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Palladium-Catalyzed Coupling of Allylboronic Acids with Iodobenzenes. Selective Formation of the Branched Allylic Product in the Absence of Directing Groups

Sara Sebelius, Vilhelm J. Olsson, Olov A. Wallner, and Kálmán J. Szabó*

Department of Organic Chemistry, Stockholm University, SE-106 91 Stockholm, Sweden

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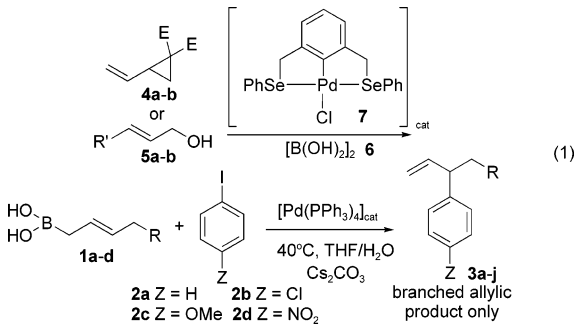
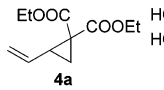
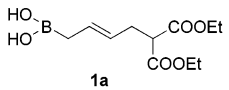
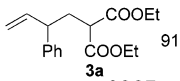
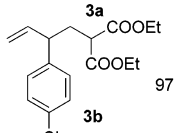
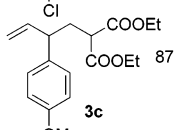
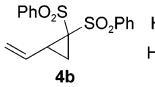
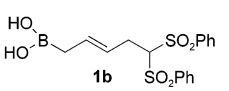
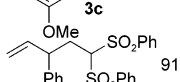
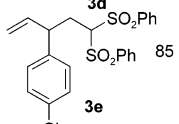
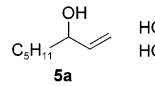
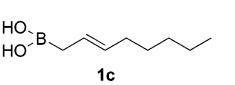
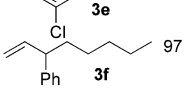
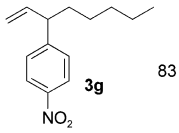
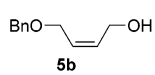
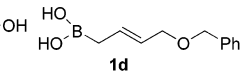
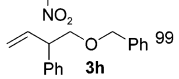
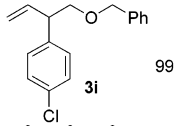
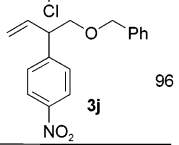
Palladium-catalyzed allylic substitution has become a widely applied methodology in organic synthesis.[1] A majority of the palladium-catalyzed nucleophilic allylation reactions proceed via (η^3-allyl)palladium intermediates.[1] Therefore, in case of employment of unsymmetrical allylic precursors, the control of the regioselectivity of the catalytic reactions may be problematic. In particular, when the reactions proceed through monosubstituted allyl−palladium intermediates, the nucleophiles preferentially attack the less hindered allylic terminus, affording the linear allylic product.[1f−h] As this product is achiral, there has been a considerable interest to revert the regioselectivity of this process to obtain the corresponding branched allylic isomer and thus create the basis for new palladium-catalyzed asymmetric transformations.[2] There have been two main strategies for conducting the nucleophilic attack toward formation of the branched allylic isomers: (i) application of directing groups in the allylic substrate;[2a−f] or (ii) application of specially designed ligands to bias the (η^3-allyl)palladium intermediates of the reaction.[2g−i]



(1)

