Free and Polymer-Bound Tricyclic Azaphosphatranes $HP(RNCH_2CH_2)_3N^+$: Procatalysts in Dehydrohalogenations and Debrominations with NaH

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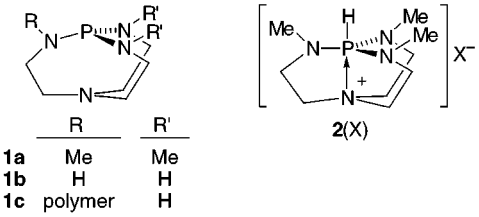
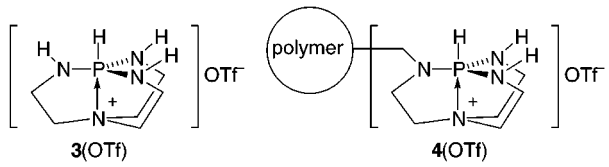
The commercially available nonionic base $P(CH_3NCH_2CH_2)_3N$ (**1a**) was shown earlier to be superior to DBU as a stoichiometric reagent for the conversion of primary and secondary alkyl halides to alkenes (Arumugam, S.; Verkade, J. G. *J. Org. Chem.* **1997**, *62*, 4827). The precursor cation $HP(CH_3NCH_2CH_2)_3N^+$ (**2**) to **1a**, which is more stable and less expensive, is reported herein to be an efficient procatalyst for these reactions and also for the debromination of vicinal dibromides using NaH as a relatively inexpensive stoichiometric hydride source in CH_3CN at room temperature. In dehydrohalogenations requiring more than ca. 10 h, the CH_2CN^- ion also acts as a base. By itself, NaH does not function well or at all under the same conditions. A catalytic cycle is proposed in which hydride deprotonates cation **2** liberating catalytic **1a**. The cations $HP(HNCH_2CH_2)_3N^+$ (**3**) and $HP[N(polymer)CH_2CH_2]N(CH_2CH_2NH)_2^+$ (**4**) are also shown to function as procatalysts for the efficient dehydrohalogenation of RX and for the debromination of vicinal dibromides. The preparation of the heterogeneous procatalyst **4**(OTf) is also described.

Introduction

The introduction of double bonds into organic systems via the elimination of hydrogen halides is a widely applicable transformation.[1] Although typical organic bases such as Et_3N, *N*,*N*-dimethylaniline, pyridine, and quinoline have been employed as dehydrohalogenation reagents, they often result in unsatisfactory yields. Over the past 30 years, DBU and DBN have become popular dehydrohalogenation reagents owing to their nonnucleophilic nature and greater basicity.[2,3] However, these reagents frequently require heating and must be used in stoichiometric excess. Moreover, yields are often only moderate. Dehalogenations have been used as a means for the purification of olefins,[4] for the temporary protection of double bonds,[5] and for generating a new double bond as part of a synthetic sequence.[6] Dehalogenations from vicinal dihalides are promoted by a variety of nucleophiles, including halide and hydride ions, as well as neutral sulfur, phosphorus, nitrogen, and oxygen compounds.[7] Recently[8,9] we found that the commercially available proazaphosphatrane **1a**, reported for the first time by our group,[10] is superior to DBU as a dehydrohalogenation reagent for primary and secondary alkyl halides. Solid **2**(X), which is produced in these reactions (X = Cl, Br, OTf) can be converted back to **1a** by treatment with KO-*t*-Bu.[11]





Here we report that NaH deprotonates **2**(Cl), **3**(OTf), and **4**(OTf), thus allowing for the possibility that neutral **1a**−**c** can act as a catalyst in dehydrohalogenations. By itself NaH is not an efficient dehydrohalogenation reagent, but it is considerably less expensive than other bases such as DBN, DBU, or KO-*t*-Bu. Because **2**(Cl) is stable to air for months without degradation, it seemed to us that it, as well as **3**(OTf) and **4**(OTf), could function as procatalysts for dehydrohalogenations of alkyl halides in the presence of NaH. Here we report that 0.1 equiv of any of these procatalysts and excess NaH (2.5 equiv) in CH_3CN are efficient dehydrohalogenation media at room temperature and that these mixtures also debrominate vicinal dibromides effectively.

