A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition Chemie

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Accepted Article

Title: Palladium-Catalyzed Fluoroarylation of gem-Difluoroalkenes

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201705321
Angew. Chem. 10.1002/ange.201705321

Link to VoR: http://dx.doi.org/10.1002/anie.201705321
http://dx.doi.org/10.1002/ange.201705321

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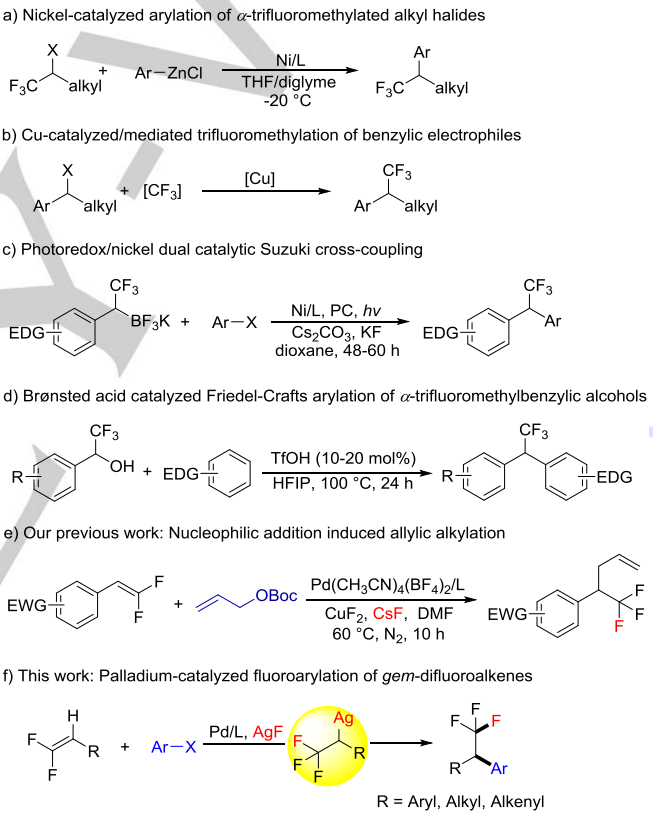
Palladium-Catalyzed Fluoroarylation of *gem*-Difluoroalkenes

Hai-Jun Tang,[a] Ling-Zhi Lin,[a] Chao Feng,*[a] and Teck-Peng Loh*[b]

Abstract: Pd-catalyzed fluoroarylation of *gem*-difluoroalkenes with aryl halides is disclosed. By taking advantage of the in situ generated *α*-CF_3-benzylsilver intermediates derived from the nucleophilic addition of silver fluoride onto *gem*-difluoroalkenes, the present strategy bypass the employment of strong base, thus enabling a mild and general synthetic protocol for the ready access of non-symmetric *α,α*-disubstituted trifluoroethane derivatives.

The importance of discovering practical and effective synthetic protocols for the ready assembly of CF_3-containing frameworks could not be overstated, especially taking into consideration of their wide application in pharmaceutical as well as agrochemicals research.[1] Thanks to the innovative design of reactivity-oriented trifluoromethylation reagents,[2] a large number of flexible protocols have been uncovered allowing the expedient introduction of CF_3 group into structurally diversified architectures. In this context, while considerable efforts have been devoted to the construction of the C(sp^2)-CF_3 bond,[3] relatively less attention has been paid to the formation of C(sp^3)-CF_3 counterpart especially for those containing a benzylic trisubstituted carbon center with CF_3 being one of the substituents.[4]

Arguably, the direct benzylic C-H trifluoromethylation would be the privileged strategy, however, the success of such protocol is quite substrate-restricted, which severally limits its more general applications.[5] Whereas elegant works from the groups of Fu,[6] Molander,[7] Moran,[8] Hu,[9] Altman,[10] Nishibayashi,[11] Prakash and Olah[12] have provided effective and orthogonal synthetic potential for the access to 1,1,1-trifluoro-2-arylalkane derivatives, disadvantages owing to the reliance on the use of sensitive coupling reagents as well as substrate scope limitations are still prominent, which in turn eroded the diversity of molecular skeletons that could be accomplished (Scheme 1a-1d). Of note, among the protocols discovered, synthetic strategies which leveraged on the elaboration of *α*-trifluoromethyl-derived alkyl nucleophiles are appealing but far less well developed. The underdevelopment of such tactic is ascribed to potential challenges such as the low stability of these anionic intermediates and their notorious reluctance to participate in transmetalation,[7] as well as the predisposition of *β*-defluorination in most cases.[13] As such, the development of novel strategies which ameliorate the present dilemma would be highly desirable and compelling. To this end, we envisioned integrating in situ generated *α*-trifluoromethylated alkyl anion with aryl halide through transition metal catalysis, while obviating the otherwise elusive deprotonative arylation protocol in this specific context.[14] Inspired by our recent work on the allylation of in situ generated *β*-trifluorocarbanion intermediates (Scheme 1e),[15] we describe herein our progress in the palladium-catalyzed fluoroarylation[16] of *gem*-difluoroalkenes, which granted a strategically novel access to non-symmetric diaryl-, alkylaryl- as well as alkenylaryl-trifluoroethane derivatives (Scheme 1f). Notably, the present work represent a rare example of introduction of *α*-trifluoromethylated alkyl segments through two electron transmetalation process.



