C–H Activation

DOI: 10.1002/anie.201400420

A Convenient Photocatalytic Fluorination of Unactivated C–H Bonds**

*Shira D. Halperin, Hope Fan, Stanley Chang, Rainer E. Martin, and Robert Britton**

Abstract: *Fluorination reactions are essential to modern medicinal chemistry, thus providing a means to block site-selective metabolic degradation of drugs and access radiotracers for positron emission tomography imaging. Despite current sophistication in fluorination reagents and processes, the fluorination of unactivated C–H bonds remains a significant challenge. Reported herein is a convenient and economic process for direct fluorination of unactivated C–H bonds that exploits the hydrogen abstracting ability of a decatungstate photocatalyst in combination with the mild fluorine atom transfer reagent N-fluorobenzenesulfonimide. This operationally straightforward reaction provides direct access to a wide range of fluorinated organic molecules, including structurally complex natural products, acyl fluorides, and fluorinated amino acid derivatives.*

The incorporation of a fluorine atom into an advanced drug candidate is a common strategy in medicinal chemistry.[1,2] Oftentimes, a single hydrogen to fluorine substitution improves druglike properties by blocking undesired metabolism at a specific site, increasing lipophilicity or binding affinity, or altering drug absorption, distribution, or excretion.[1] In addition to the medicinal advantages often presented by fluorination, valuable pharmacokinetic information can be gleaned from non-invasive positron emission tomography (PET) imaging of ^{18}F-labeled drugs in vivo.[3] The critical role fluorine plays in the drug discovery process is highlighted by the fact that one-third of the so-called blockbuster drugs are fluorinated in at least one position.[4] Since the fluorination of cortisone[5] signalled a new era of fluoropharmaceuticals, further advances have relied on the discovery of mild fluorination reagents which can be handled safely and obviate the use of fluorine gas or its surrogates.[2,6] While present sophistication in the field includes the addition of electrophilic fluorine to alkenes,[6,7] and fluorination of aryl triflates[8] and palladium aryl complexes,[9] there is much interest in the development of reactions that effect the direct fluorination of C–H bonds. In this context, success has been realized in allylic[10] and benzylic[11] fluorination. However, the identification of reagent systems that effect selective fluorination of unactivated C(sp^3)–H bonds, or those not adjacent to sp^2-hybridized carbon atoms or other functional groups, which facilitate the formation of radicals or anions, remains a significant challenge.[12]

Recently, Groves and co-workers disclosed a protocol for the fluorination of unactivated C–H bonds through a radical process which relies on a manganese porphyrin catalyst working in concert with an oxidant (iodosylbenzene), AgF, and a catalytic amount of tetrabutylammonium fluoride (TBAF).[12] The groups of Lectka[13] and Inoue[14] have also demonstrated that N-oxyl radicals are capable of catalyzing the fluorination of C(sp^3)–H bonds in unfunctionalized cycloalkanes (e.g., cyclohexane, cyclooctane) when using Selectfluor as the fluorine-transfer reagent. An earlier report by Sandford, Chambers, and co-workers also describes a catalyst-free electrophilic fluorination reaction of hydrocarbons using Selectfluor in refluxing MeCN.[15] For the reasons discussed above, we have been interested in developing a convenient protocol for the direct fluorination of unactivated C(sp^3)–H bonds, and were particularly intrigued by a process that would involve the generation and trapping of alkyl radicals with fluorine-transfer reagents. In this regard, Sammis and co-workers have calculated[16] the homolytic N–F bond dissociation energy (BDE) for several electrophilic fluorinating reagents, including *N*-fluorobenzenesulfonimide (NFSI; $BDE_{NF} = 63\ kcal\,mol^{-1}$), and demonstrated the utility of NFSI in fluorine transfer to alkyl radicals generated through decarboxylative processes.[17] Considering that [^{18}F]-NFSI can be readily prepared from the reaction of [^{18}F]F_2 and $NaN(SO_2Ph)_2$,[18] the development of a NFSI-based fluorination of unactivated C(sp^3)–H bonds could also serve as a platform technology for the production of new radiotracers for PET imaging. Bearing this in mind, we envisioned a reaction which combines the hydrogen abstraction ability of a polyoxometalate with a fluorine-transfer reagent to directly transform unactivated C(sp^3)–H bonds into C–F bonds.

