Electrophilic Routes to Tertiary Adamantyl and Diamantyl Phosphonium Salts

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In appreciation of the scientific contributions of Alfredo Ricci, with warm regards

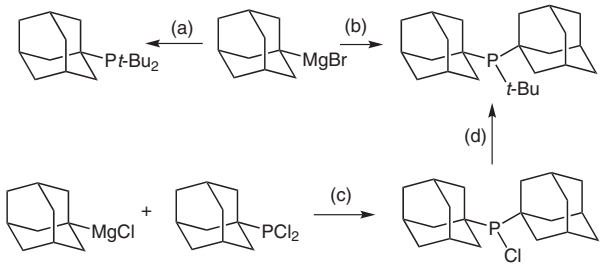
Abstract: In highly nonpolar media both 1-adamantyl and 1-diamantyl triflates are sufficiently stable to react with nucleophiles in a controlled manner. Several tertiary phosphonium triflate salts with a single adamantyl or diamantyl residue were prepared directly in this way, starting with the secondary phosphine. Three compounds with the 1-phosphodiamantane structure were characterised by X-ray.

Key words: ligands, phosphorus, electrophilic addition, adamantly, diamantyl

We report a simple method for C–P bond synthesis that introduces a 1-adamantyl group under mild conditions using the highly reactive 1-adamantyl triflate as electrophile. The method has been further extended to 1-diamantyl triflate, making phosphines derived from higher diamondoids readily accessible.

Beginning with the application of tri-*tert*-butylphosphine,[2] the use of very bulky ligands has played an important and sustained role in palladium catalysis. Their involvement reduces the coordination number of palladium in catalytic intermediates and promotes monoligated species.[3] By tuning the electronic and steric properties of the ligand, catalytic reactivity is markedly altered and may give access to otherwise inaccessible reaction pathways.[4]

1-Adamantyl (Ad)-based phosphine ligands can possess distinct reactivity from their *tert*-butyl analogues.[5] At present many phosphines with $AdPR_2$ and Ad_2PR structures are known and have been applied in catalysis, but Ad_3P is not.[6] QM analysis of the structure of Ad_3P confirms the presence of a high level of steric strain.[7] The chemistry employed in synthesis of *tert*-butyl and 1-adamantyl phosphines is generally distinct (Scheme 1). For *t*-Bu_3P, *tert*-butyllithium or the corresponding Grignard reagent are employed in a one-step or two-step synthesis starting from PCl_3.[8] A synthesis of Ad-*t*-Bu_2P involves copper-promoted reaction between *t*-Bu_2PCl and AdMgCl; Ad_2-*t*-BuP can be synthesised similarly.[9] An earlier route to the latter requires two sequential nucleophilic steps.[10] $AdPCl_2$ is reacted first with AdMgCl, and then with *t*-BuLi to form the desired ligand. In general however, there is a more attractive route to bis-1-adamantyl phosphines through the route made practical by Beller and co-workers, and one that is widely used. The direct electrophilic phosphinylation of adamantane (PCl_3, $AlCl_3$, then $LiAlH_4$) provides access to the precursors Ad_2PX (X = H, Cl).[11]



Scheme 1 Existing synthetic routes to tri-tertiary 1-adamantyl phosphines; ref. 9. *Reagents and conditions*: (a) ClP-*t*-Bu_2, LiBr, CuI (cat.), Et_2O, 0 °C; (b) same as (a) with Cl_2P-*t*-Bu; ref. 10; (c) *n*-heptane, heat; (d) Me_3CLi.

1-Adamantyl triflate has been known since 1980, and is isolable.[12] It's stability is remarkable, since tertiary sulfonates are highly reactive, and tertiary triflates otherwise unknown. For example, *tert*-butyl tosylate has been prepared and reacted in situ, but never characterised.[13] The rigid bridging environment of the 1-adamantyl moiety clearly confers stability to the triflate derivative, since the stability of the 1-adamantyl cation is closer to an unconstrained tertiary than to a secondary carbocation.[14]

