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Catalytic Appel reactions*

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Abstract: Organophosphorus chemistry plays a key role in the modern synthesis of organic compounds. The formation of phosphine oxides from phosphines often drives reactions to completion. However, these oxides also result in waste and purification issues. Organophosphorus catalysis aims to address these problems, and in this paper we present our progress in developing and utilizing new organophosphorus catalysts. More specifically, the in situ reduction of a range of cyclic phosphine oxides was explored, leading to the development of dibenzophospholes as new organophosphorus catalysts and the application thereof in the phosphorus-mediated substitution of alcohols by halides, which is also known as the Appel reaction. We show that the electronic fine-tuning of the catalyst is crucial for the success of the reaction and that the development of reactions using the in situ reduction protocol all depends on finding the right balance in the reactivities of the reaction components. This balance has been successfully found for the bromination of alcohols, and significant progress has been made for the chlorination reactions.

Keywords: Appel reaction; bromination; chlorination; organocatalysis; triphenylphosphine.

INTRODUCTION

Nucleophilic substitution reactions are of great importance in synthetic pathways and offer many possibilities for stepwise construction of complex molecules. Of particular interest is the direct substitution of a hydroxyl functionality due to its naturally high abundance and facile introduction in molecules. However, because of its poor leaving group ability, alcohols are typically activated prior to substitution by for instance protonation, sulfonylation or phosphorylation. Mainly because of their broad substrate scope, mild conditions, and stereospecificity, phosphorus-mediated alcohol substitutions are widely utilized. Well known in this category are the Mitsunobu reaction and the closely related Appel reaction [1]. Although first published by Downie, Holmes, and Lee [2] and investigated by several other groups [3], the direct substitution of alcohols by halides is commonly credited to the late Prof. Rolf Appel. It is for his extensive research on the use of chlorotriphenylphosphonium chloride in numerous other applications [4–10] and his excellent review [11] and book chapter [12] that chemists generally refer to *Appel reaction* [13], *conditions* [14], or *reagent* [15] when using the CX_4/PPh_3 mixture in a reaction. This eventually evolved into the name "Appel reaction" specifically for the substitution of alcohols under these conditions [16,17].

The use of phosphorus in organic synthesis has been well established in the last century. Pioneered by Michaelis and Arbuzov, as reflected in their named reaction [18], it was further developed by numerous organophosphorus chemists, most notably by George Wittig who received the Nobel Prize

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in 1979 for "his development of the use of phosphorus-containing compounds into important reagents in organic synthesis" [19]. The Wittig, Mitsunobu, and Appel reactions are highly ranked on the list of useful organic transformations, and the importance of the phosphorus element is clearly underlined by the widespread use of these reactions in industrial processes as well [20]. The driving force for conversions mediated by this element is often the formation of the strong P–O bond. The inherent low reactivity of the resulting phosphine oxides makes them rather useless for further use and their reduction back to the corresponding phosphines requires unfavorable harsh conditions [20b,21]. This, and the fact that these phosphine oxides significantly hamper the purification of the desired products, led to numerous creative strategies as immobilization [22], extraction [23], or further conversion [24] of these by-products. Although these attempts have shown their usefulness in several cases, the poor atom economy can in principle only be solved by using substoichiometric amounts of the phosphorus reagent [25]. An additional argument is that, as the so-called phosphate rock is depleting, prices of phosphorus reagents are likely to steadily increase over the coming years [26].

Especially during the last decade, remarkable progress has been made in the catalytic use of phosphorus reagents [27]. As illustrated in Fig. 1, two main strategies have emerged: one in which the oxidation state remains constant during the catalytic cycle (i.e., activation strategy) and one in which the P(V)-species is reduced in situ to a reactive P(III)-species (i.e., in situ reduction strategy). The activation strategy was pioneered by Campbell et al. (catalyst **1a**) for the polymerization of carbodiimides and reintroduced by Marsden et al. (catalyst **1b**) for the construction of heteroatomatic compound through an aza-Wittig reaction [28]. Both reactions make use of a reaction of phosphine oxide with an isocyanate, leading to CO_2 and an iminophosphorane intermediate that subsequently reacts further with either a second isocyanate or a carbonyl functionality. Another activation principle enabled the group of Denton to substitute alcohols by halides under Appel conditions [29]. To this end, phosphine oxide readily reacts with oxalyl chloride to form the chlorotriphenylphosphonium chloride that further reacts with the alcohol to give alkyl chlorides. By the addition of LiBr in the reaction, they could successfully

