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Radical addition reactions of chiral phosphorus hydrides

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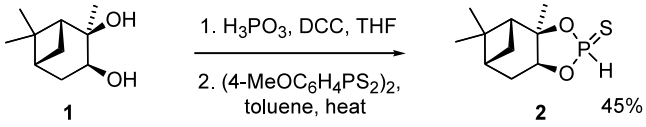
Abstract—Intermolecular radical addition of a (1*R*,2*R*,3*S*,5*R*)-(−)-pinanediol-derived thiophosphite leads to the diastereoselective formation of organophosphorus adducts. Addition of the intermediate phosphonothioyl radical to electron-rich alkenes or alkynes occurs with retention of configuration at phosphorus.

The addition of phosphorus-centred radicals to alkenes has long been utilised as an important method for preparing organophosphorus adducts.[1] Of particular recent interest has been the addition of phosphonyl or phosphonothioyl radicals, $R_2P(O)^{\bullet}$ or $R_2P(S)^{\bullet}$, respectively, to electron-rich alkenes.[2] This work, particularly that by Piettre et al., has shown that thiophosphites can add more efficiently to alkenes than phosphites and this has been attributed to the greater stability of the thiophosphonothioyl radical (compared to the phosphonyl radical). The P–H bond in a thiophosphite is therefore expected to be weaker and our studies on the cyclisation of dienes have recently supported the view that diethyl thiophosphite is a more effective hydrogen-atom donor than diethyl phosphite.[3]

Following our initial studies using achiral thiophosphites,[3] our attention turned towards the use of chiral thiophosphites in radical addition reactions. Phosphonyl radicals have been shown to have a pyramidal structure[4] and studies by Mislow[5] and Aaron[6] showed that addition of phosphonyl radicals to alkenes occurs with complete retention of configuration at phosphorus. This suggested that the radical addition of chiral thiophosphites to alkenes could afford a stereoselective approach to synthetically useful organothiophosphonates. The synthesis of non-racemic organophosphorus derivatives has attracted considerable recent attention because of the biological activities associated with this class of compound as well as their use in the preparation of catalytic antibodies.[7]

Our initial studies began with the synthesis of thiophosphite **2**, which was prepared by coupling phosphonic acid with (1*R*,2*R*,3*S*,5*R*)-(−)-pinanediol **1**[8] in the presence of dicyclohexylcarbodiimide[9] (Scheme 1).[10] The intermediate chiral phosphite (formed as a 1:1 mixture of diastereoisomers) was then treated with Lawesson's reagent[2f] to afford the desired thiophosphite **2** as a 9:1 mixture of inseparable diastereoisomers (as indicated by the ^{1}H NMR spectrum) in an overall yield of 45%. This procedure was repeated a number of times and on each occasion the ratio of diastereoisomers of **2** was found to vary, although it was generally in the region of 4–9:1.[11] It is unclear why different isomer ratios were observed (under the same conditions) although the reaction temperature is an important factor—heating an 8:1 mixture of isomers of **2** in toluene for 3 days leads to epimerisation and the formation of a 2:1 mixture.



Scheme 1.

Thiophosphite **2** was then reacted with a series of electron-rich alkenes (at rt in THF in the presence of triethylborane) in order to give organophosphorus adducts **5** via the intermediate radicals **3** and **4** as shown in Scheme 2. When a 4:1 diastereomer mixture of **2** was reacted with 1-octene, the desired regioselective radical addition reaction occurred to give **6a** in

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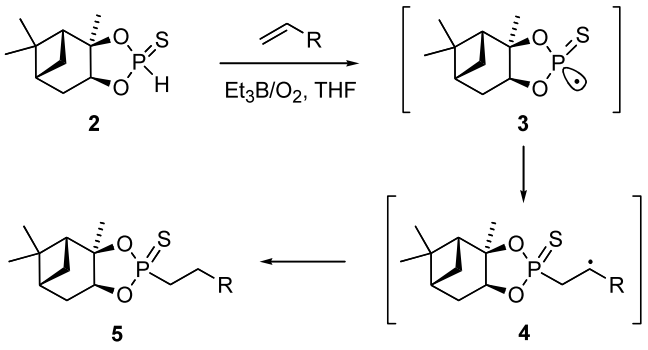


Scheme 2.

93% yield (Fig. 1).[12] The ^{1}H and ^{31}P NMR spectra of **6a** showed the presence of two diastereoisomers in the ratio of 4:1. As the product and starting material diastereoisomer ratios were the same this suggested that the radical addition had occurred with retention of configuration at the phosphorus atom. A similar result was obtained when **2** was reacted with methylenecyclohexane (under the same reaction conditions as for 1-octene). Hence a 5:1 mixture of diastereoisomers of **2** gave rise to a 5:1 mixture of diastereomers of the organophosphorus adduct **6b** (as indicated by the NMR spectra) in 83% yield.

