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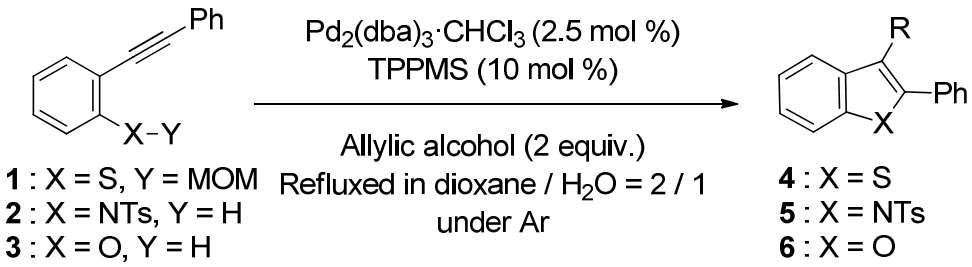
Palladium-catalyzed allylative cyclization of (*o*-alkynylphenyl) (methoxymethyl) sulfides **1**, *o*-alkynylanilines **2** and *o*-alkynylphenols **3** using simple allylic alcohols in aqueous media afforded 3-allylbenzo[*b*]thiophenes **4**, 3-allylindoles **5** and 3-allylbenzofurans **6** in good yields.



1 : X = S, Y = MOM
2 : X = NTs, Y = H
3 : X = O, Y = H

4 : X = S
5 : X = NTs
6 : X = O

Cite this: DOI: 10.1039/c0xx00000x

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COMMUNICATION

Direct use of allylic alcohols for palladium-catalyzed synthesis of 3-allylbenzo[*b*]thiophenes, benzofurans and indoles in aqueous media

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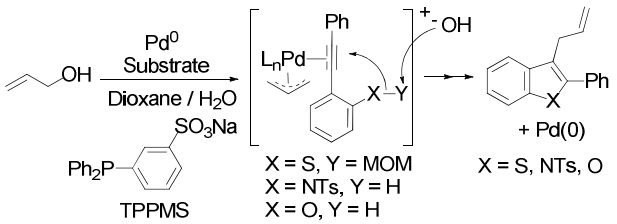
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Allylative cyclization of (*o*-alkynylphenyl) (methoxymethyl) sulfides, *o*-alkynylanilines and *o*-alkynylphenols catalyzed by π-allyl palladium species generated from simple allylic alcohols is described. 3-Allylbenzo[*b*]thiophenes, 3-allylindoles and 3-allylbenzofurans were obtained in good yields using aqueous media under neutral conditions.

Benzo[*b*]thiophenes, benzofurans and indoles are important classes of heterocycles in the pharmaceutical sciences. They are found in a variety of drugs and biologically active compounds.[1] Transition metal-catalyzed reactions using a π-allylmetal intermediate are regarded as the most important transformations in organic synthesis.[2] In most cases, activated allylic alcohol derivatives (*e.g.*, allylic halides, carbonates and esters) have been used as π-allylmetal sources. Since the beginning of the 21st century, catalytic activation (or activation by hydrogen-bonding of solvent) of allylic alcohols to produce π-allylmetal intermediates has attracted much attention from an environmental point of view.[3] A number of reactions using simple allyl alcohol as a π-allylmetal source have been reported, such as allylic substitution reactions,[4a-l] carbonylation reactions,[4m] coupling reactions with boronic acids[4n] and coupling reactions with terminal alkynes.[4o] Although palladium-catalyzed synthesis of 3-allylindoles and 3-allylbenzofurans using activated allylic compounds as π-allyl palladium sources have been reported,[5] direct use of simple allylic alcohols is more attractive with respect to the environmental benefit.[6] To our knowledge, utilization of the π-allylpalladium intermediates derived from simple allylic alcohols for alkyne activation is extremely rare.[7]



Scheme 1 Outline of this work.

