chemistry
Volume 12, Number 1, 2001

Electron-Rich $O=PR_3$ Compounds: Catalysts for Alcohol Silylation

Xiaodong Liu and John G. Verkade

Department of Chemistry, Iowa State University, Ames, IA 50011

Received 18 July 2000; revised 29 August 2000

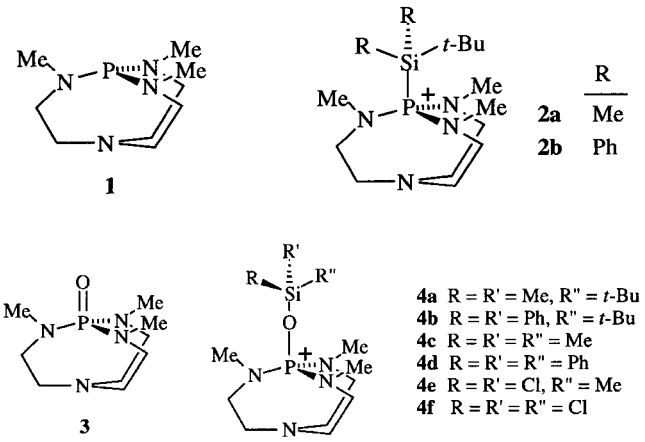
ABSTRACT: *The catalytic effect of a group of $R_3P=O$ compounds was studied in a mild procedure for the silylation of primary alcohols, secondary alcohols, hindered secondary alcohols, and of hindered phenols in the presence of t-butyldimethylsilyl chloride (TBDMSCl) and t-butyldiphenylsilyl chloride (TBDPSCl). It was found that $R_3P=O$ is an efficient catalyst in such reactions when R is a good electron-donating group, such as Me_2N or n-Bu and as an $NMe(CH_2)$ moiety in $N(CH_2CH_2NMe)_3P=O$ (**3**). However, $R_3P=O$ is a weak or ineffective catalyst when R is a poor electron-donating group, such as Ph or O-n-Bu or as a CH_2N-o-$CH_2C_5H_4N$ moiety in $N(CH_2CH_2N$-o-$CH_2C_5H_4N)_3P=O$. Compound* **3***, synthesized by oxidation of commercially available $N(CH_2CH_2NMe)_3P$, displayed the best catalytic properties for alcohol silylation in terms of efficiency, stability, and safety.*
 Heteroatom Chem 12:21–26, 2001

INTRODUCTION

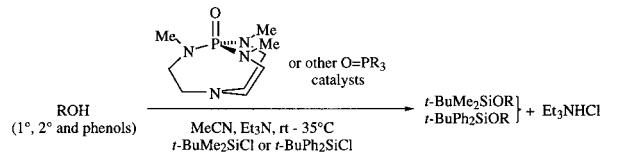
Protection of the organic hydroxyl group is necessary for avoiding undesired reactions with oxidizing agents and electrophiles during the course of multistep syntheses [1]. Among the many trialkylsilyl reagents used to protect this functionality, *t*-butyldimethylsilyl chloride (TBDMSCl) and *t*-butyldiphenylsilyl chloride (TBDMSCl) are two of the most popular [2]. A variety of methods has been reported for the derivatization of alcohols with the TBDMS and TBDPS moieties [3]. These reactions have been most satisfactorily achieved by reacting the alcohol with a molar excess of imidazole using dimethyl formamide (DMF) as a solvent [4,5], or with catalysts such as DMAP [2f], 1,1,3,3-tetramethylguanidine [2a], and ethyldiisopropylamine [2e]. More recently, the silylation of primary and secondary alcohols in 69–99% yields using TBDPCl in DMF with catalysts, such as $AgNO_3$, NH_4NO_3, or NH_4ClO_4 has been described [3d].

Proazaphosphatranes of type **1** [6] have been shown to be very strong nonionic bases that function as superior deprotonating agents [7], as superior catalysts [8], and as efficient promoters [9] in a variety of synthetically useful organic transformations. For the very effective and mild silyl protection of a wide variety of OH-containing organic substrates catalyzed by **1** [8b], a mechanism involving intermediates **2a** and **2b** detected with **1** was postulated on the basis of NMR evidence. In an earlier study of the chemistry of **3**, we discovered that the phosphoryl group of this compound is capable of catalyzing the conversion of isocyanates to isocyanurates [10] and that it is also a good donor to Lewis acids including silanes, forming cationic adducts such as **4a–f** [11]. This prompted us to evaluate the catalytic activity of **3** in alcohol silylation reactions.