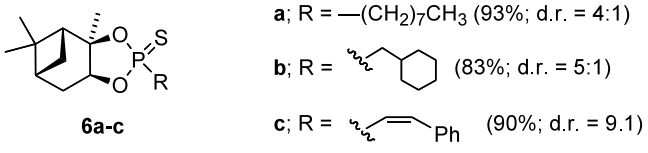


Figure 1.

Radical addition to the alkyne bond of ethynylbenzene is also possible and when a 9:1 mixture of isomers of **2** was reacted with this alkyne, a 9:1 mixture of diastereoisomers of **6c** was formed in 90% yield. Interestingly, the ^{1}H NMR spectrum of **6c** suggested the exclusive formation of the *Z*-isomer as indicated by a coupling constant of 14 Hz between the alkenic hydrogens.[13] The importance of using a thiophosphite rather than a phosphite in these types of addition reactions should be emphasised. Thus whereas reaction of ethynylbenzene with diethyl thiophosphite produced the expected *Z*-adduct in 67% yield, the corresponding reaction using diethyl phosphite did not produce any of the desired product.[14]

Addition of **2** to prochiral alkenes was then investigated. For example, reaction of a 9:1 mixture of diastereoisomers of **2** with 2-methyl-2-propenyl phenyl ether gave **7** as an inseparable mixture of 4 diastereoisomers in 80% yield (Fig. 2). Analysis of the ^{1}H and ^{31}P NMR spectra indicated a 9:9:1:1 ratio of the four diastereoisomers of **7**. This suggests that although the configuration of the phosphorus stereogenic centre is retained, there is no control over the formation of the new carbon stereogenic centre in adduct **7**. Hydride **2** can therefore react equally well with either face of the intermediate carbon-centred radical (of type **4**). A similar result was obtained when a 9:1 mixture of isomers of **2** was reacted with ethylidenecyclohexane. This gave a 9:9:1:1 mixture of diastereoisomers of **8** in a combined yield of 80%. It therefore appears that the intermediate phosphorus-centred radical **3** (derived from **2**) can equally well approach either side of the double bond in ethylidenecyclohexane.

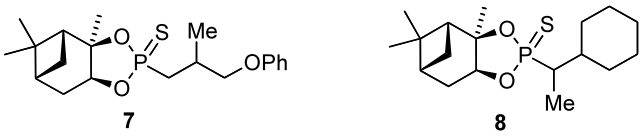
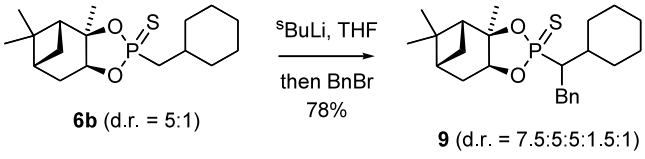


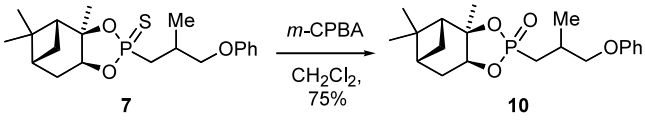
Figure 2.

The organophosphorus adducts derived from these radical addition reactions are useful synthetic intermediates. For example, α-alkylation reactions[7,15] are possible and this was investigated by deprotonation of **6b** at −78°C followed by treatment with benzyl bromide (Scheme 3). This gives rise to 4 diastereoisomers of **9** in the ratio of 7.5:5.5:1.5:1 (as indicated by the NMR spectra) and so there is little diastereoselectivity (1.5:1) in the alkylation. Further deprotonation and alkylation of **9** (using MeI or allyl bromide), in order to form a quaternary stereogenic centre, was unsuccessful and only starting material was recovered (as a 5:5:1:1 mixture of isomers).



Scheme 3.

It should also be noted that the thiophosphonate derivatives can be converted into phosphonates as shown in Scheme 4. Thus, reaction of (a 9:9:1:1 mixture of isomers of) **7** with *m*-CPBA[16] resulted in the formation of phosphonate **10** in good yield as a 9:9:1:1 mixture of isomers. This result is consistent with previous work, which has shown that oxidation of thiophosphonates using *m*-CPBA occurs with overall retention of configuration at phosphorus.[17]



Scheme 4.

