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Novel, Stereoselective and Stereospecific Synthesis of Allenylphosphonates and Related Compounds *via* Palladium-Catalyzed Propargylic Substitution

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Abstract: We have developed a novel method for the synthesis of allenylphosphonates and related compounds based on a palladium(0)-catalyzed reaction of propargylic derivatives with H-phosphonate, H-phosphonothioate, H-phosphonoselenoate, and H-phosphinate esters. The reaction is stereoselective and stereospecific, and provides a convenient entry to a vast array of allenylphosphonates and their analogues with diverse substitution patterns in the allenic moiety and at the phosphorus center. Some mechanistic aspects of this new reaction were also investigated.

Keywords: allenes; allenylphosphinates; allenylphosphonates; H-phosphonate diesters; palladium; propargylic substitution; S_N2' reactions

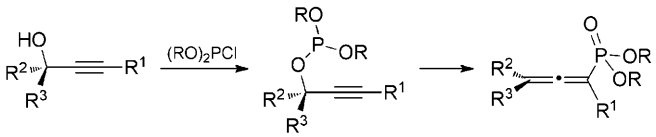
Introduction

In the last decade, the chemistry of allenes has emerged as a flourishing research area in organic chemistry.[1] In addition, due to the discovery of this structural fragment in many natural products, these chemical entities have started to attract also the increasing attention of pharmaceutical research.[2] With the development of novel synthetic methods,[3] with a prominent position of metal-catalyzed reactions,[4] allenes became useful intermediates in the chemical synthesis, frequently enabling a rapid molecular complexity increase in a single reaction step.[3a,5] The transfer of the axial chirality to a newly formed stereogenic center in a product observed for such reactions,[1,6] opens new possibilities in stereoselective synthesis.

As part of our interest in the synthesis of biologically important phosphorus compounds, we embarked recently on investigations of allenylphosphonates and related compounds. The attractive feature of these compounds is diverse reactivity that, with substituent-loading capability and axial chirality of the allene unit, makes them potentially useful synthetic intermediates. Due to the electron-acceptor nature of a phosphonate group, allenylphosphonates undergo facile and selective additions of various *N*-,[7] *O*-,[8] and *S*-nucleophiles,[9] as well as selective total[10] or partial[11] hydrogenation, radical reactions,[12] as well as Diels–Alder[13] and other cycloadditions.[14] Allenylphosphonates can be further functionalized by metal-catalyzed reactions[15] and the phosphonate group in these compounds can be employed in the Horner–Wadsworth–Emmons olefination.[16] Activation of the allene moiety with electrophilic reagents leads to cyclization producing oxaphospholanes,[17] and many of the above reactions can be combined in tandem processes[18] enabling, for instance, the synthesis of complex heterocycles.[7c,15b,19]

Phosphorus-containing compounds have always been attractive targets in biological and medicinal chemistry,[20] as they may serve as analogues of biologically important compounds, e.g., nucleic acids, phospholipids, phosphorylated sugars, or be used as enzyme inhibitors. Although an allene moiety has been extensively used in pharmacologically active compounds,[2] allenylphosphonates have not been explored yet in this context. We believe that this can be attributed to the lack of universal synthetic methods meeting the requirements of preparation of complex natural products analogues.

Except for some special cases,[13b,21] the synthesis of allenylphosphonates has been dominated by [2,3]-sigmatropic rearrangement reactions.[1] Discovered in

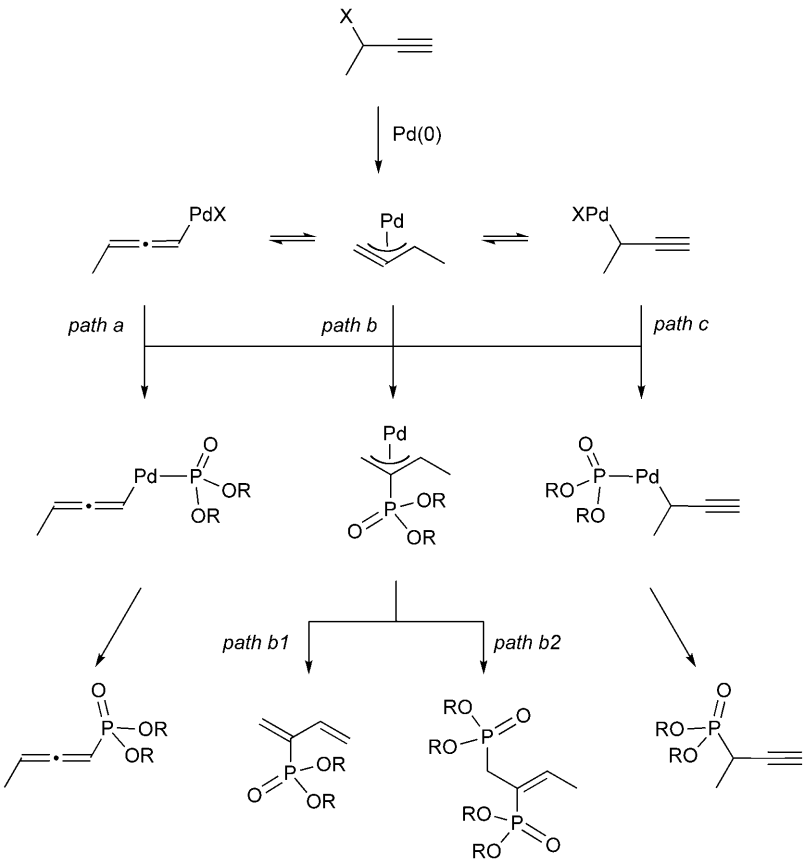


Scheme 1. Synthesis of allenylphosphonates *via* [2,3]-sigmatropic rearrangement.

the early 1960s, these involve propargylic phosphite esters that spontaneously rearrange to allenylphosphonates (Scheme 1)[22] with complete center to axial chirality transfer from the propargylic alcohol to the allene.[23] The method has a very broad scope with respect to the precursor propargylic alcohols used and it enables the synthesis of allenylphosphonates with various substitution patterns in the allene moiety. Despite these advantages, the method suffers from a serious drawback, namely, the limited number of phosphonate derivatives that can be prepared. Phosphorus compounds that are used for the synthesis of propargylic phosphites are phosphorochloridites, highly reactive compounds, prone to hydrolysis and oxidation, and thus only simple alkyl derivatives can be used for the preparation of allenylphosphonates. This feature limits the applicability of the procedure to the synthesis of only symmetrical allenylphosphonates bearing two identical, usually simple alkyl, substituents at the phosphorus center.

In order to overcome the limitations of these methods based on the sigmatropic rearrangement, we turned our attention to an in this context completely unexplored transition metal-catalyzed propargylic substitution (S_N2') reaction as a means for the synthesis of allenylphosphonates. Although, this is a well established synthetic approach to a variety of allenes,[1,24] the reaction has never been used for the formation of a carbon-phosphorus bond. An appealing feature of this type of palladium- or copper-catalyzed reaction is that often stereoselectivity and chirality transfer from the propargylic substrate to the allene moiety is observed.[1] Since Pd-catalyzed C–P bond formation has been shown to work well[25] in the synthesis of biologically important phosphorus compounds,[26] and mechanistic aspects of the reaction have been studied in depth,[27] we expected that these may lend themselves to a new methodology for the construction of complex allenylphosphonate derivatives.

