Stereoselective Synthesis of α-Phosphorylated Spiranes

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Abstract: α-Oxospiranes have been converted into vinyl triflates for phosphorylation and arylation by palladium-catalyzed cross-coupling reactions. With diethyl phosphite, the coupling provided olefinic mono- and diphosphonated spiranes. Saturation of conjugated aryl and phosphoryl alkene bonds was stereoselective when effected by catalytic hydrogenation. The double bond in conjugated alkenylphosphonates was in general more difficult to reduce than conjugated aryl derivatives. In mixed substrates, regioselectivity in the saturation of conjugated olefinic bonds was obtained.

Keywords: spirane-α-phosphonic esters, spirane bridges, cross coupling, phosphorylation, stereoselective hydrogenation

The central carbon atom in spiranes is shared between two orthogonally annulated rings that constitute the spirane. Small ring spiranes have a rigid framework, which provides a potentially useful skeleton for attachment of highly configurationally oriented substituents, especially in the α,α'-positions next to the spiro center. Spiranes with sterically rigidified pharmacophoric groups become accessible. Also, configurationally oriented coordinating functions in a spirane will provide ligands for metal complexation such as in metalloccenes and semimetalloccenes. Target molecules in this work have been spirane-bridged structures, as shown in Figure 1, which are reminiscent of certain ligands in metalloccenes. We have for some time been engaged in the development of methodologies that allow ready access to functionalized spiranes.1–3

Substitution reactions in spiranes at the α-positions are difficult to effect because of the quaternary carbon nature of the spirocenter. When the α-carbon is sp2-hybridized, however, addition of a nucleophile at this carbon can take place.4 In another variation, we have shown that the introduction of a substituent at sp2-hybridized α-carbons in spiranes can be effected smoothly when an α-oxo function is initially converted into a triflate; subsequent palladium-catalyzed cross-coupling allows the introduction of aryl groups.4

The substrate 1 in Scheme 1 is available from the corresponding 1,6-dioxospirane by monoacetalization and triflation.1 For triflation at the α-carbon, either N-phenylbis(trifluoromethanesulfonimide) (PhNTf2) or trifluoromethanesulfonic anhydride (Tf2O) can be used. The milder reagent N-phenylbis(trifluoromethanesulfonimide) is generally better.

Scheme 1

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In the literature we have found no reference to C–P bond formation in an α-position in spiranes. By way of cross-coupling reactions between an enol triflate we provide a method for C–P bond formation. Some cross-coupling reactions in C–P bond formation are shown in Scheme 1. Cross coupling between phosphorus and carbon reactants has recently been reviewed. In early work C–P bond formation was between vinyl or aryl halides and dialkylphosphinates. Diarylphosphine oxides have also been employed in C–P bond formation with appropriate halides or triflates in palladium-mediated reactions.

The first work on phosphorylations in the present study was with the acetal-protected triflate 1, which was reacted with diphenylphosphine oxide; various palladium complexes failed to effect cross coupling. With the more nucleophilic diethyl phosphite reagent7 and 3.4% tris(dibenzylideneacetone)dipalladium–chloroform complex [Pd2(dba)3·CHCl3] for catalysis, the phosphonate product 2 was isolated in 78% yield after 14 hours at 85 °C; with tetrakis(triphenylphosphine)palladium(0) [Pd(PPh3)4] (10%) as catalyst, only 40% transformation was seen after 7 days. The diphosphonate 5 could not be made in a satisfactory yield directly from the corresponding 1,6-ditriflate. The latter was available from the corresponding diketone. In the stepwise procedure for the preparation of the diphosphonate shown in Scheme 1, the monophosphonate 2 was deprotected by chemoselective cleavage of the acetal function by 3 M hydrochloric acid, and the ketone 3 subjected to triflation reactions. With one equivalent of base, very little triflation occurred. However, with 2.2 molar equivalents of lithium hexamethyldisilazanide and N-phenylbis(trifluoromethanesulphonimide), 53% of the triflated phosphonate 4 was obtained. When the amount of the triflate reagent was halved, no triflated product 4 was isolated. This finding may be rationalized as due to initial deprotonation and formation of a mixed tricic acid–phosphonic acid anhydride. The latter is subsequently deprotonated and triflated in the cyclohexane ring. The mixed anhydride function is cleaved by alkali during the work up of the reaction. The coupling between the triflated phosphonate 4 and the phosphorus reagent gave the diphosphonate 5 in a moderate yield, 36% after two days. A number of alternative conditions and catalyst systems were tried without much success. The presence of lithium bromide was essential as a catalyst stabilizer.

