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Introduction

Selective single C–F bond arylation of trifluoromethylalkene derivatives[†]

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A strategically novel single C–F bond functionalization of CF_3 -derived molecules, which shows a prominent advantage for the expedient construction of difluoromethylene-bridged organic scaffolds, is disclosed. The reported protocol consists of S_N2' amination, *N*-alkylation and palladium-catalyzed allylic substitution reactions, which enables straightforward arylation and alkenylation of vinyltrifluoromethane derivatives. Furthermore, this strategy is characterized by its broad substrate scope with respect to both CF_3 -alkene and arylboronic acid derivatives.

Trifluoromethyl (CF₃) ranks among the most popular fluorinated alkyl groups and finds wide applications in pharmaceutical chemistry, materials science, and agrochemistry owing to its unique physicochemical properties.¹ As such, the development of effective synthetic methods for the incorporation of CF₃ into organic molecules has witnessed a remarkable advancement during the past few decades.² In addition, trifluoromethylated compounds could also virtually serve as promising progenitors for the direct assembly of *gem*-difluoroalkene bridged organic frameworks, which widely occur in drugs and bioactive compounds, provided that selective single C–F bond transformation of the CF₃ group could be readily accomplished (Fig. 1).^{3,4}

Compared with conventional synthetic methods that resort to halodifluoromethylated precursors, the direct utilization of CF₃congeners tends to be more beneficial considering both stepeconomy and starting material accessibility.5 While synthetically more appealing, the development of efficacious scenarios, which are amenable to the selective functionalization of the single C(sp³)-F bond of the CF₃ group, progresses very slowly and still remains a daunting challenge. The underlying reason for this situation comes in part from the extremely high bond dissociation energy (BDE) of C-F bonds⁶ (e.g., 128 kcal mol⁻¹ for HCF₃) but more from the difficulty to well control the chemoselectivity by suppressing post-defluorination. The intrinsic fact that the strength of C-F bonds becomes attenuated progressively with the shrinking of F-substitutions on the same carbon atom also adds to such a difficulty.7 Therefore, it is not surprising that in most reported examples of CF3-derivative transformations, nonfluorinated products were always produced by unselective triple C-F bond cleavage.⁸

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Notwithstanding the prominent challenges encountered in the selective C-F bond functionalization of CF₃-containing molecules, prominent studies by making use of different strategies were disclosed during the past several years.^{4,9} For example, by taking advantage of intramolecular F-abstraction by an *in situ* generated neighboring silylium group, Hosoya and co-workers reported an elegant example of C-F bond allylation of ortho-silvlated ArCF3 derivatives.4a Very recently, photoredox-catalysis was also revealed to be a promising choice for this aim. In this respect, the groups of König4b and Jui4c have successfully utilized this manifold for the smooth generation of an α, α -difluorobenzylic radical intermediate, which further engaged in subsequent intramolecular cyclization or intermolecular alkylation reactions (Scheme 1a). In spite of these groundbreaking studies of the selective functionalization of CF₃-derivatives, the analogous transformation with respect to trifluoromethylalkenes, however, still remains elusive. The discrepancy of reactivity between electronically activated C=C



Fig. 1 Representative bioactive CF₂-containing molecules.

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b) S_N2' type C-F bond activation of CF₃-alkenes



c) Our design: ipso-C–F bond functionalization of CF₃-alkenes



Ammonium as nucleoruge in panadium-engaged ionization
 Regioselective coupling with gem-difluoroallylpalladium

Scheme 1 Selective single C–F bond functionalization of CF₃-derivatives. (a) C–F bond functionalization of CF₃-arenes. (b) S_N2' type C–F bond activation of CF₃-alkenes. (c) Our *ipso*-C–F bond functionalization of CF₃-alkenes.

