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Palladium-Catalyzed Carboamination of Allylic Alcohols Using a Trifluoroacetaldehyde-Derived Tether

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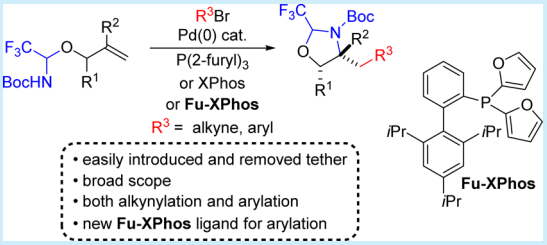
Supporting Information

ABSTRACT: The selective palladium-catalyzed carboamination of allylic alcohols is reported on the basis of the use of an easily introduced trifluoroacetaldehyde-derived tether. Aminoalkynylation reactions were realized using alkynyl bromides and commercially available phosphine ligands. For aminoarylations, a new biaryl phosphine ligand, "Fu-XPhos", was introduced to overcome a competitive Heck pathway. The carboamination products were obtained in high yields and diastereoselectivity. The tether could be easily removed to give value-added amino alcohol building blocks.

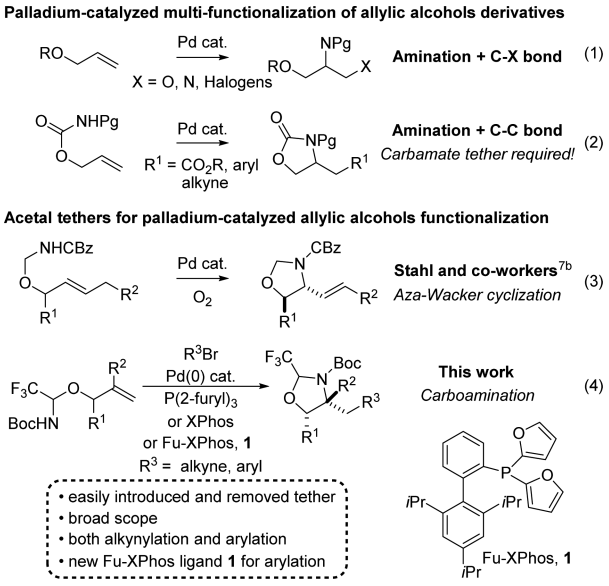


Allylic alcohols are broadly available and versatile building blocks in organic synthesis.[1] The inductive or directing effect of the alcohol or its derivatives can be used to achieve selective functionalization of the alkene double bond. In particular, amination reactions have been intensively investigated as they give access to 1,2- and 1,3-amino alcohols,[2] which are essential building blocks for the synthesis of bioactive natural and synthetic compounds.[3] Palladium catalysis has been especially successful in this respect, leading to synthetically highly useful multifunctionalization reactions such as aminohydroxylation[4] or diamination[5] (Scheme 1, eq 1). Reactions allowing the simultaneous formation of a carbon−nitrogen and a carbon−carbon bond have been less investigated, despite their high potential for the synthesis of more complex building blocks. Important breakthroughs have been achieved by the use of carbamate- or imidate-based tethers on the alcohol (Scheme 1, eq 2).[6] Nevertheless, the reported scope of these transformations remains narrow, and the tethers often require harsh conditions for cleavage. In this respect, the use of hemiaminal tethers would appear highly attractive for the functionalization of allylic alcohols, as they can be more easily removed. In fact, Hiemstra and co-workers and Stahl and co-workers have pioneered the use of such tethers for Wacker-type oxidative cyclization reactions (Scheme 1, eq 3).[7] Nevertheless, several separated steps were still needed to install and remove such tethers, and they were never used for more complex transformations involving multiple bond-forming events.

Recently, our group introduced (hemi)aminal tethers derived from trifluoroacetaldehyde for the carboamination of allylic amines to give amino alcohols and diamines.[8] We wondered if the same strategy could be applied to allylic alcohols. In this case, the lower nucleophilicity of alcohols compared to amines was expected to be a major challenge for the efficiency of tether installation.