Results and Discussion

That NaH can deprotonate cation **2** in CH_3CN to give **1a** is shown by a ^{31}P NMR spectrum of a CH_3CN solution

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(1) Baciocchi, E. In *The Chemistry of Functional Groups, Supplement D*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1983; Part 2, p 1173.
(2) Oediger, H.; Möller, F.; Eiter, K. *Synthesis* **1972**, 591.
(3) Hermecz, I. *Adv. Heterocycl. Chem.* **1987**, *42*, 100.
(4) Soday, F. J.; Boord, C. E. *J. Am. Chem. Soc.* **1933**, *55*, 3293.
(5) Solo, A. J.; Singh, B. *J. Org. Chem.* **1965**, *30*, 1658.
(6) Allred, E. L.; Beck, B. R.; Voorhees, K. J. *J. Org. Chem.* **1974**, *39*, 1426.
(7) Baciocchi, E. In *The Chemistry of Functional Groups, Supplement D*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1983; Part 2, p 161.
(8) Mohan, T.; Arumugam, S.; Wang, T.; Jacobson, R. A.; Verkade, J. G. *Heteroat. Chem.* **1996**, *7*, 455.
(9) Arumugam, S.; Verkade J. G. *J. Org. Chem.* **1997**, *62*, 4827.
(10) Schmidt, H.; Lensink, C.; Xi, S.-K.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1989**, *578*, 75.
(11) Tang, J. S.; Verkade, J. G. *Tetrahedron Lett.* **1993**, *36*, 2903.

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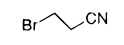
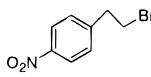
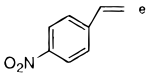
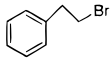
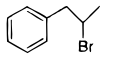
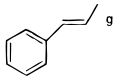
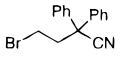
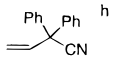
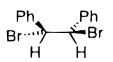
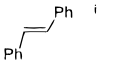
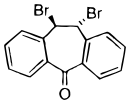
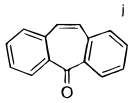
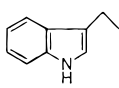
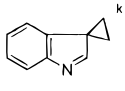
Table 1. Dehydrobromination and Debromination of Alkyl Halides with 2(Cl)/NaH, 3(OTf)/NaH, 4(OTf)/NaH, and NaH Alone

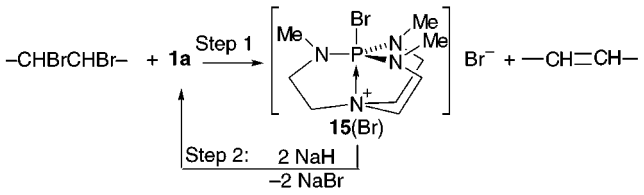
substrate	product[a]	reaction time (h)	eluent	% conversion[b] (yield[c])			
				2(Cl)/NaH	**3**(OTf)/NaH	**4**(OTf)/NaH	NaH only
 **5**	 [d]	0.6	na	99	99	99	82
 **6**	 [e]	1	hexanes	99	99 (94)	95 (92)	43
 **7**	 [f]	2	hexanes	99 (92)	99	97 (91)	72
 **8**	 [g]	2	hexanes	98 (91)	99	95 (90)	25
 **9**	 [h]	2		60	59	37	3
		6	CH_2Cl_2	99 (95)	78	97 (92)	19
 **10**	 [i]	2	CH_2Cl_2	99 (94)	98	98 (92)	39
 **11**	 [j]	2	CH_2Cl_2	99 (92)	99	97 (90)	25
 **12**	 [k]	1	- [l]	99 (85[m])	99	99 (90[n])	81
$CH_3(CH_2)_4CH(Br)CH_3$ **13**	$CH_3(CH_2)_4CH{=}CH_2$[o] *trans*-$CH_3(CH_2)_3CH{=}CHCH_3$[p]	36	na	22 65	24 70	8 25	<1
 **14**	 [q]	100	na	0	0	0	0

