Radical Coupling

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Monofluoroalkenylation of Dimethylamino Compounds through Radical–Radical Cross-Coupling

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Abstract: *An unprecedented and challenging radical–radical cross-coupling of α-aminoalkyl radicals with monofluoroalkenyl radicals derived from gem-difluoroalkenes was achieved. This first example of tandem C(sp^3)–H and C(sp^2)–F bond functionalization through visible-light photoredox catalysis offers a facile and flexible access to privileged tetrasubstituted monofluoroalkenes under very mild reaction conditions. The striking features of this redox-neutral method in terms of scope, functional-group tolerance, and regioselectivity are illustrated by the late-stage fluoroalkenylation of complex molecular architectures such as bioactive (+)-diltiazem, rosiglitazone, dihydroartemisinin, oleanic acid, and androsterone derivatives, which represent important new α-amino C–H monofluoroalkenylations.*

The monofluoroalkene substructure plays a unique role in various fields of current research.[1] It shows a high potential as a fluorinated synthon in organic synthesis[2] and is valuable as a peptide bond mimic in medicinal chemistry, drug discovery (Figure 1),[3] and high-performance materials.[4] These features have triggered the development of synthetic methods to complement existing strategies.[5] Conceptually, the development of a general, mild, and efficient catalytic C–H bond monofluoroalkenylation method would constitute a novel and practical approach since it could enable access to an array of structurally diverse monofluoroalkenes. Recently, the groups of Hoarau[6] and Loh[7] reported the transition-metal-catalyzed monofluoroalkenylation of aromatic C(sp^2)–H bonds, thereby streamlining access to trisubstituted alkenyl fluorides (Scheme 1 a,b). However, a general catalytic late-stage monofluoroalkenylation of inert C(sp^3)–H bonds to tetrasubstituted monofluoroalkenes has not been reported so far and represents a new challenge (Scheme 1, lower part).

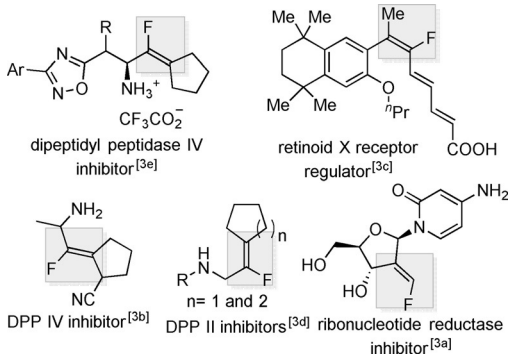
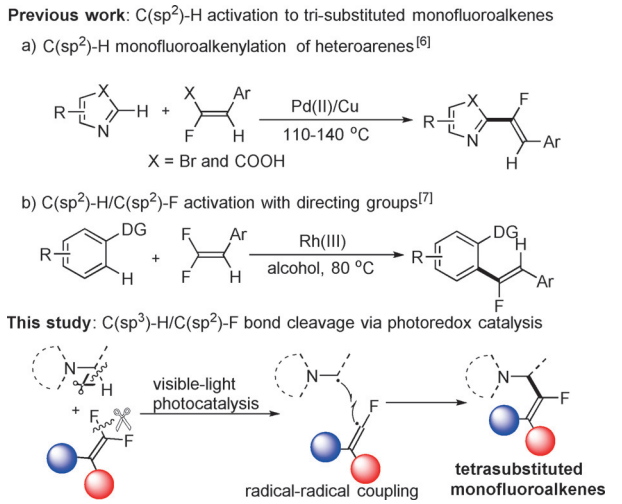


Figure 1. Selected bioactive multisubstituted monofluoroalkenes.



Scheme 1. Selective monofluoroalkenylation of unreactive C–H bonds.

The tertiary amine substructure is prevalent in natural products and pharmaceutically agents (about 20 % of the 200 top-selling pharmaceutical products contain this unit).[8] However, they were generally considered to be unreactive coupling partners until recent efforts toward α-C(sp^3)–H bond functionalization changed that view.[9] The development of a mild and general method for the selective C(sp^3)–H monofluoroalkenylation of complex tertiary amine skeletons would thus be highly attractive and meaningful for both organic and medicinal chemistry. Recently, we[10a] and others[11] have described a new radical–radical recombination of α-aminoalkyl radicals for C–C coupling reactions under photoredox catalysis.[12] We now report the recombination of α-aminoalkyl radicals with monofluoroalkenyl radicals, which readily enables the late-stage modification of complex bioactive molecules by photoredox catalysis.