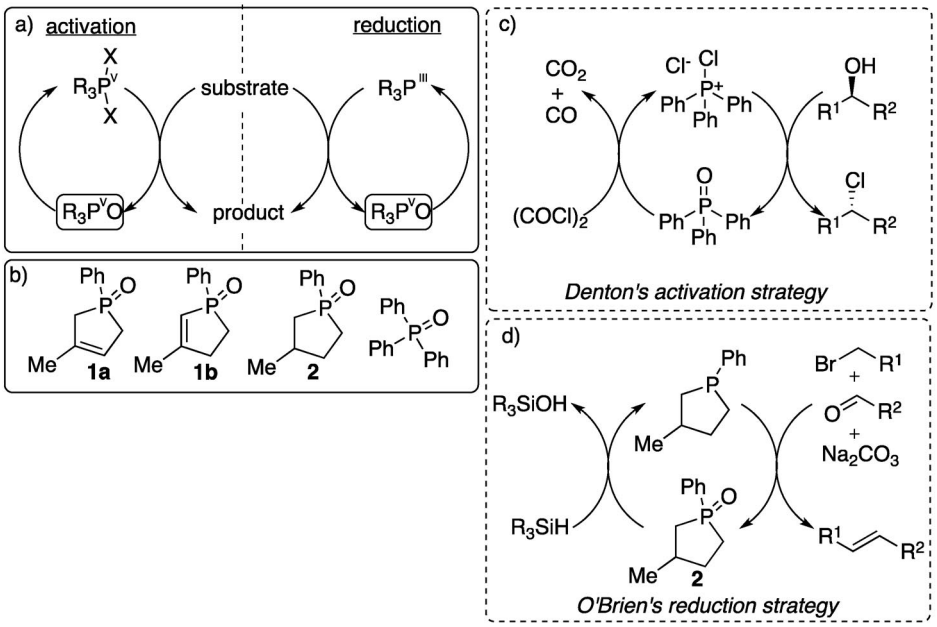


Fig. 1 (a) Overview of approaches in organophosphorus catalysis, and (b) the catalysts involved. Examples: (c) catalytic Appel reaction via the activation strategy by Denton et al., and (d) catalytic Wittig reaction via in situ reduction by O'Brien et al.

alter the reaction to give alkyl bromides [29a]. Furthermore, the phosphine oxide activation with oxalyl chloride also enabled them to convert epoxides and oximes into alkyl dichlorides and nitriles, respectively [30].

The in situ reduction strategy was introduced by O'Brien et al. in the first catalytic Wittig reaction [31]. To this end, the key cyclic phosphine oxide **2** was reduced in situ to the corresponding phosphine, followed by conversion into an ylide and subsequent Wittig reaction. Remarkably, diphenylsilane (Ph_2SiH_2) or trimethoxysilane [$(MeO)_3SiH$] reduced the phosphoryl compound selectively, without affecting the aldehyde and other reagents. Another example was given by Woerpel's group as they used the reduction approach in a triphenylphosphine-catalyzed reduction of alkyl silyl peroxides using in situ generated titanium hydride [32]. Although the number of applications of catalytic phosphorus-mediated reactions is still limited at this moment, we recognized that the concept of in situ reduction offers great potential for broader applicability. We therefore entered the field by studying new potential phosphine catalysts and developed this further into catalytic brominations and a catalytic Staudinger reduction [33]. In this paper, we report our evaluation of a variety of organophosphorus catalysts, the bromination reactions, and new developments in the chlorination of alcohols via a catalytic Appel reaction.

CATALYST DEVELOPMENT

In preceding studies performed by O'Brien and Keglevich, it was suggested that the ring size was of a crucial importance for mild phosphine oxide reduction. In order to verify this hypothesis and to obtain more insight into the importance of a 3-methyl substituent and the degree of saturation of the seven-membered rings (**6**), our research started with the synthesis of cyclic phosphine oxides **2–6** and their reductions with Ph_2SiH_2 (Fig. 2).

