Tsuji- Trost-type *O*-allylation of α-hydroxyphosphonates : An expedient entry into phosphono oxaheterocycles

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Tetrahydrofurans and pyrans substituted at the 2 position by a phosphonate moiety represent an important class of compounds which exhibit a wide range of biological activities. We report here a general access to these cyclic derivatives *via* a one-pot sequential Pudovik/Tsuji-Trost type *O*-allylation/Ring-Closing Metathesis starting from readily available aldehydes.

Five and six-membered oxygen heterocycles substituted by a phosphonate group at the 2 position have attracted considerable attention over the years owing to the interesting biological activities exhibited by many sugars bearing a phosphonate at the anomeric position (Figure 1). Their structural analogy with various natural sugars possessing a β-phosphate has led to the development of general strategies for the preparation of these non-isosteric hydrolytically stable analogues, which were shown to display important antiviral[1] and anticancer[2] activities as well as glycosyltransferase inhibition (Figure 1).[3] The phosphonate group can also mimic the carboxylic moiety found at the C1 position of certain sugars such as the sialic acids, which are involved in the regulation of many biological phenomena.[4]

In the light of their biological potential, it is not surprising that numerous synthetic routes have been explored for the formation of these phosphono derivatives. Besides methods involving substitution at C1 of a pyranose or a furanose with a phosphite in the presence of a Lewis acid (Scheme 1, **A**),[5] various studies have explored the cyclization of α-hydroxyphosphonate intermediates *via* either a substitution reaction[6] or the addition on an alkene,[2a] an alkyne,[7] or a carbonyl moiety (Scheme 1, **B**).[8] Alternative pathways have also been reported including the cyclization of α,β-unsaturated ketophosphonates through a hetero Diels-Alder reaction (Scheme 1, **C**),[9] the addition of homoenolates to acyl phosphonates[10] or the cyclization of γ-hydroxy keto phosphonates.[11] Less explored strategies rely on the cyclization of an alkoxymethylene phosphonate anion,[12] the
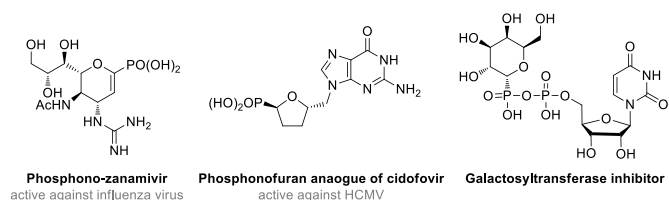
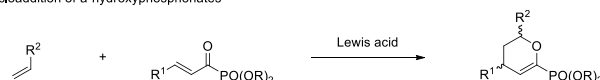**Figure 1.** Some biologically active phosphonopyrans and furans.
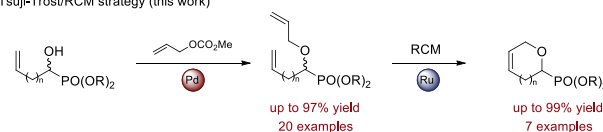

Scheme 1. Strategies to access phosphono-oxaheterocycles.