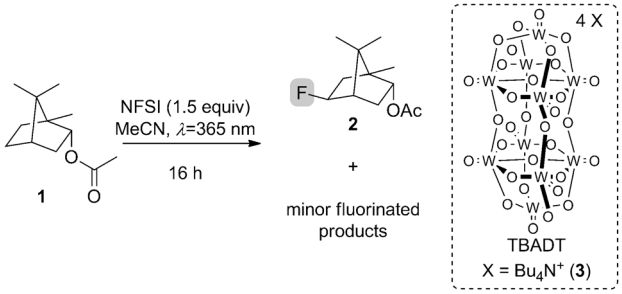
A variety of polyoxometalates have proven effective as photocatalysts in oxidative transformations,[19] and the decatungstate anion $W_{10}O_{32}^{4-}$ has been studied extensively for these purposes.[20-22] The tetrabutylammonium salt of decatungstate (TBADT; **3**; Table 1) is a well-characterized polyoxometalate catalyst which is particularly efficient at abstracting hydrogen atoms from saturated hydrocarbons[21] and has been utilized in carbon–carbon bond formation,[23] oxidation of alcohols,[24] epimerization of unactivated C–H centers,[25] and carbonylation reactions.[26] From a practical

[*] S. D. Halperin, H. Fan, S. Chang, Prof. R. Britton
Department of Chemistry, Simon Fraser University
Burnaby, British Columbia (Canada)
E-mail: rbritton@sfu.ca
Dr. R. E. Martin
Medicinal Chemistry, Small Molecule Research, Pharma Research & Early Development (pRED), F. Hoffmann-La Roche AG
Grenzacherstrasse 124, 4070 Basel (Switzerland)

[**] This work was supported by an NSERC Discovery Grant to R.B., a MSFHR Career Investigator Award to R.B., and NSERC Postgraduate Scholarships for S.D.H., H.F., S.C.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201400420.

Table 1: Demonstration and optimization of the TBADT-catalyzed fluorination of bornyl acetate (**1**).



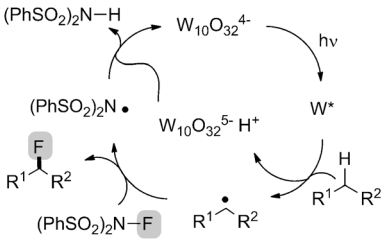
Entry	TBADT [mol%]	Conc. [M]	Additive[a]	Yield [%][b]
1	2	0.2	none	23 (32)
2	1	0.2	none	9 (12)
3	0	0.2	none	0
4	2	1.0	none	31 (43)
5	2	2.0	none	33 (46)
6	2	2.0	Na_2CO_3	37 (52)
7	2	2.0	$NaHCO_3$	40 (56)[c]

[a] Used 0.1 equiv. [b] Yield of isolated **2**; combined yield of isolated fluorinated products within parentheses. [c] An additional 30% of starting material was recovered from this reaction.

perspective, TBADT is readily prepared in one step through a complex self-assembly process from inexpensive sodium tungstate[21] and absorbs light at wavelengths that do not interact with common organic reagents (e.g., $\lambda = 350$–400 nm). Photocatalysis with TBADT also involves mild reaction conditions (e.g. room temperature, wet solvents) and is functional-group tolerant. Herein we report the discovery of an operationally simple and economic photocatalytic system for the direct fluorination of unactivated C(sp^3)–H bonds, and it exploits the hydrogen abstraction ability of TBADT and fluorine-transfer capacity of NFSI. Considering both the steric bulk and redox potential of decatungstate catalysts,[27] this process may mimic in vivo oxidative metabolism by selecting C–H bonds prone to metabolic degradation and replacing them with C–F bonds, a potentially transformative reaction for lead optimization in medicinal chemistry.

As depicted in Table 1, we initially investigated combinations of TBADT and NFSI in acetonitrile for the fluorination of bornyl acetate, which contains 11 unique and unactivated C(sp^3)–H bonds. Photoexcitation of the decatungstate catalyst was achieved by irradiating the reaction mixture with two 15 Watt black light bulbs (centered at $\lambda = 365$ nm). We were delighted to find that by using 2 mol% of TBADT and a small excess of NFSI, bornyl acetate was converted into the the fluoroacetate **2** in modest yield (23%). Increasing the reaction time (up to 60 h) had little effect on this result, whereas reduction in catalyst loading significantly impacted the yield of **2** (entry 2), and no product was observed in the absence of TBADT or light. We next examined the effect of the reaction concentration and found that fluorination proceeded optimally at high concentrations of bornyl acetate (e.g., 2.0 M, entry 5). Finally, as acetamide side products, presumably derived from acetonitrile displacement of fluoride, were also observed, various inorganic bases (e.g., Na_2CO_3, $NaHCO_3$, K_2CO_3) were added in an effort to consume the small amounts of coincident hydrofluoric acid deemed deleterious to the desired process. Optimally, the addition of a catalytic amount of base (< 20 mol%) substantially increased conversion, and when 10 mol% of $NaHCO_3$ was employed (entry 7), bornyl acetate was fluorinated in a total yield of 56% (ca. 80% yield considering the unreacted starting material).

