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NMR Studies and electrophilic properties of triphenylphosphine–trifluoromethanesulfonic anhydride; a remarkable dehydrating reagent system for the conversion of aldoximes into nitriles

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ABSTRACT

NMR Studies on the reaction of triphenylphosphine with various amounts of triflic anhydride at 0 °C is described. The reagent structure resulting from mixing 1.3 equiv of Ph_3P with Tf_2O (1.0 mmol) has been established as an equilibrium mixture consisting mainly of triphenyl(trifluoromethylsulfonyloxy)phosphonium trifluoromethanesulfinate and the corresponding bis(triphenyl)oxodiphosphonium trifluoromethanesulfinate dimer. The electrophilic properties of the system have been exploited in the development of a mild method for converting aldoximes into nitriles. The dehydration occurs at 0 °C under very mild conditions by initial activation of the oxime oxygen, followed by treatment with a base and subsequent elimination of triphenylphosphine oxide. The substrate scope and functional group tolerance of this useful method are explored.

The synthetic utility of the trifluoromethanesulfonyl (triflyl) group as an effective oxygen activator has been extensively studied and its many proven applications are well documented.[1] Among such applications, the conversion of triphenylphosphine oxide into bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate for use as a general oxygen activator has attracted interest, particularly from the Hendrickson group.[2] They demonstrated that triphenylphosphine oxide reacts smoothly under very mild reaction conditions with triflic anhydride to afford the bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate salt (**1**), currently known as Hendrickson's reagent (Scheme 1, Eq. 1). The structure was erroneously assigned as the triphenyl(trifluoromethylsulfonyloxy)phosphonium trifluoromethanesulfonate salt and was later corrected by Aaberg et al.[2,3] The oxodiphosphonium salt **1** was found to undergo rapid complexation with a wide range of oxygenated substrates and was capable of dehydrating alcohols, amides and aldoximes, and activating carboxylic acids towards nucleophilic attack.[4] Unfortunately, further exploration of the full synthetic potential of **1**, or variations thereof, as mild electrophilic activators was not aggressively pursued. Only recently has the synthetic utility of Hendrickson's reagent as a mediator of thiazoline[5] and imidazoline[6] ring formation been highlighted by You and Kelly[6] and demonstrated by Doi and Takahashi in the total synthesis of apratoxin A.[7]

$$Ph_3P{=}O + Tf_2O \xrightarrow{a} \underset{\mathbf{1}}{(Ph_3P^+)_2O.2OTf^-} \quad \text{Hendrickson's reagent} \qquad (1)$$

$$Ph_3P + Tf_2O \xrightarrow{b} \underset{\mathbf{2}}{(Ph_3P^+)OTf} + Tf^- \text{ or } \underset{\mathbf{3}}{(Ph_3P^+)_2O.2Tf^-} \qquad (2)$$

Scheme 1. Reagents and conditions: (a) Ph_3PO/Tf_2O; 2:l stoichiometry, 0 °C, CH_2Cl_2; (b) envisioned conditions for the preparation of **2**: Ph_3P/Tf_2O; 1:l stoichiometry, 0 °C or rt, CH_2Cl_2.

In our quest for an economical, rapid, efficient and mild approach for the conversion of aldoximes into nitriles, we became interested in using triphenyl(trifluoromethylsulfonyloxy)phosphonium trifluoromethanesulfinate (**2**) (Scheme 1, Eq. 2) as an alternative oxygen activator and dehydrating reagent devoid of intrinsic nucleophiles in order to circumvent the formation of unwanted by-products. Species released during the reaction are triphenylphosphine oxide, trifluoromethanesulfonate (triflate) and trifluoromethanesulfinate (triflinate) ions. In principle, such a reagent

