Tetraalkylphosphonium Trihalides. Room Temperature Ionic Liquids As Halogenation Reagents[§]

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Six room temperature ionic liquids (RTILs) comprised of a tetraalkylphosphonium cation (tridecyl-methyphosphonium or trihexyltetradecylphosphonium) and a trihalide anion (Br_3^-, $BrCl_2^-$, or $ClBr_2^-$) have been prepared and characterized. Their ability to effect halogenation reactions with a variety of substrates has been explored. In general, halogenation reactions of alkenes proceed with high yields and stereo- and regioselectivities, whether performed in the absence or presence of a solvent (chloroform). Reactions of an alkyne and electrophilic substitution on an aromatic ring have been investigated as well. The facile preparation of the salts, their ease of handling, and the simplicity of product isolation should make these RTILs useful additions to the repertoire of halogenation reagents and the reagents of choice for specific transformations.

Introduction

Organic molecules containing halogen atoms are found in many products, such as pharmaceuticals, agrochemicals, and materials for advanced technologies. In organic synthesis, they are important intermediates in reactions involving carbon−carbon bond formation, organometallic preparations (e.g., Grignard and organo-lithium reagents) and metal cross-coupling reactions.[1,2] A common method to insert halogen atoms into organic substrates, whether they be free-radical processes or polar additions to olefinic groups or electrophilic substitutions on aromatic ones, involves the use of dihalogen molecules which have high vapor pressures or are gases at room temperature and 1 atm of pressure.

Because the dihalogens are corrosive, poisonous, and can be dangerous to handle, methods that require their transport and manipulation are difficult. A comparison of many halogenation techniques and a determination of their environmental impacts with an approach related to the Sheldon factor[3] have appeared recently.[4] Although reactions employing dihalogen molecules are among the most studied in organic chemistry,[4,5] questions still remain about how they occur in specific cases, especially those involving addition of a mixed halogen molecule,[6] reaction media with varied structures,[7]

(1) De Meijere, A.; Diederich, F., Eds. *Metal-catalyzed Cross-coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004.
(2) (a) Yao, Q.; Kinney, E. P.; Yang, Z. *J. Org. Chem.* 2003, *68*, 7528–7531. (b) Seyferth, D. *Organometallics* 2009, *28*, 1598–1605.

(3) (a) Andraos, J. *Org. Process Res. Dev.* 2005, *9*, 149–163. (b) *Ibid.* 404−431. (c) Sheldon, R. A. *CHEMTECH* 1994, *3*, 38–47.
(4) Eissen, M.; Lenoir, D. *Chem.—Eur. J.* 2008, *14*, 9830−9841 and references cited therein.
(5) (a) Brown, R. S. *Acc. Chem. Res.* 1997, *30*, 131–137. (b) Ruasse, M. F. *Adv. Phys. Org. Chem.* 1993, *28*, 207–291. (c) Lenoir, D.; Chiappe, C. *Chem.—Eur. J.* 2003, *9*, 1037–1044.
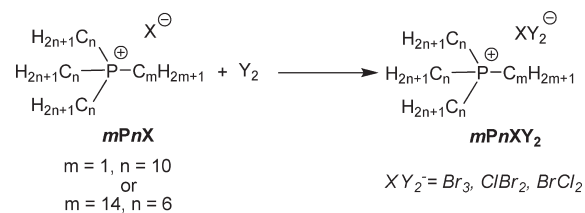(6) In chloroform solution: (a) Chiappe, C.; Del Moro, F.; Raugi, M. *Eur. J. Org. Chem.* 2001, 3501–3510. In aqueous solution: (b) Wang, T. X.; Kelley, M. D.; Cooper, J. N.; Beckwith, R. C.; Margerum, D. W. *Inorg. Chem.* 1994, *33*, 5872–5878.
(7) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A*, 5th ed.; Springer: New York, 2007; pp 485−497.

and reagents with the halogen atoms as part of a larger species.[4,8–11]

In that regard, the high polarity of ionic liquids makes them interesting media in which to conduct and investigate the selectivity and reactivity of ionic halogenation reactions, such as the aforementioned addition and substitution reactions.[12] Also, ionic liquids avoid many of the problems associated with the volatility of common organic media, and many ionic liquids can be separated easily from products and/or catalysts and reused.[13] Another approach to mediating the selectivity and reactivity of halogenations involves using trihalide anions, XY_2^- (X, Y = Cl, Br, I), as the halogen reagent,[11] and studies that combine trihalide ions and ionic liquids as the medium have been conducted.[11e] Finally, the trihalide anion has been made a part of ionic liquids so that the solvent alone is an efficient halogenating material.[14] For example, halogenations in salts of tetraalkylammonium[15] and imidazolium[16] trihalides have been used

(8) For bromination reactions involving Br_2: (a) Rajasingh, P.; Cohen, R.; Shirman, E.; Shimon, L. J. W.; Rybtchinski, B. *J. Org. Chem.* **2007**, *72*, 5973–5979. (b) Suresh, P.; Annalakshmi, S.; Pitchumani, K. *Tetrahedron* **2007**, *63*, 4959–4967. (c) Okada, Y.; Yokozawa, M.; Akiba, M.; Oishi, K.; O-kawa, K.; Akeboshi, T.; Kawamura, Y.; Inokuma, S.; Nakamura, Y.; Nishimura, J. *Org. Biomol. Chem.* **2003**, *1*, 2506–2511. (d) Das, J. P.; Say, S. *J. Org. Chem.* **2002**, *67*, 7861–7864. (e) Adimurthy, S.; Ramachandraiah, G.; Bedekar, A. V.; Ghosh, S.; Ranu, B. C.; Ghosh, P. K. *Green Chem.* **2006**, *8*, 916–922. (f) Nair, V.; Panicker, S. B.; Augustine, T.; George, T. G.; Thomas, S.; Vairamani, M. *Tetrahedron* **2001**, *57*, 7417–7422.