There is also an interesting mechanistic aspect of a Pd-catalyzed synthesis of *C*-allenes vs heteroatom-substituted allenes (e.g., allenylphosphonates). Apart from a transmetallation of the equilibrating allenyl- and propargyl-palladium species[28] (Scheme 2, paths a



Scheme 2. Possible reaction pathways during Pd-catalyzed propargylic substitution with phosphonate nucleophiles.

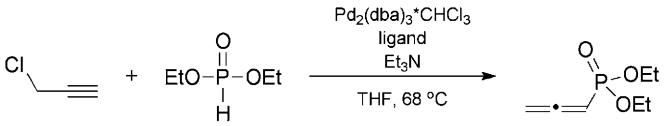
and c; formation of an allenyl- and propargyl-palladium-phosphonate intermediates, respectively), a 'soft' heteroatom nucleophile may attack a central carbon atom of the ligand (Scheme 2, path b).[24,29] For phosphorus nucleophiles, in the first instance, an allenylphosphonate (or propargylphosphonate) should be formed after reductive elimination, while in the second scenario, formation of either diene (*via* β-hydride elimination, path b1) or bisphosphonate (path b2) might be favoured. As shown by the work of Kozawa et al. on amide nucleophiles, the outcome of the reaction can be controlled by the supporting ligands used.[30]

Herein, we report studies on a palladium-catalyzed propargylic substitution reaction with H-phosphonates and related compounds as nucleophiles, aiming at the development of a new methodology for C–P bond formation, and to expand the scope of accessible allenylphosphonates, particularly those of potential biochemical relevance. A preliminary account of this work has recently been published as a short communication.[31]

Results and Discussion

Our exploratory studies on the reaction of propargylic halides with H-phosphonate diesters in the presence of Pd(0) as a catalyst revealed formation of allenylphosphonates rather than the corresponding propargylphosphonates.[31] Since the degree of the conversion with propargyl bromide was rather low (*ca.* 30%), apparently due to its reaction with triethylamine that was used as a base, in the subsequent studies less reactive propargylic derivatives (chlorides, tosylates, etc., Table 2) were employed.

Table 1. Evaluation of ligands.[a]



1a **2** **3**

Entry	Ligand	Reaction time[b]
1	$Pd(PPh_3)_4$[c]	no reaction
2	PPh_3	no reaction
3	dppp	no reaction
4	dppf	3 h
5	DPEPhos	1.5 h
6	Xantphos	2 h
7	BINAP	6 h

[a] Abbreviations: dppp = 1,3-bis(diphenylphosphino)propane, dppf = 1,1′-bis(diphenylphosphino)ferrocene, DPEPhos = bis(2-diphenylphosphin)diphenyl ether, Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene, BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphtyl (racemic). *Reaction conditions:* 0.28 mmol **1a**, 0.25 mmol **2**, 0.30 mmol Et_3N, 1.5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, 3 mol% bidentate or 6 mol% monodentate ligand, 1 mL THF (0.25 M), 68 °C.

[b] >95% conversion (^{31}P NMR).

[c] No $Pd_2(dba)_3{\cdot}CHCl_3$ was used.

Optimization of the Reaction Conditions

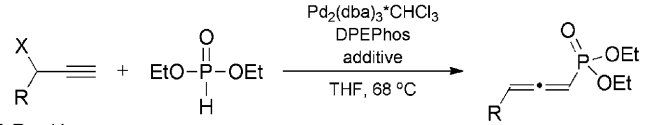
In order to evaluate different ligands for their efficacy to promote the formation of allenylphosphonates, the reaction between propargyl chloride (**1a**) and diethyl H-phosphonate (**2**) was studied in THF as a solvent at 68 °C, in the presence of Et_3N as a base (Table 1).

The screening revealed that only bidentate ligands with large bite angles were able to promote a conversion into the allenylphosphonate (Table 1, entries 4–7), and the highest reaction rate was observed for DPEPhos. To our delight, the desired allenylphosphonate **3** was always the sole product of the reaction, irrespective of the bidentate ligand used.

To investigate and optimize further the experimental conditions, the reactions with primary (**1**) and secondary (**4**) propargylic derivatives bearing different leaving groups [Cl, MeOC(O)O, TsO, AcO] were carried out. In all cases 3 mol% palladium loading was used together with DPEPhos ligand. For some entries also an effect of a base (Et_3N) and anionic additives was studied (Table 2).

The data from Table 2 provide practical guidelines for designing a synthetic method based on this reaction and also bear some mechanistic hints (see below). As it is apparent from entry 1, the propargylic chlorides showed relatively high reactivity, that did not depend on the presence or absence of an alkyl substituent on C-1 (primary *vs.* secondary propargylic derivatives). As expected, this reaction required the presence of a stoichiometric amount of a base (Table 2, entry 1 *vs.* entry 2). Propargylic carbonates, on the other hand, did not require an external base, and exhibited significant differences in rates between primary *vs.* secondary substrates (entry 3), with the later one reacting much faster (30 min *vs.* 7 h). The tosyl derivatives (**1c** and **4c**, Table 2, entry 4) were less reactive than the corresponding chlorides and in case of a primary propargylic derivative (**1c**), a partial isomerization of the product to 1-alkynylphosphonate derivative[32] was observed, apparently due to prolonged exposure to the base, necessary for reaching the full conversion. Finally, propargylic acetates were investigated (entries 6 and 7). These were found to be rather poor substrates for the reaction and in the presence of Et_3N, a large fraction of the products isomerized to the corresponding 1-alkynylphosphonates due to the very long reaction times (Table 2, entry 6). In the absence of a base, the reactivity improved, but

Table 2. Effect of the leaving group and additives.[a]



1 R = H
4 R = n-C_5H_{11}
a X = Cl, **b** X = OCO_2Me
c X = OTs, **d** X = OAc

2

3 R = H
5 R = n-C_5H_{11}

Entry	Leaving group	Additive[b]	Reaction time[c]	
			R = H	R = n-C_5H_{11}
1	Cl	Et_3N	1.5 h	1.5 h
2	Cl	–	no reaction	no reaction
3	OCO_2Me	–	7 h	30 min
4	OTs	Et_3N	10 h[d]	5 h
5	OTs	–	very slow reaction	very slow reaction
6	OAc	Et_3N	48 h[d]	24 h[d]
7	OAc	–	24 h[e]	8 h[e]
8	OTs	Et_3N, Cl^-	1.5 h	1.5 h
9	OTs	Et_3N, OAc^-	45 min	45 min

[a] *Reaction conditions:* 0.28 mmol **1** or **4**, 0.25 mmol **2**, 1.5 mol% $Pd_2(dba)_3{\cdot}CHCl_3$, 3 mol% DPEPhos, 1 mL THF (0.25 M), 68 °C.
[b] 0.30 mmol Et_3N or 0.075 mmol (30 mol%) $(n\text{-}Bu)_4N^+$ $anion^-$.
[c] > 95% conversion (^{31}P NMR).
[d] Partial isomerization of the product to 1-alkynylphosphonate (*ca.* 50%).
[e] Formation of 1,3-dienylphosphonate and other by-products (total, *ca.* 40%).

acidification of the reaction mixtures by the AcOH formed during the course of the reaction, led to formation of multiple side-products (Table 2, entry 7).[33]