double bonds with C-F bonds in these molecules, towards either radical or anionic species, is believed to be the fundamental root for such a dilemma. This competitively dominant reaction profile is visually illustrated by a considerable amount of precedents of the S_N2'-type defluorofunctionalization of CF₃-alkene derivatives over the past several years, which, however, only enables the introduction of functionalities into the distal olefinic carbon atom, thus affording gem-difluoroalkene products (Scheme 1b).96-k Thus far, the general approach for ipso-C-F functionalization of trifluoromethylalkenes has yet to be achieved. Inspired by the well-established S_N2' reaction manifold of CF₃-alkenes, we envision the feasibility of using amines as a traceless mediator for ipso-C-F bond functionalization of these molecules. We assume that with a sequence of S_N2' amination and N-alkylation, gem-difluoroallyl ammonium 3 could be obtained directly from CF₃-alkene derivatives. In view of the precedents of using ammonium functionalities as the leaving groups in transitionmetal-catalyzed cross-coupling reactions,10 we anticipate that an elegant combination of S_N2' amination, N-alkylation and palladium-catalyzed allylic substitution could potentially provide an expedient strategy for the construction of α, α -difluoroallylarenes,¹¹ provided that nucleophilic substitution of gem-difluoroallylpalladium species could be steered to occur selectively on the fluorine-containing carbon atom (Scheme 1c).

Results and discussion

To test our hypothesis, we started our investigation by using 1methoxy-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene **1a** as the model substrate (Table 1). The $S_N 2'$ amination reaction of **1a**



Entry	Ligand	Additive (mol%)	Yield ^b [%]
1	X-Phos	CuI (30%)	41
2	$P(4-CF_{3}C_{6}H_{5})_{3}$	CuI (30%)	50
3	$P(C_6F_5)_3$	CuI (30%)	39
4	C-Phos	CuI (30%)	32
5	$P(4-CF_3C_6H_4)_3$	CuI (10%)	5
6	$P(4-CF_{3}C_{6}H_{4})_{3}$	CuI (50%)	56
7	$P(4-CF_3C_6H_4)_3$	CuI (100%)	72
8	$P(4-CF_{3}C_{6}H_{4})_{3}$	CuI (200%)	80
9	$P(4-CF_3C_6H_4)_3$	CuI (250%)	80
10	$P(4-CF_{3}C_{6}H_{4})_{3}$	$CuBr \cdot Me_2S$ (200%)	83
11	$P(4-CF_{3}C_{6}H_{4})_{3}$	CuTc (200%)	31
12	$P(4-CF_{3}C_{6}H_{4})_{3}$	CuOAc (200%)	29
13 ^c	$P(4-CF_{3}C_{6}H_{4})_{3}$	$CuBr \cdot Me_2S$ (200%)	85
$14^{c,d}$	$P(4-CF_{3}C_{6}H_{4})_{3}$	$CuBr \cdot Me_2S$ (200%)	99
$15^{c,e}$	$P(4-CF_3C_6H_4)_3$	$CuBr \cdot Me_2S$ (200%)	95 (92) ^f

^{*a*} Reaction conditions (unless otherwise specified): **3a** (0.1 mmol, 1.0 equiv.), PhB(OH)₂ (2.0 equiv.), Pd(PPh₃)₄ (10 mol%), ligand (20 mol%), additive (30 mol%), K₂CO₃ (2.0 equiv.), 1,4-dioxane (1 mL), 80 °C, and 20 h. ^{*b*} Yields determined by ¹⁹F-NMR spectroscopy using trifluoromethylbenzene as an internal standard. ^{*c*} Cs₂CO₃ instead of K₂CO₃. ^{*d*} 5 Å molecular sieve (100 mg). ^{*e*} Pd(PPh₃)₄ (1 mol%) and P(4-CF₃C₆H₄)₃ (2 mol%). ^{*f*} Isolated yield.