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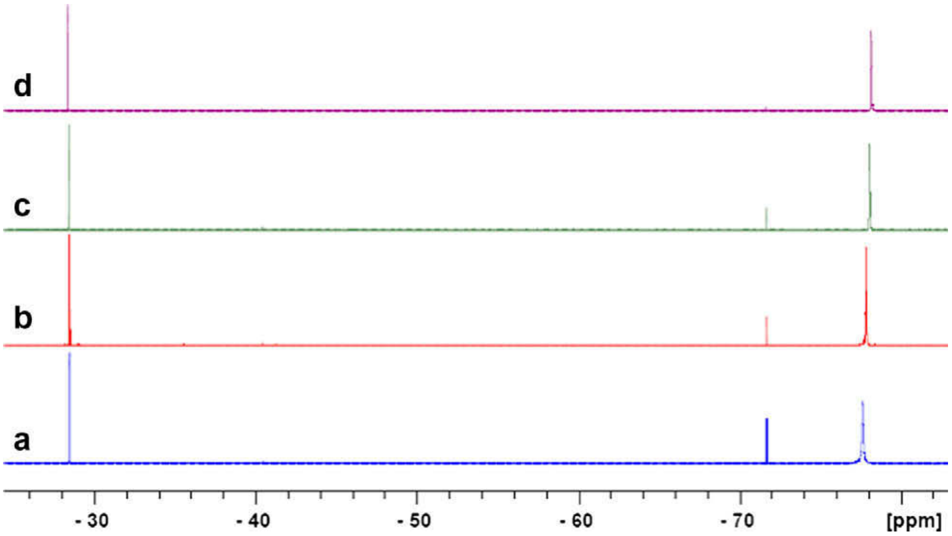
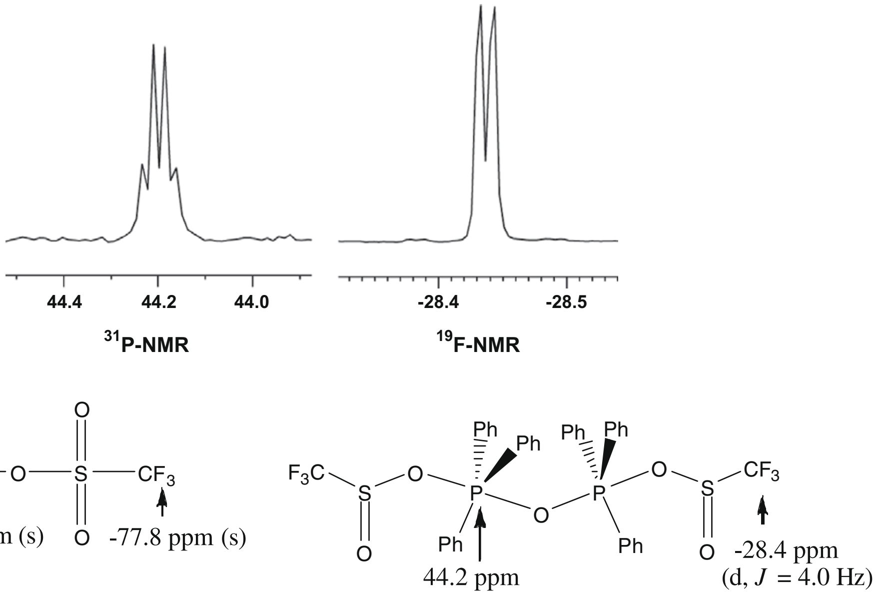


Figure 1. ^{19}F NMR spectra from the reaction of various equivalents of Ph_3P with Tf_2O in CH_2Cl_2 at 0 °C over a period of 10 min. (a) Ph_3P (1.0 equiv) + Tf_2O (1.0 equiv); (b) Ph_3P (1.1 equiv) + Tf_2O (1.0 equiv); (c) Ph_3P (1.2 equiv) + Tf_2O (1.0 equiv); (d) Ph_3P (1.3 equiv) + Tf_2O (1.0 equiv).

should be accessible via reaction of readily available and inexpensive triphenylphosphine (Ph_3P) with an equimolar amount of triflic anhydride. In sharp contrast to Hendrickson's reagent (**1**), which is prepared by triflating the phosphine oxide oxygen, reagent **2** is obtained by direct triflation of the phosphorus atom of triphenylphosphine (Scheme 1). Although reagent **2** first appeared in the literature some time ago, its preparation, characterization, electrophilic properties and synthetic applications remain unreported.[8]