 Aryl coupling into the triflated six-membered ring in substrate 4 using Suzuki conditions provided the arylation 1-phosphonate 6 in a moderate yield (Scheme 2). Initial coupling reactions using Stille conditions were unsatisfactory. Compound 8 is a regioisomer of the previous product 6 and was prepared by a palladium-catalyzed coupling between the 1-aryl-6-triflate 7 and diethyl phosphate in moderate yield. The triflate 7 was available from previous work.

The substituents in the spiranes so far prepared are attached to an sp2-hybridized α-carbon and hence are coplanar with the spirane rings. The substituents have an internal orthogonal relationship. Previously, a benzoannulated spiro[4.4]nonane, 1,1′-spirobiindane-7,7′-dihol, was described as an intermediate for ligand formation. In a spirane, the a,a′-substituents at sp3-hybridized carbons can have a cis,cis-, a cis,trans-, or trans,trans-relationship. In the cis,cis-configuration the substituents are spaced for efficient coordination towards a central metal atom as in a sandwich system. The cis,cis-configuration, however, leads to a significant repulsive interaction between the substituents, and is, in general, thermodynamically the most unfavorable structure of the three geometrical isomers. A solution for the preparation of cis,cis-structures is shown in Scheme 3. Substituents are attached at the α-position to an olefinic carbon. For steric reasons in heterogenous hydrogenation, the less sterically shielded face of a spirane ring becomes associated with the catalyst. A subsequent transfer of hydrogen from the metal to the double bond forces the substituent into a cis-position. The reactions in the present case were fully stereoselective in that only one product was seen and was assigned the cis,cis-structure (vide infra). Hence the stereoselectivity for hydrogenation in the present series corresponds to our findings in a,a′-dicarbon substituted olefinic spiro[4.4]-series.

In the phosphonate series, initial heterogeneous hydrogenation of the double bond over palladium or platinum in the acetal-phosphonate 2 (Scheme 1) failed. Neither form/palladium complexes nor metal hydrides showed any promise. Further work with bulky acetal derivatives was abandoned. Instead the 6-oxo derivative 3, after removal of the acetal function, was the substrate. The α,β-unsaturated phosphonate 3 could be hydrogenated chemoslectively over Adams catalyst to the cyclopentyl derivative 9 in 65% yield at atmospheric pressure. The reaction was slow and was stopped after 20 hours. Several attempts were made to prepare the saturated spirane 11. With Adams catalyst at room temperature and hydrogen at 60 bar, the product was the α,β-unsaturated phosphonate 10, which was isolated in 45% yield after 22 hours. When the hydrogenation was continued at 65–80 °C, some of the
fully reduced spirane 11 (ca. 30%) was seen in a heterogeneous product mixture after one day (NMR spectroscopy). With palladium on charcoal under atmospheric hydrogen pressure, however, the fully reduced product 11 was isolated from substrate 6 in 50% yield after eight days at room temperature. The isolated product appeared to be homogeneous. Its stereochemistry has not been verified to be cis,cis since the product was not a solid and therefore not suitable for X-ray analysis. The substrate 6 is a racemate, and stereoselective cis-hydrogenation will provide 11 as drawn in the (1R,5R,6S)-form, and its enantiomer. The product is a racemate and therefore appears to be homogeneous. A similar conclusion would result from the less likely trans,trans-addition. A mixed cis,trans mechanism would lead to a stereochemically heterogeneous product mixture of diastereomers with different properties. The reduction product 11 has therefore been assigned the cis,cis-configuration. The assignment of regioselective saturation of the styrene double bond in the substrate 6 to furnish product 10, was based on NMR spectroscopy. Two doublets at δ = 136 and 154 were present in the 13C NMR spectrum with coupling constants 176 Hz for vicinal 31P–13C and 11 Hz for β-vinyl 13C–31P coupling, respectively. Hence the remaining double bond is part of an α,β-unsaturated phosphonic acid system.