This asymmetric approach to organophosphorus derivatives should be applicable to other chiral thiophosphites as chiral substituents can be easily introduced on to phosphorus.[7] This includes (−)-menthyl groups and reaction of the known dimenthyl phosphite **11**,[18] with Lawesson's reagent resulted in the formation of **12** (Fig. 3) in 95% yield (as a single diastereomer). Phosphite **11** can be prepared in ≥95% yield by reaction

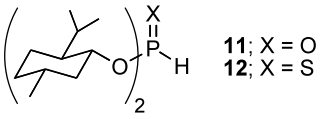


Figure 3.

of (−)-menthol with PCl_3/Et_3N followed by hydrolysis[16] or alternatively, by coupling (−)-menthol with phosphonic acid in the presence of DCC.[9]

Reaction of thiophosphite **12** (3.5 equiv.) with 1-octene (1 equiv.) in the presence of triethylborane (in cyclohexane at rt) followed by oxidation using *m*-CPBA resulted in the formation of phosphite **13** in an excellent 85% yield (Fig. 4). On treatment with ^{s}BuLi at −78°C followed by benzyl bromide this afforded the expected alkylated product **14** in 65% yield (as a 1:1 mixture of diastereoisomers). In a similar manner, reaction of **12** with 2-methyl-2-propenyl phenyl ether (1 equiv.) followed by *m*-CPBA gave **15** in 47% yield as an equal mixture of two diastereoisomers as indicated by the ^{1}H NMR spectrum.

13; R = H
14; R = Bn

15

Figure 4.

This work has shown for the first time that radical addition of chiral thiophosphites to alkenes occurs with retention of configuration at phosphorus. Addition to a variety of electron-rich alkene double bonds is possible and this offers a mild, efficient and selective approach to asymmetric organothiophosphonates, which are useful intermediates in organic synthesis.

Acknowledgements

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10. All spectra were in accord with the structures assigned.
11. The configuration of the phosphorus chiral centre in the major diastereoisomer of **2** was tentatively assigned as *S*. This was based on a NOESY experiment, which showed a correlation between the P–H and OC–CH_3 groups.
12. 1-Octene (20 mg, 0.19 mmol) and a 1 M solution of triethyl borane in hexanes (0.056 mL, 0.056 mmol) were added to a stirred solution of thiophosphite **2** (110 mg, 0.46 mmol) as a 4:1 mixture of diastereoisomers in tetrahydrofuran (2 mL) under an atmosphere of nitrogen at room temperature. After 6 h, further triethylborane (0.056 mL, 0.056 mmol) was added and the mixture stirred for 48 h while adding triethylborane portionwise (3×0.056 mL, 0.056 mmol) over this period. The mixture was then concentrated in vacuo. Purification by column chromatography on silica (hexane:ethyl acetate; 8:2) afforded (1*R*,2*R*,6*S*,8*R*)-2,9,9-trimethyl-4-octyl-3,5-dioxa-4λ^5-phosphatricyclo[6.1.1.0.^{2,6}]decane-4-thione **6a** (60 mg, 93%) as a colourless oil as a 4:1 mixture of diastereoisomers as indicated by the ^{1}H and ^{31}P NMR spectra. R_f 0.4 (hexane:ethyl acetate; 8:2): ν_{max} (CH_2Cl_2) 2929 (s), 2856 (s), 1267 (s), 943 (s) cm^{-1}. The major diastereoisomer was indicated by: δ_H (300 MHz, $CDCl_3$) 4.48 (1H, m, OC*H*), 2.45–1.25 (20H, m, 9×CH_2 and 2×C*H*), 1.54 (3H, s, CH_3), 1.32 (3H, s, CH_3), 0.88 (3H, t, J=6 Hz, CH_3), 0.85 (3H, s, CH_3); δ_C (75.0 MHz, $CDCl_3$) 91.6 (d, J_{CP}=4 Hz, O*C*CH), 80.5 (d, J_{CP}=2.7 Hz, O*C*HCH$_2$), 52.2 (d, J_{CP}=4 Hz, OC(CH$_3$)*C*H), 39.9 (*C*H), 38.6 (d, J_{CP}=92 Hz, P*C*H$_2$), 35.3 (*C*H$_2$), 32.2 (*C*H$_2$), 30.7, 30.5, 29.5, 29.4 (4×*C*H$_2$), 28.9 (POC*C*H$_3$), 27.6 (*C*H$_2$), 27.5, 24.6 (2×*C*H$_3$), 23.0 (*C*H$_2$), 14.5 (CH$_2$CH$_2$*C*H$_3$); δ_P (97.4 MHz, $CDCl_3$) 121.0; m/z (CI, NH_3) 345 (M+H$^+$, 100%); HRMS found 345.2018. $C_{18}H_{34}O_2PS$ requires for MH, 345.2017). The presence of the minor diastereoisomer was indicated by: δ_H (300 MHz, $CDCl_3$) 4.25 (1H, m, OC*H*); δ_P (97.4 MHz, $CDCl_3$) 121.1.
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