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Palladium-catalyzed haloallylation of aromatic ynol ethers with allyl chlorides: a highly regio- and stereoselective approach to (1*E*)-α-chloroenol ethers†

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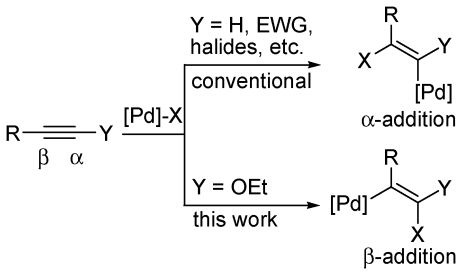
Described herein is a Pd-catalyzed haloallylation of aromatic ynol ethers and allyl chlorides, allowing facile access to (1*E*)-α-chloroenol ethers in a highly regio- and stereoselective manner. The synthetic utility of this method is demonstrated well by the synthesis of the stereodefined multisubstituted enol ethers and α-allylated carbonyl compounds.

The transition-metal-catalyzed reactions have become one of the most powerful tools for the effective construction of carbon–carbon or carbon–heteroatom bonds in organic chemistry.[1] In this respect, the halopalladation of acetylenes is receiving considerable attention because of the highly efficient and atom-economic formation of carbon–carbon and carbon–halide bonds in a single step.[2,3] Among these, particularly good selectivities and high yields were obtained for terminal alkynes and alkynes with electron-withdrawing groups. Less developed are the reactions with unsymmetrical internal alkynes, because the control of regiochemistry is usually problematic.

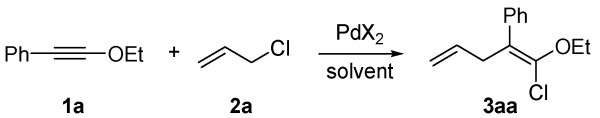
Fundamentally, the halopalladation of internal alkynes can proceed *via* two different types of pathways, *i.e.*, α-addition (palladium α to the Y group) and β-addition (Scheme 1). To address this issue, quite recently, we successfully extended the halopalladation reaction into unsymmetrical internal alkynes by substituting the acetylenes with halogen atoms, where the halopalladation of the C≡C triple bond exclusively undergoes the α-addition pathway.[4] In contrast, the regioselective halopalladation of acetylenes featuring the β-addition pathway has not been achieved yet. Clearly, it would enhance the scope and synthetic utility of halopalladation reaction if methods permitting the β-addition products were developed. In this communication, we report a highly regio- and stereoselective palladium-catalyzed haloallylation[5] of aromatic ynol ethers with the formation of a β-addition adduct as the key intermediate.

We initially investigated the reaction parameters by conducting the haloallylation reaction of 1-ethoxy-2-phenylacetylene (**1a**) with allyl chloride (**2a**). To our delight, the use of 5 mol% of $PdCl_2$ in THF at 50 °C for 1 h gave (1*E*)-α-chloroenol ether **3aa** in 87% isolated yield (entry 1, Table 1). The regiochemistry of this reaction was determined by the NOE experiments. Replacement of $PdCl_2$ by other palladium catalysts, such as $Pd(OAc)_2$, $Pd(MeCN)_2Cl_2$ and $Pd(PhCN)_2Cl_2$, led to lower yields (entries 2–4, Table 1). Further survey of the solvents using $PdCl_2$ as the catalyst concluded that THF was the preferred medium for the reaction (entries 5–12, Table 1). As such, the optimal reaction conditions consisted of 5 mol% of $PdCl_2$ as the catalyst, 50 °C as the reaction temperature, and THF as the solvent.



Scheme 1 Two pathways for halopalladation of acetylenes.

Table 1 Optimization of the reaction conditions[a]



Entry	PdX_2	Solvent	Yield[b,c] (%)
1	$PdCl_2$	THF	93 (87)[c]
2	$Pd(OAc)_2$	THF	80
3	$Pd(MeCN)_2Cl_2$	THF	85
4	$Pd(PhCN)_2Cl_2$	THF	83
5	$PdCl_2$	Dioxane	62
6	$PdCl_2$	DCE	30
7	$PdCl_2$	Toluene	81
8	$PdCl_2$	CH_3CN	84 (4/1)[d]
9	$PdCl_2$	EtOH	0
10	$PdCl_2$	DMSO	0
11	$PdCl_2$	EtOAc	69
12	$PdCl_2$	DME	73

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), and Pd catalyst (0.025 mmol) in 2 mL of solvent at 50 °C for 1–3 h. [b] GC yield. [c] Isolated yield. [d] Two stereoisomers (*E*/*Z* = 4/1) were obtained.