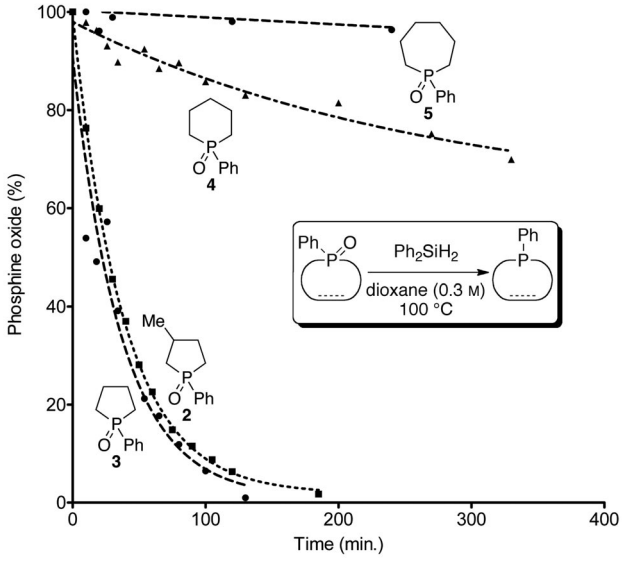


Fig. 2 Reduction of cyclic phosphine oxides by Ph_2SiH_2.

By these studies, it became clear that only five-membered phosphine oxide rings are reduced at an acceptable rate. Futhermore, the 3-methyl substituent had no significant effect on the rate [33b].

Despite the proven effectiveness of reduction of aliphatic five-membered phosphine oxides, we opted to widen the scope of phospholane-type reagents for potentially catalytic transformations. We envisioned that aromatic phospholes could be interesting candidates in this respect, due to increased

ring strain and the recovery of aromaticity after reduction. An important additional advantage of phospholes lies in the tuneability of electronic properties by introduction of substituents. Therefore, we turned our attention to dibenzophospholes and the corresponding oxides (Fig. 3, compounds **6–8** and **9–11**, respectively), which are stable at room temperature under air. Phospholes lacking fused aromatic rings were also considered but not pursued because P(V)-containing phospholes are known to dimerize by Diels–Alder reaction [34]. To investigate the effect of electron donation or withdrawal on the reactivity of the phosphorus atom, we evaluated three different phospholes with hydrogens, methoxy- or trifluoromethyl groups substituents (Fig. 3) [35]. Compounds **9–11** could be readily reduced by Ph_2SiH_2 under similar conditions as applied for phospholane oxides **2** and **3**.

It is clear that electron-withdrawing substituents (R = CF_3) significantly reduce the reduction rate with respect to unsubstituted phosphole (R = H), while a much smaller influence was detected by enhancement of electron density (R = OMe). From these data it may be surmised that Lewis basicity of the phosphoryl is of importance for the reduction potential, at least under the action of silanes. More studies to support this theory are underway.

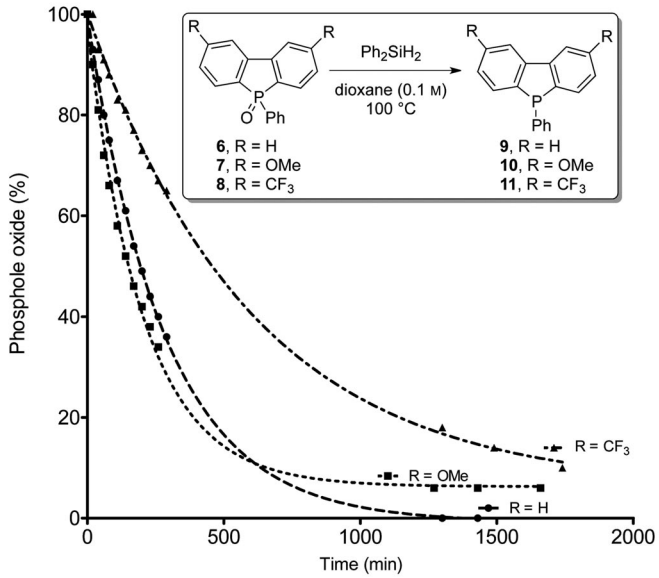


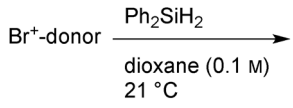
Fig. 3 Reduction of dibenzophosphole oxide by Ph_2SiH_2.

