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Unprecedented carbocyclization of 1,6-allenynes on addition of organoboronic acids under Pd-catalysis

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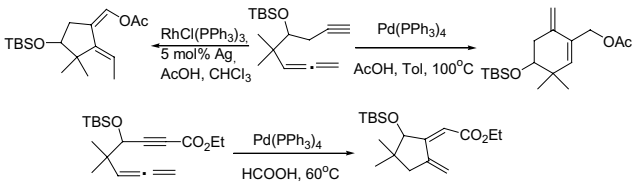
Abstract—In contrast to the ene behavior of allenes in Pauson–Khand reactions and other cyclization reactions, 1,6-allenynes undergo unprecedented carbocyclization followed by regioselective addition of organoboronic acids in the presence of $Pd(OAc)_2$ and tri-*t*-butyl phosphine under mild reaction conditions.

New methodologies for the construction of useful intermediates aimed toward the total syntheses of bioactive natural products have been developed based on allenynes.[1] Apart from intramolecular Pauson–Khand reactions,[2] allenynes have been much less involved in transition metal-mediated cyclizations than their enyne analogues.[3] These substrates exhibit different modes of cyclization when the metal catalyst is varied. For instance, 6-allen-1-ynes chemoselectively give six-membered carbocycles in the presence of $Pd(PPh_3)_4$, and five-membered carbocycles in the presence of $RhCl(PPh_3)_3$.[4,5] We recently reported that Pd(0) catalyzed 5-allen-1-yne reactions to give cycloreduction products.[6] In addition to those, we have individually studied the Pd-catalyzed hydroarylation and hydroalkenylation of alkynes,[7] allenes,[8] and their derivatives (Scheme 1).

During our studies, we found that incorporation of a specific functional group such as a keto, oxygen of hydroxyl or oxygen protected with TBS ether, nitrogen of 2-pyridyl by chelate formation, or a sterically bulky substitute could play a role in controlling the site of addition.[9] From these experiments, when we introduced a hydroxyl group at the propargyl position to the alkyne, which is conjugated to the carboxylate group, we ended up with a highly stereoselective alkylative and arylative addition followed by lactonization.[10] The regioselectivity of the reaction was controlled by employing different ligands.[11] Further, we also observed that the hydroxyl group, located either at the propargylic position or even at a remote position, influences to give the single addition product.[12] Conversely, Shengming and Zhao[13] reported that the hydroxyl group acts as a nucleophile in allenols, and in the presence of a metal catalyst gives cyclic ethers.



Scheme 1.

On the basis of our research results and evidence in the literature, it is both interesting and worthwhile to study the behavior of allenynol, where all of these variables are present in one substrate. We believe that allenynes exhibit chemodichotomy in hydropalladation and carbopalladation.

Both hydropalladation (generated from a Pd species and acid) as well as carbopalladation by RPdX (generated from a Pd species and an organoboronic acid) occur at the central carbon of the allene functionality, but the former gives a vinyl palladium species, and the latter gives a π-allyl palladium species. Because of the difference in reactivity, the vinyl palladium species forms a cycloreduction product, whereas the π-allyl palladium species undergoes further carbocyclization. Hence, we have prepared a substrate in such a way that it contains a hydroxyl group as a directing group, particularly at the propargyl position to the alkyne carboxylate, and

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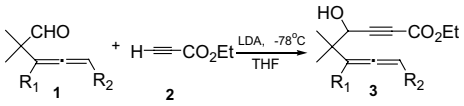
contains at the other end a highly reactive substrate such as an allene functionality. For substrate **3a**, we suspected that the organoboronic acid would add to the allene, followed by carbocyclization to afford a six-membered ring and provide a novel route to the cyclohexy-3-enylidene skeleton **5aa**.

Substrates **3a–d** were prepared by a known method.[14] LDA treatment of ethyl propiolate at 78 °C and addition of the corresponding allene-aldehydes gives the desired substrates in good yields (see Scheme 2).