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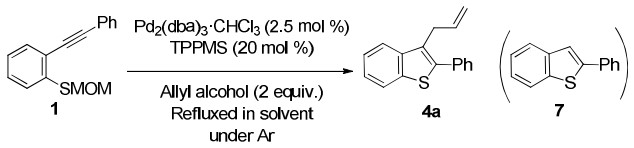
† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data. See DOI: 10.1039/b000000x/

Recently, we reported the synthesis of benzo[*b*]thiophenes, benzofurans and indoles based on palladium(II)-catalyzed cyclization-carbonylation of alkyne substrates.[8] Prompted by this precedent[4d,5] and our recent research,[8] we envisioned the direct use of allylic alcohols for the synthesis of heterocycles. Here, we report the palladium-catalyzed synthesis of 3-allylbenzo[*b*]thiophenes, 3-allylbenzofurans and 3-allylindoles in aqueous media using simple allylic alcohols as π-allylpalladium sources based on Oshima's protocols (Scheme 1).[4d]

Oshima et al. pointed out the importance of hydration of the hydroxyl group for the smooth generation of the π-allylpalladium species.[4d] Initially, we selected **1** (standard substrate), $Pd_2(dba)_3{\cdot}CHCl_3$, allyl alcohol and tppms to search for potential solvents (Table 1). Cyclized product **7** was obtained in low yield using only water (Table 1, entry 1). Next, we investigated the reaction in mixed solvents containing water, because the

Table 1. Optimization of the reaction (Synthesis of **4a**).



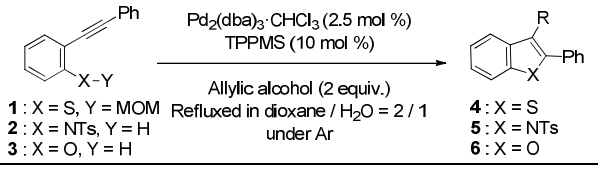
Entry	Solvent	Time (h)	Yield of **4a** (%)	Yield of **7** (%)
1	H_2O	23	trace	48
2	*i*PrOH / H_2O = 2 / 1	2	26	43
3	Hexane / H_2O = 2 / 1	23	-	-
4	DMSO / H_2O = 2 / 1	23[a]	4	25
5	THF / H_2O = 2 / 1	24	65	15
6	Dioxane / H_2O = 2 / 1	1.5	97	-
7	Dioxane	23	7	9
8[b]	Dioxane / H_2O = 2 / 1	1.5	89	-

[a] 80°C. [b] TPPMS : 10 mol %.

substrates and products were highly lipophilic, and did not

dissolve in water. Although *i*PrOH-H_2O, DMSO-H_2O and hexane-H_2O were not suitable as solvents, the use of THF-H_2O and dioxane-H_2O gave **4a** in moderate to excellent yields (Table 1, entries 2-6). In the absence of water, the reaction did not proceed, and substrate **1** was recovered (Table 1, entry 7). When the amount of tppms was reduced to 10 mol %, **4a** was obtained in 89% yield (Table 1, entry 8).

Table 2. Synthesis of 3-substituted benzo[*b*]thiophenes, 3-substituted indoles and 3-substituted benzofurans **4-6**.



Entry	Substrates	Allylic alcohols	R	Time (h)	Yield of **4-6** (%)
1	**1**	**8**		1.5	**4a** : 89
2	**2**	**8**		1.0	**5a** : 98
3	**3**	**8**		2.0	**6a** : 75[a]
4	**1**	**9**	Ph	1.0	**4b** : 91
5	**2**	**9**	Ph	1.0	**5b** : 97
6	**3**	**9**	Ph	0.5	**6b** : 89
7	**1**	**10**	*p*-MeOPh	0.5	**4c** : 95
8	**2**	**10**	*p*-MeOPh	1.0	**5c** : 97
9	**3**	**10**	*p*-MeOPh	0.5	**6c** : 80
10	**1**	**11**	*p*-NO_2Ph	1.0	**4d** : 88
11	**2**	**11**	*p*-NO_2Ph	1.5	**5d** : 99
12	**3**	**11**	*p*-NO_2Ph	0.5	**6d** : 84
13	**1**	**12**	*p*-ClPh	0.5	**4e** : 93
14	**2**	**12**	*p*-ClPh	1.0	**5e** : 93
15	**3**	**12**	*p*-ClPh	0.5	**6e** : 82
16	**1**	**13**		1.0	**4f** : 82
17	**2**	**13**		1.0	**5f** : 98
18	**1**	**14**	(Linear)[b] (Branched)	2.0	**4g**, **h** : 80 (1 : 1)

[a] 2-Phenyl benzofuran was obtained in 14% yield. [b] Small amount of *E*-isomer was contained.