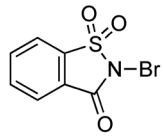
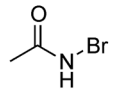
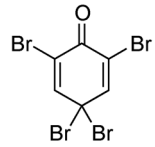
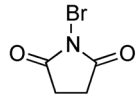
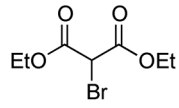
APPEL REACTION: BROMINATIONS

We commenced our investigations on the catalytic Appel reaction by utilizing the well-known bromonium donor tetrabromomethane. Thus, 2-phenylethanol was reacted with tetrabromomethane (1.5 equiv) in the presence of Ph_2SiH_2 (1.1 equiv) and **10** (10 mol %) in dioxane at 100 °C. Only 18 % conversion was observed by gas chromatography (GC), while ^{31}P NMR analysis showed many phosphorus signals as an indication of catalyst decomposition. We then used an alternative bromonium donor, *N*-bromosaccharine (NBSac) [36]. This donor led to more catalyst turnovers resulting in 60 % conversion, albeit that multiple additions of Ph_2SiH_2 and NBSac (total addition of 3.5 equiv over four additions) were required to drive the reaction to completion. The large amount of Ph_2SiH_2 that is required suggests a competitive reaction with the bromonium donor. The good conversion, however, implies that clean regeneration of dibenzophosphole indeed took place unlike the reaction with tetrabromomethane.

Since Ph_2SiH_2 was capable of smoothly reducing dibenzophosphole and showed excellent functional group selectivity in the Wittig reaction of O'Brien, we choose to continue with this reducing agent and screen other bromonium-donors (oxidizing agent) for their compatibility with Ph_2SiH_2 (reducing agent). The majority of alternative reagents, i.e., bromine (entry 1) [37], *N*-bromosuccinimide (entry 5) [38], *N*-bromoacetamide (entry 3) and 2,4,4,6-tetrabromocyclohexa-2,5-dienone (entry 4) [39], reacted quickly with Ph_2SiH_2 (Table 1). Only tetrabromomethane (entry 7) and diethyl bromomalonate (DEBM, entry 6) reacted sufficiently slow. Fortunately, in the presence of DEBM (1.5 equiv) in dioxane at room temperature, 2-phenylethanol (**12**) was converted into the corresponding bromide in 83 % yield, thereby serving as a stimulus to continue with this reagent in a catalytic Appel reaction.

Table 1 Screening of the compatibility of selected bromonium donors with Ph_2SiH_2.

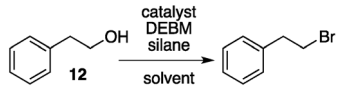


Entry	Br^+ donor	Time[a]
1	Br_2	10 min
2		15 min
3		20 min
4		30 min
5		50 min
6		4 days
7	CBr_4	no reaction

[a]Time indicates when the silane was fully consumed.

In our continuous efforts, a substoichiometric amount (10 mol %) of dibenzophosphole **9**, Ph_2SiH_2 (1.1 equiv) and DEBM (1.5 equiv) were added to alcohol **12** in dioxane at 100 °C, leading to a conversion of 65 % over 66 h (Table 2, entry 1). To increase the rate, the reaction was performed at higher concentrations, but a lower yield of (2-bromoethyl)benzene was obtained due to side reactions (entries 2 and 3). A better result was obtained using acetonitrile, which is also known to stabilize ionic intermediates for Appel reactions with tetrachloromethane, leading to faster conversions and higher yields [11]. Indeed, an excellent yield in a much shorter time was obtained (82 % in 19 h, entry 4), and even a catalyst loading of only 5 mol % still gave reasonable conversion (entry 9). The reaction proceeded also at 60 °C, but required prolonged reaction times (entry 6). As an alternative reducing agent,

Table 2 Optimization of the catalytic Appel reaction by variation of catalyst, solvent, silane, and temperature.