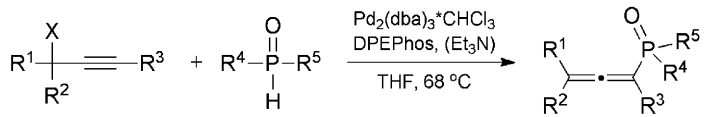
We also studied possible effects of anionic additives[26f,27a] on the outcome of the reaction with propargylic tosylates. Since tosylate anions are weakly bonding to the palladium(II) center, their replacement with the added anions (chloride or acetate) could potentially affect the transmetallation step. Indeed, addition to the reaction mixture of tetrabutylammonium chloride shortened down the reaction times to 1.5 h for both primary and secondary propargylic derivatives (Table 2, entry 8), a value identical to that observed when propargylic chlorides were used as substrates (Table 2, entry 1). Addition of external acetate anions [$(n\text{-}Bu)_4NOAc$] resulted also in a remarkable shortening of the reaction times to 45 min (Table 2, entry 9), and this indicated that the observed poor reactivity of propargylic acetates in this reaction (Table 2, entries 6 and 7) was apparently due to an inefficient oxidative addition step.

Synthesis of Allenylphosphonates and Allenylphosphinates

Having established the reactivity of different propargylic substrates under various experimental conditions, we decided to examine the scope of the reaction. Since propargylic chlorides and carbonates gave the best results without the necessity of using any additives, these two groups of substrates were used in the further investigations (Table 3).

The scope of the reaction with regard to a substitution pattern in propargylic substrates was investigated using diethyl H-phosphonate (**2**) as a *P*-nucleophile. As it is apparent from entries 1–19 (Table 3), the following trends in reactivity can be observed. The presence of one or two substituents (R^1 and R^2) at the C-1 carbon greatly increased the reaction rate of the propargylic carbonates, while it had only a minor effect on the reaction times of the corresponding propargylic chlorides. On the other hand, any substituent other than hydrogen in the terminal position of the alkyne (R^3) dramatically slowed down the reaction for both the leaving groups. These two opposite effects appeared to be approximately additive. Importantly, good conversions in case of the starting materials containing the R^3 substituent could only be achieved when carbonate was the leaving group (Table 3, entries 9, 11, 16, 17, and 19). However, in line with what was stated above, primary propargylic carbonates **9b** and **10b** with terminal substituents reacted very slowly (Table 3, entries 9 and 11, respectively), and in the latter case a microwave irradiation was required to drive the reaction to completion. Hence, except for the simple unsubstituted propargyl system (Table 3, entries 1 and 2), the propargylic carbonates

Table 3. Synthesis of allenylphosphonates and related compounds.[a]



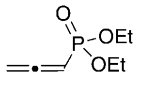
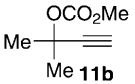
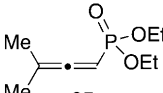
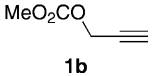
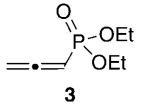
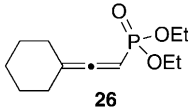
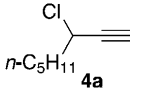
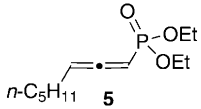
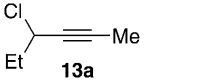
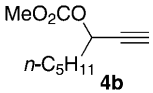
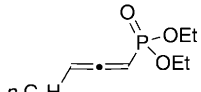
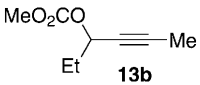
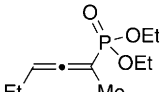
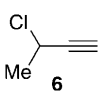
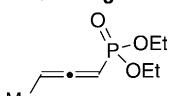
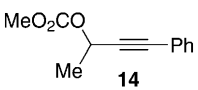
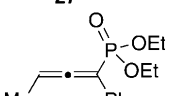
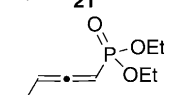
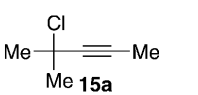
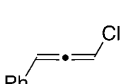
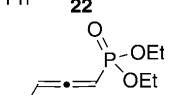
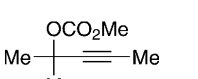
Entry	Propargylic substrate	*P*-nucleophile	Product	Reaction time (isolated yield)	Entry	Propargylic substrate	*P*-nucleophile	Product	Reaction time (isolated yield)
1	 **1a**	**2**	 **3**	1.5 h (88%)	13	 **11b**	**2**	 **25**	30 min (92%)
2	 **1b**	**2**	 **3**	7 h (79%)	14	 **12**	**2**	 **26**	1.5 h (80%)
3	 **4a**	**2**	 **5**	1.5 h (83%)	15	 **13a**	**2**	not isolated	47% conversion after 24 h
4	 **4b**	**2**	 **5**	30 min (91%)	16	 **13b**	**2**	 **27**	45 min (89%)
5	 **6**	**2**	 **21**	1.5 h (86%)	17	 **14**	**2**	 **28**	5 h (83%)
6	 **7**	**2**	 **22**	20 min (91%)	18	 **15a**	**2**	not isolated	80% conversion, 24 h
7	 **8**	**2**	 **22**	15 min (87%)	19	 **15b**	**2**	**29**	1 h (78%)
8	**9a**	**2**	na	no reaction	20	**1a**	**16**	**30**	2 h (66%)
9	**9b**	**2**	**23**	24 h (69%)	21	**1a**	**17**	**31**	16 h (78%)

Table 3. (Continued)

Entry	Propargylic substrate	*P*-nucleophile	Product	Reaction time (isolated yield)
10	**10a**	**2**	na	no reaction
11	**10b**	**2**	**24**	10 min[b] (77%)
12	**11a**	**2**	**25**	1 h (90%)
22	**1a**	**18**	**32**	16 h (84%)
23	**1a**	**19**	**33**	2 h (89%)
24	**4b**	**20**	**34**	36 h (67%)

[a] *Reaction conditions:* 1.38 mmol propargylic substrate, 1.25 mmol *P*-nucleophile, 0.019 mmol (1.5 mol%) $Pd_2(dba)_3 \cdot CHCl_3$, 0.038 mmol (3 mol%) DPEPhos, 5 mL THF (0.25 M), 68 °C. For propargylic chlorides, additionally 1.5 mmol Et_3N.

[b] 10 min microwave irradiation at 120 °C.

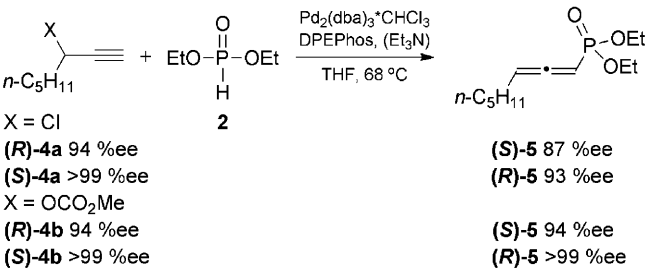
displayed higher reactivity than the corresponding chlorides. Overall, the Pd-catalyzed reaction fully matched the scope of the method based on a sigmatropic rearrangement (Scheme 1), enabling synthesis of unsubstituted (entries 1 and 2), and mono- (entries 3–11), di- (entries 12–17), and tri-substituted (entries 18 and 19, all in Table 3) allenylphosphonates. Interestingly, in a separate experiment we found that also chloroallene (**8**, Table 3, entry 7) can be efficiently used as a substrate in an analogous cross-coupling reaction.