Herein, we report the successful implementation of this strategy for the synthesis of amino alcohols, which are structurally complementary to those obtained from allylic amines. Both aminoalkynylation and aminoarylation reactions were achieved in high yields starting from preformed hemiaminal ethers. In situ formation of the tether was also possible with a slightly lower yield. In the case of aminoarylation, a new phosphine ligand ("FuXPhos", **1**) had to be designed to overcome a competitive Heck pathway. The

Scheme 1. Palladium-Catalyzed Functionalization of Allylic Alcohol Derivatives



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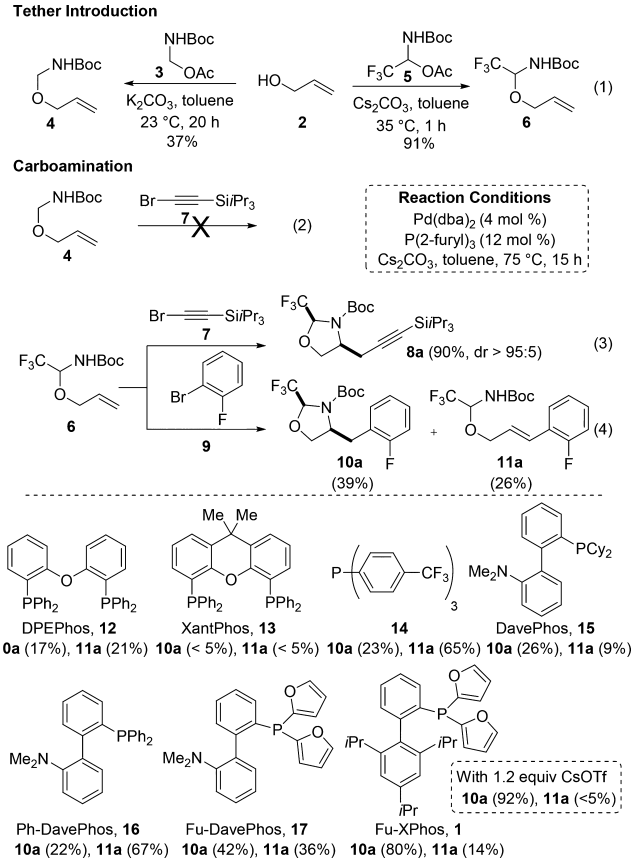
introduced tether could be easily removed under mild acidic conditions to give the free amino alcohols.

To begin our studies, we first synthesized hemiaminal ethers **4** and **6** from allylic alcohol **2** using either the reported tether precursor **3** derived from formaldehyde[7b] or the trifluoroacetaldehyde derivative **5** used in our previous studies (Scheme 2, eq 1).[8b] Interestingly, the presence of the trifluoromethyl group allowed a more efficient formation of the hemiaminal ether (91% vs 37%). The conditions developed for allylic amines were then applied to the carboalkynylation of hemiaminal ether **4** with alkynyl bromide **7**, but no product formation could be observed (Scheme 2, eq 2). In contrast, carboamination product **8a** could be obtained in 90% yield as a single diastereoiosmer after only minor optimization of the reaction conditions (Scheme 2, eq 3).[9] However, only a moderate yield of arylation product **10a** could be obtained, due to the competitive formation of Heck product **11a** (Scheme 2, eq 4).