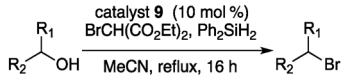
Entry	Cat.	Silane	Cat. [mol %]	Solvent	Conc. [m]	Temp. [°C]	Time [h]	Yield [%][a]
1	**9**	Ph_2SiH_2	10	dioxane	0.1	100	66	65
2	**9**	Ph_2SiH_2	10	dioxane	0.5	100	4	28
3	**9**	Ph_2SiH_2	10	dioxane	1.0	100	4	16
4	**9**	Ph_2SiH_2	10	MeCN	0.1	82	19	82
5	**9**	Ph_2SiH_2	10	DMF[b]	0.1	100	–	–
6	**9**	Ph_2SiH_2	10	MeCN	0.1	60	39	62
7	**9**	Et_3SiH	10	MeCN	0.1	82	46	9
8	**9**	$(MeO)_3SiH$	10	MeCN	0.1	82	23	5
9	**9**	Ph_2SiH_2	5	MeCN	0.1	82	72	69
10	**9**	–	10	MeCN	0.1	82	20	6
11	–	Ph_2SiH_2	–	MeCN	0.1	82	20	0
12	**10** (R = OMe)	Ph_2SiH_2	10	MeCN	0.1	82	19	68
13	**2** (O'Brien)	Ph_2SiH_2	10	MeCN	0.1	82	20	17

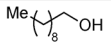
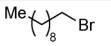
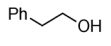
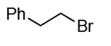
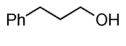
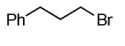
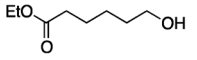
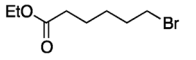
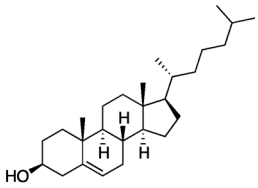
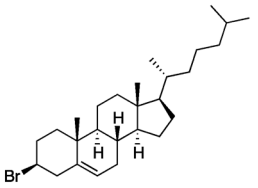
[a]GC yield based as determined with tetradecane as an internal standard, reaction was terminated after full consumption of alcohol.
[b]Ph_2SiH_2 immediately reacted with DMF.

triethylsilane was evaluated but appeared insufficiently strong to reduce **6** so that only 9 % of the bromide was obtained (entry 7). In contrast, $(MeO)_3SiH$ was able to reduce **6**, but in this case silylation of the starting alcohol **12** resulted in a low conversion (entry 8). O'Brien's precatalyst, 3-methyl-*P*-phenylphospholane oxide (**2**), led to a poor yield of bromide (entry 13), mainly due to alkylation of the in situ generated phosphine by the product bromide. The same alkylation, albeit much slower, thwarted a high yield for the more electron-rich dimethoxydibenzophosphole **10**, although the yield of the catalytic Appel reaction was acceptable (entry 12). These investigations clearly show the fine balance that has to be found for these types of catalytic reactions.

In order to further establish the scope and limititations of the catalytic Appel reaction, the optimized reaction conditions were applied to a range of substrates (Table 3). We were pleased to find that in most cases conversion of the alcohol to bromide was high. The somewhat compromised yields are due to the fact that isolation of some bromides was troublesome due to their high reactivity (entries 2 and 3). Stable bromides could, however, be isolated in moderate to good yields (entries 1 and 4–6). Sterically demanding secondary alcohols requiring an S_N2 substitution show poor reactivity (entry 7). These results show that when both S_N1 and S_N2 substitution are difficult, the conversion is limited. However, a good conversion of the secondary alcohol β-cholesterol was observed via stepwise substitution by neighboring group participation of the double bond. The formation of 3-bromocholest-5-ene by an Appel reaction with PPh_3/NBS gives stereoisomeric mixtures [40]. The catalytic Appel reaction, however, selectively gives retention of stereochemistry, indicating that stepwise substitution occurs as is also known for bromide substitution of mesylated cholesterol [41].

Table 3 Substrate scope of catalytic Appel reaction.



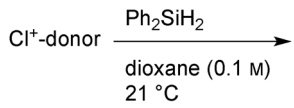
Entry	Substrate	Product	Yield [%][a]
1			72 (73)
2			55 (80)
3			45 (75)
4			71
5			63
6			72
7			20

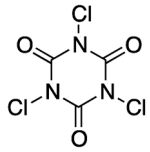
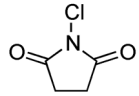
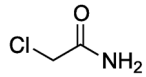
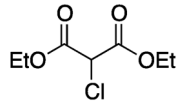
[a]Isolated yield (GC yield as determined with tetradecane as an internal standard).
[b]Full conversion, but decomposition upon loading onto silica gel.

