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Communication

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# $F^-$ Nucleophilic Addition Induced Allylic Alkylation

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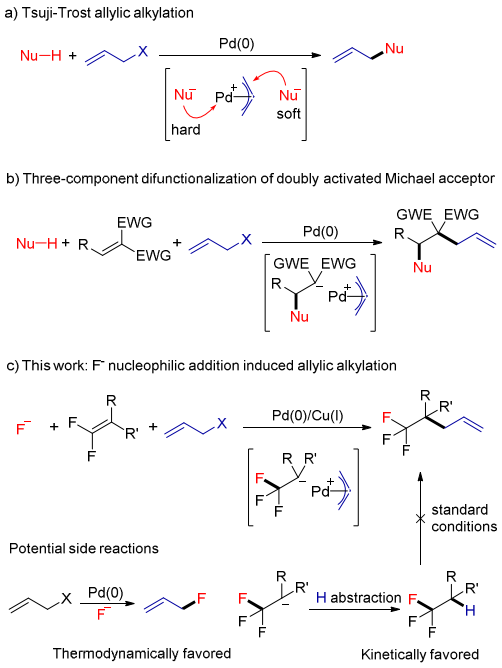
*Supporting Information Placeholder*

**ABSTRACT:** Herein, we present a novel strategy based on palladium-catalyzed allylic alkylation by taking advantage of the nucleophilic addition of external fluoride onto *gem*-difluoroalkenes as the initiation step. The merit of this protocol is highly appealing as it enables a formal allylation of trifluoroethylarene derivatives through the in situ generation of β-trifluorocarbanions, which otherwise are deemed to be problematic via deprotonative allylation manners. Furthermore, this strategy distinguishes itself by high modularity, operational simplicity and wide substrate scope with respect to allyl carbonates, giving rise to a broad array of homoallyltrifluoromethane derivatives, which otherwise would not be easily obtained using the existing synthetic methods.

Transition-metal-catalyzed allylic alkylation (AA as abbreviation) reaction represents one of the most important and fundamental C-C bond formation reactions in modern synthetic organic chemistry.[1] By enabling straightforward introduction of synthetically versatile allyl fragments to a great diversity of pro-nucleophiles, these reactions find broad applications in natural product synthesis, medicinal chemistry and materials science.[2] In this context, the palladium-catalyzed variant, also widely known as the Tsuji-Trost reaction, was particularly well explored and met with a great success during the past several decades (Scheme 1a).[3] However, the majority of reported examples were restricted to the creation of only one C($sp^3$)-C($sp^3$) bond, with only sporadic cases, which enables a nucleophilic addition induced allylic alkylation (NAAA as abbreviation), being reported.[4] By making use of the vinyl epoxide or aziridine as amphiphilic precursors under palladium catalysis, Yamamoto, Aggarwal et al. have successfully achieved the NAAA reaction with external Michael acceptors.[5] Moreover, an elegant example of three-components NAAA reaction was also disclosed by Yamamoto and coworkers, although the employment of doubly activated Michael acceptor was found to be a prerequisite (Scheme 1b).[6a] To be noted, by using this strategy Plietker and coworkers have successfully developed an efficient protocol based on nucleophilic ferrate system, which allowed the smooth alkoxy- and trifluoromethylation-allylation of doubly activated alkenes.[6b,6c] Considering the challenges and potential problems associated with NAAA reactions, for example the competing premature AA reaction of pro-nucleophile or simple conjugate addition of pro-nucleophile with Michael acceptor, it is thus quite understandable for their slow advance.

**Scheme 1. Tsuji-Trost reaction and nucleophilic addition induced allylic alkylation**

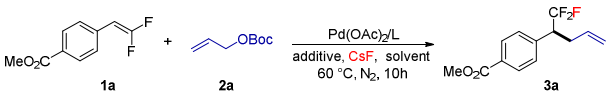



Due to the unique intrinsic nature of fluorine atom, the development of effective synthetic strategies for the introduction of fluorine or fluorine-containing functional groups to organic frameworks is of vital importance in