1-Adamantyl triflate (**2**) was synthesised from bromide **1** as shown in Scheme 2, and characterised by ^1H NMR and ^{13}C NMR in $CDCl_3$, where the triflate is moderately stable on the time scale of analysis.[12a] The most useful and distinctive feature is the low-field C1 signal at δ = 104.0 ppm. For preparative purposes, the triflate did not need to be isolated. The reaction solution in 2,2-dimethylbutane was stirred for three hours at 0 °C, and then filtered from AgBr by cannula under argon to provide a solution pure enough for preparative purposes. In the first experiments, neat $HPPh_2$ was added by syringe, the reaction mixture was allowed to warm to room temperature and stirred for two hours. Washing the precipitate with EtOAc and drying gave the pure phosphonium salt **3** as a white solid in 94% yield [mp 248–250 °C (2.5 millimolar scale)], characterised by ^1H NMR, ^{13}C NMR and ^{31}P NMR, and HRMS. A portion was oxidised to the corresponding *P*-oxide **4**,[15] with basic H_2O_2 in 67% yield.[16]

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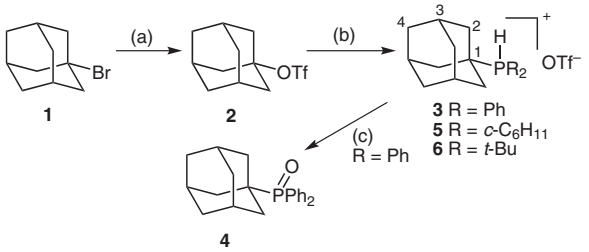


Scheme 2 1-Adamantylphosphonium salts. *Reagents and conditions*: (a) AgOTf, neohexane, 3 h, 0 °C; (b) HPR_2, r.t., 2 h; (c) 30% H_2O_2, *t*-BuOK, CH_2Cl_2, r.t., 14 h.

Encouraged by this result, related experiments with $HPCy_2$ and HP-*t*-Bu_2 were carried out, and the tertiary phosphonium salts **5** and **6** were isolated in 73% and 63% yield, respectively, and characterised as before. The synthesis constitutes a simple route to 1-adamantyl phosphine ligands, since phosphonium salts can be employed directly in Pd-catalysed reactions.[17] In **5**, where the ligand is novel, the ^{13}C NMR shows that cyclohexyl carbons adjacent to the C–P bond are diastereotopic, with 0.8 ppm separation.

The success in these syntheses encouraged their application to a more bulky diamondoid framework. Diamantane is readily accessible from rearrangement of BINOR-S, itself a dimer of norbornadiene,[18] and may be brominated specifically at the radial position to give monobromide **7**.[19] Despite this ease of precursor access, there are only two relevant reports of C–P synthesis to date. Olah and co-workers demonstrated the electrophilic phosphonylation of diamantane with $PCl_3/AlCl_3$, and isolated the phosphonic dichloride **8** (Figure 1).[20] More recently, Schreiner and co-workers have shown that phosphonylation of 1-bromodiamantane gave the disubstituted product **9** (Figure 1) in good yield.[21] This was converted into a range of simple derivatives. The lack of further examples may be due to the relative difficulty of access to 1-diamantyl lithium or magnesium derivatives.[22]

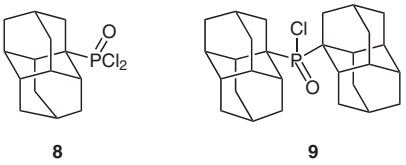
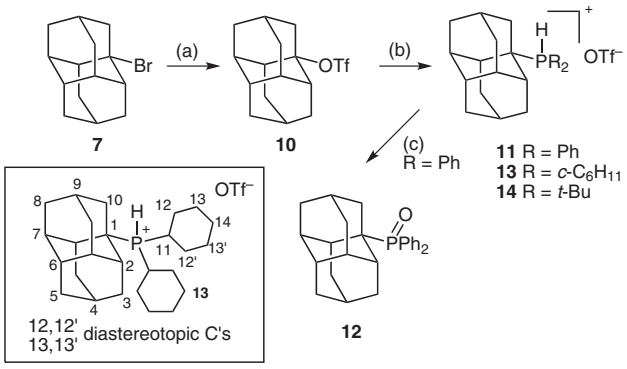