APPEL REACTION: CHLORINATION

After establishing the optimal conditions for bromination, we turned our attention to the introduction of chloride. As previously performed for bromonium donors, we first investigated the compatibility of a selection of chloronium donors and Ph_2SiH_2 (Table 4). The results clearly show that trichloroisocyanuric acid (TCCA, entry 1) and *N*-chlorosuccinimide (NCS, entry 2) are not compatible with Ph_2SiH_2. Since there is no precedence for Appel reactions with 2-chloroacetamide (entry 3), we continued our investigations with diethyl chloromalonate (entry 4) and tetrachloromethane (entry 5). By using 2-phenylethanol (**12**), we first performed classic stoichiometric Appel reactions with both tetrachloromethane and chloromalonate and 5-phenyldibenzophosphole (**9**) (Table 5). Both these reactions turned out to be rather slow and did not reach full conversion (entries 2 and 3). This is in strong contrast to the same reaction performed with triphenylphosphine (entry 1). As we had previously observed during our investigations of the bromination reactions, the nucleophilicity of the phosphorus atom is greatly reduced by incorporation in the dibenzophosphole system, but also slightly increased by placing methoxide substituents on the 2- and 8-positions. We therefore repeated the experiments, this time using 2,8-dimethoxy-5-phenyldibenzophosphole (**9**), and clearly observed an improvement in reaction rates and conversions (entries 4 and 5). However, upon turning to a catalytic variant of the Appel reaction with dibenzophosphole **10** using either chlorinating reagent, again very low conversions and reaction rates were observed (Table 5, entries 6 and 7).

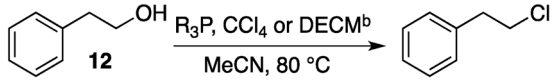
Table 4 Screening of the compatibility of selected chloronium donors with Ph_2SiH_2.



Entry	Cl^+ donor	Time[a]
1		10 min
2		50 min
3		NR
4		NR
5	CCl_4	NR

[a]Time indicates when the silane was fully consumed; NR = no reaction.

Table 5 Investigations toward chlorination of alcohols: influence of phosphine and chloronium donor.



Entry	Phosphine (equiv)	Chlorinating agent (1.5 equiv)	Silane (1.1 equiv)	Conversion [%][a]
1	PPh_3 (1.5)	CCl_4	–	100 (30 min)
2	**9** (1.5)	CCl_4	–	40 (7 h)
3	**9** (1.5)	DECM	–	14 (4.5 h)
4	**10** (1.5)	CCl_4	–	75 (2.5 h)
5	**10** (1.5)	DECM	–	68 (2.5 h)
6	**10** (0.1)	CCl_4	Ph_2SiH_2 (1.1)	10 (20 h) 20 (48 h) 30 (66 h)
7	**10** (0.1)	DECM	Ph_2SiH_2 (1.1)	14 (20 h) 25 (48 h) 33 (66 h)

[a]Conversions as determined by GC.
[b]Diethyl chloromalonate.

To investigate the underlying problem of the slow reactions more thoroughly and test the hypothesis of a too low nucleophilicity of the phosphorus atom, we performed a series of NMR experiments wherein the dibenzophospholes were subjected to the chlorinating and brominating reagents that were

used in our catalytic Appel reactions (Fig. 4). First, we mixed 2 equiv of chlorinating agent (CCl_4) with either dibenzophosphole **9** (R = H) or **10** (R = OMe) in the presence of 10 equiv of water. In case of a reaction, the chlorophosphonium chloride would be immediately hydrolyzed, and thus a reaction would become apparent by the formation of phosphine oxide (^{31}P NMR signal at 40 ppm). Clearly, the reaction with dibenzophosphole **10** (R = OMe) was much faster than with **9** (R = H). However, when we performed a reaction with the same dibenzophosphole (**9**) and either DEBM or tetrabromomethane, full conversion was obtained in less than 20 min (Figs. 4c and d). Hence, we concluded that for a successful catalytic chlorination reaction either a more electrophilic chloronium donor or a more nucleophilic phosphine are required. Since more electrophilic chloronium donors react readily with Ph_2SiH_2 (Table 4), the solution probably lies in improving the phosphorus catalyst.