(9) For asymmetric halogenations involving dihalogens: (a) Li, K. Y.; Alexakis, A. *Tetrahedron Lett.* **2005**, *46*, 5823–5826. (b) Goswarni, P.; Baruah, A.; Das, B. *Adv. Synth. Catal.* **2009**, *351*, 1483–1487. (c) Ueda, M.; Kano, T.; Maruoka, K. *Org. Biomol. Chem.* **2009**, *7*, 2005–2012. For chlorination reactions: (d) Murphy, C. D. *Nat. Prod. Rep.* **2006**, *23*, 147–152. (e) Masilamani, D.; Rogic, M. M. *J. Org. Chem.* **1981**, *46*, 4486–4489. (f) Moreno-Dorado, F. J.; Guerra, F. M.; Manzano, F. L.; Aladro, F. J.; Jorge, Z. D.; Massanet, G. M. *Tetrahedron Lett.* **2003**, *44*, 6691–6693. (g) Hajra, S.; Bhowmick, M.; Maji, B.; Sinha, D. *J. Org. Chem.* **2007**, *72*, 4872–4876. (h) Frings, M.; Bolm, C. *Eur. J. Org. Chem.* **2009**, 4085–4090. (i) Chen, J. S.; Takenaka, N. *Chem.—Eur. J.* **2009**, *15*, 7268–7276.

(10) For iodination and fluorination reactions involving dihalogens: (a) Brazdil, L. C.; Cutler, C. J. *J. Org. Chem.* **1996**, *61*, 9621–9622. (b) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826–8828.

(11) For halogenation reactions involving trihalide anions: (a) Zolfigol, M. A.; Chehardoli, G.; Salehzadeh, S.; Adams, H.; Ward, M. D. *Tetrahedron Lett.* **2007**, *48*, 7969–7973. (b) Bose, G.; Mondal, E.; Khan, A. T.; Bordoloi, M. J. *Tetrahedron Lett.* **2001**, *42*, 8907–8909. (c) Kavala, V.; Naik, S.; Patel, B. K. *J. Org. Chem.* **2005**, *70*, 4267–4271. (d) Hajipour, A. R.; Arbabian, M.; Ruoho, A. E. *J. Org. Chem.* **2002**, *67*, 8622–8624. (e) Chiappe, C.; Pieraccini, D. *J. Org. Chem.* **2004**, *69*, 6059–6064. (f) Bianchini, R.; Chiappe, C. *J. Org. Chem.* **1992**, *57*, 6474–6478. (g) Giordano, C.; Coppi, L. *J. Org. Chem.* **1992**, *57*, 2765–2766. (h) Bianchini, R.; Chiappe, C.; Lo Moro, G.; Lenoir, D.; Lemmen, P.; Goldberg, N. *Chem.—Eur. J.* **1999**, *5*, 1570–1580. (i) Smith, K.; James, D. M.; Matthews, I.; Bye, M. R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1877–1878.

(12) (a) Chiappe, C.; Pieraccini, D.; Pomelli, C. S. *Ionic Liquids in Organic Synthesis*; Malhotra, S. V., Ed.; ACS Symp. Ser. No. 950; American Chemical Society: Washington, DC, 2007; Chapter 1. (b) Pavlinac, J.; Zupan, M.; Laali, K. K.; Stavber, S. *Tetrahedron* **2009**, *65*, 5625–5662.