Figure 1

The reaction of 1-diamantyl bromide (**7**) with AgOTf in 2,2,-dimethylbutane was examined as above. AgBr was precipitated more rapidly than in the 1-adamantyl case, and the triflate **10** was formed as colourless crystals when the solvent was removed at 0 °C after cannula filtration. The solution stability was lower, albeit sufficient for spectral analysis although impurities were evident. The ^{13}C NMR spectrum showed nine distinct high-field signals as well as C1 at δ = 109.9 ppm and CF_3 at δ = 118.7 ppm (J_{CF} = 317 Hz). The reaction with $HPPh_2$ was carried out without isolation on a 1.2-millimolar scale and led to the isolation of the desired phosphonium salt **11** in 92% yield (mp 272–274 °C). The structure was confirmed by oxidation to the corresponding phosphine oxide **12**, which was recrystallised from $CHCl_3$ for X-ray analysis [Figure 2(A)]. Since the 1-diamantyl cation is in very rapid equilibrium with the less favoured 4-isomer,[23] this X-ray formally rules out an alternative structure for the phosphonium salt.

It proved possible to synthesise more bulky 1-diamantyl phosphines by using the same protocol. Using $HPCy_2$ on a 2-millimolar scale, the phosphonium salt **13** was prepared in 88% yield (mp >278 °C). In this case the ^{13}C NMR spectrum showed diastereotopic splitting for both possible sites (C12, C13), as indicated in Scheme 3. The salt could be directly recrystallised to X-ray quality from CH_2Cl_2, and the structure is shown in Figure 2(B). Finally, the C–P coupling reaction was carried out using HP-*t*-Bu_2 and the product **14** was obtained in 69% yield. Again, crystals of X-ray quality were formed by direct crystallisation from CH_2Cl_2, and the structure is shown in Figure 2(C).[24] Additional strain in the all-tertiary phosphonium salt is expressed in elongation of the P–C bonds by ca. 0.05 Å compared to the less bulky analogue **13**.[25,26]



Scheme 3 Synthesis of 1-diamantyl phosphonium salts. *Reagents and conditions*: (a) AgOTf, neohexane, 1.5 h, 0 °C; (b) HPR_2, neohexane, r.t., 2 h; (c) 30% H_2O_2, *t*-BuOK, CH_2Cl_2, r.t., 14 h.

In summary, a method for forming a single C–P bond to a tertiary ring-bridging position is demonstrated, by exploiting access to highly reactive electrophiles. This is exemplified here by the synthesis of tertiary 1-adamantyl and 1-diamantyl phosphines. The reactions described have been carried out on a small scale (2.5 mmol) allowing rapid and convenient access to quantities suitable for ligand screening protocols. We note that Takeuchi and co-workers have prepared hexane solutions containing 55 mmoles of triflate (**2**).[27] The method described should be more general, provided that the bridgehead reaction site can accommodate a carbocation of reasonable stability. Experimental details for all phosphonium salts are included; see Supporting Information.[28]