proceeded smoothly with the treatment of piperidine in the presence of n-BuLi, yielding 65% of 3,3-difluoroallylamine 2a (Table 1).12 The following methylation with MeOTf readily afforded the quaternary ammonium salt 3a in a nearly quantitative yield. Encouraged by these productive results, we moved on to evaluate the feasibility of aryl substitution with regard to quaternary ammonium salt 3a by using phenylboronic acid with different ligands and additives. Delightfully, under the reaction conditions of 10 mol% Pd(PPh₃)₄, 20 mol% X-Phos, 30 mol% CuI, and 2.0 equiv. K2CO3 in the presence of dioxane at 80 °C for 20 hours, 3a underwent regioselective allylic substitution with phenylboronic acid to afford the desired gem-difluoroallylation product 4a in 41% yield (entry 1). For improving the reaction efficiency, various ancillary ligands were then examined (entries 2-4), among which $P(4-CF_3C_6H_5)_3$ turned out to be the appropriate choice (entry 2). It is worth pointing out that the identity of the copper salt additive and its stoichiometry are of vital importance to the occurrence of allylic substitution, and the employment of 2.0 equiv. of CuBr · Me2S was ultimately revealed to be optimal (entries 5-12). Further fine tuning the reaction conditions, by using Cs₂CO₃ as a base, led to a slight improvement in the reaction yield (entry 13). While the exact role of the copper salt in the arylation step was unclear, we believed that it could promote this transformation in two aspects by acting either as the transmetalation agent to promote the transfer of the aryl group from boron to palladium or as the tertiary amine scavenger to prevent the active palladium catalyst from being deactivated by the amine byproduct. Pleasingly, the yield of **4a** increased dramatically upon the addition of 5 Å molecular sieves (entry 14).¹³ Furthermore, the catalyst loading of palladium could be lowered to 1.0 mol%, with only marginal influence on the product yield being observed (entry 15).¹⁴

With the optimized reaction conditions in hand, the reaction generality with respect to trifluoromethylalkene **1** was first examined. As tabulated in Table 2 a variety of α -CF₃-styrenes were shown to be compatible with the sequential S_N2' amination/*N*-methylation/allylic substitution. Vinyltrifluoromethane derivatives bearing alkyl, methoxyl, phenyl, trifluoromethoxy and chloride groups on the α -phenyl substituent readily participated in the amination and afforded products **2a–2h** in

46-80% yields. N-methylation of these 3,3-difluoroallylamines 2, generally proceeded with ease to furnish the quaternary ammonium salts 3a-3h in excellent yields (93-99%), and the subsequent arylation with the as-obtained ammonium intermediates also proceeded smoothly to deliver the desired products 4a-4h in 30-92% yields. Intriguingly, the diphenylamine derived substrate 1i was also compatible with this tandem reaction, with no obvious interference in N-methylation being observed. Moreover, in the case of substrate 1j, which is potentially sensitive towards the amination process because of the presence of C(Ar)-F bonds, the reaction showed excellent chemoselectivity for allylic substitution. Furthermore, polysubstituted α -CF₃-styrene derivatives were also competent substrates in this transformation as represented by the examples of 1j-1l. In addition, heterocycle-derived substrates such as benzofuran 1m and benzo[b][1,4]dioxine 1n were also well



^{*a*} See the ESI for experimental details.

accommodated and afforded the desired products **4m** and **4n** in overall moderate yields.

To further evaluate the generality of this transformation, the reaction scope of arylboronic acid was subsequently investigated (Scheme 2). By and large, arylboronic acids bearing either electron-donating or electron-withdrawing groups proved to be well amenable to this *gem*-difluoroallylation process, and the desired products **4aa–4al** could be obtained in 39–99% yields. However, arylboronic acids with *ortho*-substituents took part in this reaction sluggishly as showcased by **4am** and **4an**, thus indicating that the *gem*-difluoroallylation reaction is quite sensitive to steric hindrance. The presence of the amino functionality in the molecule of arylboronic acid was well tolerated without notable impediment to palladium catalysis (**4ao**). Furthermore, naphthylboronic acids, either α or β isomers, were revealed to be appropriate coupling partners, albeit giving rise to the desired products in yields with a contrasting



Scheme 2 Reaction scope of boronic acid.