Next, various phosphorus nucleophiles were tested, including different H-phosphonate diesters (Table 3, entries 20 and 21), and three phosphinates (entries 22–24). They all could be efficiently transformed into the corresponding allenylphosphonates and allenylphosphinates, although it became apparent that the reaction was sensitive to steric hindrance (compounds **17** and **20**, Table 3, entries 21 and 24). One should note, however, that due to essentially neutral pH of the reactions mixtures involving propargylic carbonates as substrates, long reaction times did not result in any deterioration (isomerization) of the products.

Stereochemical Aspects of Allenylphosphonate Formation

As it was mentioned in the introduction, the synthesis of allenylphosphonates *via* a sigmatropic rearrangement occurs with stereospecificity of the allenyl moiety formation. Taking into account an easy access to highly enantiomerically enriched propargylic alcohols[34] (e.g., from enzymatic kinetic resolution[35] or stereoselective addition to aldehydes[36]) this feature would be beneficial in the synthesis of complex allenylphosphonate derivatives. Therefore, we set out to investigate if the palladium-catalyzed reaction also can compete with the sigmatropic rearrangement method in this respect. In order to evaluate this possibility, enantioenriched propargylic chloride **4a** and propargylic carbonate **4b** (obtained from the corresponding alcohols), were allowed to react with diethyl H-phosphonate **2** under the developed conditions.

As it is apparent from the results presented in Scheme 3, the stereochemical outcome of the reaction depended on the leaving group present in the starting material. Using enantiomeric propargylic chlorides (*R*)- and (*S*)-**4a** as substrates resulted in allenylphosphonates (*S*)- and (*R*)-**5**, respectively (see below for the absolute stereochemistry assignment), however, the products *ee* was reduced to ~93% of that of the reactants. In contradistinction to this, propargylic carbonates (*R*)- and (*S*)-**4b** were transformed into the corresponding enantiomers of **5** with complete (within the experimental error) stereoselectivity.

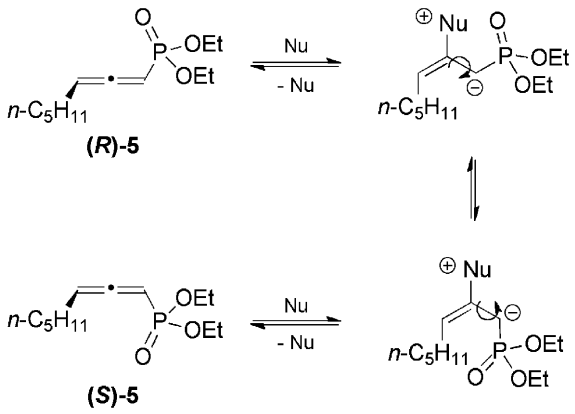


Scheme 3. Reaction of the enantioenriched propargylic chlorides (**4a**) and carbonates (**4b**) with H-phosphonate **2**.

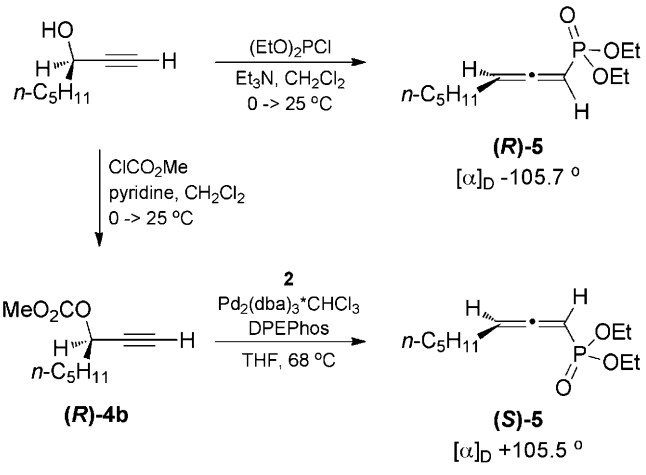
To obtain a deeper insight into origin of these differences, the stereochemical stability of allenylphosphonate **5** under different experimental conditions was examined. This revealed that compound **5** was prone to racemization by prolonged heating (in THF, at 68 °C), and this process was substantially accelerated by nucleophilic species, such as Cl^-, OAc^-, and palladium(0) [but not palladium(II)] complexes (see the Supporting Information). Such a behaviour of phosphonate **5** was not surprising since an allene moiety may undergo reversible nucleophilic addition at the β-carbon, resulting in racemization[37] as shown in Scheme 4. Since the reactions with propargylic chlorides **4a** took longer time than those with propargylic carbonates **4b** (1.5 h *vs.* 30 min, respectively, see Table 3, entry 3 vs. 4), and in the former case also Cl^- ions were present in the reaction mixture, these can account for the observed reduced stereoselectivity when propargylic chlorides were used as substrates. However, one cannot exclude a possibility that other factors may also contribute to a partial racemization during the course of the reaction.

Palladium-catalyzed S_N2' propargylic substitution is known to occur with an *anti*-stereoselectivity,[38] and the absolute stereochemistry of the allenic products is assigned on the basis of Lowe–Brewster rules,[39] correlating the absolute configuration of the carbon- and hydrogen-substituted allenes with the sign of their optical rotation. Since the applicability of these rules to phosphorus-substituted allenes is unknown, we established the absolute configuration of allenylphosphonate **5** by a stereochemical correlation method. To this end we took advantage of the fact that chiral allenylphosphonate **5** can be synthesized stereospecifically *via* an alternative method, namely by the sigmatropic rearrangement reaction, that due to its concerted character must occur in a *syn* fashion (Scheme 1). Since the allenylphosphonates **5** synthesized from the same enantiomer of the propargylic alcohol by the sigmatropic rearrangement and the Pd-catalyzed propargylic substitution had opposite configurations (Scheme 5), we tentatively concluded that the latter reaction occurs with an *anti*-stereoselectivity – similarly to the previously reported stereochemistry for the synthesis of *C*-allenes.

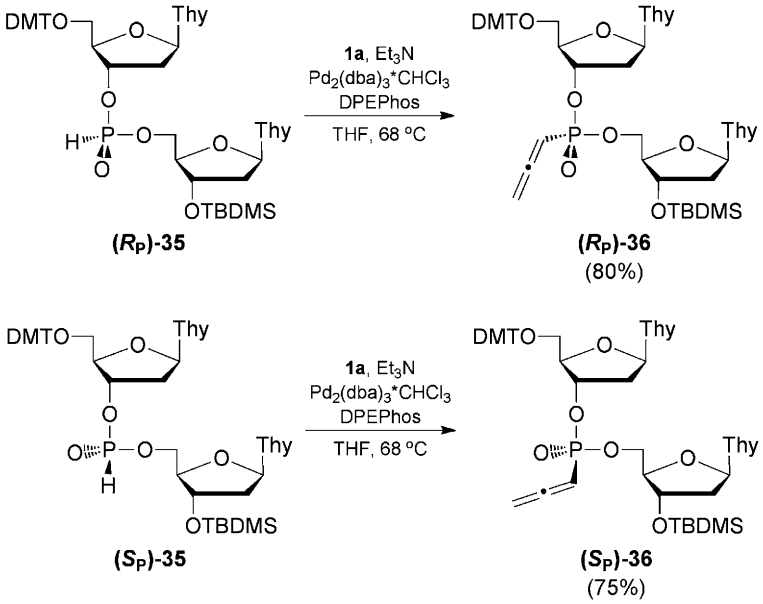
Apart from the center to axis chirality transfer described above, the other important aspect of the allenylphosphonate synthesis is chirality at the phosphorus center. Since it has been already shown that palladium-catalyzed propargylic substitution provides an easy access to allenylphosphonates with four different substituents at the phosphorus atom (Table 3, entries 22–24), therefore we decided to study the stereochemical course of the investigated reaction when the starting material contained a stereogenic phosphorus center. As model compounds for these studies we chose two diastereomeric dinucleoside H-phosphonates with opposite configurations at the phosphorus center, (R_P)-**35** and (S_P)-**35**, that were subjected separately to coupling with propargylic chloride **1a** under the developed reaction conditions (Scheme 6). It was found that the formation of dinucleoside allenylphosphonates **36** from the corresponding dinucleoside



