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Highly regio- and stereoselective palladium-catalyzed allene bifunctionalization cascade via π-allyl intermediate

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ABSTRACT

We report a palladium-catalyzed allene bifunctionalization reaction that forms C–C and either C–O or C–N bonds in one pot with excellent regio- and stereoselectivity. Carboxylic acids, amides, and hydroxide are all suitable nucleophiles. Organoboronic acid acts as hydroxide transfer reagent. An intermediate π-allyl palladium complex was isolated, which yields improved catalytic performance as well as evidence of the origin of stereoselectivity. A derivatization study emphasizes the utility of the functionalized allylic products.

1. Introduction

Polysubstituted allyl compounds are important building blocks in organic synthesis, and are common structural motifs in natural products.[1] Transition metal-catalyzed nucleophilic allylic substitution is a rapid process to construct polysubstituted allyl compounds.[2] The palladium catalyzed Tsuji–Trost reaction has been developed into a powerful tool for this transformation in recent years.[3] The π-allyl palladium intermediates are essential to the formation of allylic substitution products; such π-allyl palladium species have been thoroughly studied and reviewed by organometallic chemists.[4] Allenes possess two adjacent C=C double bonds, and can be used to construct π-allyl metal complexes with participation of electrophiles such as aryl halides. Subsequent nucleophilic substitution yields the polysubstituted allyl products.[5]

In most reports of palladium-catalyzed allene bifunctionalization reactions, the allene substituent R is an electron donating group such as alkyl/aryl, or a weak electron withdrawing group (EWG) such as carboxylic acid, ester or amide (eq. 1, Scheme 1).[5c,5d] Savic et al. demonstrated that heteroatom-based nucleophiles such as acetate could be employed in the bifunctionalization cascade, yielding allyl acetate products[9b] (eq. 2, Scheme 1). However, selectivity problems hampered further applications of this method.

Reports of nucleophilic substitution reactions utilizing allenes bearing strong EWG (such as sulfone, phosphonate and phosphine oxide) are still scarce.[6] Boronic acids are commonly used to construct C–C bonds via the transmetallation step in Suzuki-Miyaura coupling reactions.[7,8] However, examples of boronic acid employed as hydroxide source to construct C–O bonds are uncommon.[9] Herein we report a new series of palladium-catalyzed allene bifunctionalization reactions which generate substituted allylic alcohols, esters and amides employing boronic acid, carboxylic acids and amides, respectively as nucleophiles (eq. 3, Scheme 1). We observe good regioselective control and pure (*Z*)-selectivity of the double bond geometry. We isolated a possible intermediate π-allyl palladium complex and used it as catalyst, which improved the efficiency of the reaction.

2. Results and discussion

In the cascade reaction involving phenylsulfonyl allene **1a** and phenyl iodide **2a**, different palladium sources, boronic acids, phosphine ligands, and bases were screened in order to find optimal reaction conditions (Table 1). For purification purposes, the allyl alcohol product was protected using imidazole/TBSCl.[10] Optimal conditions (**entry 1**, Table 1) resulted in a 64% isolated

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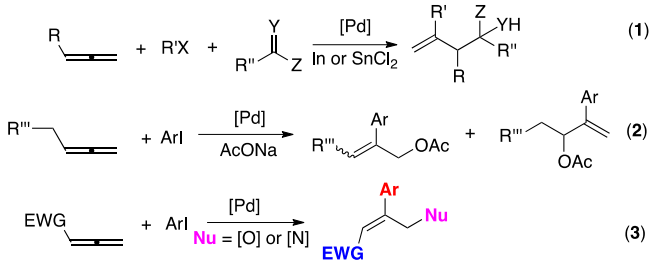
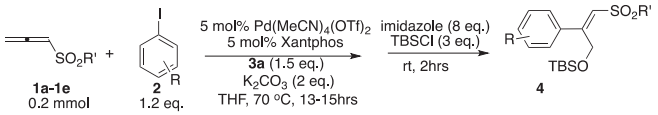


Scheme 1. Cascade reaction pathway involving allenes.

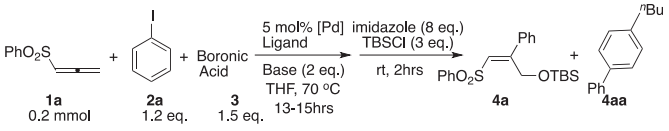


4a, R = H, R' = Ph (64%)
4b, R = 4-Me, R' = Ph (57%)
4c, R = 4-F, R' = Ph (54%)
4d, R = 4-Cl, R' = Ph, (53%)
4e, R = 4-Br, R' = Ph, (52%)
4f, R = 4-^{t}Bu, R' = Ph, (73%)
4g, R = 3-Me, R' = Ph, (59%)
4h, R = 3-Cl, R' = Ph, (50%)
4i, R = 3-OMe, R' = Ph, (50%)
4j, R = 3,5-dimethyl, R' = Ph, (56%)
4k, R = H, R' = 4-MePh (**1b**), (66%)
4l, R = H, R' = 4-OMePh (**1c**), (57%)
4m, R = H, R' = 4-BrPh (**1d**), (35%)