Reduction of the diphosphonate substrate 5 (Scheme 1) was difficult to effect. An attempted hydrogenation at 50–80 bar with temperatures in the region 50–80 °C over 20 days gave a heterogeneous product mixture, which contained some fully reduced diphosphonate (NMR) from the substrate 5. The project was not further elaborated.

The findings from the hydrogenation studies suggest that the hydrogenation of the double bond in the six-membered ring is faster than in the five-membered ring. Furthermore, the double bond in conjugation with the phenyl ring reacts faster than when conjugated with the phosphonate function. In part, this may be attributed to the larger bulkiness of the phosphonate function over the anisyl group which disfavors coordination of the double bond to the metal reducing surface.

In conclusion, our work demonstrates that palladium-catalyzed cross-coupling reactions of α- and α,α'-vinyl triflates of spiranes with phosphites provide the corresponding phosphonates. Both monophosphonated and diphosphonated spiranes can be formed. Arylation is effected similarly, and mixed phosphonated-arylated spiranes can be formed. Saturation of the α,β-unsaturated aryl and phosphonyl double bonds by catalytic hydrogenation can be effected in a stepwise manner. The products have been assigned the α,α'-cis,cis-configuration. The monophosphonates are potential precursors for ligands in semimetallocenes.

1H NMR (500 MHz) and 13C NMR (125 MHz) spectra were recorded of samples in CDCl3. Chemical shifts are reported relative to residual CHCl3 (δ = 7.24) and CDCl3 (δ = 77). Interpretation of the NMR spectra was helped by COSY, DEPT HETCOR, and COLOC techniques. The mass spectra were recorded at 70 eV ionizing potential. IR spectra were measured on a Nicolet Magna 550 spectrometer using attenuated total reflectance (ATR).

THF was dried by distillation from Na/benzophenone under N2. CH2Cl2 was dried by distillation from CaH2. Solvents were degassed by bubbling argon through. Reactions under dry conditions were run under a slight positive pressure of argon gas.
Diethyl (1,4-Dioxadispiro[4.0.4.4]tetradec-7-en-7-y]phosphonate (2)

A solution of 1 (2.20 g, 6.43 mmol), diethyl phosphite (1.16 mL, 9.01 mmol), and Et$_3$N (4.04 mL, 29.0 mmol) in DMF (20 mL) containing Pd(dba)$_2$Cl$_2$C$_6$H$_5$ (0.115 g, 0.111 mmol) was stirred at 85 °C overnight. A sat. aq NaHCO$_3$ soln (15 mL) was added to the cold mixture and it was extracted with hexane (4 × 20 mL). The combined extracts were dried (MgSO$_4$), and evaporated and the residual material subjected to flash chromatography (silica gel, EtOAc) to give the product as a yellow oil; yield: 1.74 g (82%).

IR (film): 2955 (m), 2921 (m), 2864 (s), 2727 (m), 1460 (s), 1382 (s), 1364 (s), 1257 (s), 1032 (s) cm$^{-1}$.

1$^H$ NMR (500 MHz, CDCl$_3$): $\delta$ = 1.25–1.28 (m, 1 H, CH$_2$), 1.29 (t, $J$ = 7.1 Hz, 6 H, 2 OCH$_2$CH$_3$), 1.39 (d, $J$ = 13.4 Hz, 1 H, CH$_2$, CHF$_2$), 1.51–1.57 (m, 3 H, CH$_3$, CHF), 1.64–1.68 (m, 1 H, CH$_2$), 1.72–1.78 (m, 1 H, CHF), 2.21–2.25 (m, 1 H, CHF), 2.31–2.54 (m, 4 H, 2 OCH$_2$), 3.69–3.87 (m, 3 H, OCH$_2$CH$_3$, H$_2$), 3.98–4.16 (m, 5 H, H$_2$, H$_3$, OCH$_2$CH$_3$), 6.74 (dd, $J$ = 11.8, 2.3, 1 H, H$_8$).

IR (film): 2977 (s), 2923 (s), 2864 (m), 1232 (s), 1085 (s) cm$^{-1}$.