We now report on the reactivity and behaviour of triphenylphosphine with various amounts of triflic anhydride at different temperatures, and the ability of the resulting complexes to act as very strong dehydrating reagent systems for the conversion of aldoximes into nitriles. We initially determined the appropriate stoichiometry of triphenylphosphine to triflic anhydride required to produce the electrophilic triphenylphosphonium salt **2** and whether any dimerization to complex **3** would occur. This is very critical as triflic anhydride itself is an indiscriminate electrophile and any remaining unreacted excess will mask the true identity of the electrophilic species responsible for dehydration. Thus, a dichloromethane solution of triphenylphosphine (1.0 mmol) at 0 °C was treated with one molar equivalent of triflic anhydride and the reaction progress was monitored by analyzing aliquots by ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR spectroscopy. These techniques were complementary and proved decisive in establishing the disappearance of each reagent and the emergence of new species. The ^{19}F NMR spectrum of an aliquot taken 10 min after the addition of triflic anhydride showed three signals at δ −77.8 (s), −71.7 (s) and −28.4 (d, J = 4.1 Hz) ppm integrating as 4.33:0.18:1.00 (Fig. 1, spectrum a). The singlet at δ −77.8 is most likely due to the trifluoromethanesulfinate ion and that at δ −71.7 is assigned to triflic anhydride as verified independently by the ^{19}F (δ −71.7) and ^{13}C NMR spectra (q, δ 118.3, J = 320 Hz) of a commercial sample. The doublet at δ −28.4 was attributed to bis(triphenyl)oxodiphosphonium trifluoromethanesulfinate (**3**) (Fig. 2) as was confirmed by



2

3

Figure 2. ^{19}F and ^{31}P NMR spectral evidence for complex **2** and the corresponding dimer **3**.

other experiments (vide infra). Further evidence for the formation of **3** stems from the ^{31}P NMR spectrum which showed a quartet at δ 44.2 (J = 4.0 Hz) (Fig. 2). The small value of the coupling constant suggests long-range ^{19}F–^{31}P coupling which could only exist in intermediate **2** or in the corresponding bis-triphenylphosphonium dimer **3**. The ^{31}P NMR spectrum also showed another singlet at δ 51.7 which was assigned to complex **2** (vide infra). Two other unidentified and rather weak broad singlets were observed at δ 75.1 and δ 79.5 [(^{31}P NMR δ (integration): 44.2 (0.67), 51.7 (1), 75.1 (0.28), 79.5 (0.32)] (Fig. 3, spectrum a). The signal for Ph_3P which usually occurs at δ −5.5 was not detected. Temperature control is critical as slight fluctuations led to additional new signals emerging in the ^{31}P NMR spectrum and others disappearing. For example, performing the addition at −5 °C resulted in the emergence of a new signal at δ 61.7 and the disappearance of the broad resonances observed at δ 75.1 and δ 79.5. The signals at δ 44.2 and δ 51.7 remained unchanged. On the other hand, running the reaction at room temperature under the same conditions resulted in identical signals to those observed at 0 °C, although in different ratios [(^{31}P NMR δ (integration): 44.2 (0.82), 51.7 (1), 75.1 (0.47), 79.5 (0.50) ppm; ^{19}F NMR δ (integration): −77.8 (4.1), −71.7 (0.20) and −28.4 (1) ppm)]. The ^{1}H NMR spectrum of the reaction mixture at 0 °C showed overlapping aromatic signals extending from δ 8.02–7.59, whereas the ^{13}C DEPT-135 spectrum displayed new aromatic signals due to the resulting complexes at δ 138.6 (br s, CH), 137.4 (d, J = 4.0 Hz, CH, **2**), 134.9 (d, J = 3.0 Hz, CH, **3**), 134.5 (br s, CH), 134.2 (d, J = 12.0 Hz, CH, **2**), 132.8 (d, J = 12.0 Hz, CH, **3**), 131.3 (d, J = 15.0 Hz, CH, **2**), 131.2 (br s, CH), 129.7 (d, J = 13.0 Hz, CH, **3**), with chemical shifts that differed from those of triphenylphosphine [137.1 (d, J = 11.0 Hz, C), 133.7 (d, J = 20.0 Hz, 2 × CH), 128.7 (p-CH), 128.5 (d, J = 7.0 Hz, 2 × CH)]. The ^{31}C NMR spectrum of the experimental sample showed a quartet (δ 119.3, J = 319 Hz) due to the triflinate moiety, and two other quaternary carbons appeared as doublets at δ 123.1 (d, J = 108.5 Hz, C, **3**) and δ 115.6 (d, J = 84.4 Hz, C, **2**). Interestingly, the observed large coupling constants support the presence of a P–O bond, as a similar coupling constant was observed for the quaternary carbon atom of Ph_3PO (d, J = 104.2 Hz), whereas a much smaller J value was observed for the quaternary carbon of Ph_3P (d, J = 11.0 Hz). The characteristic carbon quartet expected from the presence of remaining triflic anhydride was not observed in the ^{13}C NMR spectrum. No changes were observed in the NMR spectra when the reaction mixture was warmed to room temperature and stirred overnight.