Scheme 3 Gram-scale reaction.



Scheme 4 Synthetic transformation of gem-difluoroallylarene 4a.

difference (**4ap** and **4aq**). In addition, arylboronic acids with poly-substituents or those derived from benzoheterocycles also participated in this allylic substitution uneventfully, affording the desired products **4ar–4au** in moderate to high yields. Notably, (2-fluoropyridin-4-yl)boronic acid engaged well in this reaction and delivered the product **4av** in 50% yield. Pleasingly, alkenylboronic acids also proved to be competent reaction partners, which provide a straightforward synthetic avenue for the assembly of 3,3-difluoropenta-1,4-diene derivatives, albeit with somewhat decreased reaction efficiency. To further demonstrate the synthetic potential of the reaction protocol, elaboration of complex molecules such as estrone was carried out, which delivered the desired product **4az** in 57% yield.

The practicality of this method was showcased by the gramscale transformation of **1a**, which provided the desired product **4a** in 92% yield (Scheme 3). Moreover, a telescoped procedure that avoided intermediate purification worked well, delivering **4a** in 42% overall yield (three steps, see the ESI† for details).

As the obtained *gem*-difluoroallylarenes contain both the alkenyl and difluoromethylene functionalities, further synthetic elaborations were carried out. Osmium-catalyzed dihydroxylation of compound **4a** readily occurred to provide the product **5b** in moderate yield, without affecting the difluoromethylene moiety, while in the presence of a rhodium catalyst, **4a** underwent $S_N 2'$ type C–F bond functionalization with arylboronic esters, affording the tetra-substituted fluoroalkene **5a** in 48% yield (Scheme 4).