Scheme 1. Strategies for the construction of 1,1,1-trifluoro-2-arylalkanes.

The fluoroarylation was carried out with methyl 4-(2,2-difluorovinyl)benzoate **1a** and 1-iodo-2-methoxybenzene **2a** as the model substrates, and the representative results are shown in Table 1 (see the Supporting Information for details of the reaction optimization). Whereas the use of alkali-metal-derived fluorides all turned out to be fruitless, simply change the fluoride donor to AgF allowed us to successfully track the formation of product **3aa**, albeit in very low yield. Further systematic investigation of reaction parameters was carried out in order to improve the reaction efficiency. Solvent examination revealed that the reaction media exerted a sigficant influence on the outcome among which cyclohexane proved to be optimal. While the exact reason of the

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Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.2017xxxxx.

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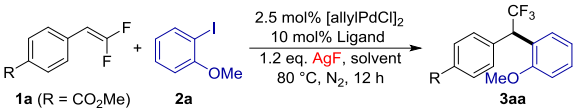
superiority of cyclohexane as the reaction media is not clear, the homogenous mixture formed from reactants **1a**, **2a** and catalyst as well as slow delivery of AgF because of its limited solubility in cyclohexane at 80 °C is, to some extent, pertinent to this outcome. It was also realized that phosphine ligands played a very important role in guaranteeing the success of this transformation with XPhos leading to the product **3aa** in 95% yield. Further investigation with respect to palladium catalyst and fluoride donor disclosed the combination of $[allylPdCl]_2$ and AgF was optimal. Notably, the replacement of AgF by a composite of KF and extra silver salts such as Ag_2CO_3 had deleterious effects in this reaction. As was not unexpected, no desired product was generated with the omission of either palladium catalyst or phosphine ligand.

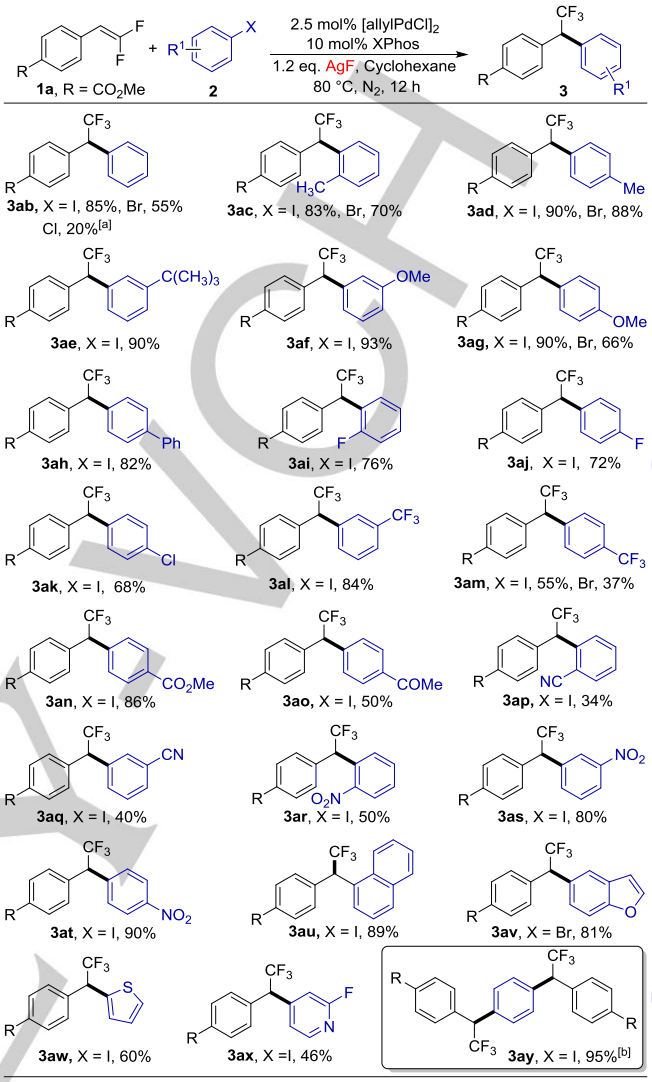
Table 1. Optimization of reaction conditions.[a]