In the next stage of our series of experiments aimed at determining the amount of Ph_3P required for the complete consumption of unreacted triflic anhydride and directed at discerning the structure of the triphenylphosphonium intermediates, 1.1 mole equiv of

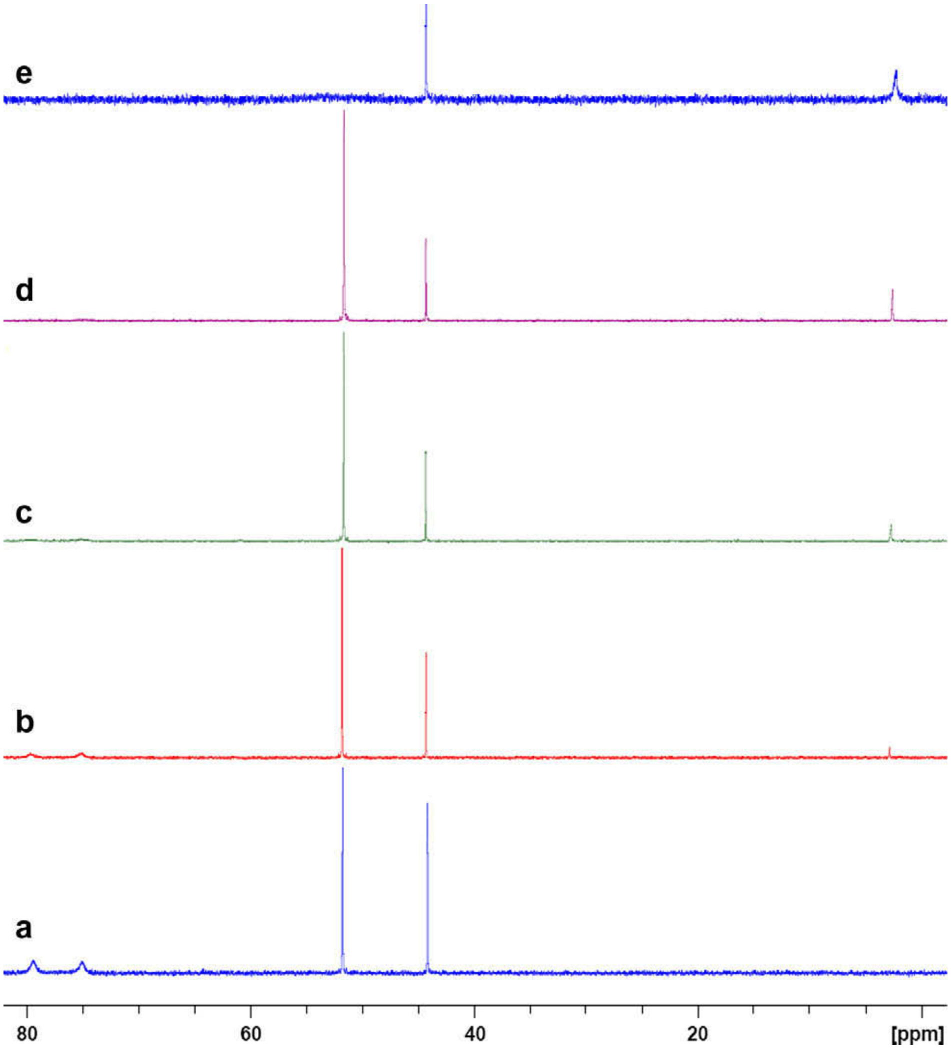
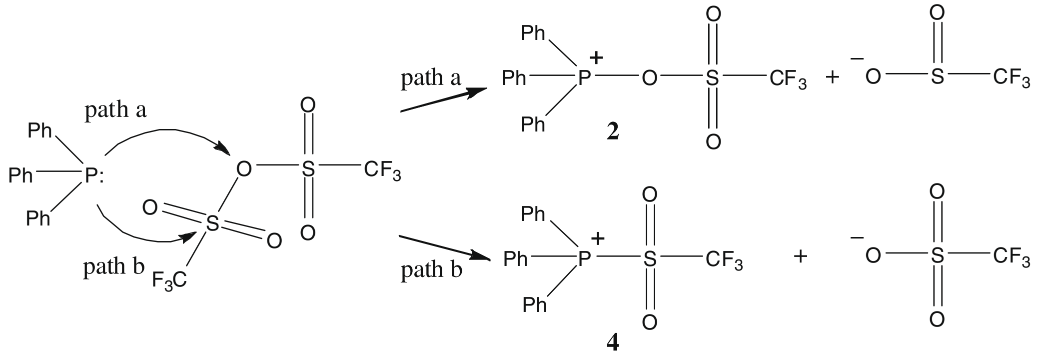