pharmaceutical and agrochemical research,[7] among which the discovery of novel synthetic approaches for the introduction of trifluoromethyl group has particularly gained much attention.[8] With our recent success of using *gem*-difluoroalkene as electrophile for the introduction of monofluoroalkene moiety,[9] we envisage the possibility of uncovering an unprecedented strategy for the modular construction of homoallyltrifluoromethane derivatives by taking advantage of palladium-catalyzed NAAA reaction (Scheme. 1c).[10] It needs to be pointed out that Hu and coworkers have recently reported a novel synthetic route to trifluoromethylated compounds with *gem*-difluoroalkene as $\alpha$-trifluoromethylated carbon-centered radical precursor.[10a] The rationales of this envisioned NAAA reaction are based on the following considerations: i) the $\alpha$-carbon atom of *gem*-difluoroalkenes are particularly electron-deficient because of the electron-withdrawing abilities of the two fluorine atoms, thus making them susceptible to external nucleophiles (here as the fluoride);[11] ii) while the addition and elimination of fluoride is a reversible process, the ensuing C-C bond formation could dramatically drive such process forward; iii) the potential side reactions such as allylic fluorination may not pose significant problem provided that the allyl fluorides could also be ionized by palladium catalyst, thus serving as a bifurcated allyl donor.[12] In addition, the kinetically more favored formation of C-C bond compared with that of C-F bond in palladium-catalyzed allylic substitution could be another factor that would guarantee the execution of this multi-component reaction. Despite reasonability of rationales envisioned, challenges associated with this proposal still remain, among which the inhibition of expected allylation by premature quenching of the in situ generated $\beta$-trifluorocarbanion is of concern.[13]

To challenge our hypothesis, the palladium-catalyzed NAAA reaction of methyl 4-(2,2-difluorovinyl)benzoate **1a** and allyl *tert*-butyl carbonate **2a** was examined with externally added fluoride salt as the nucleophile and representative results were shown in Table 1. After systematic examination of various parameters, the optimized reaction conditions was obtained: using CsF as fluoride source, $Pd(MeCN)_2(BF_4)_2$, X-Phos or XantPhos as the catalyst and assisting ligand in the presence of $CuF_2$ as additive and DMF as the solvent(see the Supporting Information for details of reaction optimization).[14] Although not mandatory, the addition of catalytic amount copper salt was revealed to have appreciable enhancement on the reaction efficiency. While the exact role of copper salt in this transformation requires further in-depth investigation, its beneficial effect could be rationalized by assuming its ability to stabilize the carbanion generated in situ.[15] Furthermore, control experiments demonstrated the indispensability of both palladium catalyst and phosphine ligand on this NAAA reaction, without either, no desired product could be obtained. It is also worth mentioning that no detectable amount of **3a** was observed when subjecting 4-(2,2,2-trifluoroethyl)benzoate to the optimized reaction conditions, which firmly rules out its potential as a reaction intermediate in the catalytic cycle. The ineffectiveness of trifluoroethylarene in this transformation is in full agreement with the current notion of allylic alkylation of organofluorine compounds, with only substrates that possess sufficiently acidic protons being competent.[16] In the present scenario, the carbanion is generated in situ *via* nucleophilic addition, thus bypassing the conventional strong base mediated deprotonation protocol.