Scheme 4. A plausible racemization mechanism of allenylphosphonate **5** in the presence of nucleophilic species.



Scheme 5. Stereochemical correlation of the allenylphosphonates **5** synthesized by the sigmatropic rearrangement and Pd-catalyzed propargylic substitution.



Scheme 6. Stereochemical course of the palladium-catalyzed propargylic substitution with *P*-chiral reactants (Thy = thymin-1-yl, DMT = 4,4′-dimethoxytrityl, TBDMS = *tert*-butyldimethylsilyl).

H-phosphonates **35** was completely stereospecific [Scheme 6, conversion of (R_P)-**35** into (R_P)-**36** and (S_P)-**35** into (S_P)-**36**], and occurred most likely with retention of configuration at the phosphorus center. Such an outcome was not unexpected, since other Pd-catalyzed cross-coupling reactions of H-phosphonates with electrophiles, such as aryl and benzyl halides, are known to be stereospecific[26c–f,40] and occur with retention of the configuration at the phosphorus center.[41]

Full control of the stereochemistry at the phosphorus center seems to be a significant advantage of the Pd-catalyzed *vs.* sigmatropic rearrangement method for the synthesis of allenylphosphonates on two counts: (i) easy preparation of H-phosphonate diesters and their analogues with defined stereochemistry at phosphorus centers, and (ii) high stereochemical stability of tetracoordinated H-phosphonates *vs.* tervalent phosphite derivatives.

Scheme 6 illustrates also the fact that the palladium-catalyzed reaction of propargylic compounds with H-phosphonate diesters can be applied to the synthesis of complex organic compounds. Since preparation of H-phosphonate diesters is well established,[42] this method may provide a convenient entry to allenylphosphonates bearing biologically important moieties attached to the phosphorus center.

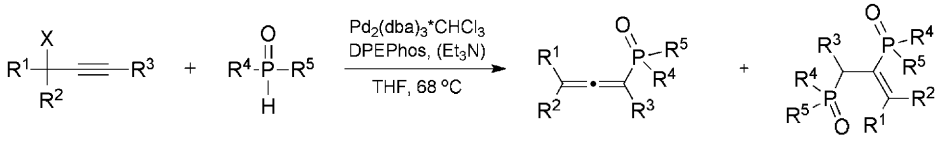
Reactions of Diphenylphosphine Oxide with Propargylic Derivatives

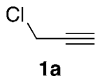
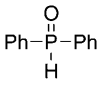
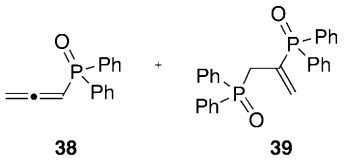
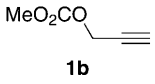
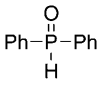
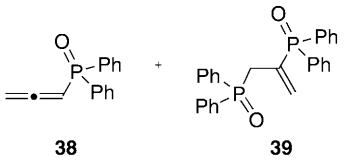
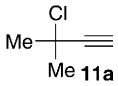
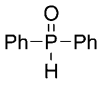
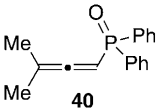
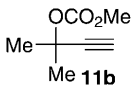
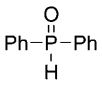
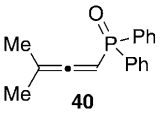
Exclusive formation of allenylphosphonates or allenylphosphinates in the reactions discussed above might indicate that in the transmetallation step (Scheme 2) H-phosphonates and H-phosphinates acted as hard nucleophiles. To explore a mechanistic part of this Pd-catalyzed reaction, we searched for a softer phosphorus nucleophile that could attack a central carbon atom of the palladium complex rather than palladium itself (path b in Scheme 2).

Indeed, when diphenylphosphine oxide **37** was subjected to the reaction with either propargyl chloride (**1a**) or carbonate (**1b**) in the presence of a palladium(0) catalyst (Table 4) approximately equimolar amounts of allenylphosphine oxide (**38**) and bis(phosphine oxide) (**39**) were obtained (Table 4, entries 1 and 2). Formation of the latter product could be explained by assuming a mechanism path 2b in Scheme 2, a reaction pathway that is favoured by soft nucleophiles (e.g., malonate anion).[29]

Since steric hindrance at C-1 should disfavour this mechanistic pathway but not those involving a transmetallation, we expected that reaction of C-1 disubstituted propargylic derivatives would afford mainly the corresponding allenylphosphine oxides. As it is apparent from entries 3 and 4 in Table 4, the reactions of dimethyl-substituted propargylic substrates (chloride **11a** and carbonate **11b**) with diphenylphosphine oxide

Table 4. Reactions of diphenylphosphine oxide with propargylic derivatives.[a]



Entry	Propargylic substrate	*P*-nucleophile	Products	Reaction time (isolated yields)
1	 **1a**	 **37**	 **38** / **39** 54 / 46	1 h (**38**: 42%; **39**: 31%)
2	 **1b**	 **37**	 **38** / **39** 61 / 39	45 min (**38:** 53%; **39**: 27%)
3	 **11a**	 **37**	 **40**	1.5 h (77%)
4	 **11b**	 **37**	 **40**	30 min (84%)

[a] *Reaction conditions:* 1.38 mmol propargylic substrate, 1.25 mmol *P*-nucleophile, 0.019 mmol (1.5 mol%) $Pd_2(dba)_3{\cdot}CHCl_3$, 0.038 mmol (3 mol%) DPEPhos, 5 mL THF (0.25 M), 68 °C. For propargylic chlorides, additionally 1.5 mmol Et_3N.

37 indeed afforded exclusively the allenylphosphine oxide **40**.