While a full mechanistic understanding of this reaction will require further experimentation, we suggest the mechanism depicted in Scheme 1, a mechanism which is consistent with both the photocatalytic reactivity of TBADT and

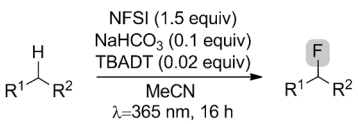


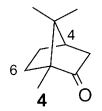
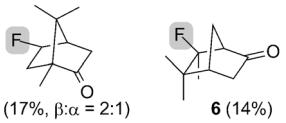
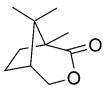
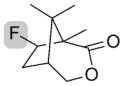
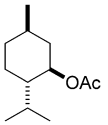
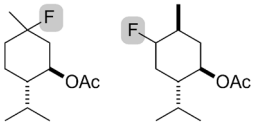
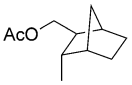
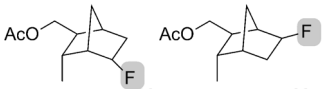
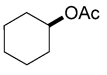
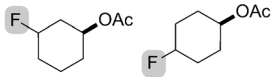
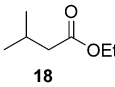
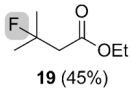
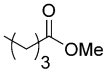
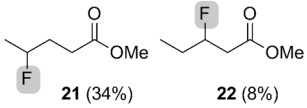
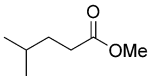
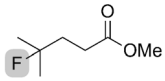
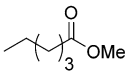
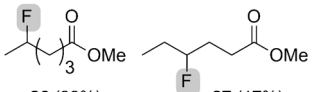
Scheme 1. Proposed catalytic cycle for the TBADT/NFSI fluorination of unactivated C(sp^3)–H bonds.

fluorine-transfer capacity of NFSI. Thus, photoexcitation of the decatungstate anion ($W_{10}O_{32}^{4-}$) produces a short-lived excited state[28] which rapidly decays to a long-lived reactive intermediate (denoted W*)[28,29] capable of hydrogen atom abstraction, thus producing $W_{10}O_{32}^{5-}H^+$. Fluorine atom transfer from NFSI to the coincident carbon-centered radical (or a single-electron transfer from the radical species to NFSI to generate a carbocation, followed by fluoride transfer[16]) provides the fluorinated product. This proposal is further supported by the fact that reaction of bornyl acetate (Table 1, entry 7) in the presence of the radical scavenger TEMPO provided no fluorinated products. Bearing in mind the size and charge of the decatungstate catalyst, the selectivity observed in the C–H fluorination of bornyl acetate is consistent with the avoidance of sterically congested C–H bonds and destabilizing electrostatic interactions.

Having demonstrated the direct C–H fluorination of bornyl acetate using the photocatalytic TBADT/NFSI system, without further optimization we explored the scope of this reaction through the fluorination of several small organic molecules, all of which possess multiple unactivated C(sp^3)–H bonds (Table 2).[30] In general, the TBADT/NFSI fluorination reaction is functional-group tolerant, and aliphatic ketones, esters, and lactones were all selectively fluorinated. The fluorination of camphor (entry 1) is notable as this substrate was incompatible with the fluorination process reported by Groves and co-workers,[12] and 6-fluoroisocamphanone (**6**), presumably from the rearrangement of a cation generated following hydrogen abstraction from C6 of camphor and SET to NFSI,[16] was also produced in this reaction. In line with observations summarized above, examination of the products

Table 2: Scope of photocatalytic fluorination.