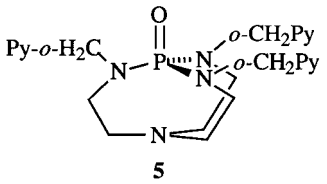
Correspondence to: John Verkade
Contract Grant Sponsor: Petroleum Research Fund, administered by the American Chemical Society.
Contract Grant Sponsor: ISU Center for Advanced Technology Development.



Herein we report on the silyl protection of a wide variety of alcohols, including primary alcohols, secondary alcohols, hindered secondary alcohols, and of hindered phenols using **3**, $O=P(NMe_2)_3$, and $O=P(n\text{-}Bu)_3$ as catalysts (equation 1) under mild conditions. Among these catalysts, **3** displays the best overall catalytic properties in terms of efficiency, stability, and safety. A comparison of the efficiency of these catalysts with the commonly used catalyst DMAP [2f] is also presented. The phosphine oxides $O=PPh_3$ and $O=P(O\text{-}n\text{-}Bu)$ and **5** [12] were found to be poor to nonfunctioning catalysts for alcohol silylation.



(1)



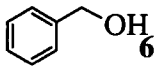
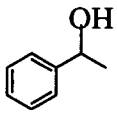
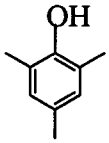
RESULTS AND DISCUSSION

In preliminary NMR monitoring reactions (see Experimental section), we found that TBDMS silylation of benzyl alcohol (**6**) is accelerated in the presence of **3**. Thus in CD_3CN, 2.1 hours were required to effect 99% silylation of **6** (according to ^1H NMR integration) in the presence of 0.5 equiv. of **3**, while 10.5 hours were required to obtain the same conversion in the absence of a catalyst. When $O=P(NMe_2)_3$, an acyclic analogue of **3**, was used as the catalyst in CD_3CN in the same reaction, only 1.3 hours were required for 99% conversion. In the nonpolar solvent C_6D_6, 11 hours were required for 99% silylation of **6** using 0.5 equiv. of **3** as a catalyst, while no reaction was observed during 12 hours in the absence of a catalyst. When the coordinating solvent DMF was used in the presence of 0.5 equiv. of **3**, silylation of **6** was complete in 1.9 hours. Although DMF seemed to be a somewhat better solvent than CH_3CN in terms of reaction rate, CH_3CN was the solvent of choice because of its lower boiling point and its ability to provide yields comparable with those obtained in DMF. For a more complete comparison, reactions were carried out on a preparative scale for three different hydroxyl compounds including primary alcohol **6**, secondary alcohol **10**, and hindered phenol **14** (Table 1) in the presence of one of the six phosphoryl compounds shown in this table. In addition, DMAP, a commonly used silylation catalyst [2f], was also compared.

Table 1 shows that $O=PR_3$ wherein R is a good electron-donating group, such as *n*-Bu, NMe_2, or $NMe(CH_2)$ (in **3**), considerably accelerates silylation for all three substrate alcohols, whereas the lack of a good electron-donating group leads to a poor catalyst ($O=PPh_3$ and **5**) or an ineffective one $O=P(O\text{-}n\text{-}Bu)_3$). In general, the catalytic efficiency for alcohol silylation of these phosphoryl compounds follows the increasing electron donor ability of the phosphoryl oxygen in the order $O=P(O\text{-}n\text{-}Bu)_3 < O=PPh_3 < \mathbf{5} < O=P(n\text{-}Bu)_3$, $O=P(NMe_2)_3$, **3**. Of all the phosphoryl compounds tested, **3** seems most effective, although the advantage is admittedly somewhat marginal compared with $O=P(n\text{-}Bu)_3$ or $O=P(NMe_2)_3$. We believe that the slight superiority of **3** in this respect may be associated with the stronger donor character of the oxygen in this compound than that in its acyclic analogue $O=P(NMe_2)_3$ owing to an $N_{ax} \rightarrow P$ transannular interaction that can occur in an intermediate or transition state [11]. However, the P=O group is more sterically hindered in the rigid cage structure of **3** by the upwardly directed Me groups, each of which resides on a planar nitrogen. Such a bulk effect may compromise the higher donor character of **3** to some extent. Thus **3** does not show a remarkable advantage over its acyclic analogues $O=P(n\text{-}Bu)_3$ and $O=P(NMe_2)_3$. The poorer performance of compound **5** is attributed to the withdrawing nature of the pyridyl groups in the $CH_2NCH_2\text{-}o\text{-}C_5H_4N$ moieties and the large cone angle swept out by the $CH_2\text{-}o\text{-}C_5H_4N$ segment of the $CH_2\text{-}o\text{-}C_5H_4N$ groups.