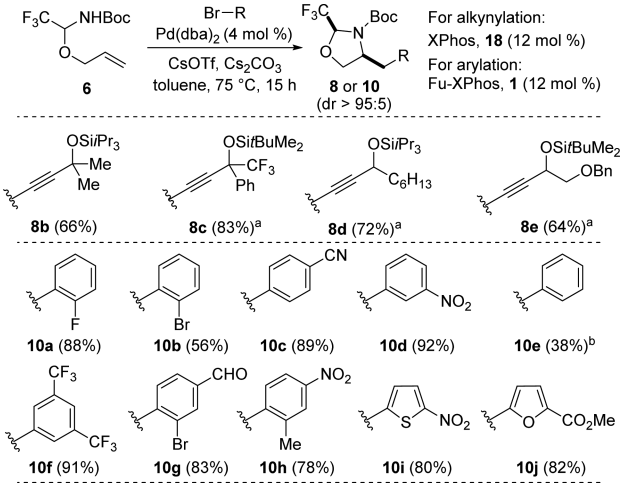
As the yield of arylation product **10a** could not be improved by changing the reaction conditions, we decided to examine other phosphine ligands. Bidentate phosphine ligands **12** and **13**, which had been successful in our previous work with allylamines,[8] gave low yields and selectivity. A good combined yield of **10a** and **11a** was obtained with electron-deficient arylphosphine **14**, but formation of the Heck product **11a** was favored. We then investigated the use of Buchwald-type biaryl monophosphine ligands.[10] Interestingly, the use of DavePhos **15** led to an increased selectivity for aminoarylation but with low overall yield. Replacing the cyclohexyl groups by benzene groups (Ph-DavePhos, **16**) restored the reactivity, but formation of the Heck product **11a** became again favored. At this point, we wondered if the favorable effect of the furyl substituent on the phosphine could be also important for Buchwald-type phosphines. The new Fu-DavePhos ligand **17** could be easily accessed in two steps. The use of **17** indeed led to an increase in selectivity and **10a** could be isolated in 42% yield. The selectivity could be further increased by using the sterically more hindered Fu-XPhos ligand **1**. Finally, the desired product **10a** could be obtained in 92% with less than 5% formation of the Heck product **11a** using cesium triflate as additive.[11]

The scope of the aminoalkynylation and arylation of hemiaminal ether **6** was then examined (Scheme 3).

Scheme 2. Preliminary Results on Tether Introduction, Carboamination, and Ligand Effect on Aminoarylation



Scheme 3. Scope of the Carboamination of Hemiaminal Ether 6[a,b]



[a]Obtained as a 50:50 mixture of diastereoisomer at the propropargylic center. [b]NMR yield.

Propargylic silyl ethers **8b–e** could be obtained in good yields in this transformation with XPhos **18** as ligand. Fu-Xphos **1** was confirmed as the best ligand for arylation. Benzene derivatives **10a–d** bearing electron-withdrawing groups such as fluorine, bromine, cyano, or nitro were isolated in high yields. The electron-withdrawing group was required to obtain good yields. Only 38% **10e** could be observed when using phenyl bromide as reagent. In this case, it was not possible to overcome completely the Heck pathway. Furthermore, both multi-substituted benzene rings **10f–h** and heterocycles **10i–j** could be accessed from hemiaminal **6**.

Substituted allylic alcohols were then examined in the aminoalkynylation and -arylation reactions (Table 1). When branched hemiaminal ether **19** was used as a 50:50 mixture of diastereoisomers, amino alcohol derivative **20** was obtained in 73% yield and 67:33 dr (Table 1, entry 1).[12] The synthesis of the corresponding aminoarylation product **21** was also successful (Table 1, entry 2). When symmetrical bisallylic hemiaminal ether **22** was used, aminoalkynylation product **23** was formed in 65% yield as a single diastereoisomer (Table 1, entry 3). The use of α,α-disubstituted olefins was also possible: Both aminoalkynylation and -arylation products **25** and **26** were obtained in good yield and diastereoselectivity (Table 1, entries 4 and 5). Finally, the more complex amino alcohol derivative **28** could be also accessed in 57% yield but with lower diastereoselectivity (Table 1, entry 6).