Transition-metal-catalyzed C–F bond functionalization has become an important strategy for coupling reactions.[13] Still, mechanistically distinct, visible-light-induced C–F bond

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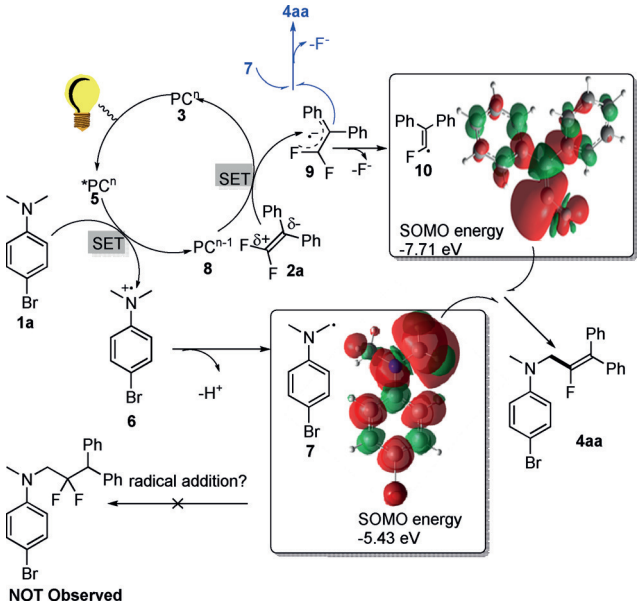
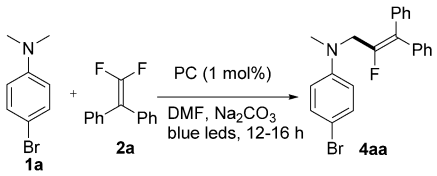
functionalization is still underdeveloped.[14] With readily formed α-aminoalkyl radicals in our mind,[15] we wondered whether we could achieve a visible-light-promoted C–F bond functionalization of tetrasubstituted *gem*-difluoroalkenes[7,13a] to produce monofluoroalkenyl radicals for radical–radical heterocoupling. A preliminary mechanistic sketch of our proposal is shown in Scheme 2. Upon irradiation, the excited-state photocatalyst **5** is formed and it then undergoes single electron transfer (SET) by accepting one electron from tertiary amine **1a** to generate radical cation **6**, which would form α-aminoalkyl radical **7** by deprotonation. Subsequent SET reduction of *gem*-difluoroalkene **2a** ($E_{1/2}^{red} = -1.04$ V vs. SCE)[16] would generate radical anion **9**, which might be prone to undergo C–F bond fragmentation to generate a fluoride and fluoroalkenyl radical **10** (similar fragmentations have already been reported for perfluoroaryl radical anions).[14b,c] DFT calculations indicate that α-aminoalkyl radical **7** has a higher SOMO energy than monofluoroalkenyl radical **10**.[16] Then, selective cross-recombination of the less reactive α-aminoalkyl radical **7** with the more reactive monofluoroalkenyl radical **10** could afford product **4aa** according to the "persistent-radical effect".[17] Alternatively, chemoselective radical C–C heterocoupling of α-aminoalkyl radical **7** with radical anion **9** and subsequent extrusion of fluoride could also efficiently deliver **4aa**. Radical addition of the α-aminoalkyl radicals to the electron-deficient *gem*-difluoroalkenes were not observed in any of our examples.[18]



Scheme 2. Proposed α-amino monofluoroalkenylation. The SOMO energies were obtained at the DFT/UM06-2X/6-311++g(d,p) level.

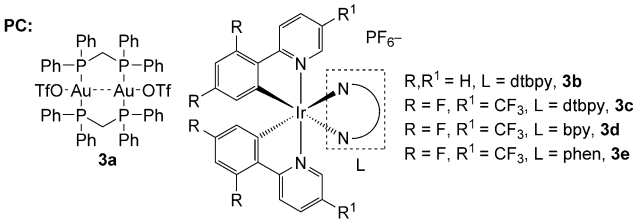
As shown in Table 1, the proposed α-C(sp^3)–H monofluoroalkenylation was indeed feasible during an initial test with $[Au_2(\mu\text{-dppm})_2]_2OTf$.[10] A further screening of various photocatalysts revealed that Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ **3c** was the optimal choice (88% yield; Table 1, entry 3). This can be rationalized by the strong oxidation potential of its long-lived excited state ($E_{1/2}[*Ir^{III}/Ir^{II}] = +1.21$ V vs. SCE) and the strong reducing ability of the corresponding Ir^{II} complex ($E_{1/2}[Ir^{III}/Ir^{II}] = -1.37$ V vs. SCE).[19] Regarding these values, both SET oxidation of **1a** ($E_{1/2}^{ox} = 0.96$ V vs. SCE)[16] and SET reduction of **2a** ($E_{1/2}^{red} = -1.04$ V vs. SCE)[16] are thermodynamically feasible. In accordance with previous reports,[10a,11,15] a slight excess of amine favored the coupling process (Table 1, entry 3 vs. entries 11 and 12). Control experiments revealed that the photocatalyst, light, and base were essential for a successful transformation (Table 1, entries 8–10).