Compared with **3**, the catalytic activity of DMAP in the silylation of alcohols is about the same for the primary alcohol **6** and the hindered phenol **14**, but is less efficient for the hindered secondary alcohol

TABLE 1 Comparison of Seven Catalysts for Alcohol Silylation

substrates	reaction time (h)	% conversions[b] no cat.	$O=P(O\text{-}n\text{-}Bu)_3$	$O=PPh_3$	**5**	$O=P(n\text{-}Bu)_3$	$O=P(NMe_2)_3$	**3**	DMAP
 **6**	0.5	70	72	80	91	98	97	98	95
 **10**	6	41	29	60	71	94	93	99	85
 **14**	12	20	22	26	33	58	53	63	65

[a]See Experimental section for conditions.
[b]Based on ^1H integrations in which the error limit is about 1% absolute. Conversions are reproducible within this error limit for at least two separate runs on each substrate.

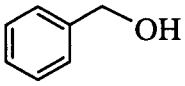
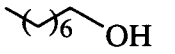
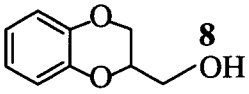
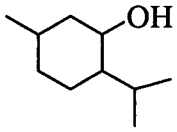
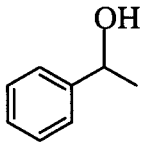
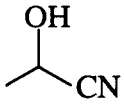
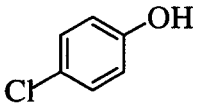
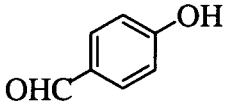
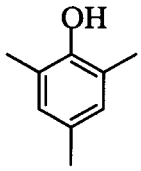
10 (see later for additional discussion). At room temperature, the silylation of **6**, **10**, and **14** using 2 equiv. of imidazole was faster than the combination of 10 mol % **3** and 1.1 equiv. of Et_3N (98% conversion vs. 90% for **6** in 0.4 hours, 97% vs. 88% for **10** in 4 hours, and 67% vs. 50% for **14** in 8 hours, respectively). However, when 10 mol % of imidazole and 1.1 equiv. of Et_3N was used, much slower conversions at room temperature were observed than with 10 mol % of **3** and 1.1 equiv. of Et_3N (67% vs. 90% for **6** in 0.4 hours, 53% vs. 88% for **10** in 4 hours, and 25% vs. 50% for **14** in 8 hours, respectively). Thus, on a mole-for-mole basis, **3** is more efficient than imidazole. That a base such as Et_3N as well as a catalyst is necessary for efficient silylations was shown by the lack of detectable silylation of **6** by TBDMSCl in the presence of 10 mol % of **3** or $O=P(NMe_2)_3$ when Et_3N was absent.

In Table 2, it is shown that **3** catalyzes the TBDMS silylation of primary alcohols **6–8** and phenols **12** and **13** within 0.5 hours at room temperature in excellent isolated yields (>91%), while the secondary alcohols **9–11** require a longer reaction time (6 hours) to give excellent yields (>91%) of silylated products. The hindered phenol **14** gave only a moderate yield of silyl ether (55%) in 12 hours. The tertiary alcohol **15** is resistant to silylation with TBDMSCl, giving no detectable yield after 48 hours. For each substrate, silylations catalyzed by DMAP and in the absence of catalyst were also conducted for comparison. It should be noted that for the primary alcohol **6**, the less hindered secondary alcohol **11**, and phenols (**12–14**), **3** shows about the same efficiency as DMAP. However, for the primary alcohols **7** and **8**, and the hindered secondary alcohols **9** and **10**, **3** is somewhat marginally more efficient than DMAP. Except for the TBDMS silylation of phenols **12** and **13**, silylations in the absence of catalysts proceed in considerably lower conversions (20–70%).