**Table 1. Optimization of reaction condition**

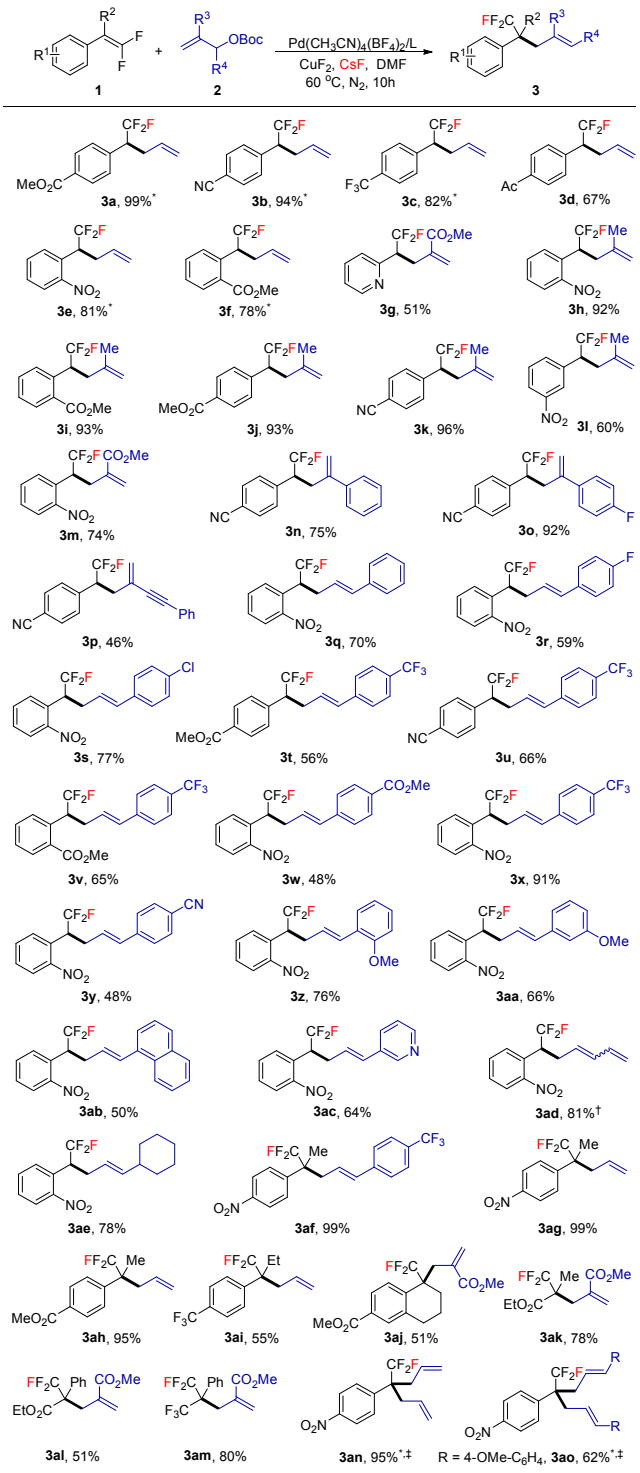



| entry | solvent | ligand | additive | **3a** (%)[a] |
|---|---|---|---|---|
| 1 | Acetone | X-Phos | CuOAc | 23 |
| 2 | DCE | X-Phos | CuOAc | trace |
| 3 | MeCN | X-Phos | CuOAc | trace |
| 4 | DMF | X-Phos | CuOAc | 67 |
| 5 | DMF | X-Phos | CuOAc | 88[b] |
| 6 | DMF | XantPhos | CuOAc | 85[b] |
| 7 | DMF | bpy | CuOAc | 0[b] |
| 8 | DMF | X-Phos | $CuF_2$ | 99[b] |
| 9 | DMF | X-Phos | $Cu(OTf)_2$ | 96[b] |
| 10 | DMF | X-Phos | - | 65[b] |
| 11 | DMF | - | CuOAc | trace[b] |
| 12 | DMF | X-Phos | CuOAc | 0[c] |

Experiments were performed with **1a** (0.15 mmol), **2a** (0.3 mmol), CsF (0.45 mmol), additive (0.015mmol), $Pd(OAc)_2$ (0.0075 mmol), monodentate ligand (0.015 mmol)/bidentate ligand (0.0075 mmol) in solvent (1.0 mL) stirring at 60 °C for 10 hours. [a]Isolated yields. [b]Using $Pd(MeCN)_4(BF_4)_2$ as catalyst. [c]No palladium catalyst was added.

With the optimized reaction conditions in hand, the reaction generalities as well as the limitations with respect to both *gem*-difluoroalkene and allyl carbonate were surveyed and the results were summarized in Table 2. In general, *gem*-difluoroalkenes with electron-withdrawing substituents reacted smoothly to afford the desired homoallyltrifluoromethane products in good to excellent yields, whereas those with electron-donating groups were reluctant to participate in such transformation, which was ascribed to the low electrophilicity of the substrates or the instability of the resulting $\beta$-trifluorocarbanions, which quickly collapsed without further engaging in allylation process. *gem*-Difluoroalkenes containing a variety of synthetically useful functionalities such as $CO_2Me$, CN, $CF_3$, Ac and $NO_2$ were amenable to this reaction and the locations of substituents were found to have appreciable influence on the reaction efficiency (**3a**-**3l**). To our pleasure, pyridine derived *gem*-difluoroalkene reacted smoothly without obvious deleterious effect on the reaction, thus giving rise to product **3g** in synthetically useful yield. For allyl carbonate, substrates with alkyl, aryl or ester substituents on the internal alkene moiety were compatible with the reaction conditions (**3h**-**3o**). Also of note was the nice

**Table 2. Reaction scope of NAAA reaction**




Experiments were performed with **1** (0.15 mmol), **2** (0.3 mmol), CsF (0.45 mmol), $CuF_2$ (0.015mmol), $Pd(MeCN)_4(BF_4)_2$ (0.0075 mmol), XantPhos (0.0075 mmol) in DMF (1.0 ml) stirring at 60 °C for 10 hours. *Using X-Phos (0.015 mmol) as ligand. †Linear/Branched = 3/1. ‡**2** (0.45 mmol) was employed.

