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Palladium-Catalyzed Propargylic Substitution with Phosphorus Nucleophiles: Efficient, Stereoselective Synthesis of Allenylphosphonates and Related Compounds

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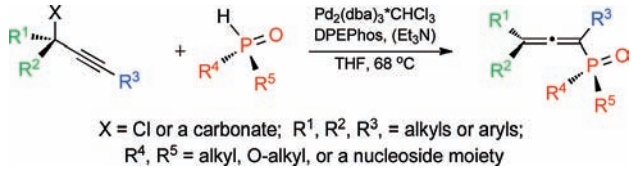
ABSTRACT



A new, efficient method is developed, based on a palladium(0)-catalyzed reaction of propargylic derivatives with various phosphorus nucleophiles, to produce allenylphosphonates and their analogues with defined stereochemistry in the allenic and the phosphonate moiety.

In recent years, allenes have rapidly evolved from curious chemical entities into one of the most flourishing research subjects in organic chemistry.[1] An allene structural motif has been discovered in many natural products and has started to attract increasing attention of pharmaceutical research.[2] Due to the development of novel synthetic methods,[3] allenes also became useful intermediates in chemical synthesis, often enabling a rapid molecular complexity increase in a single reaction step,[4] inter alia, due to an efficient transfer of chirality to the newly formed stereocenters.[1,5]

A special class of allenes constitute allenylphosphonates and related compounds that exhibit diverse reactivity[6] and hence can serve as very useful synthetic intermediates. Synthesis of allenylphosphonates has been dominated by [2,3]-sigmatropic rearrangement of propargyl phosphites,[1,7]

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(1) *Modern Allene Chemistry*; Krause, N., Hashimi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004.
(2) Hoffman-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196–1216.
(3) Ma, S. *Chem. Rev.* **2005**, *105*, 2829–2871. Sydnes, L. K. *Chem. Rev.* **2003**, *103*, 1133–1150.
(4) Ma, S.; Lu, P.; Lu, L.; Hou, H.; Wei, J.; He, Q.; Gu, Z.; Jiang, X.; Jin, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 5275–5278. Piera, J.; Närhi, K.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2006**, *45*, 6914–6917. Piera, J.; Persson, A.; Caldentey, X.; Backvall, J.-E. *J. Am. Chem. Soc.* **2007**, *129*, 14120–14121. Inagaki, F.; Sugikubo, K.; Miyashita, Y.; Mukai, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 1–6.
(5) Hoffman-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 2933–2935. Bongers, N.; Krause, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 2178–2181.
(6) Chakravarty, M.; Swamy, K. C. K. *J. Org. Chem.* **2006**, *71*, 9128–9138. Khusainova, N. G.; Mostovaya, O. A.; Berdnikov, E. A.; Litvinov, I. A.; Krivolapov, D. B.; Cherkasov, R. A. *Russ. J. Org. Chem.* **2005**, *41*, 1260–1264. Santos, J. M.; López, Y.; Aparicio, D.; Palacios, F. *J. Org. Chem.* **2008**, *73*, 550–557. Mukai, C.; Ohta, M.; Yamashita, H.; Kitagaki, S. *J. Org. Chem.* **2004**, *69*, 6867–6873. Brel, V. K.; Belsky, V. K.; Stash, A. I.; Zavodnik, V. E.; Stang, P. J. *Eur. J. Org. Chem.* **2005**, 512–521. Chakravarty, M.; Swamy, K. C. K. *Synthesis* **2007**, 3171–3178. Gu, Y.; Hama, T.; Hammond, G. B. *Chem. Commun.* **2000**, 395–396. Zapata, A. J.; Gu, Y.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 227–234.
(7) Boisselle, A. P.; Meinhardt, N. A. *J. Org. Chem.* **1962**, *25*, 1828–1833. Pudovik, A. N.; Aladzheva, I. M. *J. Gen. Chem. USSR (Engl. Transl.)* **1963**, *33*, 700–701.

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which has a broad scope with respect to the precursor propargylic alcohols used, enabling the synthesis of allenylphosphonates with various substitution patterns in the allene moiety. Despite these, the approach suffers from a serious drawback, namely, a limit in the kind of substituent that can be attached to the phosphonate center.

To overcome this limitation and to explore new avenues to carbon−phosphorus bond formation, we turned our attention to a completely unexplored, in this context, transition-metal-catalyzed propargylic substitution (S_N2') reaction as a means of synthesis of allenylphosphonates. Although this is a well established synthetic approach to a variety of allenes,[1,8] the reaction has never been used for the formation of the C−P bond. We expected that stereoselectivity and chirality transfer from the propargylic substrate observed during some allene synthesis[1] would also be preserved for phosphorus nucleophiles. Since other Pd-catalyzed C−P bond-forming reactions[9] have been shown to work well in the synthesis of biologically important phosphorus compounds,[10] and mechanistic aspects of the reaction with aryl electrophiles have been studied in depth,[11] we expected that these may lend themselves to a new method for the construction of complex allenylphosphonate derivatives.