[a] Identification was made by comparing ^1H and ^{13}C NMR spectral data with those in the references indicated. [b] Conversions were determined by ^1H NMR integration of signals for olefin products to the corresponding alkyl halides. GC−mass spectral analysis was used to confirm the olefin products and to check for detectable side products. [c] Isolated yields were obtained by chromatography, and purity was determined by ^1H NMR spectroscopy. [d] Aldrich Library of ^{13}C and ^1H FT NMR spectra, **1993**, *1*(1), 1358B. [e] Butcher, M.; Mathews, R. J.; Middleton, S. *Aust. J. Chem.* **1973**, *26*, 2067. The reaction solution turned blue within 1 min, which suggested the possibility of a side reaction between NaH and the NO_2 group in substrate. However, the GC−mass spectrum showed the olefin product lists as the only detectable product, and thus the formation of side products was assumed to be negligible. [f] Aldrich Library of ^{13}C and ^1H FT NMR spectra, **1993**, *1*(2), 23A. [g] Aldrich, Library of ^{13}C and ^1H FT NMR spectra, **1993**, *1*(2), 24A. [h] See ref 5. [i] (a) Kropp, P. J.; Crawford, S. D. *J. Org. Chem.* **1994**, *59*, 3102. (b) Aldrich Library of ^{13}C and ^1H FT NMR spectra, **1993**, *1*(2), 36A. [j] (a) Rupard, J. H.; Paulis, T. D.; Janowsky, A.; Smith, H. E. *J. Med. Chem.* **1989**, *32*, 2261. (b) Jones, A. J.; Gardner, P. D.; Grant, D. M.; Litchman, W. M.; Boekelheide, V. *J. Am. Chem. Soc.* **1970**, *92*, 2395. [k] Johansen, J. E.; Christie, D.; Rapoport, H. *J. Org. Chem.* **1981**, *56*, 4914. The reaction was carried out in dry THF instead of CH_3CN. [l] The product decomposed during attempted chromatographic separation. [m] From bulb-to-bulb distillation at 120 °C/0.1 Torr. [n] From direct filtration of the reaction mixture followed by drying under vacuum. [o] Aldrich Library of ^{13}C and ^1H FT NMR spectra, **1993**, *1*(1), 18B. [p] Aldrich Library of ^{13}C and ^1H FT NMR spectra, **1993**, *1*(1), 25B. [q] Aldrich Library of ^{13}C and ^1H FT NMR spectra, **1993**, *1*(1), 73C.

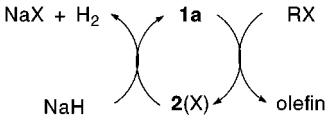
of a 3.0/1.0 equiv ratio of NaH to **2**(Cl). Only one resonance at 119 ppm corresponding to **1a** was observed after 20 min at room temperature. The combination of a catalytic amount of procatalyst **2**(Cl), **3**(OTf) or **4**(OTf) (0.1 equiv), and excess NaH (2.5 equiv) was therefore employed as a dehydrohalogenation and debromination medium for the compounds in Table 1. In the dehydrohalogenation of **7** with the above combination in CD_3CN using **2**(Cl) at room temperature, 83% and 99% conversions were obtained after 1 and 2 h, respectively, without detectable side reactions according to ^1H NMR and GC−mass spectroscopic analysis. By comparison, 2.5 equiv of NaH only, used without **2**(Cl) in the same reaction, gave rise to considerably slower reactions (i.e., 11% and 72% conversions after 1 and 2 h, respectively). This observation prompted us to test our three procatalyst systems on the additional substrates **5**−**14** in Table 1 in the presence of NaH both with and without procatalysts.

It was found that except for **14**, which afforded no detectable product in any case, the conversions (95−99%) of the products formed from substrates **5**−**12** (33−94% conversions for **13**) treated with 0.1 equiv of each procatalyst and 2.5 equiv of NaH exceeded those obtained with 2.5 equiv of NaH by itself (<1−82%) by remarkable margins. It is noted that an electron-withdrawing group β to the halogen (**5**−**8**) leads to high conversions with procatalyst/NaH in only 2 h, owing to rapid E2 elimination caused by activation of the hydrogen on the β carbon. Evidence for abstraction of such a hydrogen by **1a** was presented earlier.[9] Substrates **9** and **13** required more time to give high conversions of corresponding alkenes. Interestingly, **13** gave two isomers (1-heptene and *trans*-

Scheme 1



Scheme 2

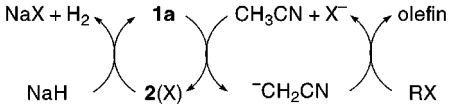


2-heptene in 87% and 94% total conversions using **2**(Cl) and **3**(OTf), respectively), whereas only one isomer (*trans*-2-heptene) was observed using 1.1 equiv of **1a**.[9] It is of interest that the dibromides **10** and **11** each gave the corresponding debrominated product with all three procatalysts. This contrasts the result for these substrates described in our earlier publication, in which only monobromoalkene was reported to form in the presence of a stoichiometric quantity of **1a**.[9] Repetition of these experiments with **10** and **11** in the presence of a stoichiometric amount of **1a** now reveals that their corresponding debrominated products (see Experimental Section) were undoubtedly also formed in our earlier experiments.[9]