reaction of an α-diazophosphonates with ketones[13] or on the phosphite addition to 2-nitroglycals.[14] Considering all these methods and their respective limitations, we envisioned that a ring-closing metathesis (RCM) of a properly functionalized α-hydroxyphosphonate derivative would allow a particularly straightforward access to these targets (Scheme 1, **D**). In addition, in view of the number of catalytic methods reported in the literature for the addition of phosphites to aldehydes,[15] including various highly enantioselective ones,[16] this strategy could eventually allow an asymmetric approach to these target molecules. We report here our results, which have not only led to the synthesis of a variety of phosphono oxaheterocycles, but also to the development of an unprecedented Pd-catalysed *O*-allylation of Pudovik adducts.
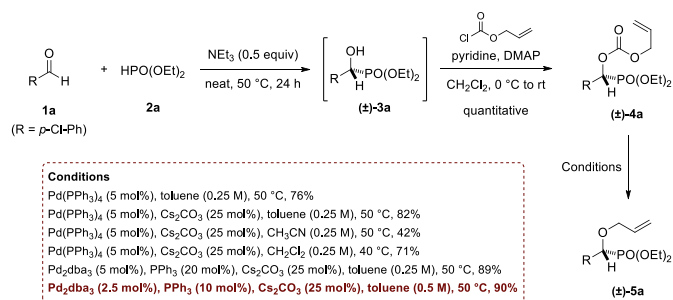
Scheme 2. Synthesis and *O*-allylation of α-hydroxyphosphonate **4a** through intramolecular Pd-AA.
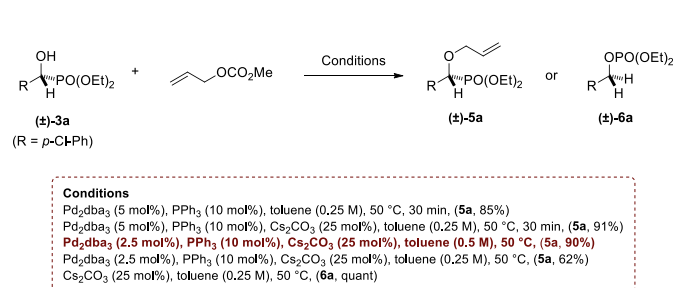

Scheme 3. *O*-Allylation of α-hydroxyphosphonate **3a** through intermolecular Pd-AA.

We became interested in this sequential Pudovik/Tsuji-Trost type *O*-allylation/RCM following an on-going project in the group focused on the development of new palladium-catalysed allylic alkylation (AA) processes.[17] Indeed, when applying typical Pd-AA conditions to an allyl carbonate derived from an α-hydroxyphosphonate, we were surprised to observe the formation of the corresponding *O*-allylated product as we expected the alkoxide intermediate to undergo a phospha-Brook rearrangement and subsequent *C*-allylation. This result was all the more interesting that under basic conditions, which are usually required in traditional *O*-allylation reactions with allyl bromides or chlorides, decomposition of the starting material through phosphonate elimination[18] or phospha-Brook rearrangement[19] is usually observed. We therefore decided to investigate this allylation reaction further.

To alleviate any potential decomposition of the α-hydroxyphosphonate, we initiated this study by evaluating the palladium-catalysed extrusion of carbon dioxide from allylcarbonate **4a**. The latter was prepared in quantitative yield from *p*-chlorobenzaldehyde **1a** and diethyl phosphite **2a** in a two-steps sequence (Scheme 2).[20] Interestingly, when **4a** was treated with 5 mol% of Pd(PPh₃)₄ in toluene (0.25 M), we were pleased to observe the formation of the corresponding *O*-allylphosphonate **5a** in 76% yield. Addition of a small amount of Cs_2CO_3 (0.25 equiv) slightly improved the yield (82%), whereas the use of a more polar solvent such as CH_3CN appeared detrimental (42%). The best conditions were obtained with a Pd₂dba₃ (2.5 mol%)/PPh₃ (10 mol%) combination in toluene (0.5 M) as the desired *O*-allylated product **5a** was obtained in up to 90% isolated yield. The same conditions could be successfully applied to the analogous 4-methoxy derivative **4b**, affording the corresponding *O*-allylated product **5b** in 78% yield (not shown in Scheme 2).

To optimize this sequence further, we decided to evaluate the direct intermolecular allylation of the Pudovik adduct **3a** with allyl methyl carbonate. Compared to the oxyallylation of standard alcohols, we expected that an intramolecular hydrogen bonding would increase the acidity of **3a** and thus allow the Tsuji-Trost allylation to proceed without requiring the use of allyl *tert*-butyl carbonate as observed for 2-hydroxy esters.[21] This was indeed the case as, when **3a** was treated with allyl methyl carbonate under the conditions settled previously, the phosphonoether **5a** was obtained in a comparable 85% yield (Scheme 3). Here again, a slight beneficial effect of added Cs_2CO_3 was observed (91%). Though the combined effect of the added base together with the

palladium catalyst is difficult to explain, the efficiency of the palladium catalysis under these conditions is clearly pictured by the fast phospha-Brook conversion of **3a** into **6a** when the same reaction was conducted without palladium under otherwise identical conditions.