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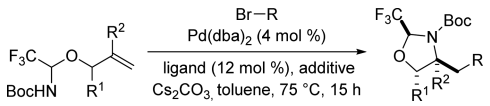
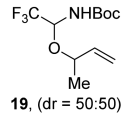
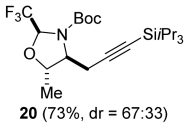
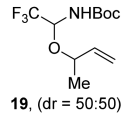
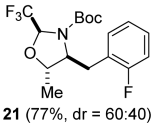
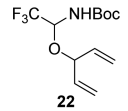
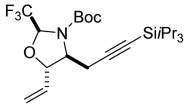
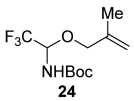
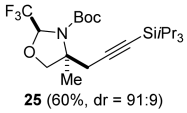
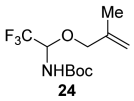
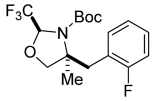
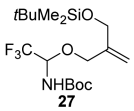
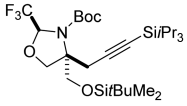
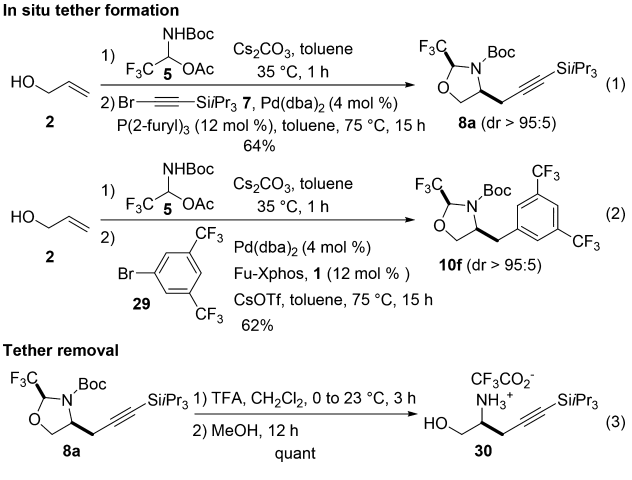
Table 1. Amino-Alkynylation and -Arylation of Substituted Allylic Alcohols



entry	substrate	RBr	ligand additive	product (yield, dr)
1	 **19**, (dr = 50:50)	**7**	P(2-furyl)$_3$ -	 **20** (73%, dr = 67:33)
2	 **19**, (dr = 50:50)	**9**	**1** CsOTf	 **21** (77%, dr = 60:40)
3	 **22**	**7**	P(2-furyl)$_3$ -	 **23** (65%, dr > 95:5)
4	 **24**	**7**	**18** -	 **25** (60%, dr = 91:9)
5	 **24**	**9**	**1** CsOTf	 **26** (61%, dr > 95:5)
6	 **27**	**7**	**18** -	 **28** (57%, dr = 73:27)

To further increase the efficiency of the carboamination process, we then investigated if the hemiaminal tether could be installed in situ. Both the aminoalkynylation and -arylation were indeed successful in the one-pot process, and products **8a** and **10f** were obtained in 64% and 62% yield, respectively (Scheme 4, eqs 1 and 2). Nevertheless, a significant decrease in yield was observed when compared to the use of isolated hemiaminal **6**. Finally, the introduced tether could be removed easily by treatment with trifluoroacetic acid (TFA) followed by methanolysis to give the ammonium salt in quantitative yield (Scheme 4, eq 3).

Scheme 4. In Situ Tether Formation and Tether Removal



In conclusion, we have reported the first carboamination of allylic alcohols based on the use of a trifluoroacetaldehyde tether. Both alkynylation and arylation products could be obtained in good yield and diastereoselectivity, giving amino alcohol derivatives with complementary substitution patterns compared to those obtained from allylic amines. The hemiaminal tethers were easily introduced and could be removed in a single step to give amino alcohols in quantitative yields. These results further highlight the versatility of tethers derived from trifluoroacetaldehyde and set the basis for the development of further highly selective transformations of olefins in future works.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01524.

Experimental procedures and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(12) The relative stereochemistry of the major diastereoisomers of compounds **21**, **23**, and **25** could be established by 2D NMR experiments, and the structure of the other major diastereoisomers was assigned by analogy. The relative stereochemistry of the minor diastereoisomer of **21** could be assigned as *all-cis*. Only two diastereoisomers were observed in entries 1−3.

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