Synthesis of Thio and Seleno Analogues of Allenylphosphonates

To expand the scope of this reaction further, we turned our attention to H-phosphonothio- and H-phosphonoselenoate diesters, as possible phosphorus nucleophiles, since compounds containing sulfur or selenium bound to the phosphorus are attractive synthetic targets due to often favorable biochemical properties.[43]

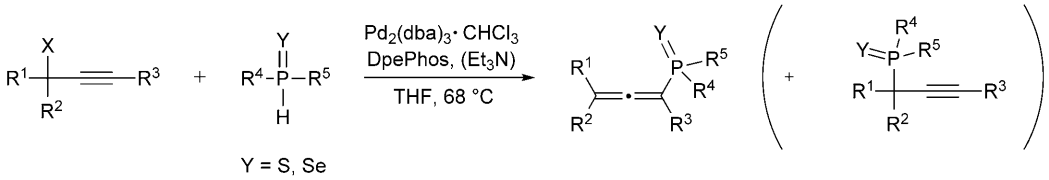
First, the reaction of different propargylic derivatives with a model diethyl H-phosphonothioate (**41**) was carried out using the developed synthetic protocol (Table 5, entries 1–5). Somewhat surprisingly, in contradistinction to diethyl H-phosphonate, that in the reaction with simple propargylic derivatives produced exclusively allenylphosphonates, the thio congener **41** diverted the reaction towards propargylphosphonothioate derivatives. For primary propargylic compounds containing chloride or carbonate as a leaving group, the reaction afforded a mixture of the desired allenylphosphonothioate (e.g., **44**) and the isomeric propargylphosphonothioate (e.g., **45**; Table 5, entries 1 and 2). A similar outcome of the reaction was also observed for dinucleoside H-phosphonothioate **42** (Table 5, entry 6) and for terminally substituted propargylic carbonate **9b** (Table 5, entry 3).[44] In the absence of the palladium catalyst, no reaction could be observed between propargylic substrates (**1a**, **1b**, and **9b**) and H-phosphonothioate **41**. These results suggested that for H-phosphonothioate nucleophiles transmetallation of the propargylpalladium(II) complexes became a feasible reaction pathway (Scheme 2, path c).

Since isomeric allenyl- and propargylphosphonothioates (**44** *vs.* **45**, **46** *vs.* **47**, **50** *vs.* **51**) turned out to be inseparable using standard experimental techniques, we attempted to suppress the formation of undesirable, in this context, propargylphosphonothioates. On a mechanistic ground, it seemed likely that transmetallation of propargylpalladium(II) complexes should be sensitive to steric hindrance from substituents on C-1, and thus mono- and di-substituted propargylic derivatives might favour transmetallation of allenylpalladium(II) species, and in consequence, formation of allenylphosphonothioates. Indeed, the reaction of propargylic derivatives bearing one or two C-1 substituents (R^1 and R^2) with H-

phosphonothioate **41** resulted in exclusive formation of allenylphosphonothioates **48** and **49** which were isolated in *ca.* 60% yield (Table 5, entries 4 and 5).

With this knowledge, we decided to examine if more complex H-phosphonothioates can also be used in this reaction. To this end, we subjected two separate diastereomers of dinucleoside H-phosphono-

Table 5. Synthesis of allenylphosphonothio- and allenylphosphonoselenoates.[a]



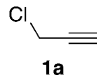
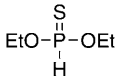
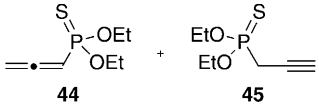
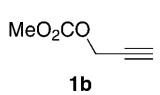
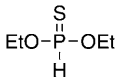
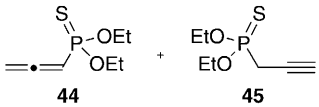
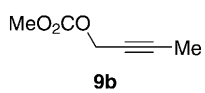
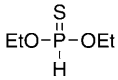
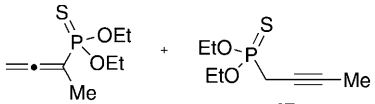
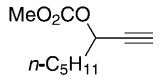
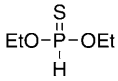
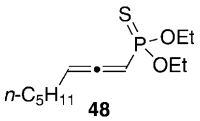
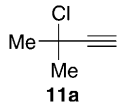
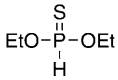
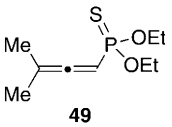
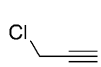
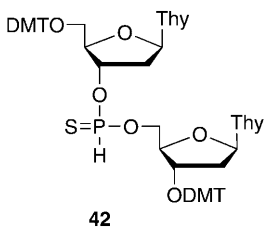
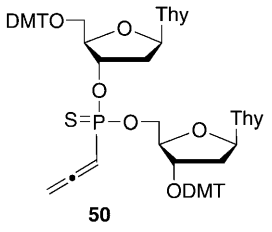
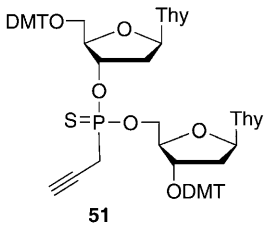
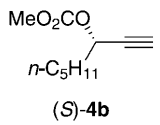
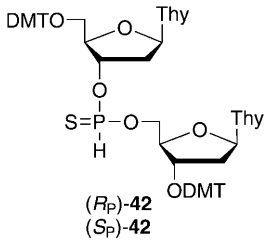
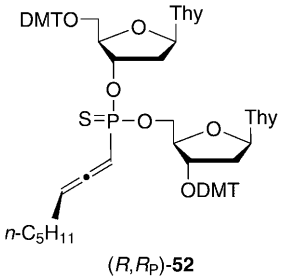
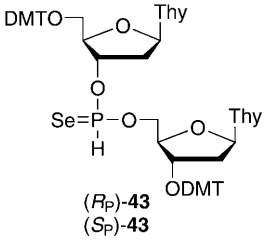
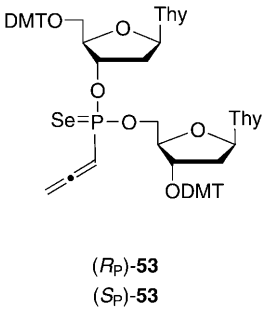
Entry	Propagylic substrate	*P*-nucleophile	Product	Reaction time (isolated yield)
1	 **1a**	 **41**	 **44** + **45** 72 / 28	5 h (inseparable mixture)
2	 **1b**	 **41**	 **44** + **45** 70 / 30	7 h (inseparable mixture)
3	 **9b**	 **41**	 **46** + **47** 83 / 17	24 h (inseparable mixture)
4	 **4b**	 **41**	 **48**	30 min (59%)
5	 **11a**	 **41**	 **49**	1.5 h (64%)
6	 **1a**	 **42**	 **50** 70 / 30 +  **51**	1 h (inseparable mixture)
7	 (*S*)-**4b**	 (*R*P)-**42** (*S*P)-**42**	 (*R*,*R*P)-**52** (*R*,*S*P)-**52**	2 h [(*R*P)-**52** 74%; (*S*P)-**52** 71%]

Table 5. (Continued)

Entry	Propagylic substrate	*P*-nucleophile	Product	Reaction time (isolated yield)
8	 **1a**	 (R_P)-**43** (S_P)-**43**	 (R_P)-**53** (S_P)-**53**	10 min [(R_P)-**53** 57%; (S_P)-**53** 67%]