Figure 3. ^{31}P NMR spectra from the reaction of various equivalents of Ph_3P with Tf_2O in CH_2Cl_2 at 0 °C over a period of 10 min. (a) Ph_3P (1.0 equiv) + Tf_2O (1.0 equiv); (b) Ph_3P (1.1 equiv) + Tf_2O (1.0 equiv); (c) Ph_3P (1.2 equiv) + Tf_2O (1.0 equiv); (d) Ph_3P (1.3 equiv) + Tf_2O (1.0 equiv); (e) Ph_3P (2.0 equiv) + Tf_2O (1.0 equiv).

Ph_3P and triflic anhydride (1.0 mmol) was reacted at 0 °C under the conditions used earlier. The ^{19}F NMR spectrum of an aliquot taken after 10 min showed the same three signals observed earlier [δ −77.8 (s), −71.7 (s) and −28.4 (d)], with an integration ratio of 4.01:0.09:1.0 (Fig. 1, spectrum **b**). Clearly, some triflic anhydride remains unreacted, although it is present in a relatively smaller amount than that observed earlier with the equimolar reaction of both reagents. The addition of 1.2 mole equiv of Ph_3P to triflic anhydride (1.0 mmol) produced the expected three signals in the ^{19}F NMR spectrum with an integration ratio of 3.69:0.06:1.0 (Fig. 1, spectrum c), whereas the addition of 1.3 mole equiv of Ph_3P resulted in the complete consumption of triflic anhydride yielding two signals only [δ −77.8 (s) and δ −28.4 (d)] in a ratio of 3.57:1.0 (Fig. 1, spectrum **d**). This clearly indicates that Ph_3P and triflic anhydride react in 1.3:1 stoichiometry as >95% of the latter was consumed immediately after the start of the reaction. It is noted that the ratio between the two signals at δ −77.8 and δ −28.4 ppm decreased consistently with additional Ph_3P as is clearly shown in spectra a–d, Figure 1. The ^{31}P NMR spectra for the preceding series of reactions are shown in Figure 3 and indicate that 1.1 equiv of Ph_3P produces the same four intermediates observed earlier as well as traces of an as yet unidentified species appearing upfield with a chemical shift of δ 2.42 [^{31}P NMR δ (integration): 2.42 (0.08), 44.2 (0.57), 51.7 (1), 75.1 (0.25), 79.5 (0.19); (Fig. 3, spectrum **b**)]. With 1.2 equiv of Ph_3P, the broad singlets at δ 75.1 and δ 79.5 disappeared almost completely whereas those at δ 44.2 and δ 2.42 ppm experienced a reduction and enhancement in integration, respectively [^{31}P NMR δ (integration): 2.42 (0.16), 44.2 (0.46), 51.7 (1); (Fig. 3, spectrum **c**)]. Finally, utilizing the optimum amount of Ph_3P (1.3 equiv) needed for the complete



Scheme 2. Plausible pathways for the reaction of Ph_3P with Tf_2O.