Table 1: Initial studies towards a C(sp^3)–H monofluoroalkenylation.[a]



Entry	Photocatalyst (PC)	^{19}F NMR yield[b]
1[c]	**3a**	10%
2	**3b**	96% (85%)
3	**3c**	>99% (88%)
4	**3d**	62%
5	**3e**	43%
6	Ru(bpy)$_3$Cl$_2$ **3f**	9%
7	Ir(ppy)$_3$ **3g**	12%
8	–	0
9[d]	**3c**	0
10[e]	**3c**	16%
11[f]	**3c**	85% (71%)
12[g]	**3c**	60%

[a] 0.1 mmol scale with 1.5 equiv **1a**. [b] With 2-bromo-4-fluorobenzaldehyde as an internal standard. The isolated yield is given in brackets. [c] UVA light. [d] In the dark. [e] Without Na_2CO_3. [f] 1.2 equiv amine. [g] 0.1 mmol **1a** with 1.5 equiv **2a**.



Under these optimized reaction conditions (Table 1, entry 3), we examined the substrate scope with respect to the applied tertiary amines (Table 2). In general, the monofluoroalkenylation method has a very broad scope. Both acyclic and cyclic *N*-Ar and aliphatic tertiary amines selectively underwent monofluoroalkenylation to give the corresponding products **4aa–ax** in 50%–97% yield. The result of the X-ray single-crystal structure analysis of **4ap** is shown in Figure 2. The reaction showed excellent functional-group compatibility; esters, aldehydes, nitriles, halides, amides, alcohols, ethers, acetals, and heteroaromatic rings were tolerated. Selective monofluoroalkenylation of the strong primary α-C(sp^3)–H bonds was preferred even in the presence of weaker secondary and tertiary C–H bonds (**4aq–ax**). Notably, the prevalence of the 1,1-diaryl-2-fluoroethenyl motif in pharmaceuticals lead structures underlines the potential of products **4aa–ax** in the context of drug

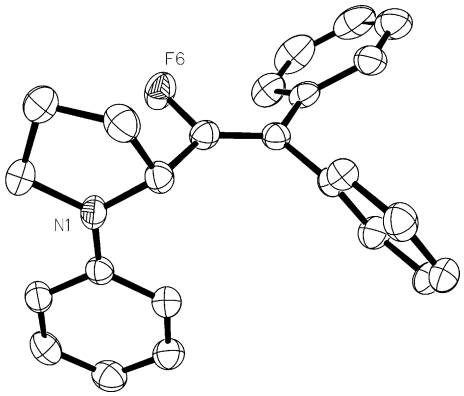
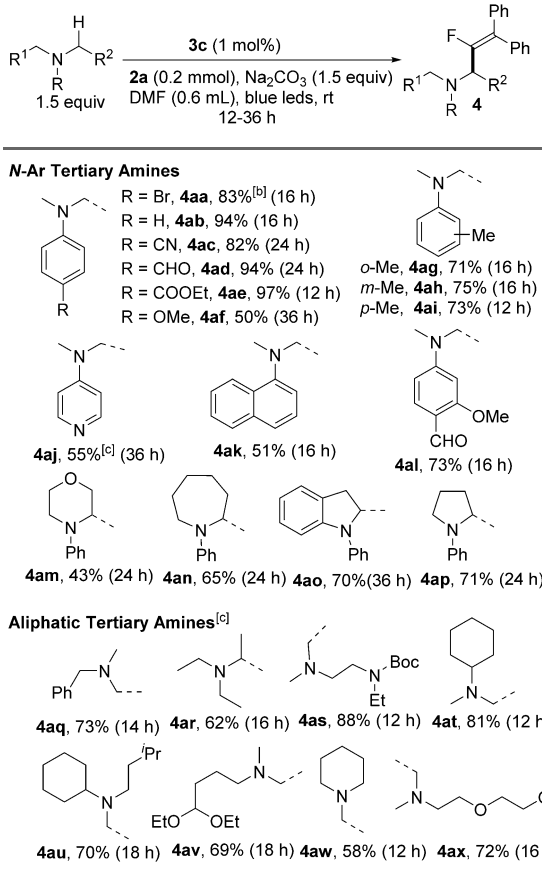


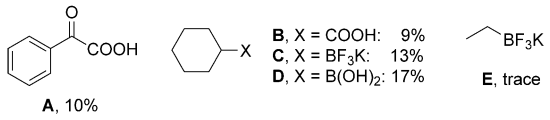
Figure 2. Solid-state molecular structure of **4ap**.[20]

Table 2: Scope with regard to the applied tertiary amines.[a]