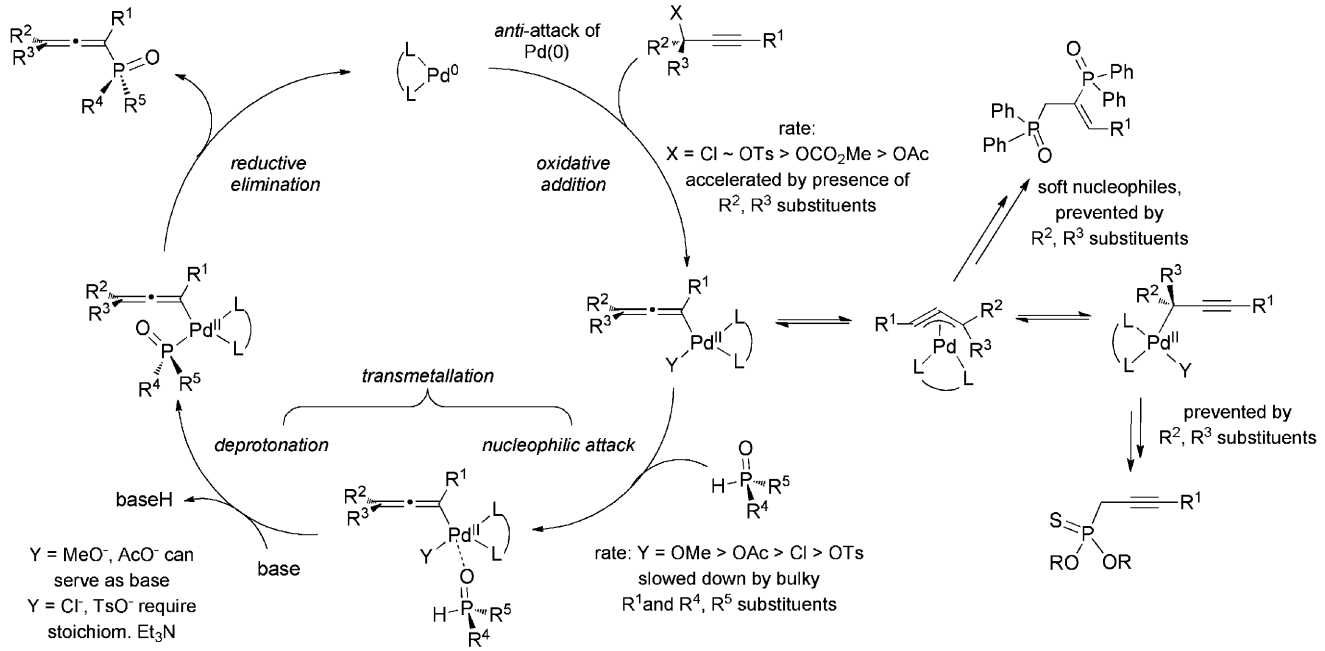
[a] *Reaction conditions:* 1.38 mmol propargylic substrate, 1.25 mmol *P*-nucleophile, 0.019 mmol (1.5 mol%) $Pd_2(dba)_3{\cdot}CHCl_3$, 0.038 mmol (3 mol%) DPEPhos, for propargylic chlorides additionally 1.5 mmol Et_3N, 5 mL THF (0.25 M), 68 °C; abbreviations: Thy = thymin-1-yl, DMT = 4,4′-dimethoxytrityl.

thioate **42**, with opposite configuration at the phosphorus center, to the reaction with a single enantiomer of propargylic carbonate **4b** (Table 5, entry 7). To our delight, the synthesis of allenylphosphonothioates (R,R_P)-**52** and (R,S_P)-**52** was uneventful and completely stereospecific at the phosphorus center, although due to a longer reaction time (2 h), a slight epimerization of the allene moiety occurred (see above).

Finally, separate diastereomers of a dinucleoside H-phosphonoselenoate **43** were used as phosphorus nucleophiles in the reaction with propargyl chloride (Table 5, entry 8). In this instance, a rapid, stereospecific reaction (10 min) took place, but in contrast to H-phosphonothioate diesters, only allenylphosphonoselenoates **53** were formed formation.[45]

Catalytic Cycle for the Pd(0)-Promoted Allenylphosphonates Formation

The presented above results suggest that the palladium-catalyzed propargylic substitution involving H-phosphonate diesters and related compounds follows a mechanistic pathway similar to that of other nucleophiles. Details of this mechanism are depicted in Scheme 7.



Scheme 7. A proposed mechanism for the palladium-catalyzed propargylic substitution with *P*-nucleophiles.

The catalytic cycle starts with an oxidative addition of a propargylic substrate to Pd(0) complex in an *anti* fashion, and this step is responsible for the overall reaction stereochemistry. The rate of the oxidative addition depended on the leaving group X, as well as on the presence of substituents (R^2, R^3) at C-1. When the oxidative addition was slow, it became apparently a turnover-limiting step of the reaction, for example, for propargylic acetates (Table 2, entries 6 and 7) and primary propargylic carbonates (Table 2, entry 3 –**1b**; Table 3, entries 2, 9, 11). In all other cases, the overall reaction rates seemed to be determined by efficiency of the next, and the most mechanistically interesting step, i.e., the transmetallation (ligand exchange).

It has been shown before by means of kinetic[27e] and mass spectrometry[46] studies, that formation of Pd(II)-phosphonate complexes from H-phosphonates (transmetallation) is a two-step process. First, an H-phosphonate is, most likely, coordinated to the palladium *via* the phosphoryl oxygen, which increases the acidity of the phosphorus-bound proton and facilitates its abstraction by a base. The incipient phosphonate anion is then immediately intercepted by the palladium, leading to the exclusive formation of a palladium(II)-phosphonate complex.

We believe that such a course of the transmetallation is a key to the observed selective formation of allenylphosphonates, in favour of other possible products (e.g., paths a and c *vs.* path b in Scheme 2, respectively). The somewhat unexpected behaviour of H-phosphonates as 'hard' nucleophiles can be explained by the fact that only negligible amounts of a free phosphonate anion are present in the reaction mixture, therefore no products due to its external attack on the allenylpalladium species are formed. The only exception from this trend was the case of diphenylphosphine oxide, that apparently, due to lack of, or attenuated, back-donation from the C–P bonds, exhibited a higher acidity, enabling formation of larger amounts of the corresponding anion, that attacked the central carbon atom a Pd-complex (Scheme 2, path b) and led eventually to the bisphosphine oxide formation (Table 4, entries 1 and 2).

Our previous studies on the palladium-catalyzed cross-coupling reactions involving H-phosphonate nucleophiles revealed that transmetallation (ligand exchange) often determines the overall rate of the reaction. We have found that the rate of this mechanistic step is sensitive to a steric bulk,[26f,27e] and strongly depends on the kind of the anion present in the Pd(II) complex.[27a,e] Direct transposition of these findings to the propargylic substitution reaction studied herein seems to be a viable action, as it leads to a plausible explanation of the experimental data. Thus, the expected reactivity order of the allenylphosphonate complexes ligated by different anions shown in Scheme 7, is consistent with the results in Table 2 (especially, the experiments involving anionic additives were very helpful in that respect – Table 2, entries 8 and 9). In particular, the accelerating effect of the acetate additives (Table 2, entry 9) is in agreement with our previous findings that the palladium(II) complexes bearing an acetate ligand undergo the transmetallation much faster than those bearing chloride.[26f,27a,e] Notably, palladium(II) complexes with an MeO^- ligand displayed the highest reactivity, which made the propargylic carbonates the substrates of choice for this reaction. The increase in the reaction time, when terminally substituted propargylic derivatives (Scheme 7, R^3) and/or *P*-nucleophiles bearing bulky groups (R^4, R^5) were used as the substrates, is also fully understandable in this context.