Entry	Solvent	Ligand	**3aa**[%][b]
1	MeCN	XPhos	trace
2	DCE	XPhos	28%
3	1,4-Dioxane	XPhos	82%
4	Cyclohexane	XPhos	95% (84%)[c]
5	Cyclohexane	XPhos	trace[d]
6	Cyclohexane	BrettPhos	trace
7	Cyclohexane	Xantphos	35%[e]
8	Cyclohexane	XPhos	21%[f]
9	Cyclohexane	-	NR
10	Cyclohexane	XPhos	NR[g]

[a] Unless otherwise noted, the reactions were carried out under reaction conditions: **1a** (0.15 mmol), **2a** (0.3 mmol), AgF (0.18 mmol), $[allylPdCl]_2$ (0.00375 mmol), ligand (0.015 mmol), solvent (1.0 mL), 80 °C, 12 h. [b] Yield was determined by ^{1}H NMR using mesitylene as internal standard. [c] Isolated yield is in parenthesis. [d] $Pd(OAc)_2$ as the catalyst. [e] ligand (0.0075 mmol). [f] Using KF in stead of AgF and adding 0.6 eq. Ag_2CO_3. [g] No palladium catalyst was added. XPhos: 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl; BrettPhos: 2-(Dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl; Xantphos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene.

With the optimized reaction condition in hand, the reaction generalities and limitations with respect to aryl halides were surveyed, and the results were summarized in Scheme 2. According to experimental results, both aryl iodides and bromides are suitable for this reaction, whereas relatively low yield of product was obtained in the case of aryl chloride. For aryl iodide, both electron-donating and electron-withdrawing group containing substrates worked well in this reaction. For example, substrates with electron-donating substituents such as Me, *t*-Bu and OMe were all applicable and provided the desired products in good to excellent yields. In addition, the substitution position showed little influence on the reaction efficiency. In the case of *para*-phenyl phenyl iodide, the reaction proceed smoothly and furnished the product **3ah** in 82% yield. With respect to electron-deficient aryl halides, synthetically important functionality, such as F, CF_3, CO_2Me, COMe, CN and NO_2 were all well tolerated in this reaction.



Scheme 2. Reaction scope of aryl halides. Unless otherwise noted, all experiments were performed with **1a** (0.15 mmol), **2** (0.30mmol), AgF (0.18 mmol), $[allylPdCl]_2$ (0.00375 mmol), XPhos (0.015 mmol) in cyclohexane (1 mL) stirring at 80 °C for 12 h. Yields of isolated products were listed. [a] Yield was determined by ^{1}H NMR using mesitylene as internal standard. [b] **1a** (0.60 mmol), **2y** (0.15 mmol), AgF (0.36 mmol) was employed.

Aryl halides with extended aromatic system, such as **2u**, participated in this reaction without any difficulty and afforded the desired product **3au** in 89% yield. It is noteworthy that heterocyclic aromatic substrates such as those derived from thiophene, benzofuran and pyridine were also well accommodated without any obvious detrimental effect on the catalytic efficiency of this transformation, delivering the desired products in moderate to good yields (**3av**-**3ax**). Interestingly, *p*-phenylene bistrifluoroethane derivative **3ay** could be smoothly generated in 95% yield by a consecutive two-fold fluoroarylation using 1,4-diiodobenzene as the arylation reagent with excess amount of **1a**.