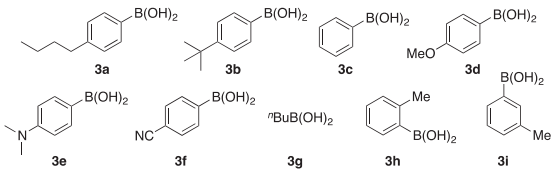
Scheme 2. Substrate scope.

yield of desired product **4a**, but we were unable to completely suppress the biphenyl product **4aa** formed by the direct C-C coupling of phenyl iodide **2a** and boronic acid **3a**. For the palladium source, $[Pd(MeCN)_4](OTf)_2$ outperformed its counterparts $Pd_2(dba)_3$ and $Pd(OAc)_2$ (**entries 1**–**3**, Table 1). Arylboronic acids of varying structure were also screened (entries **4**–**9**, Table 1); use of *ortho* methyl-substituted phenyl boronic acid (**3h**) yielded only a trace amount of desired product **4a**, and *meta*-methylphenyl boronic acid (**3i**) gave 26% isolated yield of **4a** (entries **10**–**11**, Table 1). The optimal boronic acid was *p*-*n*-butylphenylboronic acid (**3a**). Screening different phosphine ligands (entries **12**–**17**, Table 1) revealed Xantphos to be the preferred choice. The success of Xantphos may be attributed to its wide bite angle and rigid carbon skeleton, which can help to increase the ability of Pd to bind the C–C double bond of the functionalized allene substrates.[11] Changing the base from potassium carbonate to KF or K_3PO_4 did not lead to improved yields (entries **18**–**19**, Table 1).

Table 1
Optimization of palladium catalyzed cascade reaction.



Entry	[Pd]/5 mol%	[P]/10 mol%	Boronic acids **3**	Base	**4a**[a] (%)	**4aa** (%)
	[Pd]/[P] = 1:2					
1	$[Pd(MeCN)_4](OTf)_2$	Xantphos	**3a**	K_2CO_3	64	26
2	$Pd_2(dba)_3$	Xantphos	**3a**	K_2CO_3	28	–
3	$Pd(OAc)_2$	Xantphos	**3a**	K_2CO_3	9	–
4	$[Pd(MeCN)_4](OTf)_2$	Xantphos	**3b**	K_2CO_3	46	–
5	$[Pd(MeCN)_4](OTf)_2$	Xantphos	**3c**	K_2CO_3	26	–
6	$[Pd(MeCN)_4](OTf)_2$	Xantphos	**3d**	K_2CO_3	49	–
7	$[Pd(MeCN)_4](OTf)_2$	Xantphos	**3e**	K_2CO_3	trace	–
8	$[Pd(MeCN)_4](OTf)_2$	Xantphos	**3f**	K_2CO_3	25	–
9	$[Pd(MeCN)_4](OTf)_2$	Xantphos	**3g**	K_2CO_3	trace	–
10	$[Pd(MeCN)_4](OTf)_2$	Xantphos	**3h**	K_2CO_3	trace	–
11	$[Pd(MeCN)_4](OTf)_2$	Xantphos	**3i**	K_2CO_3	26	–
12	$[Pd(MeCN)_4](OTf)_2$	PPh_3	**3a**	K_2CO_3	trace	34
13	$[Pd(MeCN)_4](OTf)_2$	dppe	**3a**	K_2CO_3	trace	trace
14	$[Pd(MeCN)_4](OTf)_2$	dppp	**3a**	K_2CO_3	trace	18
15	$[Pd(MeCN)_4](OTf)_2$	dppf	**3a**	K_2CO_3	trace	6
16	$[Pd(MeCN)_4](OTf)_2$	dppbz	**3a**	K_2CO_3	trace	trace
17	$[Pd(MeCN)_4](OTf)_2$	DPEphos	**3a**	K_2CO_3	trace	25
18	$[Pd(MeCN)_4](OTf)_2$	Xantphos	**3a**	KF	26	–
19	$[Pd(MeCN)_4](OTf)_2$	Xantphos	**3a**	K_3PO_4	trace	–
20	$[Pd(MeCN)_4](OTf)_2$	Xantphos	THF/H_2O (3:0.1/mL)	K_2CO_3	Complicated	–



THF was dried by sodium/benzophenone and used in glove box (O_2 < 0.1 ppm and H_2O < 0.1 ppm).
[a] There is no need to purify the allyl alcohol precursor. Isolated yield of two steps were shown. -TBS = -$SiMe_2(^tBu)$; -OTf = -SO_2CF_3;