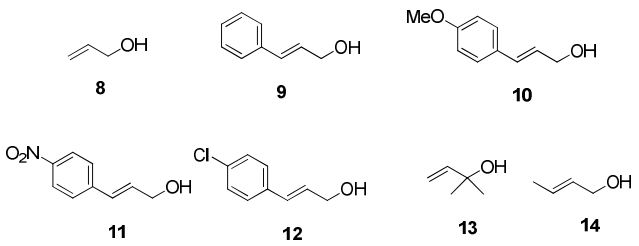
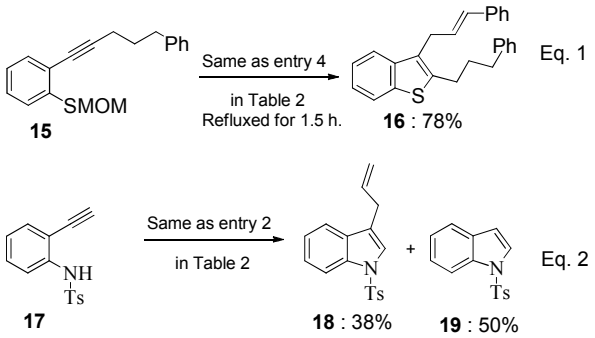
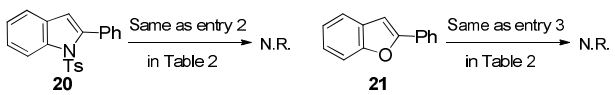


Figure 1. Allylic alcohols for Table 2.



Scheme 2 Reaction of **15** and trerminal alkyne **17**.

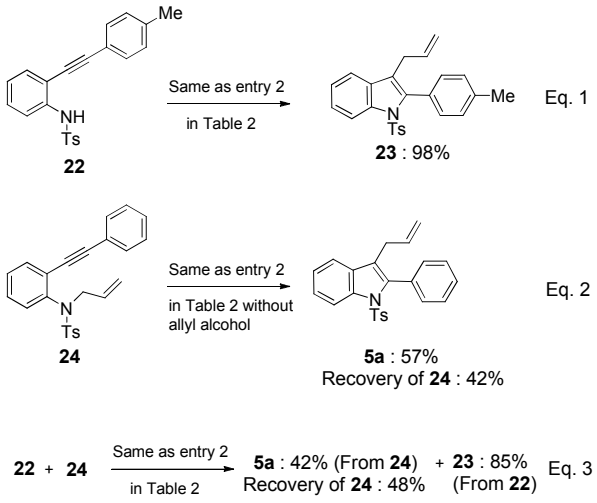
Having elucidated the optimum conditions for the reaction, we then employed several allylic alcohols **8-14** and substrates **1-3** for the synthesis of 3-substituted benzo[*b*]thiophenes, 3-substituted indoles and 3-substituted benzofurans (Table 2, Fig. 1). The reaction of *o*-alkynylaniline **2** with allyl alcohol **8** proceeded well, and **5a** was obtained in excellent yield (Table 2, entry 2). The use of *o*-alkynylphenol **3** resulted in a reduced yieldof **6a** (75%) with 2-phenylbenzofuran obtained in 14% yield as a by-product (Table 2, entry 3). These products were easily separated by silica gel column chromatography. In the case of cinnamyl alcohol **9**, the attempted reactions occurred smoothly, affording **4b**, **5b** and **6b** in 89-97% yields (Table 2, entries 4-6). The allylic alcohols **10** and **11** bearing both electron-donating and electron-withdrawing substituents gave good results, similar to that of parent cinnamyl alcohol (Table 2, entries 7-12). Chloro substituents on the phenyl group were tolerated under the reaction conditions (Table 2, entries 13-15). In the case of 2-methyl-3-butene-2-ol **13**, linear **4f** and **5f** were obtained as sole products due to steric hindrance (Table 2, entries 16 and 17). On the other hand, the reaction of allylic alcohol **14** with **1** afforded an inseparable mixture of linear and branched products **4g** and **4h** (1:1) in 80% yield (Table 2, entry 18). Replacement of the aryl groups at the alkyne terminus with an alkyl group and hydrogen atom afforded a slightly lower yield of **16** (78%) (Scheme 2, Eq. 1). In the case of terminal alkyne **17**, **18** was obtained in 38% yield together with **19** (50%) (Scheme 2, Eq. 2).



Scheme 3 Control experiment 1.