We believe the pathway shown in Scheme 1 for **2**(Cl) reasonably accounts for the formation of these debrominated products. Thus, step 1 occurs in the stoichiometric experiment, and this is followed by step 2 under catalytic conditions. As with the use of PPh_3 in such reactions,[12] initial nucleophilic attack of the phosphorus of **1a** on a bromine is followed by the formation of cation **15**[13] with elimination of the second bromine from the substrate as Br^-. When **2**(Cl)/NaH is used, **15**(Br) can be further reduced and deprotonated by NaH to regenerate **1a**. In two separate ^1H NMR experiments, 10 mol % of **2**(Cl)/2.5 equiv of NaH and 2.0 equiv of PPh_3 were used to debrominate **10** in CD_3CN at 35 °C. It was found that debromination by **2**(Cl)/NaH is much more efficient than by PPh_3, giving 99% conversion vs <30% conversion in 2 h. The literature describes the use of PPh_3 for debromination promoted under considerably harsher conditions (xylene/150−160 °C/250 min), and the yield is only moderate (76%).[12]

A possible dehydrohalogenation pathway for substrates requiring extended reaction times (beyond ca. 10 h) in the presence of **1** in CH_3CN is described in an earlier paper, in which evidence was put forth that the CH_2CN^- abstracts a proton from the substrates.[9] Thus, the main phosphorus-containing compound observed in the dehydrohalogenation of **13** in D_3CCN is the deuterio analogue of **2**, which displayed a triplet signal at −10.0 ppm in the ^{31}P NMR spectrum.[9] Catalytic cycles that account for the aforementioned direct and indirect dehydrohalogenations are shown in Schemes 2 and 3, respectively, for cation **2**. The first step in Scheme 2 involves NaH deprotonation of cation **2** to give **1a**, the effective dehydrohalogenation agent for substrates with activating groups. The signal at 119 ppm in the ^{31}P NMR spectrum

Scheme 3



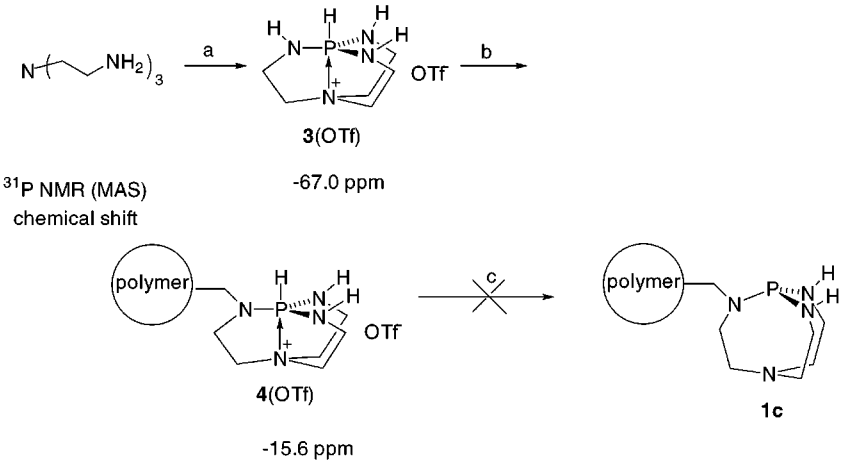
observed at the end of these reactions is characteristic of **1a**. In the second step, **1a** reacts with activated alkyl halides to give corresponding olefin products. That the first step in Scheme 2 is rate-determining is supported by the detection of only a single ^{31}P NMR signal at −10.0 ppm before completion of the reaction. This peak corresponds to cation **2** as noted above. The peak at 119 ppm corresponding to **1a** was not observed until the reaction was complete, which is in accord with the supposition that the concentration of **1a** during the reaction is low and that the reaction rate of alkyl halides with **1a** is fast compared with the regeneration of **1a** from **2** by NaH. A similar conclusion can be drawn from the cycles in Scheme 3 in which the process on the left is again the slow step. In this scheme, however, deprotonation of CH_3CN by **1a** is faster than deprotonation of RX by **1a**. All of the reactions were accompanied by the formation of H_2 gas bubbles. It should be mentioned that procatalyst **2**(Cl) can be rather simply recovered chromatographically (see Experimental Section).