Subsequently, the reaction scope with regard to *gem*-difluoroalkene was investigated, and the results are listed in Scheme 3. *gem*-Difluorostyrenes containing electron-withdrawing substituents such as ester, trifluoromethyl, cyano, nitro group

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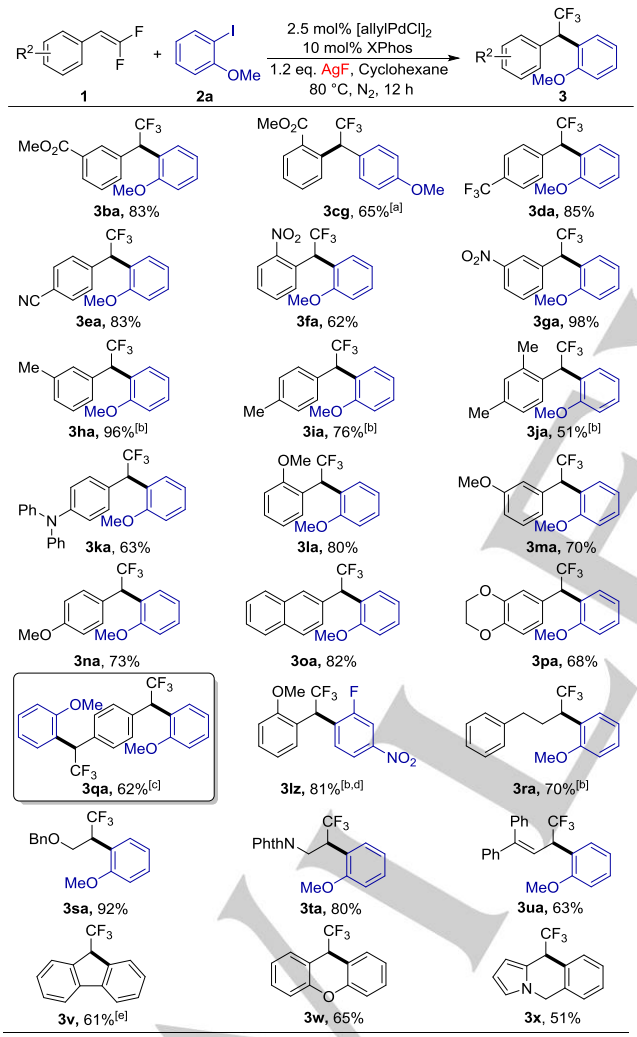
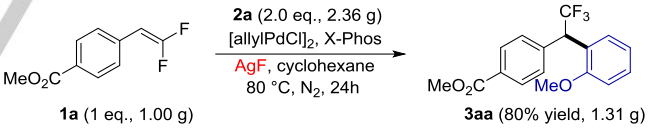
were well compatible to the reaction conditions. Of note, that the location of the substitient on the phenyl ring influenced the reaction efficiency. For example, when carrying out the reaction between *o*-CO_2Me derived *gem*-difluorostyrene **1c** and *o*-iodoanisole **2a**, no desire fluoroarylation product could be obtained, probably due to the steric effect, which impeded either the transmetalation or reductive elimination step. In line with this assumption, switching the aryl iodide from *o*-iodoanisole **2a** to *p*-iodoanisole **2g** enabled the reaction to proceed smoothly and delivered product **3cg** in 65% yield. Excitingly, the present reaction was not restricted to electronically biased *gem*-difluorostyrene substrates with those bearing electron-donating substituents engaging in this reaction uneventfully, which is in stark contrast to our recent work.[15] Notably, *gem*-difluorostyrenes with methyl, methoxy and *N*,*N*-diphenylamino



Scheme 3. Reaction scope of *gem*-difluoroalkenes. Unless otherwise noted, all experiments were performed with **1** (0.15 mmol), **2a** (0.30mmol), AgF (0.18 mmol), $[allylPdCl]_2$ (0.00375 mmol), XPhos (0.015 mmol) in cyclohexane (1 mL) stirring at 80 °C for 12h. Yields of isolated products were listed. [a] *p*-iodoanisole **2g** was employed instead of **2a**. [b] **1** (0.30 mmol), **2** (0.15 mmol) was employed. [c] **2a** (0.60 mmol), **1q** (0.15 mmol), AgF (0.36 mmol) was employed. [d] Using 2-fluoro-1-iodo-4-nitrobenzene instead of **2a**. [e] Intramolecular annulation of **2v-2x**.