(13) (a) Abedin, S. Z. E.; Endres, F. *Acc. Chem. Res.* **2007**, *40*, 1106–1113. (b) Rogers, R. D.; Voth, G. A. *Acc. Chem. Res.* **2007**, *40*, 1077–1078. (c) *Ionic Liquids III: Fundamentals, Progress, Challenges, and Opportunities*; Rogers, R. D., Seddon, K. R., Eds.; ACS Symp. Ser. Nos. 901−902; American Chemical Society: Washington, DC, 2005. (d) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667–3692.
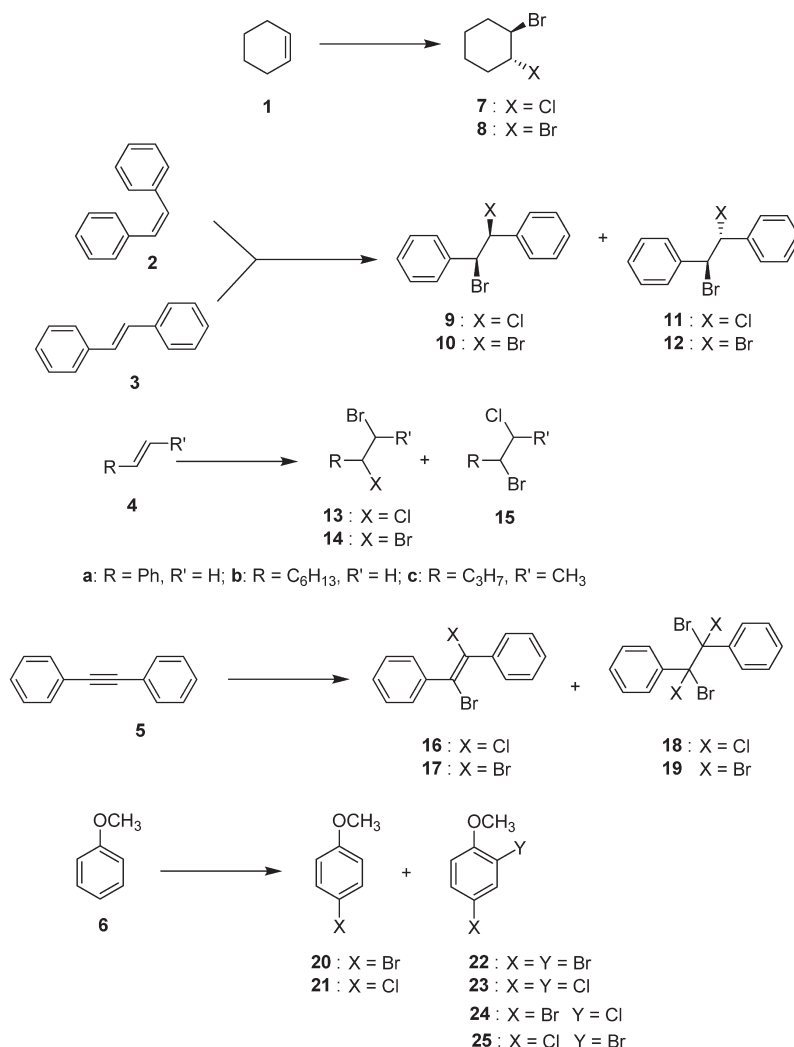
(14) Halogenation reactions involving trihalide ionic liquids: (a) Ma, K.; Li, S.; Weiss, R. G. *Org. Lett.* **2008**, *10*, 4155–4158. (b) Chiappe, C.; Leandri, E.; Pieraccini, D. *Chem. Commun.* **2004**, 2536–2537. (c) Borikar, S. P.; Daniel, T.; Paul, V. *Tetrahedron Lett.* **2009**, *50*, 1007–1009. (d) Salazar, J.; Dorta, R. *Synlett* **2004**, *7*, 1318–1320. (e) Bortolini, O.; Bottai, M.; Chiappe, C.; Conte, V.; Pieraccini, D. *Green Chem.* **2002**, *4*, 621–627. (f) Kessat, A.; Babadjamian, A. *Eur. Polym. J.* **1996**, *32*, 193–199. (g) Cristiano, R.; Walls, A. D.; Weiss, R. G. To be submitted for publication.

(15) Bora, U.; Chaudhuri, M. K.; Dey, D.; Dhar, S. S. *Pure Appl. Chem.* **2001**, *73*, 93–102.

(16) (a) Chiappe, C.; Conte, V.; Pieraccini, D. *Eur. J. Chem.* **2002**, *16*, 2831–2837. (b) Chiappe, C.; Pieraccini, D. *J. Org. Chem.* **2004**, *69*, 6059–6064.

SCHEME 1. Preparation of Tetraalkylphosphonium Trihalide Salts, *mP*n*XY*$_2$

to examine the role of the cation and anion structures on the kinetics of the reactions, the stability of the reaction intermediates, and, thus, the reactivity and selectivity of the substrates.

As part of our continuing studies of phase properties and uses of phosphonium salts,[17] we developed recently an ionic liquid, tridecylmethylphosphonium tribromide (**1P10Br$_3$**), that functions as a brominating reagent in a stacked, "phase-vanishing"[18] reactor that exploits the diffusion of molecular bromine and the densities and immiscibilities of bromine, a fluorous liquid, the ionic liquid, and alkane/substrate layers.[14a] Our use of phosphonium rather than ammonium or imidazolium salts is motivated by the fact that P^+ has a larger size, a greater polarizability, and a lower binding energy with anions than N^{+} [17] and the phosphonium salts are structurally simpler molecules than the imidazolium salts. These attributes make phosphonium salts attractive and interesting alternative halogenation reagents.

Here, we describe the preparation of six room temperature ionic liquids, *mP*n*XY*$_2$ (Scheme 1), made from combinations of two tetraalkylphosphonium cations (tridecylmethyphosphonium and trihexyltetradecylphosphonium) and three trihalide anions (Br_3^-, $BrCl_2^-$, and $ClBr_2^-$) and their use as both solvents and halogenation reagents for bromination and bromo-chlorination reactions with unsaturated substrates. Both the regio- and stereoselectivities of these reactions with a wide variety of substrates and the influence on these parameters of different aliphatic chains of the *mP*n*XY*$_2$ are discussed. It is shown that the reactions proceed in high yields and selectivities under mild conditions and that the nature of the mixed halogenations can be controlled somewhat.

Results and Discussion

Synthesis and Characterization of Phosphonium Trihalides. The *mP*n*XY*$_2$ were prepared as shown in Scheme 1. Trihalide