We have now found that the palladium-catalyzed arylation of functionalized allylboronic acids leads to a selective formation of the branched allylic isomers without employment of directing groups or specially designed ligands. Accordingly, under standard Suzuki−Miyaura coupling conditions,[4] allylboronic acids **1a**−**d** readily undergo palladium(0)-catalyzed substitution reactions with aryl iodides **2a**−**d**, affording the corresponding terminal alkenes **3a**−**j** (eq 1). The reaction of allylboronic acid **1a** with iodobenzene proceeds smoothly at 40 °C, affording coupling product **3a** in 16 h with high yield (entry 1). The application of iodobenzene is important to obtain a high yield, as coupling of bromobenzene or phenyltriflate (in place of **2a**) with **1a** results in only trace amounts of **3a** under the applied mild conditions. Para-substituted iodobenzenes reacted similarly to **2a** (entries 2 and 3), indicating that the electronic effects of the aryl substituents have no significant effect on the outcome of the coupling reaction. Exchange of the carbethoxy substituents in **4a** to bulky phenyl sulfonyl groups (**4b**) did not affect the regioselectivity of the reaction (entries 4 and 5). Furthermore, allylboronic acids with an alkyl (**1c**) and benzyloxy group (**1d**) reacted readily with the same selectivity as **1a** and **1b**

Table 1. Regioselective Coupling of Allylboronic Acids with Aryl Iodides[a]

entry	precursor	allylboronic acid[b]	Ar-I	product	yield [%][c]
1	 **4a**	 **1a**	**2a**	 **3a**	91
2	**4a**	**1a**	**2b**	 **3b**	97
3	**4a**	**1a**	**2c**	 **3c**	87
4	 **4b**	 **1b**	**2a**	 **3d**	91
5	**4b**	**1b**	**2b**	 **3e**	85
6	 **5a**	 **1c**	**2a**	 **3f**	97
7	**5a**	**1c**	**2d**	 **3g**	83
8	 **5b**	 **1d**	**2a**	 **3h**	99
9	**5b**	**1d**	**2b**	 **3i**	99
10	**5b**	**1d**	**2d**	 **3j**	96

[a] The coupling reactions of **1** and **2** were conducted in the presence of Cs_2CO_3 and $Pd(PPh_3)_4$ (5 mol %) in a mixture of THF and water for 16 h at 40 °C. [b] The allylboronic acids were prepared according to refs 3a,b (see also Supporting Information). [c] Isolated yield.

(entries 6−10) even when nitrobenzene derivative **2d** was employed as the coupling component (entries 7 and 10).

Because of the mild reaction conditions (40 °C), the catalytic transformations proceed with high functional group tolerance as carbethoxy, phenylsulfonyl, aromatic chloro, and nitro groups remained unchanged under the catalytic transformations. Allylation of ortho-chloroiodobenzene with **1a** was also attempted (cf. entry 2). However, this reaction gave only traces of the ortho-chloro

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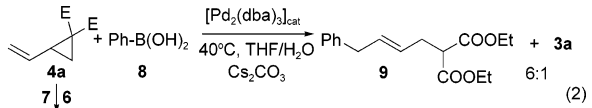
analogue of **3b**, indicating that the coupling reaction is probably sensitive to the ortho substitution of the iodobenzene component.

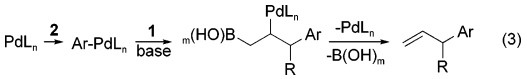
The allylboronic acid precursors can easily be obtained[3a,b] by boronation reaction of vinyl cyclopropanes[3a] (such as **4a**,**b**) and allyl alcohols[3b] (such as **5a**,**b**) with diboronic acid (**6**) in the presence of catalytic amounts of pincer complex **7**.[3c] Although, allylboronic acids are remarkably stable[3a,b,5a] in the presence of water, air, weak bases, and acids, they rapidly decompose under solvent-free conditions.[3a,b,5b] Nevertheless, we have found that allylboronic acids **1a**−**d** can be sufficiently purified by ether extraction of the water-diluted reaction mixture of the boronation process. The allylboronic acids are stable in ether and other solvents unless their solution is evaporated to dryness. Thus, the coupling reactions were carried out by addition of the corresponding iodoarenes (**2a**−**d**), $Pd(PPh_3)_4$, Cs_2CO_3, and THF to the wet etheral extract of **1a**−**d** followed by reduction of the solvent volumes. A successful coupling reaction of **1** and **2** requires the use of $Pd(PPh_3)_4$, while pincer complex **7** proved to be inefficient to catalyze the coupling process.