In our earlier work,[14] attempts to isolate the neutral form **1b** from **3**(OTf) resulted in oligomeric product, suggesting that intermolecular oligomerization occurs subequent to the deprotonation step. However, as shown in Table 1, **3**(OTf) is as effective as **2**(Cl) for both dehydrohalogenation and debromination, which suggests the formation of **1b** as an intermediate that reacts more quickly with the substrate than it does intermolecularly to form the oligomer. Additional evidence supporting the formation of **1b** stems from an NMR experiment in which a ^{31}P NMR signal was observed at 91 ppm upon adding 2.0 equiv of KO-*t*-Bu to **3**(OTf) in THF at room temperature. The catalytic reaction pathways for **3**(OTf) are analogous to those shown in Schemes 2 and 3. Although this procatalyst cannot be recovered after use in such reactions owing to oligomerization of **1b**, **3**(OTf) is much less expensive to synthesize than **2**(Cl) and is very comparable in efficiency.

Whereas the syntheses of **2**(Cl)[10] and **3**(OTf)[14] have been reported, that of **4**(OTf) (Scheme 4) has not. Although the protonated form of **4**(OTf) was successfully synthesized, attempts to isolate its neutral form **1c** by deprotonation with KO-*t*-Bu or NaH, at room temperature or 60 °C, for 1−6 days have thus far failed for reasons that are not clear. Survival of cation **4** is signaled by its CPMAS ^{31}P NMR chemical shift at −15.9 ppm (see Experimental Section). However, the results in Table 1 show that 0.1 equiv of **4**(OTf) in the presence of excess NaH (2.5 equiv) in CH_3CN effectively allowed both dehydrohalogenation and debromination, although more slowly than **2**(Cl) and **3**(OTf) (Table 1). Thus, we believe that in the presence of NaH, **1c** is generated in situ and that it functions as the catalyst. The advantage of this approach in which both the NaH and the procatalyst and catalyst are insoluble is the easy isolation of spectroscopically pure products (ca. 95%) by filtration of the reaction mix-

(12) Devlin, C. J.; Walker, B. J. *J. Chem. Soc., Perkin* **1972**, 1249.
(13) Mohan, T.; Wan, Y.; Verkade, J. G. *J. Fluorine Chem.* **1995**, *71*, 185.
(14) Laramay, M. A. H.; Verkade, J. G. *Z. Anorg. Allg. Chem.* **1991**, *605*, 163.

Scheme 4



a. $P(NMe_2)_3$, HOTf, CH_2Cl_2, RT,Ar, 30 min, 99%.
b. Merrifield's peptide resin, DMF, 110°C, 6 days.
c. KO-*t*-Bu or NaH, THF, RT or 60°C, 1 - 6 days.

ture followed by evaporation. Moreover, the procatalyst is easily recovered by washing and drying the filter cake.

Experimental Section

CH_3CN and CD_3CN were distilled from CaH_2. All other solvents were used as purchased. All chemicals were obtained from Aldrich Chemicals and were used without purification unless otherwise noted. All reactions were carried out at room temperature under Ar. Both **2**(Cl)[10] and **3**(OTf)[14] were prepared according to our previously published methods.

Preparation of Polymer-Based Azaphosphatrane 4(OTf). Under Ar, a mixture of **3**(OTf) (4.15 g, 12.8 mmol), Merrifield's peptide resin (5.00 g, 1% cross-linked 200−400 mesh, ca. 2.5 mmol Cl/g), and 60 mL of DMF was vigorously stirred at 110 °C for 6 days. Then the reaction mixture was cooled to room temperature, and 40 mL of MeOH was added. After the mixture was shaken for 5 min, it was filtered to give a solid, which was successively washed with THF, Et_3N, MeOH, THF, Et_2O, THF, and Et_2O (10 mL each). After drying in vacuo, 4.56 g of a pale yellow-brown solid **4**(OTf) was obtained. Solid-state ^{31}P NMR (MAS): δ −15.6 ppm. Elemental analysis: P 3.27, N 5.15. P:N ratio: calcd 1.8, found, 1.6. Loading: 1.0 mmol of **3**(OTf)/g of **4**(OTf).