Conclusions

In summary, we have developed a novel method, which enables the selective single C–F bond arylation/alkenylation of trifluoromethylalkene derivatives. By directly making use of CF₃alkenes as the reaction substrates and strategically merging S_N2' amination, *N*-alkylation and palladium-catalyzed allylic substitution, an unprecedented synthetic protocol for easy access to α, α -difluoroallylarene/alkene structures was formulated. Furthermore, the high regioselectivities of both amination and allylic substitution processes are deemed responsible for the success of this transformation. Because of its wide substrate scope and practicality, this method is expected to find more potential applications in the discovery of new lead compounds for pharmaceutical innovations.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- (a) W. K. Hagmann, J. Med. Chem., 2008, 51, 4359–4369; (b)
 D. O'Hagan, J. Fluorine Chem., 2010, 131, 1071–1081; (c)
 W. Zhu, J. Wang, S. Wang, Z. Gu, J. L. Aceña, K. Izawa, H. Liu and V. A. Soloshonok, J. Fluorine Chem., 2014, 167, 37–54; (d)
 E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and
 N. A. Meanwell, J. Med. Chem., 2015, 58, 8315–8359.
- 2 (a) X. Liu, C. Xu, M. Wang and Q. Liu, Chem. Rev., 2015, 115, 683–730; (b) H. Egami and M. Sodeoka, Angew. Chem., Int. Ed., 2014, 53, 8294–8308; (c) E. Merino and C. Nevado, Chem. Soc. Rev., 2014, 43, 6598–6608; (d) A. Studer, Angew. Chem., Int. Ed., 2012, 51, 8950–8958; (e) S. Barata-Vallejo and A. Postigo, Coord. Chem. Rev., 2013, 257, 3051–3069.
- 3 (a) F. Xue, H. Li, S. L. Delker, J. Fang, P. Martasek, L. J. Roman, T. L. Poulos and R. B. Silverman, J. Am. Chem. Soc., 2010, 132, 14229–14238; (b) N. Tadashi, M. Takeshi, G. Wakana, K. Masaaki, M. Nobuaki, M. Yasushi and H. Hideaki, Biol. Pharm. Bull., 2003, 26, 1691–1695; (c) C. L. Lynch, C. A. Willoughby, J. J. Hale, E. J. Holson, R. J. Budhu, A. L. Gentry, K. G. Rosauer, C. G. Caldwell, P. Chen, S. G. Mills, M. MacCoss, S. Berk, L. Chen, K. T. Chapman, L. Malkowitz, M. S. Springer, S. L. Gould, J. A. DeMartino, S. J. Siciliano, M. A. Cascieri, A. Carella, G. Carver, K. Holmes, W. A. Schleif, R. Danzeisen, D. Hazuda, J. Kessler, J. Lineberger, M. Millerc and E. A. Emini, Bioorg. Med. Chem. Lett., 2003, 13, 119–123; (d) N. A. Meanwell, J. Med. Chem., 2011, 54, 2529–2591.
- 4 (a) S. Yoshida, K. Shimomori, Y. Kim and T. Hosoya, Angew. Chem., Int. Ed., 2016, 55, 10406-10409; (b) K. Chen, N. Berg,
 R. Gschwind and B. König, J. Am. Chem. Soc., 2017, 139, 18444-18447; (c) H.-B. Wang and N. T. Jui, J. Am. Chem. Soc., 2018, 140, 163-166; (d) H. Dang, A. M. Whittaker and
 G. Lalic, Chem. Sci., 2016, 7, 505-509.
- 5 (a) Y.-B. Yu, G.-Z. He and X. Zhang, Angew. Chem., Int. Ed., 2014, 53, 10457–10461; (b) Q.-Q. Min, Z. Yin, Z. Feng, W.-H. Guo and X. Zhang, J. Am. Chem. Soc., 2014, 136, 1230–1233; (c) Y.-L. Xiao, Q.-Q. Min, C. Xu, R.-W. Wang and X. Zhang, Angew. Chem., Int. Ed., 2016, 55, 5837–5841; (d) J.-W. Gu, W.-H. Guo and X. Zhang, Org. Chem. Front., 2015, 2, 38–41; (e) Y.-L. Xiao, W.-H. Guo, G.-Z. He, Q. Pan and X. Zhang, Angew. Chem., Int. Ed., 2014, 53, 9909–9913; (f) T. L. Andersen, M. W. Frederiksen, K. Domino and T. Skrydstrup, Angew. Chem., Int. Ed., 2016, 55, 10396–10400.