1$^H$ NMR (500 MHz, CDCl$_3$): $\delta$ = 1.25–1.28 (m, 1 H, CH$_2$), 1.29 (t, $J$ = 7.1 Hz, 6 H, 2 OCH$_2$CH$_3$), 1.39 (d, $J$ = 13.4 Hz, 1 H, CH$_2$, CHF$_2$), 1.51–1.57 (m, 3 H, CH$_3$, CHF), 1.64–1.68 (m, 1 H, CH$_2$), 1.72–1.78 (m, 1 H, CHF), 2.21–2.25 (m, 1 H, CHF), 2.31–2.54 (m, 4 H, 2 OCH$_2$), 3.69–3.87 (m, 3 H, OCH$_2$CH$_3$, H$_2$), 3.98–4.16 (m, 5 H, H$_2$, H$_3$, OCH$_2$CH$_3$), 6.74 (dd, $J$ = 11.8, 2.3, 1 H, H$_8$).

IR (film): 2977 (s), 2923 (s), 2864 (m), 1232 (s), 1085 (s) cm$^{-1}$.

1$^H$ NMR (500 MHz, CDCl$_3$): $\delta$ = 1.25–1.28 (m, 1 H, CH$_2$), 1.29 (t, $J$ = 7.1 Hz, 6 H, 2 OCH$_2$CH$_3$), 1.39 (d, $J$ = 13.4 Hz, 1 H, CH$_2$, CHF$_2$), 1.51–1.57 (m, 3 H, CH$_3$, CHF), 1.64–1.68 (m, 1 H, CH$_2$), 1.72–1.78 (m, 1 H, CHF), 2.21–2.25 (m, 1 H, CHF), 2.31–2.54 (m, 4 H, 2 OCH$_2$), 3.69–3.87 (m, 3 H, OCH$_2$CH$_3$, H$_2$), 3.98–4.16 (m, 5 H, H$_2$, H$_3$, OCH$_2$CH$_3$), 6.74 (dd, $J$ = 11.8, 2.3, 1 H, H$_8$).

IR (film): 2977 (s), 2923 (s), 2864 (m), 1232 (s), 1085 (s) cm$^{-1}$.
NMR (500 MHz, CDCl3): δ = 1.23 (t, J = 7.5 Hz, 3 H, OCH2CH3), 1.27 (t, J = 7.5 Hz, 3 H, OCH2CH3), 1.43–1.52 (m, 1 H, H3), 1.59–1.69 (m, 3 H, H4, H9, H10), 1.91–2.03 (m, 2 H, H3, H9), 2.08–2.13 (m, 2 H, H8), 2.15–2.18 (m, 1 H, H10), 2.43–2.48 (m, 1 H, H4), 3.70 (s, 3 H, OCH3), 3.92–4.09 (m, 4 H, 2 OCH2CH3), 5.42 (dd, J = 3.9, 3.8 Hz, 1 H, H7), 6.42 (m, 1 H, H2), 6.73 (dd, J = 7.9, 7.5 Hz, 2 H, H3*, H5*), 7.08 (ddd, J = 7.9, 7.8, 1.7 Hz, 1 H, H4*), 7.21 (dd, J = 7.4, 1.5 Hz, 1 H, H6*).

13C NMR (125 MHz, CDCl3): δ = 16.3 (d, J = 4.7 Hz, 1 C, OCH2CH3), 16.4 (J = 5.7 Hz, 1 C, OCH2CH3), 19.3 (C9), 25.5 (C8), 32.5 (d, J = 21.4 Hz, 1 C, C5), 37.4 (C10), 40.3 (C1, 110.3, C3*), 119.3, 127.5 (C4* or C7), 127.7 (C7 or C4*), 131.7 (C13*), 132.7 (C6*), 138.2 (d, J = 18 Hz, 1 C, C1), 138.4 (C6), 150.5 (d, J = 13.9 Hz, 1 C, C2), 157.2 (C2*).

MS (70 eV): m/z (%): 376 (9) [M]+, 160 (10), 159 (19), 129 (11), 91 (7).