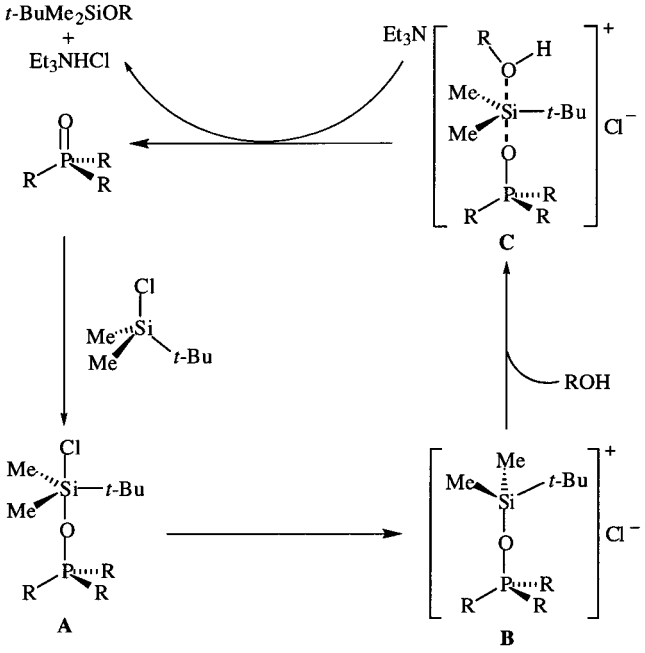
Table 3 shows that with 0.10 equiv. of **3** as a catalyst at 35°C, the primary alcohols (**6** and **7**) and phenol (**12** and **13**) are silylated with TBDPSCl within 6 hours and 4 hour, respectively, in high conversions (95–99%), while the secondary alcohol **9** is more difficult to silylate, giving 74% conversion over 24 hours. It is noted that **11** and the acid-sensitive alcohol **8** require longer reaction times but give good conversions (94% and 97%, respectively) to silylated products. The hindered secondary alcohol **10** is reluctant to silylate with TBDPSCl, giving only a 30% conversion of product in 24 hours.

Although several mechanistic pathways can be considered that rationalize the ability of electron rich $O=PR_3$ compounds to catalyze hydroxyl silylation, we believe the one shown in Scheme 1 is the most plausible on the basis of present evidence. This pathway could be facilitated in the case of the somewhat superior catalyst **3**, by transannulation of the bridgehead nitrogen to the phosphorus to form intermediates **B** and/or **C** wherein phosphorus is five-coordinate. An analogous pathway has been suggested as a working hypothesis in the ring opening of epoxides with $SiCl_4$ promoted by $O=P(NMe_2)_3$ [13]. Further support for the pathway in Scheme 1 comes from our previously reported isolation and

TABLE 2 Comparison of **3** and DMAP in Alcohol Silylation with TBDMSCl[a]

Substrate		Reaction Time (h)	Conversions[b] (yields[c]) (%)		
			3[d]	DMAP[d]	No cat.
	**6**	0.5	98 (91)	95	70
	**7**	0.5	98 (92)	88	45
	**8**	2	97 (91)	90	44
	**9**	6	97 (93)	60	31
	**10**	6	99 (91)	85	41
	**11**	6	99 (94)	99	65
	**12**	0.2	99 (95)	99	91
	**13**	0.2	99 (94)	99	90
	**14**	12	63 (55)	65	20
t-BuOH	**15**	48	–[e]	–[e]	–[e]

[a]See Experimental section for conditions.
[b]Based on ^{1}H integrations of characteristic resonances. The conversions are reproducible for at least two separate runs on each substrate. The error limit is about 1% absolute.
[c]After column chromatography, the purity was >95% by ^{1}H NMR spectroscopy. The yields are the highest values observed in each case.
[d]10 mol% catalyst.
[e]No detectable reaction.



SCHEME 1

characterization of **4e** and **4f** [11]. ^1H and ^{31}P NMR spectroscopic data suggest the presence of transannulation in these compounds as well as in **4c** and **4d** [11]. Further supporting the cycle in Scheme 1 in which ion formation is involved is the fact that the catalyzed silylations occur in the polar solvent CH_3CN. By contrast, silylation is much slower in benzene (see first paragraph of this section). There is considerable evidence in the literature indicating that pentacoordinate silicon compounds tend to be more reactive to nucleophilic substitution than four-coordinate silicon species [14]. This evidence also supports the cycle in Scheme 1.