- 6 J. Burdeniuc, B. Jedlicka and R. H. Crabtree, *Chem. Ber.*, 1997, **130**, 145–154.
- 7 (a) K. B. Wiberg and P. R. Rablen, *J. Am. Chem. Soc.*, 1993, 115, 614–625; (b) D. O'Hagan, *Chem. Soc. Rev.*, 2008, 37, 308–319; (c) C. P. Andrieux, C. Combellas, F. Kanoufi, J.-M. Savéant and A. Thiébault, *J. Am. Chem. Soc.*, 1997, 119, 9527–9540.
- 8 (a) V. J. Scott, R. Çelenligil-Çetin and O. V. Ozerov, J. Am. Chem. Soc., 2005, 127, 2852–2853; (b) K. Fuchibe and T. Akiyama, J. Am. Chem. Soc., 2006, 128, 1434–1435; (c) C. Douvris and O. V. Ozerov, Science, 2008, 321, 1188–1190; (d) J. Terao, M. Nakamura and N. Kambe, Chem. Commun., 2009, 6011–6013; (e) T. Stahl, H. F. T. Klare and M. Oestreich, J. Am. Chem. Soc., 2013, 135, 1248–1251; (f) J. Zhu, M. Perez, C. B. Caputo and D. W. Stephan, Angew. Chem., Int. Ed., 2016, 55, 1417–1421.
- 9 (a) R. Doi, M. Ohashi and S. Ogoshi, Angew. Chem., Int. Ed., 2016, 55, 341-344; (b) K. Fuchibe, H. Hatta, K. Oh, R. Oki and J. Ichikawa, Angew. Chem., Int. Ed., 2017, 56, 5890-5893; (c) S. B. Lang, R. J. Wiles, C. B. Kelly and G. A. Molander, Angew. Chem., Int. Ed., 2017, 56, 15073-15077; (d) T. Ichitsuka, T. Fujita and J. Ichikawa, ACS Catal., 2015, 5, 5947-5950; (e) W. Dai, Y. Lin, Y. Wan and S. Cao, Org. Chem. Front., 2018, 5, 55–58; (f) Y. Lan, F. Yang and C. Wang, ACS Catal., 2018, 8, 9245-9251; (g) T. Fujita, M. Takazawa, K. Sugiyama, N. Suzuki and J. Ichikawa, Org. Lett., 2017, 19, 588-591; (h) T. Ichitsuka, T. Fujita, T. Arita and J. Ichikawa, Angew. Chem., Int. Ed., 2014, 53, 7564-7568; (i) Y. Liu, Y. Zhou, Y. Zhao and J. Qu, Org. Lett., 2017, 19, 946–949; (j) M. Wang, X. Pu, Y. i. Zhao, P. Wang, Z. Li, C. Zhu and Z. Shi, J. Am. Chem. Soc., 2018, 140, 9061-9065; (k) P. Gao, C. Yuan, Y. Zhao and Z. Shi, Chem, 2018, 4, 1-11.
- 10 (a) L.-G. Xie and Z.-X. Wang, Angew. Chem., Int. Ed., 2011, 50, 4901–4904; (b) P. Maity, D. M. Shacklady-McAtee, G. P. Yap, E. R. Sirianni and M. P. Watson, J. Am. Chem. Soc., 2013, 135, 280–285; (c) T. Moragas, M. Gaydou and R. Martin, Angew. Chem., Int. Ed., 2016, 55, 5053–5057; (d) D. Y. Wang, Z. K. Yang, C. Wang, A. Zhang and M. Uchiyama, Angew. Chem., Int. Ed., 2018, 57, 3641–3645; (e) Y.-Q.-Q. Yi, W.-C. Yang, D.-D. Zhai, X.-Y. Zhang, S.-Q. Li and B.-T. Guan, Chem. Commun., 2016, 52, 10894–10897.
- 11 (a) J. Tsuji, I. Shimizu, I. Minami, Y. Ohashi, T. Sugiura and K. Takahashi, J. Org. Chem., 1985, 50, 1523–1529; (b)
 K. J. Schwarz, C. M. Pearson, G. A. Cintron-Rosado, P. Liu and T. N. Snaddon, Angew. Chem., Int. Ed., 2018, 57, 7800– 7803; (c) Y. Chen, J. P. Romaire and T. R. Newhouse, J. Am. Chem. Soc., 2015, 137, 5875–5878; (d) B. Zhang and X. Zhang, Chem. Commun., 2016, 52, 1238–1241; (e)
 G. P. Boldrini, M. Mengoli, E. Tagliavini, C. Trombini and A. Umani-Ronchi, Tetrahedron Lett., 1986, 27, 4223–4226.
- 12 (a) T. A. Hamlin, C. B. Kelly, R. M. Cywar and N. E. Leadbeater, *J. Org. Chem.*, 2014, **79**, 1145–1155; (b) J.-P. Bégué, D. Bonnet-Delpon and M. H. Rock, *Synlett*, 1995, **6**, 659–660.
- 13 The addition of external H_2O was found to be detrimental to the arylation reaction.
- 14 For the proposed reaction mechanism of arylation step, see the ESI[†] for details.