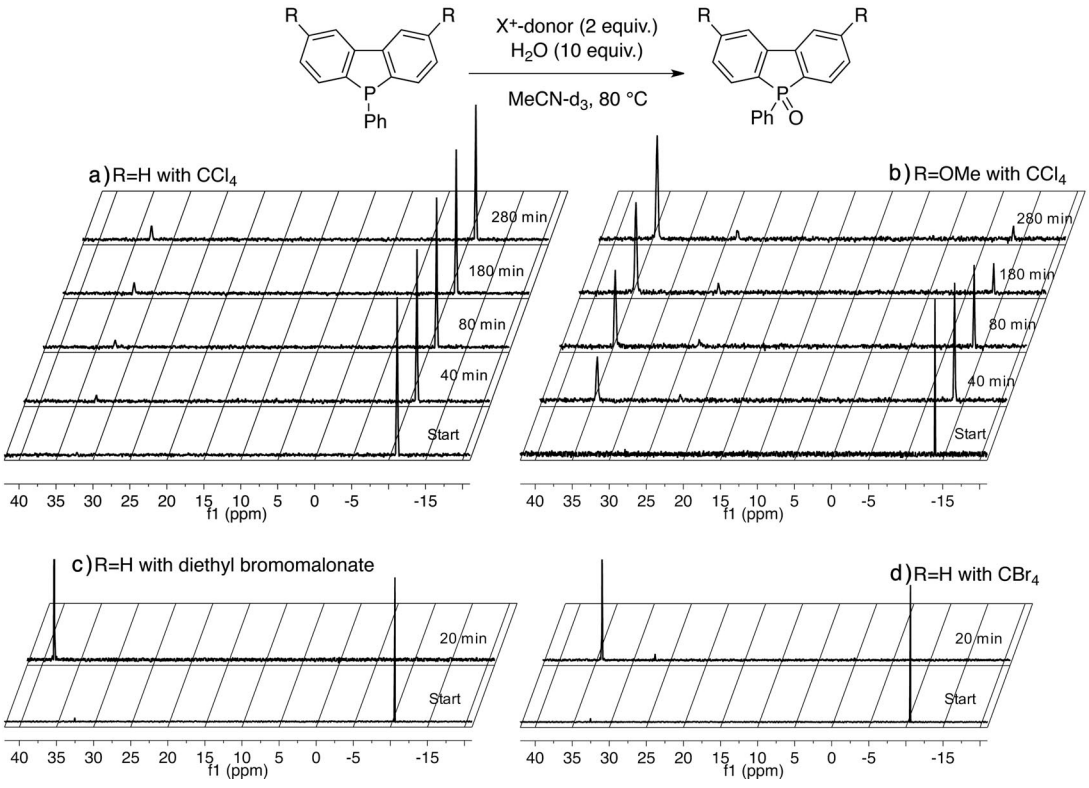


Fig. 4 Stacked ^{31}P NMR spectra of the reactions of dibenzophospholes **9** (R = H) and **10** (R = OMe) with halonium donors. Phosphines resonate at ca. 9 ppm and phosphine oxides at ca. 40 ppm. (a) Phosphole **9** with CCl_4 shows almost no reaction; (b) phosphole **10** with CCl_4 shows a much faster reaction; (c) reaction of phosphole **9** with DEBM and (d) CBr_4 give a much faster reaction.

CONCLUSIONS

The development of organophosphorus-catalyzed Appel reactions using the in situ reduction protocol all depends on finding the right balance in the reactivities of the reaction components. The phosphine should readily react with the halonium donor, while it refrains from reacting with the alkyl halide product. At its turn, the halonium donor (an oxidizing agent) has to be reasonably unreactive toward the silane (reducing agent) while the silane has to retain its capability to reduce the phosphine oxides. This balance has been successfully found for the bromination of alcohols. Significant progress has been

made for the chlorination reaction, and currently we are looking into improving the organophosphorus catalyst to obtain the same selectivity and activity as is obtained for the bromination.

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