The employed allylboronic acids do not contain any known[2] directing groups, and the employed catalyst, $Pd(PPh_3)_4$, is one of the most commonly used palladium(0) sources, in which the PPh_3 ligands are not expected to affect the regioselectivity. Nevertheless, the catalytic allylation process affords selectively the branched allylic product. To study a possible directing effect of the carbethoxy group in **1a**, we carried out a classical allylic substitution reaction of **4a** with phenyl boronic acid in the presence of $Pd_2(dba)_3$ as catalyst.[6a] This process provided predominantly the linear product **9** and only traces[6b] of the branched allylic isomer **3a** (eq 2). This regioselectivity is typical for the classical nucleophilic substitution of **4a** proceeding via (η^3-allyl)palladium intermediate.[7a] On the other hand, when **4a** was converted first to allylboronic acid **1a** and then coupled with iodobenzene (**2a**), the regiochemistry of the process is reverted, providing solely the branched product **3a** (entry 1, eq 2). Accordingly, the regioselectivity of the coupling reaction of **4a** can be fully controlled by the appropriate choice of the reaction partners. Furthermore, the above results (eq 2) clearly indicate that the carbethoxy groups lack any directing effects for the formation of the branched allylic isomer **3a**. Obviously, the alkyl group of **1c** also lacks the directing effect on the regioselection of the arylation reaction (entries 6 and 7). Furthermore, the polar benzyloxy group in **1d** is expected to direct the nucleophilic attack to the less substituted allylic terminus if (η^3-allyl)palladium intermediates were involved in the catalytic process.[1g,h] Hence, the reaction proceeds with an excellent regioselectivity, providing the branched product. All these findings suggest that the above-described coupling of allylboronic acids **1a**−**d** and aryl iodides **2a**−**d** does not proceed via (η^3-allyl)palladium intermediates.



(2)

A similar mechanistic conclusion was reported by Hallberg and Nilsson[7b] studying the palladium-catalyzed coupling reaction of the parent allylpinacolborane with iodobenzene **2a**. Allylpinacolborane is apparently less reactive than allylboronic acid derivatives since the reaction required harsh conditions, typically 100 °C reaction temperature and 25 h reaction time. In this reaction, several isomeric products were formed, suggesting that the reaction is initiated by oxidative addition of **2a** to the palladium(0) catalyst followed by carbopalladation of the allyl boronate and subsequent elimination of the palladium boronate.[7b] We believe that a similar mechanism applies for the palladium-catalyzed coupling of functionalized allylboronic acids with iodobenzenes (eq 1), as well. This mechanism would also explain the selective coupling of **1a**−**d** with **2a**−**d** (eq 1) involving a highly regioselective carbopalladation process followed by β-boronate elimination by palladium (eq 3).



(3)

In summary, we have shown that the palladium-catalyzed coupling of allylboronic acids with aryl iodides can be achieved under standard Suzuki−Miyaura coupling conditions. The reactions proceed with a remarkably high regioselectivity, providing the branched allylic isomers. In contrast to palladium-catalyzed nucleophilic substitution reactions proceeding via (η^3-allyl)palladium intermediates, this process does not require directing groups in the allyl moiety to achieve substitution at the substituted allylic terminus. As the coupling reaction of allyl boronic acids with iodobenzenes generates a new stereogenic carbon, the presented method creates the basis for development of new asymmetric allylation processes.

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Supporting Information Available: Experimental procedures as well as characterization and NMR spectra of the products. This material is available free of charge via Internet at http://pubs.acs.org.

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(6) (a) The reaction of **4a** with **8** catalyzed by $Pd(PPh_3)_4$ proceeds extremely slowly, giving only traces of **9**. (b) The **9**:**3a** ratio in the crude product was determined by ^{1}H NMR spectroscopy.

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