substituents, regardless of their substitution position, all proved to be productive substrates, providing the desire products in good yields. Furthermore, *gem*-difluoroalkene derived from 2-naphthyl aldehyde also nicely paticipated in this reaction and afforded product **3oa** in 82% yield. In analogy to the synthesis of *p*-phenylene bistrifluoroethane derivative **3ay** by using 1,4-diiodobenzene **2y** and *gem*-difluoroalkene **1a**, similar structural skeleton **3qa** could also be readily generated through an alternative coupling mode via the coupling of bisdifluoroalkene substrate **1q** and aryl iodide **2a**. To our pleasure, besides electronically deactivated aromatic *gem*-difluoroalkenes, aliphatic ones were applicable in this reaction, thus highlighting the wide applicability of the present protocol (**3ra**-**3ta**). It is also noteworthy that *gem*-difluorodiene was amenable to this reaction, and in the case of substrate **1u**, the coupling product **3ua** was isolated in 60% yield. In addition to the aforementioned fluoroarylation reactions that take place via intermolecular aryl group installation, *gem*-difluoroalkenes with tethered aryl halide pendent was also competent substrates and engaged in this reaction through intramolecular delivery of aryl group (**3v**-**3x**). For instance, when biphenyl *gem*-difluoroalkene **2v** was subjected to the standard reaction conditions, the desired product **3v** encompassing a fluorine framework was obtained in 61% yield, whereas in the cases of **2w** and **2x**, the desired heterocyclic products were uneventfully generated, albeit in moderate yields. While the reaction shows sufficient generality, scope limitation with respect to *gem*-difluoroalkene still remains, for example, *gem*-difluoroalkene derived from picolinaldehyde, ketones and those being too sterically demanding proved incompetent at the present stage.[17] In order to showcase the practicability of this fluoroarylation reaction, a gram-scale reaction between **1a** and **2a** was carried out, which gave rise to product **3aa** in 80% yield (scheme 4).



Scheme 4. Gram-scale reaction.

Being aware of the generation of radical species from homolysis of organosilver intermediates,[9,18] further control experiments to elucidate the reaction mechanism with respect to the transmetalation step either through one-electron or two-electron type were carried out. According to Hu' report,[9,18b] the adduct of AgF and *gem*-difluoroalkenes could generate trifluorobenzyl radicals. However, in the present reaction the addition of radical scavengers, such as TEMPO, BHT and 1,1-diphenylethylene all did not show any impediment in the reaction efficiency, which firmly ruled out the possibility of involvement of radical intermediate in this reaction. Therefore, based on the experimental results, we tentatively proposed the reaction mechanism shown in Scheme 5. The reaction starts from oxidative addition of aryl halides to palladium catalyst to generate the arylpalladium complex **I**. Meanwhile, benzylsilver intremediate **II** could be generated in situ from nucleophilic addition of AgF onto

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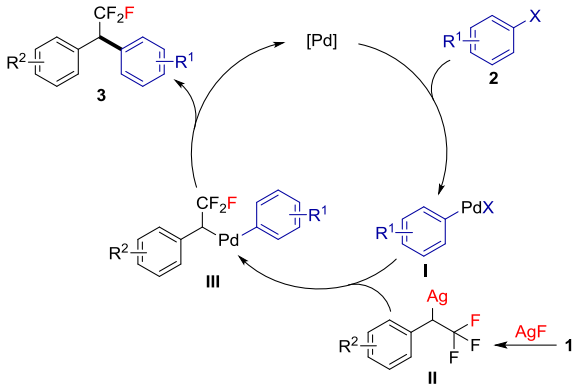
gem-difluoroalkene. Subsequently, the conventional polar two-electron transmetalation of intermediate **II** to arylpalladium **I** occurs to afford intermediate **III**, which further undergoes reductive elimination to provide the desired product **3** and regenerate the active catalyst.



Scheme 5. Proposed reaction mechanism.

In conclusion, we have developed a novel synthetic method for the access of 1,1,1-trifluoro-2-arylalkane derivatives based on the fluoride nucleophilic addition induced arylation of *gem*-difluoroalkenes. By taking advantage of the in situ generation of *α*-trifluoromethyl benzylsilver intermediate as nucleophilic coupling partner, this strategy obviates otherwise troublesome strong base enableddeprotonative protocol. Further extension of the present transformation into asymmetric version will be the objective of our continuing work.

Acknowledgements

We thank the “1000-Youth Talents Plan”, a Start-up Grant (39837110) from Nanjing Tech University and financial support by SICAM Fellowship by Jiangsu National Synergetic Innovation Center for Advanced Materials.

Keywords: *gem*-difluoroalkene • palladium • fluorination • arylation • cross-coupling

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By taking advantage of the in situ generation of α-trifluoromethyl benzylsilver intermediate, a general synthetic protocol for the preparation of 1,1,1-trifluoro-2-arylalkane derivatives through palladium-catalyzed fluoroarylation of *gem*-difluoroalkenes was reported. Notably, this work represents a rare example of introduction of α-trifluoromethylated alkyl segments through two electron transmetalation process.

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