(17) (a) Abdallah, D. J.; Bachman, R. E.; Perlstein, J.; Weiss, R. G. *J. Phys. Chem. B* **1999**, *103*, 9269–9278. (b) Abdallah, D. J.; Robertson, A.; Hsu, H.-F; Weiss, R. G. *J. Am. Chem. Soc.* **2000**, *122*, 3053–3062. (c) Abdallah, D. J.; Weiss, R. G. *Chem. Mater.* **2000**, *12*, 406–413. (d) Abdallah, D. J.; Lu, L.; Cocker, M. T.; Bachman, R. E.; Weiss, R. G. *Liq. Cryst.* **2000**, *27*, 831–837. (e) Hui, C.; Kwait, D. C.; Gönen, Z. S.; Weslowski, B. T.; Abdallah, D. J.; Weiss, R. G *Chem. Mater.* **2002**, *14*, 4063–4072. (f) Abdallah, D. J.; Wauters, H. C.; Kwait, D. C.; Khetrapal, C. L.; Nagana Gowda, G. A.; Robertson, A.; Weiss, R. G. *Ionic Liquids IIIB: Fundamental, Progress, Challenges and Opportunities*; Rogers, R. D., Seddon, K. R., Eds.; ACS Symp. Ser. No. 902; American Chemical Society: Washington, DC, 2005; Chapter 21. (g) Ma, K.; Somashekhar, B. S.; Nagana Gowda, G. A.; Khetrapal, C. L.; Weiss, R. G. *Langmuir* **2008**, *24*, 2746–2758. (h) Ma, K.; Lee, K.-M.; Minkova, L.; Weiss, R. G. *J. Org. Chem.* **2009**, *74*, 2088–2098. (i) Shahkhatuni, A. A.; Ma, K.; Weiss, R. G. *J. Phys. Chem. B* **2009**, *113*, 4209–4217. (j) Ma, K.; Shahkhatuni, A. A.; Somashekhar, B. S.; Nagana Gowda, G. A.; Tong, Y.; Khetrapal, C. L.; Weiss, R. G. *Langmuir* **2008**, *24*, 9843–9854.

(18) (a) Ryu, I.; Matsubara, H.; Yasuda, S.; Nakamura, H.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 12946–12947. (b) Rahman, M. T.; Kamata, N.; Matsubara, H.; Ryu, I. *Synlett* **2005**, 2664–2666. (c) Jana, N. K.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 3787–3790.

SCHEME 2. Halogenation Reactions of Substrates with $mPnXY_2$ Reagents

anions were generated in the salts by reaction of a $mPnX$ with 1 mol equiv of a dihalogen molecule, Y_2, in a closed flask protected from light. Although this reaction is slightly exothermal, it can be carried out in the absence or presence of an aprotic solvent such as dichloromethane, even when the $mPnX$ is a solid. Without solvent, the reactants should be stirred well to ensure that the reaction is complete; crystals of the phosphonium halide slowly "melt" as they are converted to a liquid trihalide salt.

All of the $mPnXY_2$ with $m = 1$ and $n = 10$ ($1P10XY_2$) and $m = 14$ and $n = 6$ ($14P6XY_2$) are room temperature ionic liquids (**RTILs**). Preliminary investigations with some other trihalide salts—$4P4Br_3$, $4P4BrI_2$, $1P14I_3$, and $1P14BrI_2$—were abandoned when it was found that they were solids at room temperature or when it was found that the trichloride preparations (from $mPnCl$ and Cl_2) did not lead to salts that could be characterized well; they may be useful in other halogenation processes, however. The liquid range of the RTIL trihalides is very broad although some may become glasses at very low temperatures: differential scanning calorimetry (DSC) analyses did not show any cooling exotherms to temperatures as low as −60 °C and thermogravimetric analyses (TGA) indicated <1% weight loss up to 100 °C. Thermal decomposition of $14P6Br_3$ and the previously

reported $1P10Br_3$[14a] involve loss of Br_2 and reformation of the original monobromide salts, $mPnBr$: the weight loss curve for $1P10Br_3$ (see the Supporting Information) shows a small loss starting at ca. 100 °C and then abruptly increasing at 175 °C to ca. 24%; the weight percent of Br_2 in the salt is 22.35%. The changes that occur upon heating are more complex in the cases of the mixed halides (N.B., TGA curves for $1P10ClBr_2$ and $1P10BrCl_2$ in the Supporting Information); more than one step in the weight loss is clearly evident. Although dihalogen molecules appear to be released, their nature is not clear and may be a combination of BrCl, Br_2, and/or Cl_2. An additional test of stability was conducted in which $1P10BrCl_2$ was placed in a N_2 stream for 30 min at 25 °C; the weight loss after this time, <0.3% (see the Supporting Information), indicated that the trihalide remained intact.

The structures of the RTILs were characterized by ^{1}H and ^{31}P NMR spectrometry and elemental analyses (see the Experimental Section and the Supporting Information). Visually, qualitative evidence for trihalide formation is found in comparison of the appearances of the $mPnX$ precursors and their $mPnXY_2$ products. For example, $1P10ClBr_2$ is a red-orange liquid and $1P10Cl$ is a white solid. The transformations of the solids into liquids was expected

as a consequence of the larger sizes and greater electron delocalizations (resulting in looser association with the cationic centers) of the trihalide anions.[19] For example, the chemical shifts of the protons of the methylene and methyl groups linked to the phosphorus atom of **1P10Cl** appear at 2.48−2.42 (m, 6H, C$\underline{H}_2$−P) and 2.14 (d, J = 13.6 Hz, 3H, P−C$\underline{H}_3$) ppm, respectively, while those for **1P10ClBr$_2$** are shifted upfield to 2.34−2.27 (m, 6H, C$\underline{H}_2$−P) and 2.00 (d, J = 12.8 Hz, 3H, P−C$\underline{H}_3$) ppm.[20] Similarly, the ^{31}P resonance shifts from 32.64 ppm in **1P10Cl** to 31.95 ppm in **1P10ClBr$_2$**. Although the elemental analyses are within acceptable limits, the observed hydrogen/carbon ratios are always larger than the calculated ones. This may be an indication that traces of water are present in the salts.[17h]

Bromination and Bromo-Chlorination Reactions. Halogenation reactions at room temperature in solvent-free conditions or in solutions were performed in the dark (to avoid radical reactions[21]) and in closed vessels on the structurally diverse substrates in Scheme 2 with the salts indicated in Table S1 (Supporting Information). The mixtures were stirred only in those cases where the substrate and salt did not form a solution.