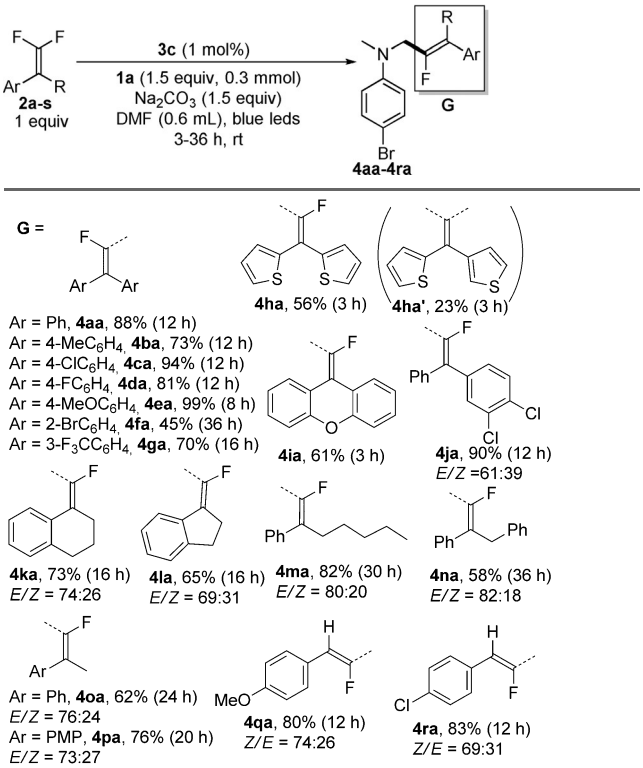
[a] Yields of isolated product. [b] 1 mmol scale. [c] 3 equiv tertiary amines were used due to lower reactivity.

discovery.[21] However, with α-oxo acids,[22a] alkyl carboxylic acid,[22b] and alkyl trifluoroborates or boronic acids[22c] instead of tertiary amines, only small amounts or traces of the desired products were observed under the same conditions (Scheme 3). We speculate that replacement of the α-amino-alkyl radicals by more short-lived acyl or alkyl radicals is unfavorable for the radical recombination process.[23]



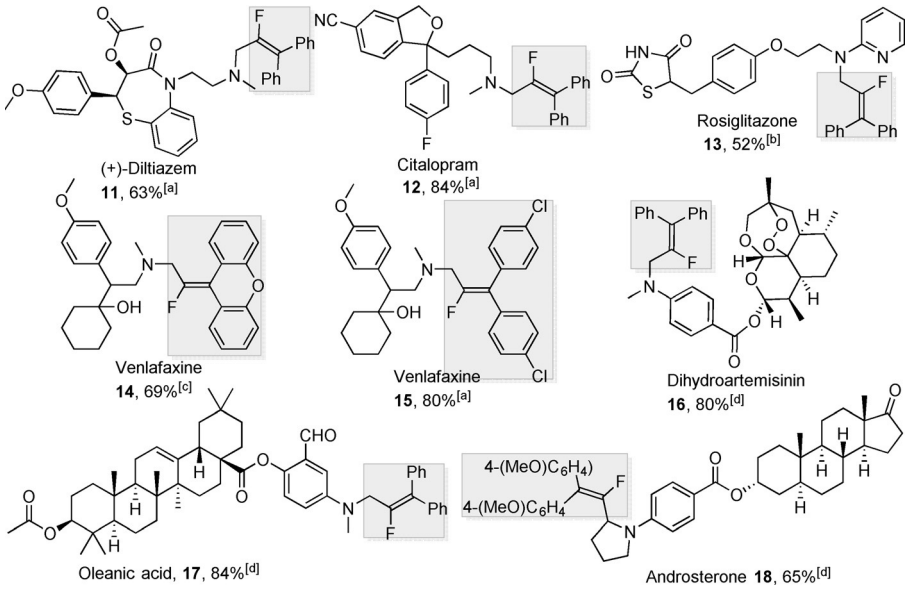
Scheme 3. Exploration of other coupling partners. Reaction conditions: **3c** (1 mol%), **2a** (0.2 mmol), **A-E** (1.5 equiv), Na_2CO_3 (1.5 equiv), DMF (0.6 mL), blue LEDs, RT.

Table 3: Substrate scope with regard to the *gem*-difluoroalkenes.[a]



[a] Yields of isolated product and the major product are shown. The *E*/*Z* ratio was determined by ^{19}F NMR analysis of reaction mixture.

gem-Difluoroalkenes are readily available building blocks.[24] A variety of *gem*-difluoroalkenes were converted (Table 3). Both electron-donating and electron-withdrawing groups in the *ortho*, *meta*, and *p*ara positions of the attached aromatic rings were compatible, affording the corresponding tetrasubstituted alkenyl fluorides **4aa–ja** in satisfactory yields (up to 99%).[25] With an electron-rich thiophene moiety, besides the desired product **4ha**, an interesting double C–F bond functionalization delivered the C_2-symmetrically tetra-substituted alkene **4ha′** in significant amounts. In the case of unsymmetrical *gem*-difluoroalkenes as starting materials, moderate *E*/*Z* selectivity was obtained (**4ja–pa**, ratio up to 82:18). The observed stereoselectivity is consistent with our initial hypothesis of a radical–radical coupling model as depicted in Scheme 2. The diastereoisomeric ratio is kinetically controlled through trapping of the transient fluroalkenyl radical and, owing to the extremely fast radical recombination process, it is poorly controllable. Trisubstituted *gem*-difluoro-

