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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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F^- Nucleophilic-Addition-Induced Allylic Alkylation

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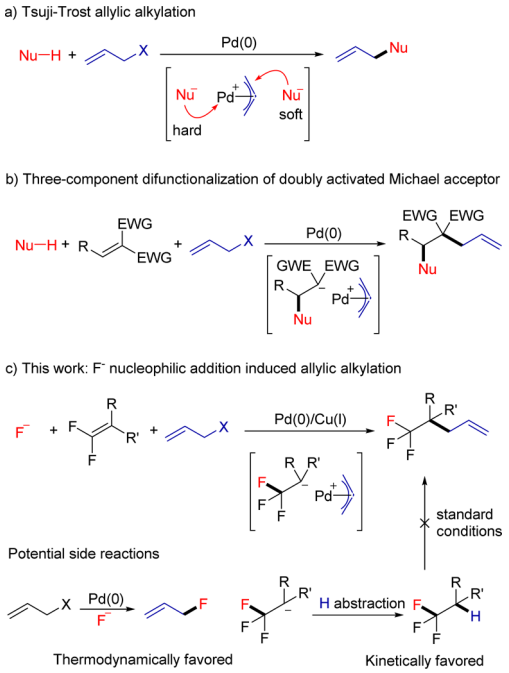
Supporting Information

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 in deprotonative allylation. 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 existing synthetic methods.

Transition-metal-catalyzed allylic alkylation (AA) is 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 pronucleophiles, AA has found 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, has been particularly well explored and met with 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 enabling nucleophilic-addition-induced allylic alkylation (NAAA) being reported.[4] By making use of vinyl epoxides or aziridines as amphiphilic precursors under palladium catalysis, Yamamoto,[5a] Aggarwal,[5b] and Hou[5c] have successfully achieved NAAA reactions with external Michael acceptors. Moreover, an elegant example of a three-component NAAA reaction was also disclosed by Yamamoto and co-workers, although the use of a doubly activated Michael acceptor was found to be a prerequisite (Scheme 1b).[6a] Using this strategy, Plietker and co-workers successfully developed an efficient protocol based on a nucleophilic ferrate system that allowed the smooth alkoxylation− and trifluoromethylation−allylation of doubly activated alkenes.[6b,c] In view of the challenges and potential problems associated with NAAA reactions, such as the competing premature AA reaction of the pronucleophile or simple conjugate addition of the pronucleophile and the Michael acceptor, their slow advance is quite understandable.

Scheme 1. Tsuji−Trost Reaction and Nucleophilic-Addition-Induced Allylic Alkylation



Because of the unique intrinsic nature of the 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 the trifluoromethyl group has particularly gained much attention.[8] With our recent success of using *gem*-difluoroalkenes as electrophiles for the introduction of monofluoroalkene moieties,[9] we envisaged the possibility of uncovering an unprecedented strategy for the modular construction of

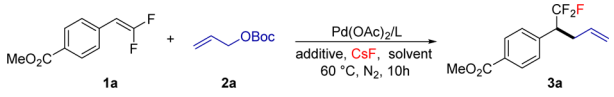
Received: October 27, 2016
Published: November 28, 2016

DOI: 10.1021/jacs.6b11205
J. Am. Chem. Soc. 2016, 138, 15869−15872

homoallyltrifluoromethane derivatives by taking advantage of a palladium-catalyzed NAAA reaction (Scheme. 1c).[10] It needs to be pointed out that Hu and co-workers have recently reported a novel synthetic route to trifluoromethylated compounds with *gem*-difluoroalkenes as α-trifluoromethylated carbon-centered radical precursors.[10a] The rationales for this envisioned NAAA reaction are based on the following considerations: (i) the α-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 a process forward; (iii) potential side reactions such as allylic fluorination may not pose a significant problem provided that the allyl fluorides could also be ionized by the palladium catalyst, thus serving as a bifurcated allyl donor.[12] In addition, the kinetically more favored formation of C−C bonds compared with C−F bonds in palladium-catalyzed allylic substitution could be another factor that would guarantee the execution of this multicomponent reaction. Despite the reasonability of the rationales envisioned, challenges associated with this proposal still remain, among which the inhibition of expected allylation by premature quenching of the in situ-generated β-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 are shown in Table 1. After systematic examination of various

Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	ligand	additive	yield of **3a** (%)[b]
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[c]
6	DMF	XantPhos	CuOAc	85[c]
7	DMF	bpy	CuOAc	0[c]
8	DMF	X-Phos	CuF_2	99[c]
9	DMF	X-Phos	$Cu(OTf)_2$	96[c]
10	DMF	X-Phos	–	65[c]
11	DMF	–	CuOAc	trace[c]
12	DMF	X-Phos	CuOAc	0[d]