With these conditions in hand, the efficiency of the procedure was evaluated with a set of aliphatic and aromatic α-hydroxy phosphonates **4**, all prepared under solvent-free conditions from the corresponding aldehydes and phosphites (Table 1, entries 1-11). As a general trend, the Pudovik step is quantitative and only requires a simple evaporation and filtration over silica gel to afford a phosphite-free starting material suitable for the following Tsuji-Trost allylation step.

Various electron-rich and poor aromatic aldehydes were thus successfully converted to the target products in good to excellent yields ranging from 67 to 97% (Table 1, entries 1-3 and 5-8). The sequence was also applicable to a variety of heterocyclic (Table 1, entries 9-11), aliphatic (Table 1, entry 4) and styrene derivatives (Table 1, entry 13), yielding once again the desired products in good to excellent yields (60-96%). Unfortunately, these conditions were not suitable for the α-hydroxy phosphonates derived from ketones as shown by the low yield obtained in the allylation of **5h** (Table 1, entry 7) and the recovery of acetophenone.

Conversely, variation of the allyl component was well tolerated with phenyl-substituted products **5k'** and **5l** obtained in 60 and 64% yield respectively (Table 1, entries 11-12), while the replacement of diethyl phosphite by dimethyl phosphite did not drastically alter the outcome of the reaction (Table 1, entry 2).

Next, we turned our attention to the synthesis of various phosphono oxaheterocycles by subjecting Pudovik adduct's bearing a pendent olefin to RCM conditions. To this end, we prepared a range of dienes of various length **3n-q** and subjected them to standard RCM conditions using Grubbs' second generation catalyst, **GII** (4 mol%), in refluxing CH_2Cl_2 (100 mM concentration) (Table 2). Under these conditions, small rings were obtained in good yields ranging from 81 to 92% (Table 2, entries 1-4). This strategy was also amenable to the synthesis of larger macrocycles including 14-, 15- and 16-phosphono oxaheterocycles, but required more dilute conditions (1 mM) to avoid any undesired oligomerization (Table 2, entries 5-7). Of note is the efficient formation of [12] and [13]metacyclophanes **7f** and **7g** which were obtained in 69 and 99% yield respectively.

Table 1. Scope of the *O*-allyl hydroxyphosphonate synthesis.[a]

Reaction scheme: R¹CHO (1b-m) + HPO(OR²)₂ (2), NEt₃ (0.5 equiv), neat, 50 °C, 24 h → hydroxyphosphonate (±)-3b-m; then R³CH=CHCH₂OAc, Pd₂dba₃, PPh₃, Cs₂CO₃, toluene, 50 °C, 30 min → (±)-5b-m.