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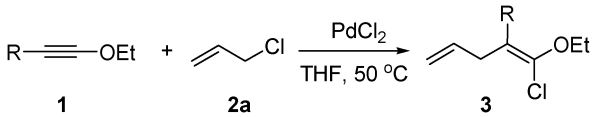
Table 2 Pd-catalyzed haloallylation of ynol ethers with **2a**[a]



Entry	1	R	3	Yield[b] (%)
1	**1a**	Ph	**3aa**	87
2	**1b**	4-Pr–C_6H_4	**3ba**	78
3	**1c**	4-Me–C_6H_4	**3ca**	85
4	**1d**	4-Br–C_6H_4	**3da**	81
5	**1e**	3-Br–C_6H_4	**3ea**	76
6	**1f**	2-Br–C_6H_4	**3fa**	68
7	**1g**	4-Cl–C_6H_4	**3ga**	83
8	**1h**	2-Cl–C_6H_4	**3ha**	79
9	**1i**	4-F–C_6H_4	**3ia**	82
10	**1j**	3-OMe–C_6H_4	**3ja**	74
11	**1k**	2,4-Cl_2–C_6H_3	**3ka**	76
12	**1l**	3,4-OMe_2–C_6H_3	**3la**	72
13	**1m**	2-Thienyl	**3ma**	77
14	**1n**	2-Naphthyl	**3na**	75
15	**1o**	*n*-C_5H_{11}	**3oa**	0

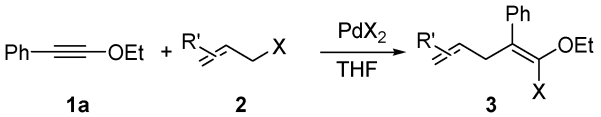
[a] Reaction conditions: **1** (0.5 mmol), **2a** (1.5 mmol), $PdCl_2$ (0.025 mmol) in 2 mL of THF at 50 °C for 1–3 h. [b] Isolated yield.

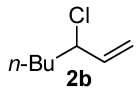
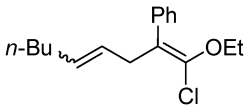
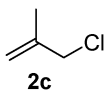
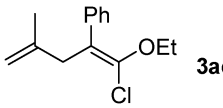
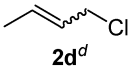
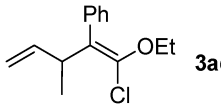
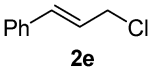
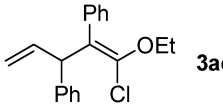
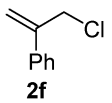
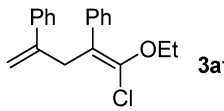
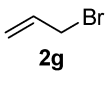
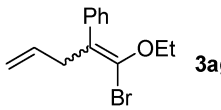
With the optimized reaction conditions identified, the scope and limitations of this approach were then investigated in detail with other alkynyl ethers. As summarized in Table 2, the reaction was suitable for a wide range of aromatic ynol ethers. Both electron-rich and electron-deficient aromatic alkynyl ethers were smoothly converted into the (1*E*)-α-chloroenol ether products in good yields with excellent stereoselectivity (Table 2). For example, ynol ethers **1b** and **1c** resulted in the desired (1*E*)-α-chloroenol ethers **3ba** and **3ca** in 78% and 85% yields, respectively (entries 2 and 3, Table 2). The reaction of sterically hindered ynol ethers **1f** and **1h** occurred uneventfully as well, producing (1*E*)-α-chloroenol ethers **3fa** and **3ha** in 68% and 79% yields, respectively (entries 6 and 8, Table 2). Heteroaromatic ynol ether, **1m**, for example, led to the (1*E*)-α-chloroenol ether **3ma** in 77% yield (entry 13, Table 2). However, to our disappointment, the reaction of aliphatic ynol ether **1o** failed to give the desired product, due to its oligomerization under the standard reaction conditions (entry 15, Table 2).

The versatility of this method was further examined by the reactions of **1a** with various allylic halides (Table 3). As shown in Table 3, 3-chloro-1-heptene (**2b**) produced the α-chloroenol ether **3ab** in 82% yield with a 1.8/1 mixture of two stereoisomers (entry 1, Table 3). Furthermore, the reaction is sensitive to the steric and electronic effects of allyl halides. For example, 2-methyl-substituted allyl chloride (**2c**) smoothly reacted with **1a** at 50 °C for 2 h to give the desired product **3ac** in good yield, while the reaction of crotyl chloride (**2d**) had to be performed at 70 °C for 10 h to complete the conversion (entries 2 and 3, Table 3). Additionally, both cinnamyl chloride (**2e**) and its isomer **2f** were intact under the reaction conditions even at a higher temperature of 70 °C (entries 4 and 5, Table 3).

On the other hand, α-bromoenol ether **3ag** could be generated in 83% yield using allyl bromide (**2g**); however, a mixture of two stereoisomers (1*E*/1*Z* = 4/1) was isolated (entry 6, Table 3). In comparison to the (1*E*)-α-chloroenol ether products, the inconsistency of this reaction in terms of stereoselectivity could

Table 3 Pd-catalyzed haloallylation of **1a** with **2**[a]

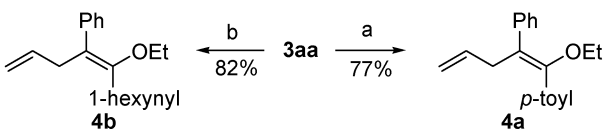


Entry	2	3		Yield[b] (%)
1	 **2b**		**3ab**	82[c]
2	 **2c**		**3ac**	73
3[e]	 **2d**[d]		**3ad**	71
4[e]	 **2e**		**3ae**	0
5[e]	 **2f**		**3af**	0
6[f]	 **2g**		**3ag**	83[g]

[a] Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), $PdCl_2$ (0.025 mmol) in 2 mL of THF at 50 °C for 1–10 h. [b] Isolated yield. [c] 4*E*/4*Z* = 1.8/1. [d] 2*E*/2*Z* = 2/1. [e] The reaction was carried out at 70 °C for 10 h. [f] 5 mol% of $PdBr_2$ was used. [g] 1*E*/1*Z* = 4/1.