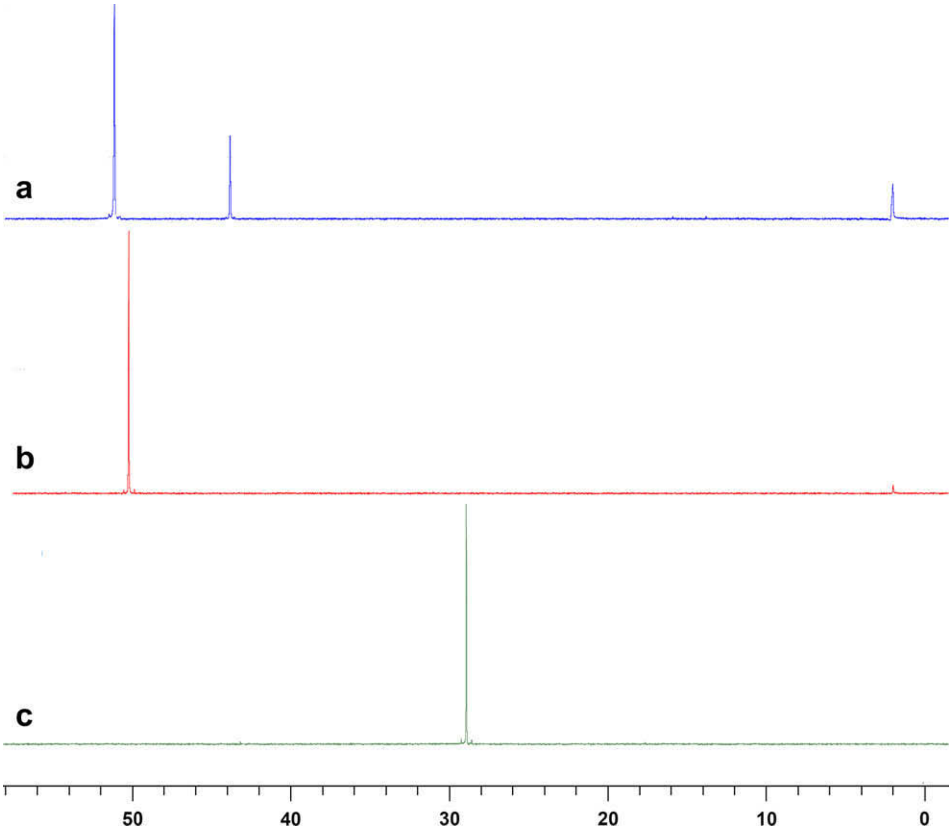


Figure 4. ^{31}P NMR reaction profile for the conversion of 2,6-dichlorobenzaldehyde oxime into 2,6-dichlorobenzonitrile under the conditions given in Table 1; (a) Ph_3P (1.3 equiv) + Tf_2O (1.0 equiv), 0 °C, 10 min; (b) 2,6-dichlorobenzaldehyde oxime (1.0 equiv) was added to the reaction mixture at 0 °C; (c) the reaction mixture was treated with Et_3N (2 equiv).

reaction of triflic anhydride resulted in the same three signals observed above [^{31}P NMR δ (integration): 2.42 (0.24), 44.2 (0.40), 51.7 (1); (Fig. 3, spectrum **d**)]. It is noted from Figure 3 that as the amount of Ph_3P was increased, there was a consistent reduction in the integration of the signal at δ 44.2 and an apparent enhancement of that at δ 2.42. The ^1H NMR spectrum of the reaction mixture exhibited chemical shifts ranging from δ 8.02–7.59, whereas the ^{13}C DEPT-135 spectrum displayed, in addition to the usual six aromatic CH doublets of **2** and **3**, three new aromatic CH doublets stemming from the minor compound with a ^{31}P chemical shift of δ 2.42 ppm [^{13}C NMR δ 135.5 (d, J = 3.0 Hz, CH), 134.0 (d, J = 10.0 Hz, CH), 130.5 (d, J = 15.0 Hz, CH)].

The final reaction of our series of experiments at 0 °C involved treating triflic anhydride (1.0 mmol) with 2 equiv of Ph_3P and analyzing an aliquot of the reaction mixture after 10 min by NMR. Spectrum **e** of Figure 3 clearly shows that the excess Ph_3P reacted completely as demonstrated by the absence of a signal at δ −5.41. The signal for complex **2** was virtually undetectable as the ^{31}P NMR spectrum showed a major signal for dimer **3** and a minor one for the species which was observed earlier at δ 2.42 (integration; 1.00:0.33, respectively). The ^{19}F NMR spectrum showed the two signals at δ −77.8 (s) and δ −28.4 (d) and indicated that triflic anhydride had been totally consumed, whereas the ^{13}C NMR spectrum demonstrated the expected signals as observed earlier for the above-mentioned two products. The disappearance of **2** is understandable as excess Ph_3P converts it into the corresponding bis(triphenyl)oxodiphosphonium dimer **3**. It is worthwhile noting that when the same reaction was conducted at room temperature, the same two species were formed in almost similar ratios.