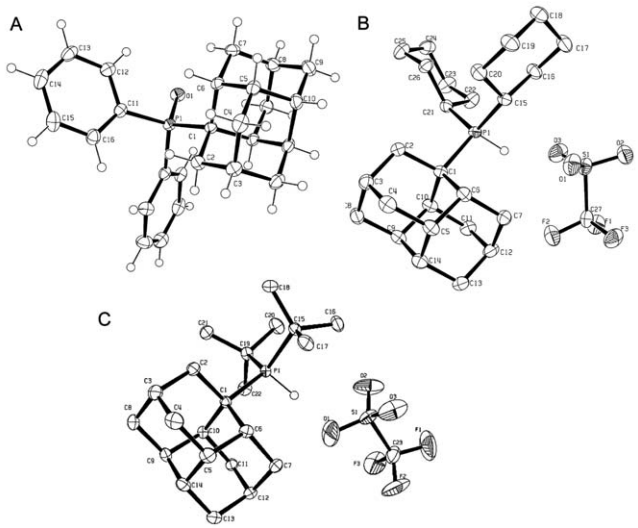


Figure 2 Three X-ray structures of phosphodiamantanes; A: **12**; B: **13**; C: **14**; crystallographic numbering. ORTEP-3 diagrams are shown with ellipsoids at 40% probability. Key data: **12**: R = 0.0353, wR = 0.0408; **13**: R = 0.0410, wR = 0.0479; **14**: R = 0.0517, wR = 0.0622.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(28) Experimental data:
Caution: The tertiary triflates **2** and **10** are powerful electrophiles and should be treated with care; avoid contact.
Sample Preparation 11 and **12** via **10**: Anhydrous AgOTf (105 mg, 0.4 mmol) was added to a solution of 1-bromodiamantane (100 mg, 0.37 mmol) in anhyd 2,2-dimethylbutane (10 mL) at 0 °C and stirred with exclusion of light for 1.5 h. The solution was filtered under argon by cannula and the solvent was removed under vacuum at 0 °C to afford 1-diamantyl triflate(**10**) as colourless crystals. ^1H NMR (500 MHz, $CDCl_3$, 25 °C): d = 1.54–2.40 (m). ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): d = 118.7 (q, J_{CF} = 316.7 Hz, CF_3), 109.9 (C1), 43.6 (C10), 42.9 (C2), 42.4 (C7), 37.9 (C5), 36.8 (C8), 36.4 (C6), 32.8 (C3), 32.1 (C9), 24.8 (C4).
After repeating on a 1.2-millimolar scale and cannula filtration $HPPh_2$ (210 mg, 196 μL, 1.12 mmol)was added and the solution was warmed to r.t. After 2 h stirring at r.t., a white solid precipitated. Solvent was removed and the solid

was washed with EtOAc and dried in vacuo to give 1-diamantyldiphenylphosphonium triflate(**11**) as a white solid (506 mg, 92% yield); mp 272–274 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): d = 9.24 (d, 1 H, HP, J_{HP} = 506 Hz), 8.07 (m, 4 H, H12), 7.74 (m, 2 H, H14), 7.64 (m, 4 H, H13), 2.57 (d, J_{HH} = 14.2 Hz, 2 H, H3), 2.17 (br m, 1 H, H4), 2.04 (br m, 3 H, H7, H9), 1.92 (br m, 2 H, H2), 1.85 (br m, 2 H, H8), 1.81 (br m, 1 H, H6), 1.77 (br m, 5 H, H10, H3, H8), 1.64 (br m, 3 H, H8, H5). ^{31}P NMR (162 MHz, $CDCl_3$, 25 °C): d = 3.6. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): d = 134.8 (d, J_{CP} = 2.7 Hz, C14), 134.5 (d, J_{CP} = 9.4 Hz, C12), 130.4 (d, J_{CP} = 12.3 Hz, C13), 114.2 (d, J_{CP} = 78.3 Hz, C11), 42.9 (d, J_{CP} = 37.9 Hz, C1), 37.9 (C10), 37.7 (C2), 37.6 (C6), 36.5 (C8), 36.4 (C7), 36.1 (C5), 32.7 (d, J_{CP} = 3.8 Hz, C3), 25.2 (d, J_{CP} = 9.7 Hz, C9), 24.6 (C4). A portion was oxidised: triflate **11** (160 mg, 0.42mmol), *t*-BuOK (246.8 mg, 2.2 mmol) in CH_2Cl_2 (20 mL), together with 30% H_2O_2 (1.0 mL) were stirred for 14 h. After workup and flash chromatography (EtOAc) 1-diamantyldiphenylphosphine oxide(**12**) was obtained (124 mg, 76% yield); mp 261–262 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): d = 7.99 (m, 4 H, H12), 7.49 (m, 6 H, H13, H14), 3.11 (d, J_{HH} = 12.7 Hz, 2 H, H3), 2.03 (br m, 2 H, H2), 1.91 (br m, 1 H, H4), 1.31 (br m, 1 H, H9), 1.76 (br m, 2 H, H7), 1.70 (br m, 5 H, H5, H6, H8), 1.59 (br m, 4 H, H8, H10), 1.43 (d, J_{HH} = 12.9 Hz, 2 H, H3). ^{31}P NMR (162 MHz, $CDCl_3$, 25 °C): d = 39.6. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): d = 132.4 (d, J_{CP} = 7.5 Hz, C12), 132.2 (d, J_{CP} = 88.3 Hz, C11), 131.1 (d, J_{CP} = 2.5 Hz, C14), 128.1 (d, J_{CP} = 10.7 Hz, C13), 42.7 (d, J_{CP} = 66.9 Hz, C1), 39.3 (C5), 38.9 (C8), 38.8 (d, J_{CP} = 4.0 Hz, C7), 37.6 (C6), 37.5 (d, J_{CP} = 1.4 Hz, C2), 37.3 (C10), 34.1 (C3), 25.9 (d, J_{CP} = 11.2 Hz, C9), 25.2 (C4). HRMS (ES$^+$): *m*/*z* calcd for $C_{26}H_{29}PO$: 389.2034; found: 389.2041.