The substrates **1**−**6** were chosen because all of the expected (and found) products and their NMR spectra are known; product ratios are based on integration ratios from NMR spectra and, in some cases, they were verified by GC analyses; see the Supporting Information. These reactions were performed neat and in CDCl$_3$ solutions in order to compare the results in media of different polarity and different trihalide ion concentrations. From the observation that the selectivities were similar in both neat and chloroform solution reactions, we conclude that they are not very sensitive to polarity, at least within the range investigated here. It is known that very little dissociation of trihalides (N.B., a contribution to reaction from dissociation of BrCl$_2^-$ cannot be discounted; vide infra) occurs in chloroform[6,11e,f] and the use of CDCl$_3$ allowed the progress and course of the reactions to be followed directly by NMR spectroscopy: because the ^1H signals for the ***m*P*n*X** and ***m*P*n*XY$_2$** salts are between 1.8 and 2.4 ppm and the diagnostic proton resonances of the unsaturated substrates and their halogenated products are in a very different (downfield) region, from 3.5 to 8.0 ppm., the percent of conversion to products could be determined easily from integration ratios of peak areas.

Unlike many other types of ionic liquids,[13] the ***m*P*n*XY$_2$** are miscible with low polarity organic solvents such as hexanes and ethyl ether. Although this enhanced solubility opens some interesting possibilities for applications and mechanistic studies, it closes another, the ability to separate the RTILs from the reaction products by extracting with a low polarity solvent. Also, the water/methanol/hexane mixture used previously to separate products from the RTIL **14P6Br**[22] did not function here. However, products could be separated easily from the ionic liquids by chromatography through silica gel, using hexane or 6:1 hexane:ethyl acetate as the eluent.

The data, reported in Table S1 (Supporting Information) show that reactions involving addition to a double bond were highly stereoselective and *anti*: With **14P6Br$_3$**, ratios of *anti: syn* addition products were as high as 99:1 and only *trans*-1,2-dibromocyclohexane (**8**) was found as the product from cyclohexene (**1**). Halogenations of *cis*-stilbene (**2**) were more rapid than those of its *trans*-isomer (**3**), and both gave *anti* addition products, the *d,l* (**10**) and *meso* (**12**) stereoisomers for dibromo products and *threo* (**9**) and *erythro* (**11**) stereoisomers for bromo-chloro products, respectively. These results are indicative of a similar reaction pathway for most of the alkene substrates studied, probably involving a bridged intermediate.[23] By contrast, bromination of **2** by the RTIL, **1P10Br$_3$**, using two and four layer reactors,[14a] yielded the *syn*-addition product preferentially (but the expected *anti*-addition product of **3**). When reaction of **2** was conducted with **14P6Br$_3$** in a two-layer fashion, the *syn*-addition product was formed preferentially again, although only a 26% product yield was isolated.

Reactions involving ClBr$_2^-$ and BrCl$_2^-$ again led to *anti*-addition products, but with mixtures of bromo-chloro and dibromo products whose ratio depended upon the RTIL and the substrate. Only very low yields of dichloro products were formed and only with **14P6BrCl$_2$** as the reagent and *cis*-stilbene (**2**) or *trans*-stilbene (**3**) as the substrate (entries 31 and 37, Table S1, Supporting Information). Reactions with BrCl$_2^-$ yielded predominantly bromo-chloro products and very small amounts of dibromo products. The greater than statistical incorporation of bromine may be a consequence of its higher polarizability and nucleophilicity as well as its enhanced electrophilicity when linked to the more electronegative chlorine atoms.

By contrast, reaction of cyclohexene (**1**) with **1P10ClBr$_2$** gave a 6:4 mixture of bromo-chloro (**7**) and dibromo (**8**) products, both of which were *trans*. The addition was very fast—the orange color of the trihalide (when not in excess) occurred in a few minutes and an NMR spectrum recorded 50 min after the initiation of reactiom indicated a complete loss of substrate. In an attempt to slow the reaction in order to observe whether the ratios of bromo-chloro and dibromo products depend on the extent of substrate conversion (i.e., the ratio between **1P10ClBr$_2$** and its monohalide analogues), 1.2 mol equiv of **1P10ClBr$_2$** was reacted as one phase and substrate **1** dissolved in hexadecane as another.[14a] This method limits the reaction zone effectively to the interface between the two phases. After 10 days, ca. 95% of **1** had disappeared (Figure 1). Analyses of aliquots of the hexadecane layer removed periodically during the intervening period indicated that the **7**:**8** ratio remained ~6:4, the ratio observed in the one-phase reaction system, throughout (Figure 1 and entries 3−8, Table S1, Supporting Information). Because there must be some equilibration among the possible trihalide species in this experiment (N.B., ClBr$_2^-$, Br$_3^-$, and ClBr$_2^-$),[6] we expected a much larger variation in the **7**:**8** ratio as a function of substrate **1** conversion; the results reported in entries 8 and 9 in Table S1 (Supporting

(19) Grodkowski, J.; Neta, P. *J. Phys. Chem. A* **2002**, *106*, 11130–11134.

(20) The chemical shifts of the protons on the methyl and methylene groups attached to phosphorus in these ionic liquids are very slightly concentration dependent (Supporting Information). The concentration dependence is much less than the shift differences observed between the mono- and trihalide salts.

(21) Schönberg, A. *Preparative Organic Photochemistry*; Springer-Verlag: New York, 1968; Chapter 37.

(22) McNulty, J.; Nair, J. J.; Robertson, A. *Org. Lett.* **2007**, *9*, 4575–4578.