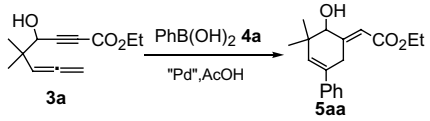
In the model study, 4-hydroxy-5,5-dimethyl-octa-6,7-diene-2-ynoic acid ethyl ester **3a** was treated with a simple boronic acid, such as phenylboronic acid **4a**, and various metal complexes, in different solvents (Table 1). The reactions went well in all solvent media and for different Pd catalysts, but using 1,4-dioxane as the solvent, in the presence of $Pd(OAc)_2$ in combination with a P(*t*-Bu)$_3$ ligand, the reaction went cleanly in terms of reaction monitoring on TLC, yield and isolation of the product.

Hence, we have used 1,4-dioxane as the solvent, $Pd(OAc)_2$/P(*t*-Bu)$_3$ as the catalyst, and temperatures of 50–60 °C for our study.[15] Isolated product structures were assigned by IR, ^{1}H NMR, ^{13}C NMR, COSY, DEPT, HMQC, MS, and HRMS analysis. In order to determine the geometry at the exocyclic double bond, we performed chemical transformations such as lactonization. These experiments suggest that it has *trans* geometry (*E*-geometry).[16]



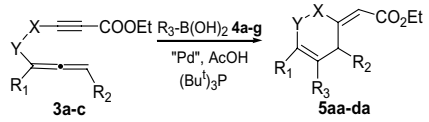
Scheme 2.

Table 1. Reaction of allenyne **3a** and phenylboronic acid **4a** with different Pd catalysts in various solvents



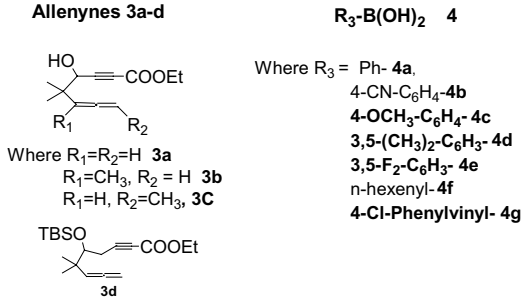
Entry	'Pd'	Solvent	Temp (°C)/time (h)	% Yield
1	$Pd(OAc)_2$/dppe	THF	50/10	34
2	$Pd(PPh_3)_4$	THF	50/4	43
3	$Pd(OAc)_2/PPh_3$	THF	50/4	44
4	$Pd_2(dba)_3$	DMF	70/2	47
5	$Pd(OAc)_2$/P(*t*-Bu)$_3$	DMF	80/3	65
6	$Pd(OAc)_2$/P(*t*-Bu)$_3$	THF	Rt/24	28
7	$Pd(OAc)_2$/P(*t*-Bu)$_3$	THF	50/4	67
8	**$Pd(OAc)_2$/P(*t*-Bu)$_3$**	**1,4-Dioxane**	**50/4**	**86**
9	$Pd(OAc)_2$/P(*t*-Bu)$_3$	EtOH	50/12	17
10	$Pd(OAc)_2$/P(*t*-Bu)$_3$	$CHCl_3$	50/10	31

Table 2. Reactions of various organoboronic acids **4a–g** with allenyne **3a–d**



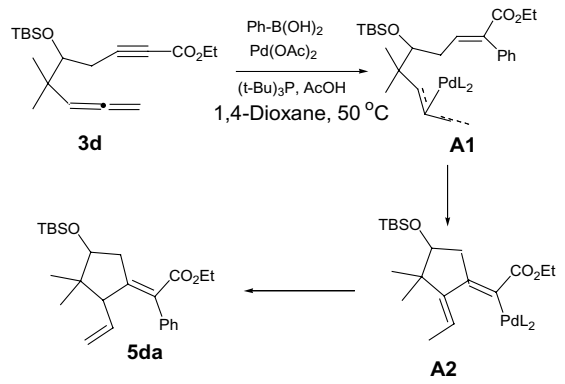
Entry	Allenyne	R_3–B(OH)$_2$	Temp (°C)/time (h)	Product	Yield (%)
1	**3a**	**4a**	50/4	**5aa**	86
2	**3a**	**4b**	50/4	**5ab**	76
3	**3a**	**4c**	50/4	**5ac**	78
4	**3a**	**4d**	50/4	**5ad**	82
5	**3a**	**4e**	50/4	**5ae**	93
6	**3a**	**4f**	50/4	**5af**	71
7	**3a**	**4g**	50/6	**5ag**	79
8	**3b**	**4a**	**50/4**	**5ba**	**81**
9	**3b**	**4f**	50/6	**5bf**	74
10	**3b**	**4g**	50/4	**5bg**	63
11	**3c**	**4a**	50/4	**5ca**	71
12	**3c**	**4f**	50/4	**5cf**	75
13	**3c**	**4g**	50/6	**5cg**	65
14	**3d**	**4a**	50/10	**5da**	61