To investigate the reaction pathway, control reactions were performed (Scheme 2). The direct allylation of indole with allylic

alcohols has been reported,[6] thus *N*-tosyl-2-phenylindole **20** and 2-phenylbenzofuran **21** were treated under the current reaction conditions (Scheme 3). No reaction took place, with **20** and **21** recovered quantitatively. These results show that the simple cyclized products were not intermediates in the present reaction. As described in the introduction, the reaction of 2-alkynylaniline with activated allylic alcohol derivatives has previously been reported,[5] with the *N*-allylaniline derivative proposed as an intermediate. Although the *N*-allylaniline derivative could not be detected by TLC analysis in the present reaction, we performed another control reaction. At first, the reaction of **22** with allyl alcohol **8** proceeded well, and **23** was obtained in 98% yield (Scheme 3, Eq. 1). Next, *N*-allylaniline derivative **24** was prepared and subjected to the reaction conditions without allyl alcohol (Scheme 3, Eq. 2). The reaction rate of **24** was slower

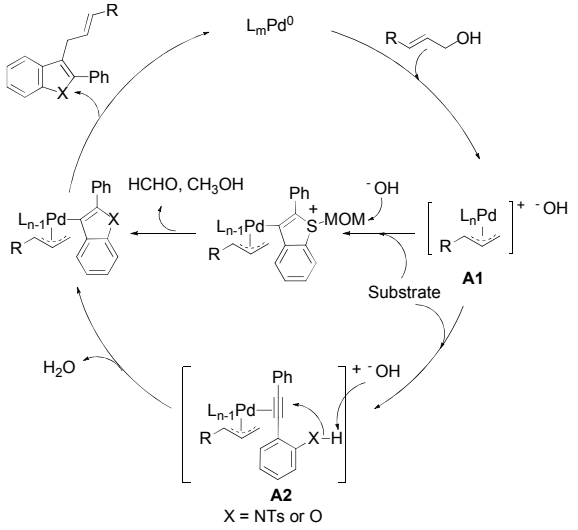


Scheme 4 Control experiment 2.

relative to that of **22**, and about half of **24** was recovered. In addition, an equimolar mixture of **22** and **24** was subjected to the reaction conditions (Scheme 3, Eq. 3). Although **22** was transformed to **23** within one hour, about half of **24** was recovered. These results suggested that the *N*-allylaniline derivative was not the intermediate in the present reaction, or at least it was not involved in the major pathway. Based on these control experiments, a plausible mechanism for the reaction is shown in Scheme 5. First, the π-allyl palladium complex **A1** is formed from allyl alcohol with the aid of hydrogen-bonding to water. The triple bond of the substrate coordinates to **A1** to produce intermediate **A2** by ligand exchange. In the case of aniline and phenol substrates **2** and **3**, the hydroxyl anion of **A1** acts as a base to remove the proton. This is followed by cyclization and subsequent reductive elimination to provide the products **5** and **6**. On the other hand, in the case of the substrates **1**, deprotection of the MOM group may occur after cyclization.[8,9]

Conclusions

In conclusion, palladium-catalyzed allylative cyclization of (*o*-alkynylphenyl) (methoxymethyl) sulfides **1**, *o*-alkynylanilines **2** and *o*-alkynylphenols **3** using simple allylic alcohols in aqueous media afforded 3-allylbenzo[*b*]thiophenes, 3-allylindoles and 3-allylbenzofurans in good yields. These reactions are general for a wide range of substrates. The reaction conditions are nearly neutral and base is not required.



Scheme 5 Plausible mechanism.

Acknowledgement

This work was supported by a JSPS KAKENHI grant (No. 15K078771).

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6 Recently, palladium catalyzed one-pot synthesis of 2,3-substituted indoles from *o*-alkynyl anilines and allylic alcohols has been reported. The mechanism is different from that of our work, 1) intramolecular cyclization lead to indolyl palladium intermediate 2) protonolysis of indolyl palladium intermediate to form 2-substituted indole 3) C3-alkylation of 2-substituted indole giving 2,3-substituted indole. In addition, allylic alcohols are restricted to 1,3-diaryl-2-propenols, two aryl groups of allylic alcohols are indispensable for allylation reaction, see: (*a*) C. Xu, V. K. Murugan and S. A. Pullarkat, *Org. Biomol. Chem.,* 2012, **10***,* 3875; Cyclization-Heck reaction sequence, see (*b*) Q. Wang, L. Huang, X. Wu and H. Jiang, *Org. Lett.,* 2013, **15**, 5940.

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