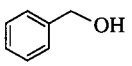
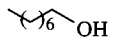
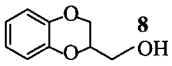
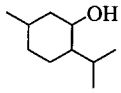
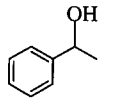
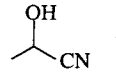
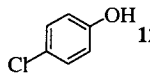
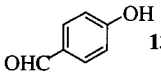
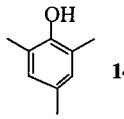
CONCLUSION

Compounds of the type O = PR_3, in which R is a good electron-donating group, are excellent catalysts for alcohol and phenol protective silylations under mild conditions using TBDMSCl and TBDPSCl. The advantages of these catalysts are (1) the yields or conversions of the silylated alcohols and phenols are generally superior, (2) acetonitrile can be used instead of the often employed but comparatively nonvolatile DMF, (3) the O = PR_3 catalysts are highly stable under the reaction conditions employed, (4) these catalysts are soluble in both polar and nonpolar solvents, and (5) **3**, though more expensive than O = $P(NMe_2)_3$, can be recovered in good yield and is less volatile than O = $P(NMe_2)_3$, which is a well-known nasal carcinogen and should be avoided if a substitute is available.

EXPERIMENTAL

CH_3CN and CD_3CN were distilled from CaH_2, and Et_2O and benzene were dried with sodium. All solvents were freshly distilled before use, and all reactions were carried out under Ar. Catalysts **3** [6] and **5** [12] were prepared according to methods developed in our laboratories. Silica gel sheets were purchased from J. T. Baker. All other chemicals were purchased from Aldrich Chemical Co. and were used as received.

TABLE 3 TBDPSCl Alcohol Silylations Catalyzed by **3**[a]

substrates		reaction time (h)	conversions[b] (%)	
			3[c]	no cat.
	**6**	6	95	47
	**7**	6	99	50
	**8**	24	97	39
	**9**	24	74	25
	**10**	24	30	9
	**11**	24	94	59
	**12**	4	97	78
	**13**	4	98	85
	**14**	50	–[d]	–[d]

[a]See Experimental section for conditions.
[b]Based on ^1H integrations in which the error limit is about 1% absolute. Conversions are reproducible within this error limit for at least two separate runs on each substrate. New compounds were characterized by ^1H, ^{13}C NMR, and HRMS(EI) spectroscopies.
[c]10 mol% catalyst.
[d]ND, No detectable reaction.

NMR Monitoring Experiments for the Catalytic Silylation of **6**

In a 5 mm NMR tube was dissolved 0.05 mmol of catalyst (when catalysts were used) in 0.75 mL of solvent (CD_3CN,C_6D_6 or DMF). To this solution was added 0.11 mmol of *t*-$BuMe_2SiCl$ followed by the addition of NEt_3 (15 μL, 0.11 mmol). After shaking the tube for 2 min, **6** (10 μL, 0.10 mmol) was added followed by recording ^{1}H NMR spectra at various time intervals. The reaction temperature was 20°C. The time interval between each spectrum was 1 min for spectra 1–20, 10 min for spectra 21–30, 30 min for spectra 31–40, 1 hour for spectra 41–45, and 4 hours for each spectrum thereafter. One minute was required to complete each spectrum.

General Procedure for Silylations with t-$BuMe_2SiCl$ (TBDMSCl) or t-$BuPh_2SiCl$ (TBDPSCl)

In a 10 mL test tube capped with a rubber septum was dissolved 0.1 equiv. of a catalyst in 2 mL of CD_3CN. To this was added 1.0 mmol of the alcohol followed by the addition of NEt_3 (0.15 mL, 1.1 mmol). After stirring the mixture for 5 min, 1.1 mmol of the silylating agent was added with continuous stirring at room temperature (25°C) for *t*-$BuMe_2SiCl$ and at 35°C for *t*-$BuPh_2SiCl$. ^{1}H NMR spectra were taken to obtain the conversion based on ^{1}H NMR integration of characteristic resonances, and the product identity was confirmed by gas chromatography–mass spectroscopy. After the reaction time stated in the tables, 0.02 mL of H_2O was added with stirring. The mixture was filtered, and the residue was washed with Et_2O (2 $\times$ 5 mL) followed by evaporating ca. 95% of the solvent under vacuum. The resulting crude silyl ether was purified chromatographically on a silica gel column using a mixture of 95% hexane and 5% ethyl acetate as the eluent. The product was obtained upon drying over anhydrous $MgSO_4$ and evaporation of the eluent. The identifying ^{1}H and ^{13}C NMR spectra compared favorably with those in the literature (see supporting information available from the author upon request).

General Procedure for the Recovery of **3**

After chromatographic separation of the silyl ether product, the silica gel column was washed with an additional 100 mL of a solution of 90% hexanes and 10% ethyl acetate followed by washing with 100 mL of CH_3OH. After collecting the pure CH_3OH fraction and evaporating the solvent under vacuum, **3** was recovered as a white solid in 60–75% yields. The ^{31}P, ^{1}H, and ^{13}C NMR spectra were identical to those of an authentic sample of **3**.