Substrates in hand were tested for Pd-catalyzed addition of various organoboronic acids (**4a–g**), followed by cyclization under the above-mentioned conditions. The results thus obtained are summarized in Table 2.

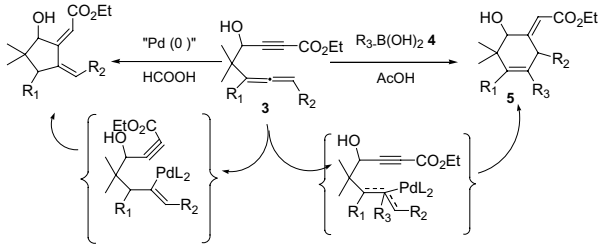


In order to check the generality of this method, **3a** was reacted with different arylboronic acids, that is, with an electron withdrawing group such as CN, **4b**, electron donating groups such as methoxy and methyl, **4c** and **4d**, fluoro substituted **4e**, phenylvinylboronic acid **4f** and alkenylboronic acid **4g**. Irrespective of the nature of the substituents on the arylboronic acids, allenyne **3a** gave **5aa–ag** in good to excellent yields. The literature reveals that substitution on the allene moiety changes the reaction pathway in PKR and other types of reactions, so we prepared C-3 and C-1 methyl-substituted analogues, allenynes **3b** and **3c** respectively. Among the boronic acids used in the present study, phenylboronic acid **4a**, alkenylboronic acid **4f** and phenylvinyl-boronic acid **4g** were taken as representative examples for further study.

Allenyne **3b** with methyl substitution on the internal double bond reacted with boronic acids **4a**, **4f**, and **4g**



Scheme 3.



Scheme 4.

and showed analogous behavior to give **5ba**, **5bf**, and **5bg** in 81%, 74%, and 63% yields, respectively. Immediately, the same reactions were applied to allenyne **3c**, giving two diastereoisomers of **5ca**, **5cf**, and **5cg** (Isomer A and Isomer B), which were isolated by a simple flash chromatographic technique.

It is surprising to us that under the same reaction conditions, **3d**, which is a homologue to **3a**, gave **5da**, instead of the anticipated cycloheptylidine ring (Scheme 3). This is mainly due to the formation of the vinyl palladation species (**A1**), instead of the π-allylpalladium species. This intermediate immediately undergoes cyclization to give intermediate (**A2**). At the final step, incorporation of the organic group from the boronic acid takes place to give **5da**.

Several features should be noted. First, these Pd-catalyzed additions/carbocyclizations work well to give the corresponding products in excellent yields. Mechanistically, the organoboronic acids first react with the Pd species to form the organopalladium complex, which then couples with the central carbon of the allene to form the π-allyl palladium complex. This undergoes further carbocyclization to give product **5** (Scheme 4).

In summary, we have demonstrated that when an organoboronic acid is added to a 1,6-allenyne system, carbopalladation takes place at the central carbon of the allene, followed by carbocyclization to the pendant alkyne to give the product. Mechanistic studies and applications of this work to the synthesis of bioactive molecules are currently under active investigation.

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.02.020.