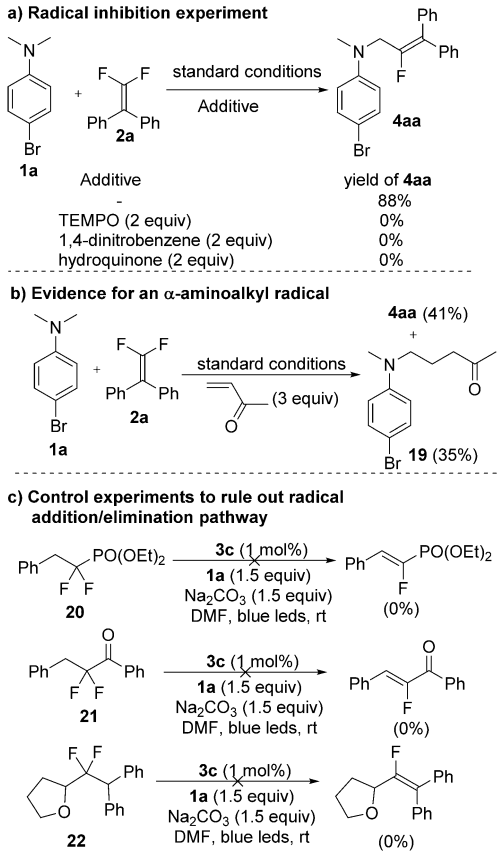


Scheme 4. Late-stage α-amino C–H monofluoroalkenylation of top-selling drugs and complex molecules. [a] 3 equiv tertiary amine. [b] 1.5 equiv tertiary amine. [c] 2 equiv tertiary amine. [d] 1.2 equiv tertiary amine.

alkenes prepared from aldehydes were also suitable coupling partners (**4qa** and **4ra**).

The challenging late-stage application of complex molecular architectures is indispensable for the development of innovative methods. As depicted in Scheme 4, a variety of top-selling drugs such as (+)-diltiazem (a potent vasodilator), citalopram (an antidepressant), rosiglitazone (an antidiabetic), and venlafaxine (an antidepressant) tolerated the monofluoroalkenylation conditions well, even in the presence of functional groups that are sensitive to oxidants or acidic/basic conditions. Products **11**–**15** were obtained in 52–84% yields with primary α-C(sp^3)–H bond selectivity. The derivatives of complex biologically important compounds such as dihydroartemisinin, oleanic acid, and androsterone can also be α-C(sp^3)–H monofluoroalkenylated while keeping other versatile functional groups (ester, aldehyde, alkene, acetal, peroxide, ketone) intact. The successful incorporation of the monofluoroalkenyl motif into such bioactive compounds could help to improve their bioactivity and other properties. These examples demonstrate that the applied method represents a powerful late-stage monofluoroalkenylation. The small drawback that an excess of tertiary amine is needed becomes tolerable if one considers that all of the monofluoroalkenylation reactions run cleanly, which significantly simplifies the recovery of unreacted amine.

With regard to the mechanism, we first performed radical inhibition experiments with various radical inhibitors. The observed inhibition is in all cases indicative of a SET-mediated radical pathway (Scheme 5a). Adding Michael acceptor but-3-en-2-one into the model reaction led to the formation of byproduct **19** in 35% yield, which strongly implies the involvement of α-aminoalkyl radical **7** (Scheme 5b).[15] In addition, the monofluoroalkenyl radical or gem-difluoroalkenyl radical anion can be trapped by different acyl or alkyl radicals as listed in Scheme 3. Although the proposed radical–radical coupling is possible at this stage, an alternative radical addition and a subsequent base-mediated elimination pathway has to be considered as well. To evaluate the possibility of this alternative mechanistic scenario, several gem-difluoro-phenylethane derivatives (**20**–**22**) bearing acidic benzylic C–H bonds were prepared as mimics for the possible intermediates that would be formed if a radical addition were to initiate the reaction. However, under the standard reaction conditions, none of the monofluoroalkene products were formed (Scheme 5c). Therefore, an addition/elimination process is less likely, and indeed a radical–radical coupling pathway dominated by the persistent-radical effect could operate.



Scheme 5. Control experiments and mechanistic studies.

In summary, we describe an unprecedented α-C(sp^3)–H monofluoroalkenylation of unactivated tertiary amines through a mild, efficient, and redox-neutral route to priv-

ileged tetrasubstituted monofluoroalkenes by photoredox catalysis. Mechanistic studies indicate a radical–radical cross-coupling reaction of α-aminoalkyl radicals with monofluoroalkenyl radicals. The mild reaction conditions, a broad scope, excellent functional-group tolerance, and exclusive selectivity for primary $C(sp^3)$–H bonds open up an opportunity for performing challenging late-stage monofluoroalkenylations of complex molecules. This merging of $C(sp^3)$–H and $C(sp^2)$–F bond functionalization with photoredox catalysis represents an important step forward for monofluoroalkenylation strategies.

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Keywords: late-stage functionalization · monofluoroalkenylation · photoredox catalysis · radical coupling · C–H activation

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Angew. Chem. **2016**, *128*, 9563–9568

[1] P. Kirsch, *Modern Fluoroorganic Chemistry*: *Synthesis Reactivity*, *Applications*, *2nd ed.*, Wiley-VCH, Weinheim, **2013**.