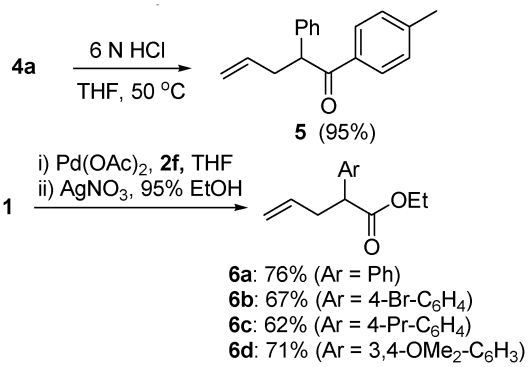
be attributed to the increased polarity of the Pd–Br bond,[3f] that is, the more polar Pd–Br bond may generate the free bromide ion and lead to the formation of a (1*Z*)-isomer through the *trans*-halopalladation process.[6]

To demonstrate the synthetic utility of this method, the resulting products were examined in the Pd-catalyzed cross-coupling reactions. For example, the Suzuki–Miyaura coupling[7] of **3aa** with 4-Me-$C_6H_4B(OH)_2$ employing Xphos[8] as the ligand gave the trisubstituted enol ether **4a** in 77% yield, while the Sonogashira coupling[9] of **3aa** with 1-hexyne afforded the enol ether **4b** in 82% yield (Scheme 2). Although there are a few methods that exist for the synthesis of the highly

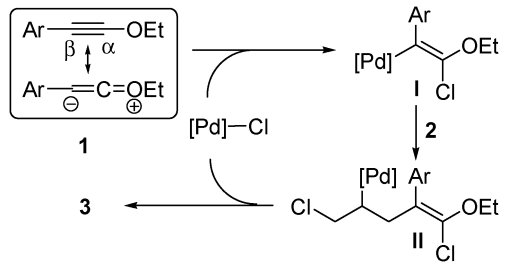


Reaction conditions: a = $Pd(OAc)_2$ (5 mol%), Xphos (10 mol%), *p*-Me-$C_6H_4B(OH)_2$ (1.5 equiv), Cs_2CO_3 (2 equiv), THF, 50 °C; b = $Pd(OAc)_2$ (5 mol%), Xphos (10 mol%), 1-hexyne (2 equiv), Cs_2CO_3 (2 equiv), THF, 60 °C.

Scheme 2 Synthesis of stereodefined enol ethers.



Scheme 3 Synthesis of α-allylated carbonyl compounds.



Scheme 4 Proposed mechanism.

substituted enol ethers,[10] this protocol provides a complementary, as well as efficient strategy to access the stereodefined multi-substituted enol ethers.

In addition, treatment of **4a** with 6 N HCl resulted in the α-allylated ketone **5** in 95% yield (Scheme 3). More interestingly, this method can be applied to the synthesis of α-allylated esters *via* the bromoallylation–hydrolysis sequence. For instance, α-bromoenol ether **3ag**, generated *in situ via* the Pd-catalyzed bromoallylation of ynol ether **1a**, was hydrolyzed with the assistance of silver nitrate to give the α-allylated ester **6a** in 76% yield (unoptimized). The generality of this strategy was preliminary demonstrated by the synthesis of functionalized aromatic α-allylated esters **6b–6d** in good yields (Scheme 3).

A plausible mechanism for this Pd-catalyzed haloallylation of aromatic ynol ethers was illustrated in Scheme 4. The first reasonable step is the insertion of ynol ether **1** into the Pd–Cl bond to generate the alkenyl palladium intermediate **I**. Very likely, the negative charge[11] on the β-carbon of ynol ethers may account for the regioselective β-addition of palladium, which is similar to the reversal of regiochemistry in the Heck reaction of electron-rich olefins.[12] Then, the carbopalladation of alkenyl palladium intermediate **I** with allyl halide **2** gives an alkyl palladium intermediate **II**, followed by the β-Cl elimination[13] to form the α-chloroenol ether **3** and to regenerate the palladium catalyst (Scheme 4).

In summary, we have developed a convenient protocol for the synthesis of (1*E*)-α-chloroenol ethers with excellent control of regio- and stereochemistry under the mild conditions. It represents the first example of halopalladation reaction featuring the β-addition pathway. Moreover, this methodology could be applied to the synthesis of stereodefined multi-substituted enol ethers and α-allylated carbonyl compounds. Further investigations on the applications of the developed protocol are underway.

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