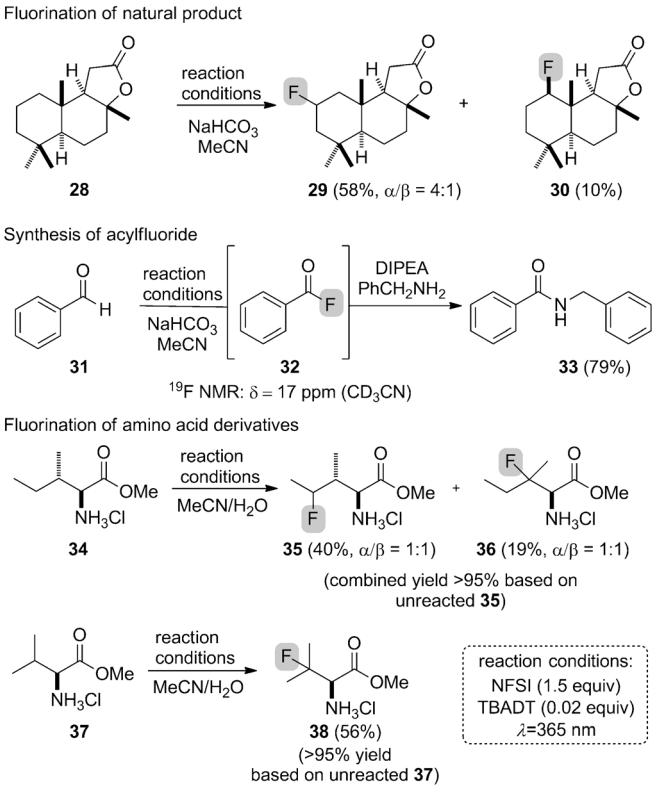


Entry	Substrate	Major product(s)[a]	Yield [%][b]
1	 **4**	 **5** (17%, β:α = 2:1) **6** (14%)	48
2	 **7**	 **8** (14%)[c]	30
3	 **9**	 **10** (13%)[c] **11** (15%, β:α = 2.4:1)[c]	43
4	 **12**	 **13** (20%)[c] **14** (20%)[c]	53
5	 **15**	 **16** (32%) **17** (18%)	50
6	 **18**	 **19** (45%)	75
7	 **20**	 **21** (34%) **22** (8%)	70
8	 **23**	 **24** (40%)	49
9	 **25**	 **26** (33%) **27** (17%)	51

[a] Yields are given within parentheses, and unless otherwise indicated, were calculated from a ^{1}H NMR spectrum recorded on the crude reaction mixture by using an internal standard. [b] Yield based on unreacted starting material; combined yield where two products are depicted. [c] Yield of isolated product.

depicted in Table 2 highlights the selectivity for fluorination at sterically accessible branched methines or methylenes which are also remote from electron-withdrawing groups. The inductive influence of electron-withdrawing groups on the selectivity of fluorination is further exemplified in the reactions of camphor (**4**, entry 1), the corresponding lactone **7** (entry 2), and bornyl acetate (**1**; Table 1), all of which fluorinate at positions most remote from carbonyl or O carboxy functions. Additionally, no difluoro compounds were detected in any of these reactions. These electronic-gearing factors are also evidenced in the monofluorination of menthyl acetate (**9**, entry 3), and occurs equally at the most sterically accessible methine and the methylene most remote from the acetoxy group. Further studies on saturated esters were consistent with these results. Thus, fluorination of ethyl isovalerate (**18**), methyl valerate (**20**), and methyl 4-methylvalerate (**23**; entries 6–8), occurred predominantly at the methylene or methine position most remote from the carboxylic ester functionality. However, further increasing the chain length resulted in a decreased selectivity, and fluorination of methyl hexanoate (**25**) provided an approximate 2:1 mixture of the C5 and C4 fluorinated esters **26** and **27** (entry 9), respectively. Notably, the conversion in fluorination reactions of linear esters was much improved by the addition of water, however, the overall yields were compromised by concomitant hydrolysis and formation of the corresponding fluoroacids.

To compare the present catalyst system with that reported by Groves,[12] the fluorination of sclareolide (**28**) was also investigated. As depicted in Scheme 2, the TBADT/NFSI system is highly efficient for fluorination of sclareolide and both catalyst/reagent systems are similar in producing (2*S*)-2-fluorosclareolide (**29**) as the major product. Considering the relatively low BDE for acylhydrides (CO-H BDE ≈ 89 kcal



Scheme 2. Site-selective fluorination of sclareolide, benzaldehyde, and amino acid derivatives. The yields for **35**, **36**, and **38** are calculated from ^{1}H NMR spectra recorded on crude reaction mixtures with the addition of an internal standard.

mol^{-1}),[31] we also explored the direct conversion of aldehydes into acylfluorides, which are a relatively stable but underutilized class of acyl halide. By employing the optimized reaction conditions, benzaldehyde (**31**) was converted into benzoylfluoride (**32**), and subsequently transformed directly into *N*-benzylbenzamide (**33**) by reaction with benzylamine. The facile conversion of an aldehyde directly into an acyl fluoride is a rare example of this potentially useful reaction, which was previously limited to strongly electrophilic fluorinating reagents (e.g., BrF_3,[32] $CsSO_4F$[33]).