**Diethyl 1-[2-Methoxyphenyl]spir[4,5]deca-1,6-dien-6-ylphosphonate (8)**

A soln of 7 (300 mg, 0.77 mmol), diethyl phosphite (0.14 mL, 1.08 mmol), Et3N (0.46 mL, 3.46 mmol, 4.5 equiv), and Pd(dba)2 (35 mg, 0.034 mmol) in DMF (3.5 mL) was heated at 80 °C for 15 h. The cold mixture and the mixture extracted with hexane (4 × 15 mL). The combined hexane extracts were dried (MgSO4) and evaporated, and the product was subjected to flash chromatography (silica gel, 20% CH2Cl2–EtOAc) to give the product as a yellow oil; yield: 139 mg (48%).

IR (film): 2931 (s), 2869 (m), 1488 (w), 1461 (m), 1236 (m), 1057 (m) cm−1.


**Diethyl cis-6-[2-Methoxyphenyl]spir[4,5][dec-1-en-1-yl]phosphonate (10)**

PO2 (5 mg, 0.02 mmol) was added to a soln of 6 (40 mg, 0.11 mmol) in EtOAc (4 mL) and the mixture was stirred under H2 (30 bar) at r.t. for 2 h. No significant reaction was observed. Another portion of the catalyst, PO2 (12 mg, 0.05 mmol), was added and the H2 pressure was increased to 60 bar. The stirring was continued at r.t. for 22 h. The catalyst was filtered off and the product was isolated as a yellow oil after flash chromatography (silica gel, 20% EtOAc–CH2Cl2), which separated the remaining substrate; yield: 18 mg (45%).

IR (film): 2923 (s), 2852 (m), 1492 (w), 1434 (m), 1238 (m), 1053 (m), 1028 (m) cm−1.

**Diethyl cis-6-[2-Methoxyphenyl]spir[4,5][dec-1-en-1-yl]phosphonate (11)**

PO2 (5 mg, 0.02 mmol) was added to a soln of 6 (40 mg, 0.11 mmol) in EtOAc (4 mL) and the mixture was stirred under H2 (30 bar) at r.t. for 2 h. No significant reaction was observed. Another portion of the catalyst, PO2 (12 mg, 0.05 mmol), was added and the H2 pressure was increased to 60 bar. The stirring was continued at r.t. for 22 h. The catalyst was filtered off and the product was isolated as a yellow oil after flash chromatography (silica gel, 20% EtOAc–CH2Cl2), which separated the remaining substrate; yield: 18 mg (45%).
$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 1.23–1.29$ (m, 6 H, CH$_2$CH$_3$), 1.29–1.34 (m, 1 H, H3), 1.34–1.41 (m, 1 H, H8), 1.46–1.53 (m, 1 H, H2), 1.55–1.62 (m, 2 H, H3 and H4), 1.63–1.77 (m, 4 H, H7, 3 H9/ H10), 1.94–2.00 (m, 4 H, 1 H2, H7, H8, H9/H10), 2.02–2.11 (m, 1 H, H1), 2.22–2.27 (m, 1 H, H4), 3.33–3.35 (m, 1 H, H6), 3.77 (s, 3 H, OCH$_3$), 3.93–4.00 (m, 4 H, 2 OC$\cdot$H), 4.18–4.21 (m, 2 H, 2 OCH$_2$), 6.81 (d, $J = 7.0$ Hz, 1 H, H5$'$), 7.08–7.13 (m, 2 H, H6$'$, H4$'$).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 16.4$ (OCH$_3$CH$_2$), 16.5 (OCH$_3$CH$_2$), 22.3 (CH$_2$), 22.4 (CH$_2$), 22.8 (CH$_2$), 23.5 (CH$_2$), 33.1 (CH$_2$), 37.8 (C6), 38.8 (CH$_3$), 40.9 (C1), 48.7 (C5), 55.4 (OCH$_3$), 60.5 (d, $J = 7.0$ Hz, 1 C, OCH$_2$CH$_3$), 61.2 (d, $J = 6.7$ Hz, OCH$_3$CH$_2$), 110.5 (C3$'$), 120.8 (C5$'$), 126.7 (C6$'$ or C4$'$), 129.3 (C4$'$ or C6$'$), 134.7 (C1$'$), 156.8 (C2$'$).

MS (EI 70 eV): $m/z$ (%) = 380 (100) [M]$^+$, 259 (21), 242 (39), 121 (53), 91 (25).

HRMS (EI): $m/z$ [M]$^+$ calcd for C$_{21}$H$_{33}$O$_4$P: 380.2116; found: 380.2121.

**References**