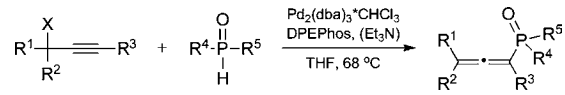
Herein we report for the first time studies on a palladium-catalyzed propargylic substitution reaction with H-phosphonates and related compounds as nucleophiles. Our aim was to develop a new synthetic method for this class of compounds and expand the scope of accessible allenylphosphonates, particularly those of potential biochemical relevance.

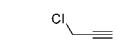
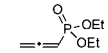
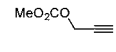
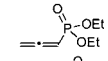
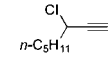
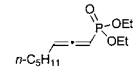
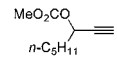
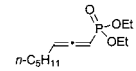
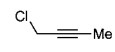
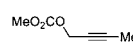
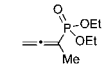
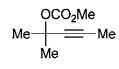
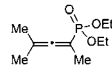
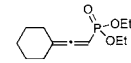
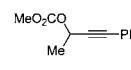
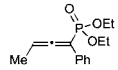
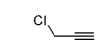
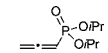
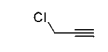
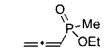
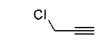
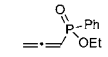
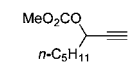
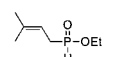
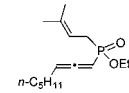
As a model reaction we chose coupling between propargyl chloride and diethyl H-phosphonate (Table 1, entry 1). The screening revealed that only bidentate ligands with wide bite angles were able to promote a conversion into the allenylphosphonate, and the highest reaction rate was observed for bis(2-phenylphosphinophenyl)ether (DPEPhos) (see Supporting Information).

The scope of the reaction turned out to be broad in terms of propargyl derivatives and the H-phosphonates used, as it was apparent from synthesis of allenylphosphonates with diverse structural features (Table 1).

In this reaction propargyl chlorides showed relatively high reactivity that did not depend on the presence or absence of substituents at C1 (Table 1, entry 1 vs 3 and 8). Propargyl carbonates did not require an external base and exhibited significant differences in rates between primary vs secondary substrates (entry 2 vs 4), with the latter one reacting much faster (7 h vs 30 min). A substituent in the terminal position of the alkyne (R^3) dramatically slowed down the reaction for both the leaving groups, and a good conversion to the corresponding allenylphosphonate could only be achieved for the carbonate derivative (entry 5 vs 6). However, introduction of substituents at C1 significantly increased the reactivity of this type of substrate (entries 7 and 9). The coupling reaction was sensitive to steric hindrance at the phosphorus center as it is apparent from entry 10 vs 1 in Table 1. Other phosphorus nucleophiles, e.g., phosphinate esters, could also be used in this reaction (entries 11−13) to produce the corresponding allenylphosphinates. Although the last two products could also technically be obtained using

Table 1. Synthesis of Allenylphosphonates and Related Compounds[a]



entry	propargylic substrate	*P*-nucleoph.	product	reaction time (yield)
1				1.5 h (88%)
2				7 h (79%)
3				1.5 h (83%)
4				30 min (91%)
5			na	no reaction
6				24 h (69%)
7				1 h (78%)
8				1.5 h (80%)
9				5 h (83%)
10				16 h (78%)
11				16 h (84%)
12				2 h (89%)
13				36 h (67%)

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

(8) Ma, S. *Eur. J. Org. Chem.* **2004**, 1175–1183. Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed.* **1995**, *34*, 2589–2612.

(9) Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041–2075. Schwan, A. L. *Chem. Soc. Rev.* **2004**, *33*, 218–224. Montchamp, J. L. *J. Organomet. Chem.* **2005**, *690*, 2388–2406.

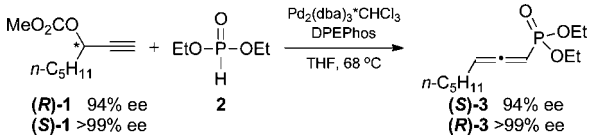
(10) Abbas, S.; Hayes, C. J. *Synlett* **1999**, *7*, 1124–1126. Abbas, S.; Bertram, R. D.; Hayes, C. J. *Org. Lett.* **2001**, *3*, 3365–3367. Johansson, T.; Stawinski, J. *Chem. Commun.* **2001**, 2564–2565. Lavén, G.; Stawinski, J. *Collect. Symp. Ser.* **2005**, *7*, 195–199. Kalek, M.; Stawinski, J. *Collect. Symp. Ser.* **2008**, *10*, 214–218. Kalek, M.; Ziadi, A.; Stawinski, J. *Org. Lett.* **2008**, *10*, 4637–4640. Kalek, M.; Jezowska, M.; Stawinski, J. *Adv. Synth. Catal.* **2009**, *351*, 3207–3216.