References and notes

1. (a) Brummond, K. M.; Chen, H. *Abstracts of Papers*, 224th ACS National Meeting, Boston, MA, United States, August 2002; 18; (b) Brummond, K. M.; Gao, D. *Org. Lett.* **2003**, *5*, 3491; (c) Alcaido, B.; Almendros, P.; Aragoncillo, C. *Org. Lett.* **2003**, *5*, 3795; (d) Zimmer, R.; Dinesh, C. U.; Nanadanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067; (e) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067.
2. (a) Cao, H.; Flippen-Anderson, J.; Cook, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 3230; (b) Brummond, K. M.; Kerekes, A. D.; Wan, H. *J. Org. Chem.* **2002**, *67*, 5156; (c) Pagenkopf, B. L.; Belanger, D. B.; O'Mahony, D. J. R.; Livinghouse, T. *Synthesis* **2000**, 1009; (d) Mukai, C.; Nomura, I.; Kitagaki, S. *J. Org. Chem.* **2003**, *68*, 1376; (e) Shibata, T.; Kadowaki, S.; Hirase, M.; Takagi, K. *Synlett* **2003**, 57; (f) Shibata, T.; Kadowaki, S.; Takagi, K. *Organometallics* **2004**, *23*, 4116.
3. Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813.
4. (a) Llerena, D.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1996**, *37*, 7027; (b) Brummond, K. M.; Chen, H.; Sill, P.; You, L. *J. Am. Chem. Soc.* **2002**, *124*, 15186; (c) Shin, S.; Rajan Babu, T. V. *J. Am. Chem. Soc.* **2001**, *123*, 8416; (d) Shibata, T.; Takesue, Y.; Kadowaki, S.; Takagi, K. *Synlett* **2003**, 268.
5. Oh, C. H.; Jung, S. H.; Rhim, C. Y. *Tetrahedron Lett.* **2001**, *42*, 8669.
6. Oh, C. H.; Jung, S. H.; Park, D. I.; Choi, J. H. *Tetrahedron Lett.* **2004**, *45*, 2499.
7. Oh, C. H.; Jung, H. H.; Kim, K. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 805.
8. (a) Oh, C. H.; Ahn, T. W.; Reddy, V. R. *Chem. Commun.* **2003**, 2622; (b) Oh, C. H.; Jung, S. H.; Bang, S. Y.; Park, D. I. *Org. Lett.* **2002**, *4*, 3325.
9. Kim, N.; Kim, K. S.; Gupta, A. K.; Oh, C. H. *Chem. Commun.* **2004**, 618.
10. Oh, C. H.; Park, S. J.; Ryu, J. H.; Gupta, A. K. *Tetrahedron Lett.* **2004**, *45*, 7039.
11. Ryu, J. H.; Oh, C. H. *Bull. Chem. Soc. Korea* **2003**, *24*, 1563.
12. Hirokazu, U.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 7329.
13. Shengming, Ma.; Zhao, S. *J. Am. Chem. Soc.* **1999**, *121*, 7943.
14. Mikami, K.; Yoshida, A. *Tetrahedron* **2001**, *57*, 889.
15. General experimental procedure: $Pd(OAc)_2$ (1.6 mg, 0.072 mmol, 0.03 equiv), 44.6 μL of tri-*t*-butylphospine (0.1 M solution in toluene), 1,4-dioxane (1 mL), an appropriate organo boronic acid **4a**–**g** (0.28 mmol), and an allenyne **3a**–**d** (0.0239 mmol) were placed into a screw cap bottle. This was stirred well at room temperature for 510 min. Then acetic acid (1.38 μL, 0.023 mmol,

0.01 equiv) was added and stirring was continued for five more minutes. The reaction mixture was heated to 50–60 °C, and monitored until the starting material was absent. The reaction mixture was then cooled to 10 °C, diluted with water, and extracted with diethyl ether (20 mL × 3). The combined organic portion was washed, first with water and finally with brine solution. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. The crude syrup thus obtained was purified by column chromatography by elution with 1:4 ethyl acetate:hexane to obtain pure products **5aa**–**da**.

16. Majewski, M.; Irvine, M. N.; MacKinnon, J. *Tetrahedron: Asymmetry* **1995**, *6*, 1837.