[2] a) G. Dutheuil, S. Couve-Bonnaire, X. Pannecoucke, *Angew. Chem. Int. Ed.* **2007**, *46*, 1290–1292; *Angew. Chem.* **2007**, *119*, 1312–1314; b) O. A. Wong, Y. Shi, *J. Org. Chem.* **2009**, *74*, 8377–8380; c) L. Debien, B. Quiclet-Sire, S. S. Zard, *Org. Lett.* **2012**, *14*, 5118–5121.

[3] a) J. Kanazawa, T. Takahashi, S. Akinaga, T. Tamaoki, M. Okabe, *Anti-Cancer Drugs* **1998**, *9*, 653–657; b) K. Zhao, D. S. Lim, T. Funaki, J. T. Welch, *Bioorg. Med. Chem.* **2003**, *11*, 207–215; c) T. Deng, S. Shan, Z.-B. Li, Z.-W. Wu, C.-Z. Liao, B. Ko, X.-P. Lu, J. Cheng, Z.-Q. Ning, *Biol. Pharm. Bull.* **2005**, *28*, 1192–1196; d) P. Van der Veken, K. Senten, I. Kertèsz, I. De Meester, A.-M. Lambeir, M.-B. Maes, S. Scharpé, A. Haemers, K. Augustyns, *J. Med. Chem.* **2005**, *48*, 1768–1780; e) S. D. Edmondson, L. Wei, J. Xu, J. Shang, S. Xu, J. Pang, A. Chaudhary, D. C. Dean, H. He, B. Leiting, K. A. Lyons, R. A. Patel, S. B. Patel, G. Scapin, J. K. Wu, M. G. Beconi, N. A. Thornberry, A. E. Weber, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2409–2413; f) C. E. Jakobsche, G. Peris, S. J. Miller, *Angew. Chem. Int. Ed.* **2008**, *47*, 6707–6711; *Angew. Chem.* **2008**, *120*, 6809–6813.

[4] a) F. Babudri, G. M. Farinola, F. Naso, R. Ragni, *Chem. Commun.* **2007**, 1003–1022; b) F. Babudri, A. Cardone, G. M. Farinola, C. Martinelli, R. Mendichi, F. Naso, M. Striccoli, *Eur. J. Org. Chem.* **2008**, 1977–1982.

[5] Most sophisticated methods for the direct synthesis of monofluoroalkenes usually require prefunctionazation of substrates and/or the use of sensitive reagents, which limits application with complex molecules: a) G. Landelle, M. Bergeron, M.-O. Turcotte-Savard, J.-F. Paquin, *Chem. Soc. Rev.* **2011**, *40*, 2867–2908; b) S. H. Lee, J. Schwartz, *J. Am. Chem. Soc.* **1986**, *108*, 2445–2447; c) C. Chen, K. Wilcoxen, N. Strack, J. R. McCarthy, *Tetrahedron Lett.* **1999**, *40*, 827–830; d) A. K. Ghosh, B. Zajc, *Org. Lett.* **2006**, *8*, 1553–1556; e) M.-H. Yang, S. S. Matikonda, R. A. Altman, *Org. Lett.* **2013**, *15*, 3894–3897; f) M. Bergeron, T. Johnson, J.-F. Paquin, *Angew. Chem. Int. Ed.* **2011**, *50*, 11112–11116; *Angew. Chem.* **2011**, *123*, 11308–11312; g) O. E. Okoromoba, J. Han, G. B. Hammond, B. Xu, *J. Am. Chem. Soc.* **2014**, *136*, 14381–14384.

[6] a) C. Schneider, D. Masi, S. Couve-Bonnaire, X. Pannecoucke, C. Hoarau, *Angew. Chem. Int. Ed.* **2013**, *52*, 3246–3249; *Angew. Chem.* **2013**, *125*, 3328–3331; b) K. Rousée, C. Schneider, S. Couve-Bonnaire, X. Pannecoucke, V. Levacher, C. Hoarau, *Chem. Eur. J.* **2014**, *20*, 15000–15004.

[7] During the preparation of this manuscript, Loh et al. reported an elegant Rh^{III}-catalyzed tandem $C(sp^2)$–H/$C(sp^2)$–F acitvation with trisubstituted gem-difluoroalkenes in alcohol solution at 80 °C: P. Tian, C. Feng, T.-P. Loh, *Nat. Commun.* **2015**, *6*, 7472.

[8] http://jon.oia.arizona.edu/njardarson/group/sites/default/files/Top200PharmaceuticalProductsByWorldwideSalesin2009.pdf.

[9] a) S.-I. Murahashi, N. Komiya, H. Terai, T. Nakae, *J. Am. Chem. Soc.* **2003**, *125*, 15312–15313; b) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 11810–11811; c) A. G. Condie, J. C. González-Gómez, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2010**, *132*, 1464–1465; d) A. S.-K. Tsang, P. Jensen, J. M. Hook, A. S. K. Hashmi, M. H. Todd, *Pure Appl. Chem.* **2011**, *83*, 655–665.