compatibility of alkynyl functionalities, for example, by using this strategy, trifluoromethyl incorporated enyne product **3p** could be selectively obtained, albeit with somewhat compromised reaction efficiency. For allylic carbonates containing substituents on the allylic positions, the allylic alkylation could potentially lead to the formation of both region- and diastereoisomers. Within our experiments, moderate to high selectivity were observed depending on the substrates employed. The substrate scope with respect to 1-arylallyl carbonate was quite broad, with electronically differentiated functional groups such as halogen, $CF_3$, CN, OMe and ester being well adapted regardless of their substitution locations (**3q**-**3aa**). The nice tolerance of halogen substituents provides a synthetic handle for further elaboration through traditional cross-coupling strategies. In addition, extended aromatic entity such as naphthyl derived substrate also uneventfully underwent this reaction and provided product **3ab** in 50% yield. Also of note, the reaction efficiency was not inhibited by heteroaryl containing allyl carbonates and when pyridine based substrate was applied, the adduct **3ac** was produced in 64% yield. Besides 1-arylallyl carbonate, alkyl and alkenyl based congeners could also be employed as effective allyl donors, for example product **3ae** could be isolated in 78% yield when 1-cyclohexylallyl carbonate was used, while in the case of diallyl carbinol counterpart, product **3ad** was produced in 81% yield, albeit with moderate stereoselectivity. It also needs to be pointed out that the present allylation protocol could also be readily extended to ketone based *gem*-difluoroalkene derivatives, allowing the expedient construction of architectures containing quaternary carbon centers with one substituent being the trifluoromethyl group (**3af**-**3ao**). In this respect, by making use of tetrahydronaphthalene derived *gem*-difluoroalkene as substrate, we were able to obtain the densely functionalized product **3aj** in 51% yield. Because of the electron delocalization ability of ester group, further electronic activation was not required in the case of *gem*-difluoroacrylate derivatives and related allylation products could be obtained in moderate to good yields (**3ak**, **3al**). It is noteworthy that when *gem*-difluoroalkene derived from trifluoroacetophenone was employed, the reaction occurred readily to produce product **3am** in 80% yield, thus providing an efficient method for the synthesis of *gem*-trifluoromethyl homoallylbenzene derivatives. Furthermore, the construction of quaternary carbon center also proved to be feasible *via* two-fold allylation processes, provided that substrates contain functionalities that are electron-withdrawing strong enough for assisting further deprotonation after introduction of the first allyl group (**3an**, **3ao**). Finally, while it is quite appealing to extend this NAAA reaction into asymmetric version, preliminary effort in this direction was unfortunately less rewarding with only marginal enantiomeric excess observed (see the Supporting Information for the details).[15] Continuing endeavor aiming at realizing asymmetric NAAA reaction is still underway in our lab.

In conclusion, by making use of palladium-catalyzed nucleophilic addition induced allylic alkylation manifold, we have successfully developed a strategically novel synthetical protocol that allows a step-economic and expedient construction of homoallyltrifluoromethane deriva-

tives without resorting to the deprotonative functionalization manner.[17] This three-component transformation is characterized by its well organized reaction sequence, thus obviating the potential side pathways which would otherwise occur between either of two reaction partners employed. It is also worth mentioning that by making use of such strategy, the reaction boundary, which restricts the allylic alkylation of trifluoromethyl-containing molecules to those with relative low p$K_a$ values, is skillfully overridden.[16]

## ASSOCIATED CONTENT

### Supporting Information

Detailed experiment procedures and compound characterization deta. "This material is available free of charge via the Internet at http://pubs.acs.org."

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### Author Contributions

[§]P. T. and C.-Q. W. contributed equally to this work.


### Notes

The authors declare no competing financial interests.

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(14) Other transition-metal-catalyzed allylic alkylation protocols such as Rh, Ir, Ni and Mo-based systems were not effective for this transformation; using nitrogenous or NHC ligands only led to formation of premature protonation byproducts, see the supporting information for details.

(15) We appreciate one reviewer's comments on a possible role of $CuF_2$ by assuming the in situ formation of fluoride cluster with CsF, which acts as a "soft" nucleophile and also the difficulty for asymmetric induction using chiral ligands as result of Cu-stabilized carbanion with considerable covalent bond character.

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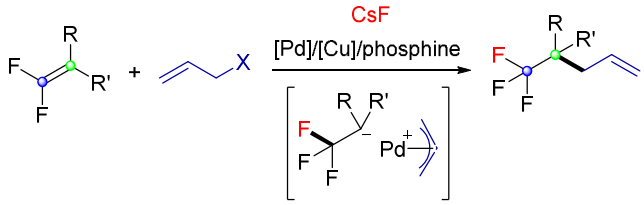


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