(23) (a) Chretien, J. R.; Coudert, J.-D.; Ruasse, M.-F. *J. Org. Chem.* **1993**, *58*, 1917–1921. (b) Bellucci, G.; Chiappe, C.; Lo Moro, G. *J. Org. Chem.* **1997**, *62*, 3176–3182.
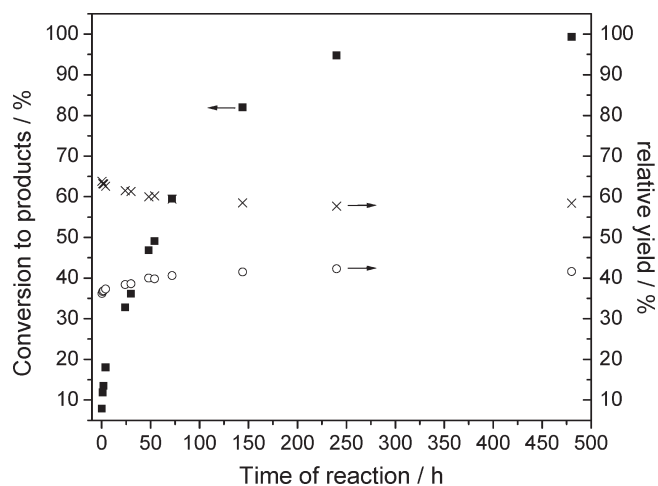
FIGURE 1. Percent conversion of **1** in hexadecane by **1P10ClBr₂** (■) and relative product yields for **7** (×) and **8** (○) as a function of reaction time. Note that the data points at shorter times have larger errors due to the smaller amounts of products present.

Information) do suggest that trihalide equilibration may play some role in the relative product yields (vide infra). In previous work, we demonstrated that no free bromine could be detected in the hexadecane layer when **1P10Br₃** was the brominating reagent,[14a] and a similar experiment here with **1P10ClBr₂** as well as with polystyrene beads containing appended methyltriphenylphosphonium tribromide groups in dichloromethane[14g] again gave no evidence for the presence of free halogen molecules in the alkane layer. On these bases, we believe that dihalogen molecules are not responsible for the actual electrophilic addition reactions, although we cannot eliminate the possibility that a very small steady-state concentration is the active species at this time.

As in this case, the relative yields of bromo-chloro products are always larger than those of the corresponding dibromo products (Table S1, Supporting Information). This result may reflect the greater strength of chloride than bromide as a nucleophile in aprotic solvents and in the gas phase.[24] To examine this point further, experiments were performed in the presence of added chloride ions in the form of **14P6Cl**. Consistent with the hypothesis above (as well as another in which the larger concentration of chloride allows it to compete more effectively to add to the product-determining intermediate, whether it be an alkene–dihalogen π-complex[6a] or a halonium or halocarbenium ion), the relative yields of the bromo-chloro products increased and those of the dibromo products decreased (see entries 12, 13, 26, 27, 28, 35, 36, 41, and 46 in Table S1, Supporting Information). Related to the latter explanation, we find that somewhat different product ratios are obtained when the molar equivalents of the trihalide salt are reduced. As an example, cyclohexene (**1**) yields a ∼6:4 bromo-chloro:dibromo product ratio in the presence of 1.2 equiv of **14P6ClBr₂** and a 1:1 ratio when only 0.6 equiv of **14P6ClBr₂** is present (entries 8 and 9 in Table S1, Supporting Information). These results are suggestive of some equilibration by different

trihalide anions,[6] but they will require additional experimentation to be understood fully.

Furthermore, addition of one chlorine and one bromine atom from $ClBr_2^-$ and $BrCl_2^-$ to terminal double bonds (N.B., styrene (**4a**) and 1-octene (**4b**)) resulted in different ratios of regioisomers (as well as different bromo-chloro: dibromo product ratios). Assuming that the initially formed intermediate is a bromonium ion or β-bromocarbocation,[25] **4a** undergoes only Markovnikov addition with $ClBr_2^-$, yielding **13a** and the dibromo product. When the trihalide employed is $BrCl_2^-$ from **1P10BrCl₂**, none of the dibromo product is detected. However, reaction of **4b** with **14P6ClBr₂** gave the dibromo product in highest yield and almost equal yields of the Markovnikov (**13b**) and anti-Markovnikov (**15b**) bromo-chloro products. As expected, addition of more chloride ions, in the form of **14P6Cl**, increased the relative yields of both **13b** and **15b** and increased slightly the ratio of anti-Markovnikov (**15b**) to Markovnikov (**13b**) addition products (entry 46 in Table S1, Supporting Information). Somewhat surprisingly, reaction of **4b** with **14P6BrCl₂** gave only bromo-chloro products, a 45:55 **13b**:**15b** mixture (entry 47 in Table S1, Supporting Information).

In general, reactions of diphenylacetylene (**5**) with the *m***P**n**XY₂** were much slower and gave lower yields than those with the alkenes. Alkynes are known to be less reactive than alkenes toward electrophilic attack, mainly because the intermediate vinyl cations are less stable than analogous saturated cations. Both the dibromo *E*-isomer **17** and the tetrabrominated **19** were formed upon reaction of **5** with **14P6Br₃** (entry 49 in Table S1, Supporting Information). Reactions of **5** (entry 50 and 51 in Table S1, Supporting Information) gave mixtures of bromo-chloro (**16**) and dibromo (**17**) products when reacted with **14P6ClBr₂** (entry 50 in Table S1, Supporting Information) and only **16** when reacted with **14P6BrCl₂** (entry 51 in Table S1, Supporting Information); neither tetrabrominated (**19**) nor mixed tetrahalo products, such as **18**, were observed.