REFERENCES

[1] Greene, T. W.; Wuts, P. G. M. Protective Groups in Organic Synthesis, 3rd ed.; Wiley & Sons: New York, 1999.

[2] (a) Kim, S.; Chang, H. Syn Commun 1984, 14 (10), 899; (b) Kim, S.; Chang, H. Bull Chem Soc Jpn 1985, 58, 3669; (c) Azipuraua, J. M.; Palono, C. Tetrahedron Lett 1985, 26, 475; (d) Lissel, M.; Weiffer, J. Syn Commun 1981, 11 (7), 545; (e) Lombardo, L. Tetrahedron Lett 1984, 25, 227; (f) Chaudhary, S. K.; Hernandez, O. Tetrahedron Lett 1979, 20, 99; (g) Olah, G. A.; Gupta, B. G.; Narang, S. C.; Malhotra, R. J Org Chem 1979, 44, 4272; (h) Kita, Y.; Haruta, J.; Fuji, T.; Segawa, J.; Tamura, Y. Synthesis 1981, 451.

[3] (a) Golinski, M.; Brock, C. P.; Watt, D. S. J Org Chem 1993, 58, 159; (b) Mazur, P.; Nakanishi, K. J Org Chem 1992, 57, 1047; (c) Gooding, O. W.; Beard, C. C.; Jackson, D. Y.; Wren, D. L.; Cooper, G. F. J Org Chem 1991, 56, 1083; (d) Hardinger, S.; Wijaya, N. Tetrahedron Lett 1993, 34, 3821; (e) Detty, M. R.; Seidler, M. R. J Org Chem 1981, 46, 1283.

[4] Corey, E. J.; Venkateswarlu, A. J Am Chem Soc 1972, 94, 6190.

[5] Hanessian, S.; Lavallee, P. Can J Chem 1975, 53, 2975.

[6] Schmidt, H.; Lensink, C.; Xi, S. K.; Verkade, J. G. Z. Anorg Allg Chem 1989, 578, 75.

[7] (a) Tang, J.-S.; Verkade, J. G. J Org Chem 1994, 59, 7793; (b) Tang, J. S.; Verkade, J. G. J Org Chem 1996, 61, 8750; (c) Mohan, T.; Arumugam, S.; Wang, T.; Jacobson, R. A.; Verkade, J. G. Heteroat Chem 1996, 7, 455; (d) Arumugam, S.; Verkade, J. G. J Org Chem 1997, 62, 4827; (e) Arumugam, S.; McLeod, D.; Verkade, J. G. J Org Chem 1998, 63, 3677; (f) Wang, Z.; Verkade, J. G. Heteroat Chem 1998, 9, 687.

[8] (a) Tang, J.-S.; Verkade, J. G. Angew Chem Int Ed Engl 1993, 32, 896; (b) D'Sa, B.; Verkade, J. G. J Am Chem Soc 1996, 118, 12,832; (c) D'Sa, B.; McLeod, D.; Verkade, J. G. J Org Chem 1997, 62, 5057; (d) D'Sa, B. A.; Kisanga, P.; Verkade, J. G. J Org Chem 1998, 63, 3961; (e) Kisanga, P.; D'Sa, B.; Verkade, J. G. J Org Chem 1998, 63, 10057; (f) Kisanga, P. B.; McLeod, D.; D'Sa, B. A.; Verkade, J. G. J Org Chem 1999, 64, 3091; (g) Ilankumaran, P.; Verkade, J. G. J Org Chem 1999, 64, 3087; (h) D'Sa, B.; Kisanga, P.; Verkade, J. G. J Org Chem 1998, 63, 3691; (i) Liu, X.; Verkade, J. G. J Org Chem 1999, 64, 4840.

[9] (a) D'Sa, B. A.; Verkade, J. G. J Org Chem 1996, 61, 2963; (b) Kisanga, P. B.; Verkade, J. G. J Org Chem 1999, 64, 4298; (c) Wang, Z.; Verkade, J. G. J Org Chem (in press).

[10] Tang, J. S.; Mohan, T.; Verkade, J. G. J Org Chem 1994, 59, 4931.

[11] Liu, X.; Verkade, J. G. Inorg Chem 1998, 37, 5189.

[12] Liu, X.; Verkade, J. G. (in press).

[13] Denmark, S. E.; Barsanti, P. A.; Wong, K.; Stavenger, R. A. J Org Chem 1998, 63, 2428.