The other aspect possibly connected to the transmetallation (ligand exchange) step is the formation of propargylphosphonothioates as side-products during the coupling of propargylic derivatives with H-phosphonothioates (Table 5, entries 1–3). It has been shown on many occasions that the η^1-allenic and η^1-propargylic palladium complexes in solution may exist in an equilibrium.[24a,38b,47] Ma et al. reported detailed studies demonstrating that these species can display different preferences towards transmetallation with various nucleophiles and that steric hindrance is a dominating factor governing the regioselectivity.[28] In line with these, it is probable that for H-phosphonothioates the transmetallation is feasible for both of these isomeric complexes, although introduction of substituents (R^2, R^3) at C-1, efficiently prevented the transmetallation of a propargylic complex, and ultimately formation of the propargylphosphonothioate derivative. The reason why H-phosphonoselenoates in the reaction with propargylic compounds afforded exclusively the corresponding allenylphosphonoselenoates, remains unclear. However, a significantly higher reactivity of these compounds in the investigated reaction than that of H-phosphonate and H-phosphonothioate diesters, indicates the kinetic importance of other factors during the transmetallation step.

As to reductive elimination, we cannot exclude this as a possible turnover-limiting step of the catalytic cycle on account of the fact that this Pd-catalyzed propargylic substitution worked only with bidentate, large bite angle phosphine ligands, that are known to accelerate reductive elimination from metalphosphonate complexes.[27c] In such a scenario, it could be the activation energy for the reductive elimination of the product that determine predominant (or exclusive) formation of allenylphosphonates *vs.* propargylphosphonates or allenylphosphonothioates *vs.* propargylphosphonothioates.

Irrespective of these mechanistic aspects, it seems that throughout the reaction a stereochemical integrity at the phosphorus center was preserved and this re-

sulted in a stereospecific outcome of the reaction (most likely, retention of configuration). Further mechanistic studies on this reaction are in progress.

Conclusions

We have developed a novel, general method for efficient preparation of allenylphosphonates and related compounds *via* a Pd(0)-catalyzed S_N2' reaction of propargylic derivatives with H-phosphonate, H-phosphonothioate, and H-phosphonoselenoate diesters or their analogues. Several ligands have been evaluated for their ability to catalyze this C–P bond formation, and the most efficient catalytic system was found to consist of $Pd_2(dba)_3{\cdot}CHCl_3$ as a palladium source and bis(2-diphenylphosphino)diphenyl ether (DPEPhos) as a supporting ligand. Some mechanistic aspects of the reaction were investigated and this permitted us to optimize the reaction conditions and suppress side-product formation. The transformation into allenylphosphonates was stereospecific at the phosphorus center (most likely retention of configuration) and occurred with a complete center to axial chirality transfer from the propargylic to the allene moiety. Since both types of substrates used for the reaction, i.e., propargylic compounds and H-phosphonate derivatives and their analogues are easily available, complex organic structures can be generated. This new protocol may expand the range of biologically important C-phosphonate analogues with predefined stereochemistry at the phosphorus center and diverse substitution patterns in the allene moiety, that can be prepared under mild conditions and in high efficiency.

Experimental Section

General

All reagents and solvents were of analytical grade, obtained from commercial suppliers and used without further purification. Propargyl carbonate (**1b**),[48] oct-1-yn-3-yl 4-methylbenzenesulfonate (**4c**),[49] oct-1-yn-3-yl acetate (**4d**),[50] 1-chlorobut-2-yne (**9a**),[51] but-2-yn-1-yl methyl carbonate (**9b**),[48] (3-chloroprop-1-yn-1-yl)benzene (**10a**),[52] methyl (3-phenylprop-2-yn-1-yl) carbonate (**10b**),[53] 3-chloro-3-methylbut-1-yne (**11a**),[54] methyl (2-methylbut-3-yn-2-yl) carbonate (**11b**),[55] 1-chloro-1-ethynylcyclohexane (**12**),[56] 4-chloro-4-methylpent-2-yne (**15a**),[57] ethyl methylphosphinate (**18**),[58] ethyl phenylphosphinate **(19)**,[59] ethyl (3-methylbut-2-en-1-yl)phosphinate (**20**),[60] 5′-*O*-(4,4′-dimethoxytrityl)thymidin-3′-yl 3′-*O*-*tert*-butylsilylthymidin-5′-yl H-phosphonate (**35**),[61] diethyl H-phosphonothioate (**41**),[62] 5′-*O*-(4,4′-dimethoxytrityl)thymidin-3′-yl 3′-*O*-(4,4′-dimethoxytrityl)thymidin-5′-yl H-phosphonothioate (**42**),[63] and 5′-*O*-(4,4′-dimethoxytrityl)thymidin-3′-yl 3′-*O*-(4,4′-dimethoxytrityl)thymidin-5′-yl H-phosphonoselenoate (**43**)[64] were prepared according to published procedures. THF was dried using a VAC solvent purifier system. All reactions were carried out using standard Schlenk techniques. Column chromatography was preformed on silica gel (Grace Davison, Davsil, 0.035–0.070 mm). The NMR spectra were registered using a Bruker Avance II 400 MHz instrument. The chemical shifts are reported in ppm, relative to solvent peaks (^1H, ^{13}C) or 2% H_3PO_4 solution in D_2O (^{31}P NMR). Assignment of the NMR signals was done on the basis of 2D correlation experiments (COSY, HSQC).

General Procedure for the Preparation of Allenylphosphonates and Allenylphosphinates

$Pd_2(dba)_3{\cdot}CHCl_3$ (19.7 mg, 0.019 mmol, 3.0 mol% Pd) and DPEPhos (20.5 mg, 0.038 mmol) were placed in the reaction vessel. The vessel was sealed and filled with N_2, by applying 2 cycles of vacuum, followed by N_2. THF was introduced *via* the septum (5 mL), followed by triethylamine (200 μL, 152 mg, 1.50 mmol; only for propargylic chlorides), *P*-nucleophile (1.25 mmol), and propargylic substrate (1.38 mmol). After heating at 68 °C for the time indicated in Table 1, the solvent was evaporated and product purified by silica gel chromatography (depending on the case, pentane:AcOEt mixture from 95:5 to 0:1 was used as the eluent).

In the case of dinucleoside allenylphosphonates (**36**, **50**, and **53**), due to high molecular weight, lower concentration of the starting materials was used (0.10 M H-phosphonate diester, instead of 0.25 M); i.e., $Pd_2(dba)_3{\cdot}CHCl_3$ (7.9 mg, 0.0076 mmol), DPEPhos (8.2 mg, 0.015 mmol), triethylamine (83 μL, 61 mg, 0.60 mmol; if necessary), H-phosphonate (0.50 mmol), propargylic chloride/carbonate (0.55 mmol), THF (5 mL). For details, see footnotes in the Table 3, Table 4 and Table 5. Characterization of the synthesized compounds is provided in the Supporting Information.

Supporting Information

Characterization data for the synthesized allenylphosphonate and allenylphosphinate derivatives (Table 3, Table 4, Table 5) and the ^1H- , ^{13}C-, and ^{31}P NMR spectra, synthesis of some propargylic precursors, and data on the stereochemical stability of allenylphosphonate **5** are available in the Supporting Information.

Acknowledgements

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