We believe that **2** is formed by the attack of the phosphorus atom of triphenylphosphine on the anhydride oxygen of triflic anhydride via path a of Scheme 2, releasing a trifluoromethanesulfinate ion as the leaving group. Triphenylphosphine can also be envisioned to undergo an alternative reaction pathway (path b) in which it reacts with the triflyl group to give an electrophilic triphenyl(trifluoromethylsulfonyl)phosphonium complex (**4**) and a negative triflate ion (Scheme 2). Complex **4** may then act as a triflyl source, negating the role of triphenylphosphine. Fortunately, this was not the case as was proven by the reaction of Ph_3P with $PhNTf_2$. The latter reagent is a source of a triflyl group and a very strong triflating agent. When an equimolar amount of Ph_3P and $PhNTf_2$ was reacted in CH_2Cl_2 at 0 °C, the former failed to react as was demonstrated by ^1H, ^{13}C, ^{19}F and ^{31}P NMR spectroscopy. For example, the ^{31}P NMR spectrum showed only one signal at δ −5.41 due to Ph_3P, and the ^{19}F NMR spectrum contained one signal at δ −70.6 corresponding to $PhNTf_2$.

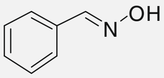
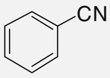
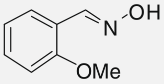
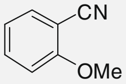
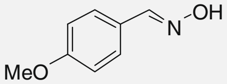
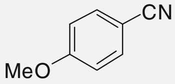
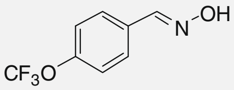
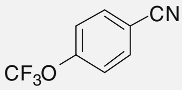
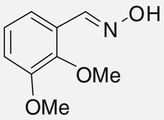
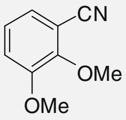
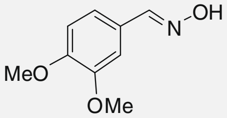
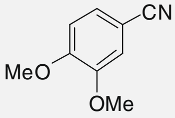
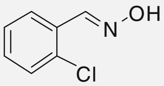
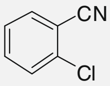
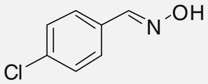
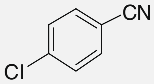
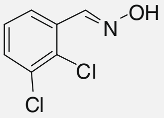
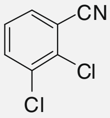
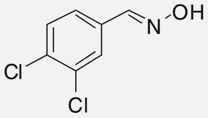
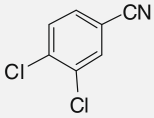
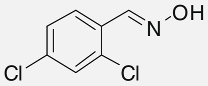
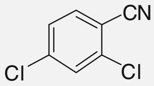
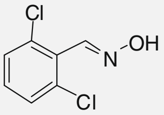
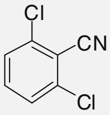
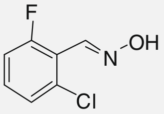
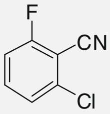
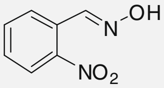
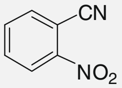
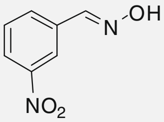
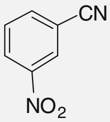
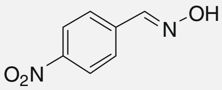
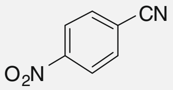
Next, we assessed the electrophilic properties of the Ph_3P/Tf_2O reagent system and its effectiveness as a general oxygen activator. 2,6-Dichlorobenzaldehyde oxime was used as a model compound in a complexation/dehydration study with the Ph_3P/Tf_2O reagent system and the progress of the reaction was monitored by ^{31}P NMR spectroscopy. The reagent system was prepared under the optimal conditions reported earlier (Fig. 4, spectrum **a**). The oxime (1.0 equiv) underwent immediate complexation at 0 °C with all three species present in the reagent system to give a single complex as observed in Figure 4, spectrum b. Finally, the addition of two equivalents of Et_3N resulted in immediate and clean dehydration of the oxime to the corresponding nitrile in high yield and eliminated $Ph_3P{=}O$ as demonstrated in Figure 4, spectrum c.