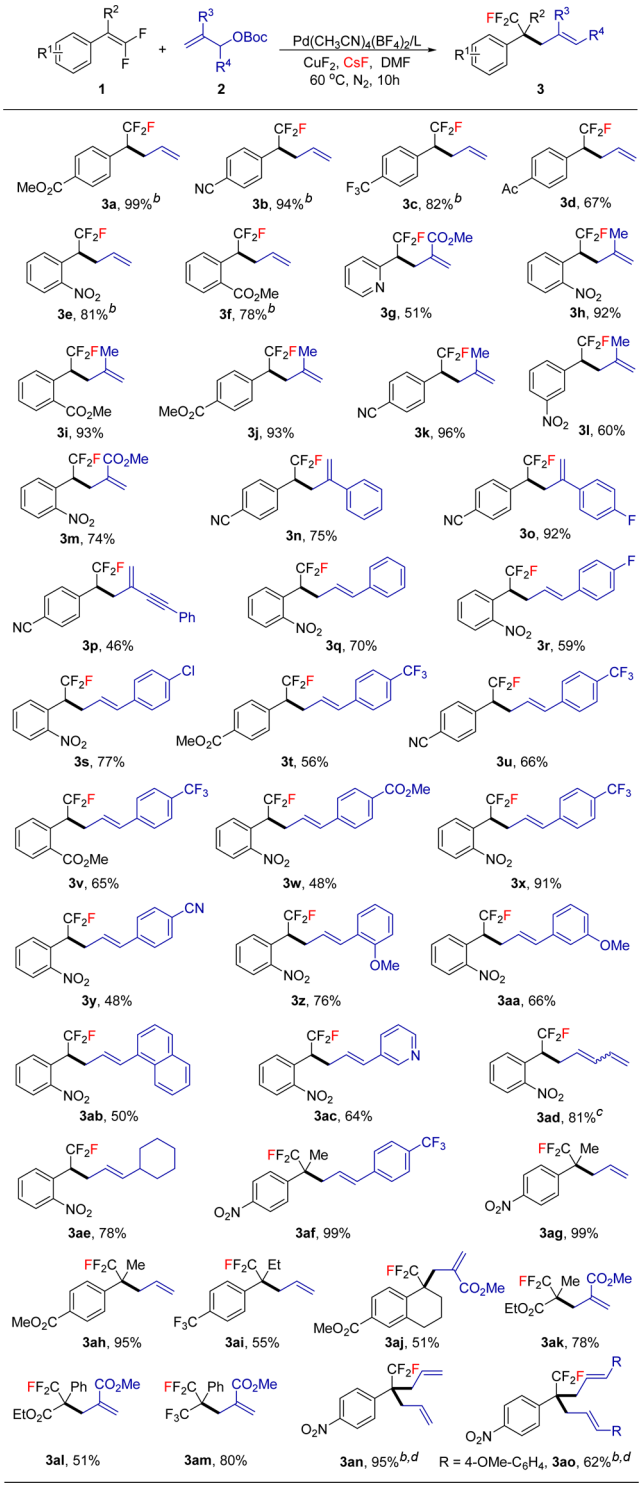
[a]Experiments were performed with **1a** (0.15 mmol), **2a** (0.3 mmol), CsF (0.45 mmol), additive (0.015 mmol), $Pd(OAc)_2$ (0.0075 mmol), and monodentate ligand (0.015 mmol)/bidentate ligand (0.0075 mmol) in solvent (1.0 mL) with stirring at 60 °C for 10 h. [b]Isolated yields. [c]Using $Pd(MeCN)_4(BF_4)_2$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

parameters, the optimized reaction conditions were obtained: CsF as the fluoride source, $Pd(MeCN)_2(BF_4)_2$ as the catalyst, and X-Phos or XantPhos as the assisting ligand in the presence of CuF_2 as an additive and DMF as the solvent (see the Supporting Information for details of the reaction optimization).[14] Although not mandatory, the addition of a catalytic amount of copper salt was revealed to provide an appreciable enhancement of the reaction efficiency. While the exact role of the 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 the palladium catalyst and the phosphine ligand in this NAAA reaction, as without either no desired product could be obtained. It is also worth mentioning that no detectable amount of **3a** was observed when 4-(2,2,2-trifluoroethyl)benzoate was subjected 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.