Electrophilic substitutions on the aromatic ring of anisole (**6**) by the *m***P**n**XY₂** were also much slower and gave lower yields than those with the alkenes. They were performed in the presence of a base, $NaHCO_3$, to capture the HX released in the reaction. In the absence of base, no product was observed with **14P6Br₃**; the phosphonium salts with $ClBr_2^-$ and $BrCl_2^-$ anions were somewhat more reactive. However, only bromine-substituted products were observed, regardless of the composition of the trihalide employed. For example, **14P6BrCl₂** converted 97% of **6** to a 92:8 mixture of 4-bromoanisole:2, 4-dibromoanisole, but only after 48 h. We attribute the propensity for bromination to the higher polarizability of bromine than chlorine and the greater electronegativity of chlorine than bromine: both factors tend to enhance the partial positive charge on bromine in the mixed trihalides, and the result here is consistent with our hypothesis that bromonium ions are the predominantly (if not exclusively) formed intermediates during the additions to alkenes (vide ante).

Conclusions

The use of two RTILs, tetralkylphosphonium cations with either tribromide or mixed bromo-chloro trihalides, as

(24) In the gas phase as well as in aprotic solvents, nucleophilicity follows the trend F⁻ > Cl⁻ > Br⁻ > I⁻. Olmstead, W. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 4219–4228.

(25) Braddock, D. C.; Hermitage, S. A.; Kwok, L.; Pouwer, R.; Redmond, J. M.; White, A. J. P. *Chem. Commun.* **2009**, 1082–1084.

halogenating reagents for alkenes, an alkyne, and an aromatic molecule has been explored. On the basis of the results obtained, these reagents offer an easily synthesized and easily handled alternative to many of the other halogenation reagents developed previously. The yields with alkenes, especially, are very high and the products are easily separated from the reagents and their byproducts. The reactions proceed with high stereo- and regioselectivities. Because these reagents are liquids at room temperature, they function well in solvent-free conditions. Additional studies are being conducted to characterize further the properties of these RTILs and to obtain more details about the mechanism of their halogenation reactions. Also, structural modifications to the phosphonium and trihalide parts will be explored.

Experimental Section

Synthesis of Phosphonium Trihalides (*m*P*n*XY_2). Tridecylmethylphosphonium Dibromochloride (1P10ClBr$_2$). In a 50 mL round-bottomed flask immersed in a room temperature water bath, bromine (0.396 g, 2.48 mmol) was added to solid **1P10Cl** (1.25 g, 2.48 mmol). The reaction mixture is stirred for 30 min in the dark in the closed vessel to afford 1.65 g (100%) of a redorange viscous liquid. ^{1}H NMR (CDCl$_3$) δ 2.34−2.27 (m, 6 H), 2.00 (d, J = 12.8 Hz, 3 H), 1.60−1.49 (m, 12 H), 1.35−1.27 (m, 36 H), 0.88 (t, J = 6.4 Hz, 9 H) ppm. ^{13}C NMR (CDCl$_3$) δ 31.84, 30.76, 30.62, 29.47, 29.30, 29.25, 28.96, 22.65, 21.83, 21.78, 20.88, 20.40, 14.09 ppm. ^{31}P NMR (CDCl$_3$) δ 31.95 ppm. Elemental Anal. Calcd for C$_{31}$H$_{66}$Br$_2$ClP: C, 55.98; H, 10.00. Found: C, 56.20; H, 10.39.

Tridecylmethylphosphonium Bromodichloride (1P10BrCl$_2$). **1P10Br** (0.51 g, 0.94 mmol) was transferred to a 50 mL three-necked round-bottomed flask equipped with an inlet for chlorine gas and an outlet containing a drying tube. The flask was cooled in a dry ice bath and chlorine gas[26] was slowly released into it. The liquid chlorine slowly dissolved the solid **1P10Br** and the mixture was kept in the dark for 1 h. After this period, it was warmed to room temperature, releasing most of the excess chlorine, and a strong stream of nitrogen was passed over the liquid to remove the remaining excess chlorine: yield 0.58 g (99%) of a green-yellowish viscous liquid. ^{1}H NMR (CDCl$_3$) δ 2.33−2.24 (m, 6 H), 1.97 (d, J = 13.2 Hz, 3 H), 1.61−1.50 (m, 12 H), 1.27 (s broad, 36 H), 0.88 (t, J = 6.4 Hz, 9 H) ppm. ^{31}P NMR (CDCl$_3$) δ 31.89 ppm. Elemental Anal. Calcd for C$_{31}$H$_{66}$BrCl$_2$P: C, 59.99; H, 10.72. Found: C, 60.24; H, 10.98.

Trihexyltetradecylphosphonium Tribromide (14P6Br$_3$). Bromine (0.614 g, 3.84 mmol) was added to neat **14P6Br** (2.16 g, 3.84 mmol) in a 25 mL round-bottomed flask. The flask was sealed with a rubber stopper and the red liquid mixture was stirred at room temperature for 6 h to give 2.72 g (98%) of a red viscous liquid. ^{1}H NMR (CDCl$_3$) δ 2.28 (m, 8 H), 1.57 (m, 16 H), 1.39−1.26 (m, 32 H), 1.02 (m, 12 H). ^{31}P NMR (CDCl$_3$) δ 33.38. Elemental Anal. Calcd for C$_{32}$H$_{68}$Br$_3$P: C, 53.12; H, 9.47. Found: C, 52.90; H, 10.04.