[10] a) J. Xie, S. Shi, T. Zhang, N. Mehrkens, M. Rudolph, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2015**, *54*, 6046–6050; *Angew. Chem.* **2015**, *127*, 6144–6148; b) J. Xie, T. Zhang, F. Chen, N. Mehrkens, F. Rominger, M. Rudolph, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2016**, *55*, 2934–2938; *Angew. Chem.* **2016**, *128*, 2987–2991.

[11] Selected examples: a) J. Xuan, T.-T. Zeng, Z.-J. Feng, Q.-H. Deng, J.-R. Chen, L.-Q. Lu, W.-J. Xiao, H. Alper, *Angew. Chem. Int. Ed.* **2015**, *54*, 1625–1628; *Angew. Chem.* **2015**, *127*, 1645–1648; b) S. B. Lang, K. M. O'Nele, J. A. Tunge, *J. Am. Chem. Soc.* **2014**, *136*, 13606–13609; c) A. McNally, C. K. Prier, D. W. C. MacMillan, *Science* **2011**, *334*, 1114–1117; d) D. Uraguchi, N. Kinoshita, T. Kizu, T. Ooi, *J. Am. Chem. Soc.* **2015**, *137*, 13768–13771; e) C. Wang, J. Qin, X. Shen, R. Riedel, K. Harms, E. Meggers, *Angew. Chem. Int. Ed.* **2016**, *55*, 685–688; *Angew. Chem.* **2016**, *128*, 695–698.

[12] a) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102–113; b) J. Xuan, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 6828–6838; *Angew. Chem.* **2012**, *124*, 6934–6944; c) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363; d) D. P. Hari, B. König, *Angew. Chem. Int. Ed.* **2013**, *52*, 4734–4743; *Angew. Chem.* **2013**, *125*, 4832–4842; e) J. Xie, H. Jin, P. Xu, C. Zhu, *Tetrahedron Lett.* **2014**, *55*, 36–48; f) D. M. Schultz, T. P. Yoon, *Science* **2014**, DOI: 10.1126/science.1239176; g) M. Reckenthäler, A. G. Griesbeck, *Adv. Synth. Catal.* **2013**, *355*, 2727–2744; recent light-mediated reactions of gold complexes: h) L. Huang, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2016**, *55*, 4808–4813; *Angew. Chem.* **2016**, *128*, 4888–4893; i) L. Huang, F. Rominger, M. Rudolph, A. S. K. Hashmi, *Chem. Commun.* **2016**, *52*, 6435–6438.

[13] a) M. Takachi, Y. Kita, M. Tobisu, Y. Fukumoto, N. Chatani, *Angew. Chem. Int. Ed.* **2010**, *49*, 8717–8720; *Angew. Chem.* **2010**, *122*, 8899–8902; b) W.-H. Guo, Q.-Q. Min, J.-W. Gu, X. Zhang, *Angew. Chem. Int. Ed.* **2015**, *54*, 9075–9078; *Angew. Chem.* **2015**, *127*, 9203–9206; c) J. Xu, E.-A. Ahmed, B. Xiao, Q.-Q. Lu, Y.-L. Wang, C.-G. Yu, Y. Fu, *Angew. Chem. Int. Ed.* **2015**, *54*, 8231–8235; *Angew. Chem.* **2015**, *127*, 8349–8353.

[14] Photocatalytic C–F bond functionalization of polyfluorinated arenes: a) S. M. Senaweera, A. Singh, J. D. Weaver, *J. Am. Chem. Soc.* **2014**, *136*, 3002–3005; b) A. Singh, J. J. Kubik, J. D. Weaver, *Chem. Sci.* **2015**, *6*, 7206–7212; c) S. Senaweera, J. D. Weaver, *J. Am. Chem. Soc.* **2016**, *138*, 2520–2523.

[15] Selected examples: a) Y. Miyake, K. Nakajima, Y. Nishibayashi, *J. Am. Chem. Soc.* **2012**, *134*, 3338–3341; b) P. Kohls, D. Jadhav, G. Pandey, O. Reiser, *Org. Lett.* **2012**, *14*, 672–675; c) S. Zhu, A. Das, L. Bui, H. Zhou, D. P. Curran, M. Rueping, *J. Am. Chem. Soc.* **2013**, *135*, 1823–1829; d) Z. Zuo, D. T. Ahneman, L. Chu,

J. A. Terrett, A. G. Doyle, D. W. C. MacMillan, *Science* **2014**, *345*, 437 – 440; e) L. Ruiz Espelt, I. S. McPherson, E. M. Wiensch, T. P. Yoon, *J. Am. Chem. Soc.* **2015**, *137*, 2452 – 2455.

[16] Please see the Supporting Information for details, including DFT calculations, optimization of reaction conditions, light on/off experiments, cyclic voltammetry measurements of **1a** and **2a**, luminescence quenching experiments, and quantum yields.