Attempted Deprotonation of 4(OTf). Under Ar, **4**(OTf) (1.0 g, ∼1.0 mmol) was added to a suspension of KO-*t*-Bu (1.12 g, 10 mmol) or 95% pure NaH (0.24 g, 10 mmol) in THF or DMF (20 mL). Then, the reaction mixture was vigorously stirred at room temperature or 60 °C for 1−6 days. The solid remaining after filtration of the reaction mixture was successively washed with THF, DMF, and THF (20 mL each). After drying in vacuo, 2.0−2.5 g of a pale brown solid was recovered. Solid-state ^{31}P NMR (MAS): δ −15.9 ppm.

General Procedure for Dehydrohalogenation or Debromination. The combination of **2**(Cl) and **3**(OTf) (0.10 mmol) or **4**(OTf) (0.10 g, ∼0.10 mmol) and NaH (0.1 g, 2.5 mmol, 60% in mineral oil) or NaH (0.10 g, 2.5 mmol, 60% in mineral oil) by itself was added to 3 mL of CD_3CN at room temperature under Ar. After stirring for 10 min, the alkyl halide (1.0 mmol) was added to the above suspension, and the resulting mixture was stirred at room temperature. The reaction was monitored by ^1H NMR spectroscopy. After the reaction time stated in Table 1, a ^1H NMR spectrum was recorded from which conversions were obtained by integration of peak areas. GC−mass spectra were recorded for some substrates to confirm the identity of the products. The reaction was then quenched by 0.1 mL of MeOH, and the resulting mixture was filtered and washed with CH_3CN (2 × 10 mL). The cake was saved for the recovery of catalyst when **4**(OTf) was employed as the procatalyst. The filtrate was dried over $MgSO_4$, followed by evaporation of about 95% of the solvent under vacuum. The resulting crude product was purified by chromatography on a silica gel column using the eluents stated in Table 1. The product was obtained upon evaporation of the solvent and was identified by ^1H and ^{13}C NMR spectroscopies.

NMR Reaction of 10 with PPh_3. In a 5 mm NMR tube was placed **10** (17 mg, 0.05 mmol) followed by a mixture of PPh_3 (27 mg, 0.10 mmol) in CD_3CN (0.75 mL). The NMR tube was placed in an ultrasonic bath for 2 h, and then the ^1H NMR spectrum was recorded. The reaction temperature was 35 °C. See Results and Discussion.

NMR Reaction of 10 with 2(Cl)/NaH. In a 5 mm NMR tube was placed **10** (17 mg, 0.05 mmol) and NaH (5.00 mg, 0.125 mmol, 60% in mineral oil) followed by a solution of **2**(Cl) (1.5 mg, 0.01 mmol) in CD_3CN (0.75 mL). The NMR tube was placed in an ultrasonic bath for 2 h, and then the ^1H NMR spectrum was recorded. The reaction temperature was 35 °C. See Results and Discussion.

NMR Reactions of 10 and 11 with 1a. In a 5 mm NMR tube was placed **10** or **11** (0.05 mmol) followed by a solution of **1a** (17 mg, 0.075 mmol) in CD_3CN (0.75 mL). Then, this NMR tube was placed in an ultrasonic bath for 2 h, and the ^1H NMR spectrum was recorded. The reaction temperature was 35 °C. ^1H NMR spectra of the reaction mixture showed that the reaction was complete in 1 h and that the products were the corresponding debrominated alkenes. These results were confirmed by GC−mass spectroscopy.

Recovery of 2(Cl). After chromatographic separation of the olefin products, the silica gel columns were washed with 100 mL of a solution of CH_2Cl_2 (95%) and CH_3OH (5%) followed by washing with 100 mL of CH_3OH. After collection of the pure CH_3OH fraction and evaporation of the solvent under vacuum, **2**(Cl) was recovered as a white solid in 60−80% yield. The ^{31}P, ^1H, and ^{13}C NMR spectra are consistent with those of a standard sample of **2**(Cl).

Recovery of 4(OTf). The filter cake from five experiments (0.50 g of **4**(OTf)) was placed in a 100 mL round-bottomed flask followed by addition of 30 mL of distilled H_2O. The resulting suspension was stirred at room temperature for 2 h and filtered. The cake was washed with H_2O, MeOH, THF, and Et_2O (20 mL each), and then it was dried in vacuo for 24 h to give **4**(OTf) as a pale yellow-brown solid (0.45 g, 90% mass recovery). Solid-state ^{31}P NMR (MAS): δ −15.7 ppm.

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