Trihexyltetradecylphosphonium Dibromochloride (14P6ClBr$_2$). The synthesis followed the same procedure described for **1P-10ClBr$_2$** with **14P6Cl** (2.64 g, 5.09 mmol) and bromine (0.814 g, 5.09 mmol): 3.45 g (100%) of an orange viscous liquid. ^{1}H NMR (CDCl$_3$) δ 2.23−2.16 (m, 8 H), 1.53−1.45 (m, 16 H), 1.27−1.17 (m, 32 H), 0.84−0.77 (m, 12 H). ^{31}P NMR (CDCl$_3$) δ 33.25 ppm. Elemental Anal. Calcd for C$_{32}$H$_{68}$Br$_2$ClP: C, 56.59; H, 10.09. Found: C, 56.90; H, 10.84.

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(26) Vogel, A. I. *A textbook of practical organic chemistry*, 3th ed.; Longman: Thetford, UK, 1974; p 183.

Trihexyltetradecylphosphonium Bromodichloride (14P6BrCl$_2$). The synthesis followed the same procedure described for **1P10BrCl$_2$** with **14P6Br** (2.16 g, 3.83 mmol) and chlorine gas: 2.45 g (100%) of a viscous yellow liquid. ^{1}H NMR (CDCl$_3$) δ 2.30−2.23 (m, 8 H), 1.59−1.53 (m, 16 H), 1.35−1.26 (m, 32 H), 0.93−0.86 (m, 12 H). ^{31}P NMR (CDCl$_3$) δ 33.29 ppm. Elemental Anal. Calcd for C$_{32}$H$_{68}$BrCl$_2$P: C, 60.56; H, 10.80. Found: C, 60.82; H, 11.12.

Representative Procedures for Halogenation Reactions. With Cyclohexene (1). Two-Phase Bromo-Chlorination (entry 2 in Table S1, Supporting Information). A solution of cyclohexene (**1**) (0.047 g, 0.58 mmol) in 2 mL of hexadecane was added directly to **1P10ClBr$_2$** (0.35 g, 0.70 mmol) in a 14 mm diameter screw cap vial. The two-phase system was kept in the dark and without stirring. Aliquots were removed periodically and analyzed by GC to follow the course of the reaction.

Reaction with Neat Ionic Liquid (entry 1 in Table S1, Supporting Information). Cyclohexene (**1**) (0.022 g, 0.27 mmol) was added to a vial containing neat **14P6Br$_3$** (0.24 g, 0.33 mmol) and the mixture was kept at room temperature in the dark for 3 h. The product, *trans*-1,2-dibromocyclohexane (0.059 g (91%)), was isolated by column chromatography (silica gel; hexanes as eluant) and identified spectroscopically, using literature assignments for comparison; see the Supporting Information.

With *cis*-stilbene (2). Reaction with Ionic Liquid in Solution (entry 18 in Table S1, Supporting Information). *cis*-Stilbene (**2**) (0.0418 g, 0.232 mmol) and **14P6ClBr$_2$** (0.190 g, 0.279 mmol) were dissolved in CDCl$_3$ (0.70 g, 0.46 mL). The reaction mixture was kept in the dark at room temperature in a closed vessel. TLC (silica gel; 6:1 hexanes:ethyl acetate as eluant) and ^{1}H NMR analyses indicated complete reaction after 1 h (see the Supporting Information). The products (0.064 g, 88%) were isolated via column chromatography (silica gel; 6:1 hexanes:ethyl acetate as eluant) and identified as a ca. 6:4 mixture of *threo*-1-bromo2-chloro-1,2-diphenylethane and *d*, *l*-1,2-dibromo-1,2-diphenylethane by their spectra, using literature assignments for comparison; see the Supporting Information.

With *trans*-Stilbene (3). Reaction with Ionic Liquid Leading to Precipitation of the Product (entry 35 in Table S1, Supporting Information). *trans*-Stilbene (**3**) (0.043 g, 0.24 mmol), **14P6Cl** (0.148 g, 0.286 mmol), and **14P6ClBr$_2$** (0.194 g, 0.286 mmol) were dissolved in CDCl$_3$ (0.71 g, 0.48 mL). The solution was kept in the dark for 12 h at room temperature in a closed vessel. Precipitation of a white solid was noted after 2 h of reaction. The solid was filtered and washed with cool CHCl$_3$ to give 0.057 g (77% yield), identified spectroscopically using literature assignments for comparison (see the Supporting Information) to be a ca. 3:1 mixture of *erythro*-1-bromo-2-chloro-1,2-diphenylethane and *meso*-1,2-dibromo-1,2-diphenylethane.

With Styrene (4a). Reaction in Solution with Additional Chloride Ions (entry 41 in Table S1, Supporting Information). Styrene (**4a**) (0.027 g, 0.26 mmol), **14P6Cl** (0.136 g, 0.262 mmol), and **14P6ClBr$_2$** (0.178 g, 0.262 mmol) were dissolved in CDCl$_3$ (0.79 g, 0.52 mL). The reaction mixture was kept in the dark at room temperature in a closed flask for 1 h, at which time, TLC (silica gel, eluant hexanes:ethyl acetate 6:1) and ^{1}H NMR analyses indicated the complete loss of styrene. The products (0.032 g, 52%) isolated via column chromatography (silica gel; 6:1 hexanes:ethyl acetate as eluant) were identified spectroscopically, using literature assignments for comparison (see the Supporting Information), as a ca. 2:1 mixture of 2-bromo-1-chloro-1-phenylethane and 1,2-dibromo-1-phenylethane.

Supporting Information Available: Thermal characterizations of ionic liquids, their NMR spectra as well as those of reaction products, and selected gas chromatograms of reaction mixtures. This material is available free of charge via the Internet at http://pubs.acs.org.