(11) Kalek, M.; Stawinski, J. *Organometallics* **2007**, *26*, 5840–5848. Kalek, M.; Stawinski, J. *Organometallics* **2008**, *27*, 5876–5888. Levine, A. M.; Stockland, R. A.; Clark, R.; Guzei, I. *Organometallics* **2002**, *21*, 3278–3284. Stockland, R. A.; Levine, A. M.; Giovine, M. T.; Guzei, I. A.; Cannistra, J. C. *Organometallics* **2004**, *23*, 647–656. Kohler, M. C.; Stockland, R. A., Jr.; Rath, N. P. *Organometallics* **2006**, *25*, 5746–5756. Kohler, M. C.; Grimes, T. V.; Wang, X.; Cundari, T. R.; Stockland, R. A. *Organometallics* **2009**, *29*, 1193–1201.

the sigmatropic rearrangement reaction,[1,7] preparation of suitable tervalent phosphorus precursors would pose considerable difficulty. On the other hand, aryl- and vinylphosphinates used in our palladium-catalyzed propargylic substitution reaction can be easily synthesized by methods develped by Montchamp et al.[12]

To investigate the stereochemistry of this reaction, enantioenriched propargyl carbonates **1** were allowed to react with diethyl H-phosphonate **2** under the developed conditions. As is apparent from the results in Scheme 1, propargyl carbonates (*R*)-**1** and (*S*)-**1** were transformed into allenylphosphonates **3** in a completely stereoselective and stereospecific manner.

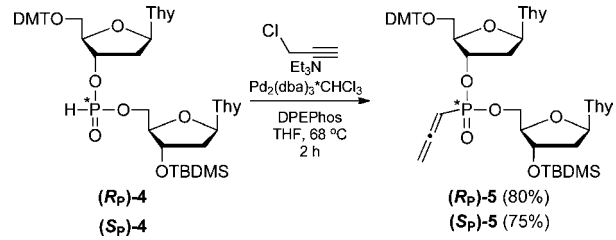
Scheme 1



Center to axis chirality transfer described above does not exhaust stereochemical features of this allenylphosphonate synthesis. The other equally important aspect is chirality at the phosphorus center. Therefore we studied a stereochemical course of the investigated reaction, when the starting material contained a stereogenic phosphorus center (Scheme 2).

To this end, two diastereomeric dinucleoside H-phosphonates, with opposite configurations at the phosphorus, (R_P)-**4** and (S_P)-**4**, were subjected separately to coupling with propargyl chloride under the developed reaction conditions (Scheme 2). It was found that each of the dinucleoside **4** diastereomers was transformed quantitatively into the corresponding diastereomer of the product [Scheme 2, (R_P)-**5** and (S_P)-**5**), respectively], and this proved that the palladium-catalyzed process was completely stereospecific, and the configuration at the phosphorus center in the product was determined by the configuration in the starting material. It

Scheme 2



is important to mention that this aspect of the allenylphosphonates synthesis, i.e., control of stereochemistry at the phosphorus atom, is completely beyond the scope of the original sigmatropic rearrangenent method.[1,7]

In conclusion, we have developed a novel method for the synthesis of allenylphosphonates and related compounds via a Pd(0)-catalyzed coupling of propargylic derivatives with H-phosphonate diesters or their analogues. The reaction represents a new means for the formation of the C−P bond and permits stereoselective and stereospecific construction of an allenic moiety with complete transfer of center to axial chirality and retention of configuration at the phosphorus center. By a proper choice of propargylic components and H-phosphonate derivatives, complex organic structures can be generated. High efficiency, mildness of the reaction conditions, and easily accessible starting materials can make this reaction a method of choice for the synthesis of various analogues of biologically important compounds with a predefined stereochemistry and substitution pattern in the allene and the phosphonate moieties.

Acknowledgment. Financial support from the Swedish Natural Science Research Council is gratefully acknowledged.

Supporting Information Available: Synthetic experimental procedures, ligand screening results, characterization data for all the compounds, and NMR spectra of synthesized allenylphosphonates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Dumond, Y. R.; Baker, R. L.; Montchamp, J. L. *Org. Lett.* **2000**, *2*, 3341–3344. Montchamp, J. L.; Dumond, Y. R. *J. Am. Chem. Soc.* **2001**, *123*, 510–511. Bravo-Altamirano, K.; Montchamp, J.-L. *Org. Lett.* **2006**, *8*, 4169–4171.