With the optimized reaction conditions in hand, the reaction scope and limitations with respect to both *gem*-difluoroalkenes and allyl carbonates were surveyed, and the results are 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 this transformation, which was ascribed to the low electrophilicity of the substrates or the instability of the resulting β-trifluorocarbanions, which quickly collapsed without further engaging in the 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 an appreciable influence on the reaction efficiency (**3a**–**l**). To our pleasure, a pyridine-derived *gem*-difluoroalkene reacted smoothly without obvious deleterious effects on the reaction, thus giving rise to product **3g** in synthetically useful yield. For allyl carbonates, substrates with alkyl, aryl, or ester substituents on the internal alkene moiety were compatible with the reaction conditions (**3h**–**o**). Also noteworthy was the nice compatibility of alkynyl functionalities. For example, by means of this strategy, trifluoromethyl-incorporated enyne product **3p** could be selectively obtained, albeit with somewhat compromised reaction efficiency. For allylic carbonates containing substituents at the allylic positions, the allylic alkylation could potentially lead to the formation of both regio- and diastereoisomers. Within our experiments, moderate to high selectivity was observed depending on the substrates employed. The substrate scope with respect to 1-arylallyl carbonates 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**–**aa**). The nice tolerance of halogen substituents provides a synthetic handle for further elaboration through traditional cross-coupling strategies. In addition, an extended aromatic entity such as a naphthyl-derived substrate also uneventfully underwent this reaction, providing product **3ab** in 50% yield. It is also noteworthy that the reaction efficiency was not inhibited by heteroaryl-containing allyl carbonates, and when a pyridine-based substrate was applied, the adduct **3ac** was produced in 64% yield. Besides 1-arylallyl carbonates, alkyl- and alkenyl-based congeners could also be employed as effective allyl donors. For example, product **3ae**

DOI: 10.1021/jacs.6b11205
J. Am. Chem. Soc. 2016, 138, 15869−15872

Table 2. Scope of the NAAA Reaction[a]



[a]Experiments were performed with **1** (0.15 mmol), **2** (0.3 mmol), CsF (0.45 mmol), CuF_2 (0.015 mmol), $Pd(MeCN)_4(BF_4)_2$ (0.0075 mmol), and XantPhos (0.0075 mmol) in DMF (1.0 mL) with stirring at 60 °C for 10 h. [b]X-Phos (0.015 mmol) was used as the ligand. [c]Linear/branched = 3/1. [d]**2** (0.45 mmol) was employed.

was isolated in 78% yield when 1-cyclohexylallyl carbonate was used, while in the case of the 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**–**ao**). In this respect, by making use of a tetrahydronaphthalene-derived *gem*-difluoroalkene as the substrate, we were able to obtain the densely functionalized product **3aj** in 51% yield. Because of the electron-delocalization ability of the ester group, further electronic activation was not required in the case of *gem*-difluoroacrylate derivatives, and the related allylation products were obtained in moderate to good yields (**3ak** and **3al**). It is noteworthy that when the *gem*-difluoroalkene derived from trifluoroacetophenone was employed, the reaction occurred readily to afford product **3am** in 80% yield, thus providing an efficient method for the synthesis of *gem*-trifluoromethyl homoallylbenzene derivatives. Furthermore, the construction of a quaternary carbon center also proved to be feasible via a twofold allylation process, provided that the substrate contains functionalities that have sufficient electron-withdrawing strength to assist further deprotonation after introduction of the first allyl group (**3an** and **3ao**). Finally, while it would be quite appealing to extend this NAAA reaction to an asymmetric version, preliminary efforts in this direction were unfortunately less rewarding, as only marginal enantiomeric excess was observed (see the Supporting Information for details).[15] Continuing endeavors aimed at realizing an asymmetric NAAA reaction are still underway in our lab.

In conclusion, by making use of a palladium-catalyzed nucleophilic-addition-induced allylic alkylation manifold, we have successfully developed a strategically novel synthetic protocol that allows the step-economical and expedient construction of homoallyltrifluoromethane derivatives without resorting to deprotonative functionalization.[17] This three-component transformation is characterized by its well-organized reaction sequence, thus obviating the potential side pathways that would otherwise occur with either of two reaction partners employed. It is also worth mentioning that by means of such a strategy, the reaction boundary that restricts the allylic alkylation of trifluoromethyl-containing molecules to those with relatively low pK_a values is skillfully overridden.[16]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b11205.

Detailed experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the "1000-Youth Talents Plan", a Start-up Grant (39837110) from Nanjing Tech University and financial

DOI: 10.1021/jacs.6b11205
J. Am. Chem. Soc. 2016, 138, 15869–15872

support by SICAM Fellowship by Jiangsu National Synergetic Innovation Center for Advanced Materials. We also thank the funding support of the State Key Program of National Natural Science Foundation of China (21432009) for generous financial support.

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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 led only to the 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 involving the in situ formation of a fluoride cluster with CsF, which acts as a "soft" nucleophile, and also the difficulty of asymmetric induction using chiral ligands as result of the Cu-stabilized carbanion with considerable covalent bond character.

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DOI: 10.1021/jacs.6b11205
J. Am. Chem. Soc. 2016, 138, 15869−15872