Entry	Abramov adduct 3	Yield[d] (%)	Carbonate	Phosphonate 5	Yield[d] (%)
1	**3b** (MeO-C₆H₄, CH(OH)PO(OEt)₂)	quant[b]	Me-C(O)-OAllyl	**5b**	85
2	**3c** (O₂N-C₆H₄, CH(OH)PO(OMe)₂)	83[c]	Me-C(O)-OAllyl	**5c**	78
3	**3d** (o-NO₂-C₆H₄, CH(OH)PO(OEt)₂)	quant[b]	Me-C(O)-OAllyl	**5d**	97
4	**3e** (Ph-CH₂CH₂CH(OH)PO(OEt)₂)	81	Me-C(O)-OAllyl	**5e**	67[e,f]
5	**3f** (Cl-C₆H₄, CH(OH)PO(OMe)₂)	quant[b]	Me-C(O)-OAllyl	**5f**	94
6	**3g** (Cl-C₆H₄, CH(OH)PO(O*i*-Pr)₂)	quant[b]	Me-C(O)-OAllyl	**5g**	90
7	**3h** (Cl-C₆H₄, C(OH)(Me)PO(OEt)₂)	77[g]	Me-C(O)-OAllyl	**5h**	21[h,i]
8	**3i** (o-Br-C₆H₄, CH(OH)PO(OEt)₂)	98[j]	Me-C(O)-OAllyl	**5i**	79
9	**3j** (pyridyl, CH(OH)PO(OEt)₂)	71[j]	Me-C(O)-OAllyl	**5j**	78[k]
10	**3k** (furyl, CH(OH)PO(OEt)₂)	quant[b]	Me-C(O)-OAllyl	**5k**	96
11	**3k** (furyl, CH(OH)PO(OEt)₂)	quant[b]	Me-C(O)-O-CH₂CH=CH-Ph	**5k'**	60
12	**3b** (MeO-C₆H₄, CH(OH)PO(OEt)₂)	quant[b]	Me-C(O)-O-CH₂CH=CH-Ph	**5b'**	64
13	**3l** (MeO-C₆H₄CH=CH-CH(OH)PO(OEt)₂)	quant[b]	Me-C(O)-OAllyl	**5l**	77[f]

[a] All the Pudovik reactions were run on a 5 mmol scale, while the Tsuji-Trost reactions were run on a 1 mmol scale. [b] When quantitative, the crude mixture was simply filtered over silica gel. [c] Very fast reaction completed in 5 min under mecanical mixing. [d] Isolated yield. [e] Reaction performed at 100 °C. [f] Reaction ran for 1.5 h. [g] Obtained with a different procedure using *n*-BuLi as a base. [h] 50% starting ketone recovered. [i] Reaction ran for 1 h. [j] Reaction performed at 50 °C during 2 h for **3i** and 12 h for **3j**. [j] Reaction ran for 12 h.

In summary, we have developed an unprecedented palladium-catalysed allylation of α-hydroxyphosphonates circumventing the phospha-Brook rearrangement that otherwise occurs in typical alkylating conditions. The broad scope tolerated by the reaction

Table 2. Scope of the *O*-allylation/RCM sequence.

Reaction scheme: allyl-OAc, Pd₂dba₃, PPh₃, Cs₂CO₃, toluene, T (°C), t (h), 3n-q → 5n-t; then GII (4 mol%), CH₂Cl₂, 40 °C → 7a-g. GII = Grubbs II catalyst.

Entry	Allylation product 5	Yield[a] (%)	Heterocyclic product 7	C (mM)	Yield[a] (%)
1	**5n**	82 (100 °C, 5 h)	**7a** (5) PO(OEt)₂	100	89
2	**5o**	40[b] (50 °C then 100 °C)	**7b** (6) PO(OEt)₂	100	82
3	**5p**	58 (80 °C, 12 h)	**7c** (7) PO(OEt)₂	100	81
4	**5q**	91 (50 °C, 2 h)	**7d** (7) (EtO)₂OP	100	92
5	**5r**	74 (50 °C, 4 h)	**7e** (14) (EtO)₂OP (*E/Z*[d] = 83:17)	1	92[c]
6	**5s**	97 (50 °C, 4 h)	**7f** (15) (EtO)₂OP (*E/Z*[d] = 77:23)	1	69[c]
7	**5t**	82 (50 °C, 4 h)	**7g** (16) (EtO)₂OP (*E/Z*[d] = 78:22)	1	99[c]

[a] Isolated yield. [b] **3o** was obtained following a double allylation process (see supporting information). [c] Required 6 mol% catalyst loading. [d] Determined by NMR analysis on the crude reaction mixture.

allowed us to access a diverse array of allyloxyphosphonates in good to excellent yields under mild conditions. This method was eventually implemented in a Pudovik/Tsuji-Trost type *O*-allylation/RCM sequence affording an expedient and high yielding entry into valuable phosphonated heterocycles of various sizes ranging from 5 to 16.

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