[17] The "persistent-radical effect" was initially discovered with "persistent" radicals, but it is also suitable for short-lived radicals in the the case of quite different lifetimes. Reviews: a) A. Studer, *Chem. Eur. J.* **2001**, *7*, 1159 – 1164; b) H. Fischer, *Chem. Rev.* **2001**, *101*, 3581 – 3610; c) D. Griller, K. U. Ingold, *Acc. Chem. Res.* **1976**, *9*, 13 – 19; selected examples: d) J. Ke, Y. Tang, H. Yi, Y. Li, Y. Cheng, C. Liu, A. Lei, *Angew. Chem. Int. Ed.* **2015**, *54*, 6604 – 6607; *Angew. Chem.* **2015**, *127*, 6704 – 6707; e) B. Schweitzer-Chaput, J. Demaerel, H. Engler, M. Klussmann, *Angew. Chem. Int. Ed.* **2014**, *53*, 8737 – 8740; *Angew. Chem.* **2014**, *126*, 8882 – 8885; f) J.-K. Cheng, T.-P. Loh, *J. Am. Chem. Soc.* **2015**, *137*, 42 – 45.

[18] We consider radical adddition of α-aminoalkyl radical to gem-difluoroalkenes followed by based-mediated fluoride elimination to be a less likely pathway but it cannot be ruled out absolutely: a) J. D. LaZerte, R. J. Koshar, *J. Am. Chem. Soc.* **1955**, *77*, 910 – 914; b) C. L. Bumgardner, J. P. Burgess, *Tetrahedron Lett.* **1992**, *33*, 1683 – 1686. Also, we found that the radical addition of a highly nucleophilic α-THF radical to **2a** for the synthesis of compound **22** is rather sluggish (the same reaction conditions with **18b** at 80 °C for 48 hours, only 2 % yield).

[19] M. S. Lowry, J. I. Goldsmith, J. D. Slinker, R. Rohl, R. A. Pascal, G. G. Malliaras, S. Bernhard, *Chem. Mater.* **2005**, *17*, 5712 – 5719.

[20] CCDC 1436926 (**4ap**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[21] M. J. Coghlan, J. E. G. Green, T. A. P. K. Jadhav, D. P. Matthews, M. I. Steinberg, K. R. Fales, M. G. Bell, WO 2004052847 A2, **2004**.

[22] a) J. Liu, Q. Liu, H. Yi, C. Qin, R. Bai, X. Qi, Y. Lan, A. Lei, *Angew. Chem. Int. Ed.* **2014**, *53*, 502 – 506; *Angew. Chem.* **2014**, *126*, 512 – 516; b) Q.-Q. Zhou, W. Guo, W. Ding, X. Wu, X. Chen, L.-Q. Lu, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2015**, *54*, 11196 – 11199; *Angew. Chem.* **2015**, *127*, 11348 – 11351; c) H. Huang, G. Zhang, L. Gong, S. Zhang, Y. Chen, *J. Am. Chem. Soc.* **2014**, *136*, 2280 – 2283.

[23] The lifetime of alkyl radicals (ethyl and cyclohexyl radical), an acyl radical (phenacyl radical), and an α-aminoalkyl radical (Et_2NCHMe) are about 180 fs, 2 ns, 20 ns and 700 ns, respectively: a) B. Wilkinson, M. Zhu, N. D. Priestley, H. H. T. Nguyen, H. Morimoto, P. G. Williams, S. I. Chan, H. G. Floss, *J. Am. Chem. Soc.* **1996**, *118*, 921 – 922; b) P. Livant, R. G. Lawler, *J. Am. Chem. Soc.* **1976**, *98*, 6044 – 6045; c) E. N. Step, N. J. Turro, *J. Photochem. Photobiol. A* **1994**, *84*, 249 – 256; d) J. C. Scaiano, *J. Phy. Chem.* **1981**, *85*, 2851 – 2855; additionally, the lifetime of an alkenyl radical was estimated to range from 0.3 to 30 ns: e) "The Stereochemistry of Cyclohexyl and Vinylic Radicals": O. Simamura, *Top. Stereochem.* **1969**, *4*, 1 – 34.

[24] a) M. Obayashi, E. Ito, K. Matsui, K. Kondo, *Tetrahedron Lett.* **1982**, *23*, 2323 – 2326; b) M. Hu, Z. He, B. Gao, L. Li, C. Ni, J. Hu, *J. Am. Chem. Soc.* **2013**, *135*, 17302 – 17305.

[25] Very recently, Zhang and co-workers reported an alternative route to fluorinated tetrasubstituted alkenes through oxidative amination of highly reactive allenes with NFSI: G. Zhang, T. Xiong, Z. Wang, G. Xu, X. Wang, Q. Zhang, *Angew. Chem. Int. Ed.* **2015**, *54*, 12649 – 12653; *Angew. Chem.* **2015**, *127*, 12840 – 12844.

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