Having established a proof of concept for the activating ability of the Ph_3P/Tf_2O reagent system, the versatility of this protocol was examined on various structurally diverse aldoximes derived from aromatic (entries 1–17, 25 and 26), heterocyclic (entries 18–20 and 24) and aliphatic (entries 21–23) substrates (Table 1). Using the optimized conditions (1.3:1 Ph_3P/Tf_2O), the dehydration proceeded rapidly at 0 °C and produced high yields of the corre-

Table 1

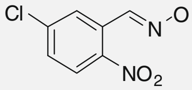
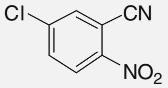
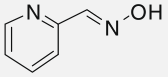
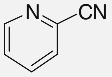
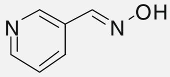
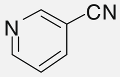
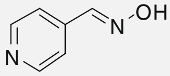
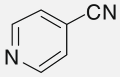
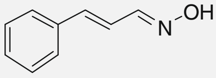
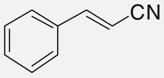
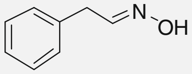
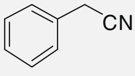
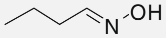
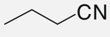
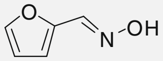
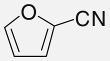
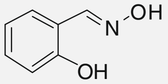
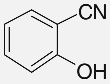
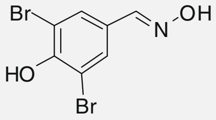
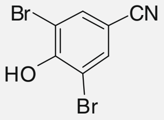
Nitriles prepared from aldoximes via reaction with the Ph_3P/Tf_2O reagent system[a]

$$RCH{=}N{-}OH \xrightarrow[Et_3N\ (2\ mmol),\ CH_2Cl_2,\ 0\ ^{\circ}C,\ 10\ min]{Ph_3P\ (1.3\ mmol),\ Tf_2O\ (1.0\ mmol)} R{-}C{\equiv}N$$

Entry	Substrate	Product	Yield[b] (%)
1			91
2			95
3			98
4			92
5			92
6			93
7			93
8			94
9			95
10			95
11			93
12			95
13			96
14			85
15			95
16			88

(*continued on next page*)

Table 1 (*continued*)

Entry	Substrate	Product	Yield[b] (%)
17			88
18			84
19			84
20			85
21			90
22			95
23			82
24			60
25			84
26			85

[a] Products were characterized by ^{1}H and ^{13}C NMR spectroscopy and compared with authentic commercial samples. The ^{1}H and ^{13}C NMR spectra matched those reported in the literature.

[b] Isolated unoptimized yields.

sponding nitriles.[9] The method tolerates a wide range of substrates and functional groups such as methoxy, trifluromethoxy, halogens and nitro. Moreover, the system exhibits some degree of chemoselectivity (entries 25 and 26) as the oxime function reacted preferentially over the phenolic hydroxy group. Interestingly, ring-activating and deactivating substituents had no significant effect on the rate of reaction as all the nitriles shown in Table 1 were produced almost immediately following the addition. All the products were characterized by ^{1}H and ^{13}C NMR spectroscopy and were compared with authentic commercial samples.

In summary, we have presented NMR evidence of the novel triphenyl(trifluoromethylsulfonyloxy)phosphonium trifluoromethanesulfinate complex and its corresponding bis(triphenyl)oxodiphosphonium trifluoromethanesulfinate dimer which are produced on mixing 1.3 equiv of Ph_3P with Tf_2O (1.0 mmol). The electrophilic properties of the system have been utilized in the development of a mild method for converting aldoximes into nitriles, rapidly at 0 °C in high yields.[10] The method tolerates a wide range of substrates and functional groups and has been shown to exhibit some degree of chemoselectivity. Hence, this method should find utility in synthesis and may prove to be a valuable alternative to known methods.

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References and notes

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10. *Typical procedure for the conversion of an aldoxime into the corresponding nitrile.* A CH_2Cl_2 solution (5 mL) of Ph_3P (1.3 mmol) was cooled in an ice bath to 0 °C and treated with Tf_2O (1.0 mmol). After stirring the mixture for 10 min, the aldoxime (1.0 mmol) was added as a neat liquid or solid, followed by the addition of Et_3N (2.0 mmol). After stirring for another 10 min, the mixture was diluted with CH_2Cl_2 (10 mL) and washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, and the residue was purified on silica gel (elution with 5% EtOAc/hexanes) to afford the nitrile in the yields shown in Table 1.