Considering the value of fluorinated amino acids to drug discovery[34] and their potential utility in PET imaging,[35] we examined the fluorination of the methyl esters derived from valine and isoleucine. While irradiation of the free base of valine methyl ester with TBADT/NFSI provided none of the desired product, we were delighted to find that after 17 h, reaction of the corresponding hydrochloride salt **37** proceeded smoothly to afford 3-fluorovaline (**38**). In this case, the reaction was necessarily carried out in a mixture of MeCN/H_2O (2:1) to ensure solubility of all reagents. Likewise, overnight irradiation of a solution of the hydrochloride salt of isoleucine methyl ester with TBADT/NFSI resulted in the formation of a diastereomeric mixture of 4-fluoro isoleucine derivatives **35** along with a small amount of the 3-fluoro amino ester **36**.

In summary, exploiting the hydrogen abstraction capability of a readily prepared and inexpensive decatungstate photocatalyst in combination with the fluorine-transfer agent NFSI, we have developed a convenient method for the fluorination of unactivated C(sp^3)–H bonds. This new process provides direct access to a variety of fluorinated organics, including natural products, acyl fluorides, and fluorinated amino acid derivatives, many of which would otherwise be inaccessible or require multistep reaction sequences. Considering the steric and electronic bias of hydrogen atom abstraction by the photoexcited decatungstate, an important aspect of this reaction system is its ability to fluorinate C–H bonds prone to oxidative metabolism, a potentially enabling capability for medicinal chemistry. Additionally, fluorination of other amino acid derivatives or indeed small peptides with [^{18}F]NFSI may well provide new radiotracers for PET imaging or improved procedures for preparing existing imaging agents.

Received: January 14, 2014
Published online: ■■ ■■, ■■■■

Keywords: amino acids · C–H activation · photochemistry · polyoxometalates · tungsten

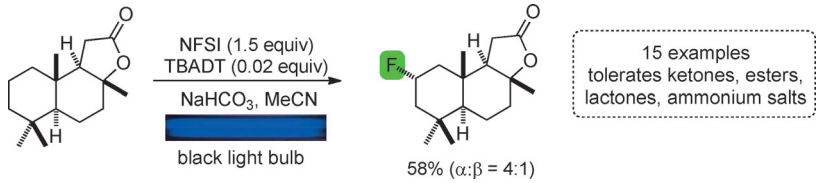
[1] W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359 – 4369.
[2] K. L. Kirk, *Org. Process Res. Dev.* **2008**, *12*, 305 – 321.
[3] S. M. Ametamey, M. Honer, P. A. Schubiger, *Chem. Rev.* **2008**, *108*, 1501 – 1516.
[4] D. O'Hagan, *J. Fluorine Chem.* **2010**, *131*, 1071 – 1081.
[5] J. Fried, E. F. Sabo, *J. Am. Chem. Soc.* **1954**, *76*, 1455 – 1456.
[6] T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem.* **2013**, *125*, 8372 – 8423; *Angew. Chem. Int. Ed.* **2013**, *52*, 8214 – 8264.
[7] T. Barker, D. L. Boger, *J. Am. Chem. Soc.* **2012**, *134*, 13588 – 13591.
[8] D. A. Watson, M. Su, G. Teverovskiy, Y. Zhang, J. Garcia-Fortanet, T. Kinzel, S. L. Buchwald, *Science* **2009**, *325*, 1661 – 1664.
[9] E. Lee, A. S. Kamlet, D. C. Powers, C. N. Neumann, G. B. Boursalian, T. Furuya, D. C. Choi, J. M. Hooker, T. Ritter, *Science* **2011**, *334*, 639 – 642.
[10] M.-G. Braun, A. G. Doyle, *J. Am. Chem. Soc.* **2013**, *135*, 12990 – 12993.
[11] J.-B. Xia, C. Zhu, C. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 17494 – 17500.
[12] W. Liu, X. Huang, M.-J. Cheng, R. J. Nielson, W. A. Goddard III, J. T. Groves, *Science* **2012**, *337*, 1322 – 1325.
[13] S. Bloom, C. R. Pitts, D. Curtin Miller, N. Haselton, M. G. Holl, E. Urheim, T. Lectka, *Angew. Chem.* **2012**, *124*, 10732 – 10735; *Angew. Chem. Int. Ed.* **2012**, *51*, 10580 – 10583.
[14] Y. Amaoka, M. Nagatomo, M. Inoue, *Org. Lett.* **2013**, *15*, 2160 – 2163.
[15] R. D. Chambers, M. Parsons, G. Sandford, R. Bowyden, *Chem. Commun.* **2000**, 959 – 960.
[16] M. Rueda-Becerril, C. C. Sazepin, J. C. T. Leung, T. Okbinoglu, P. Kennepohl, J.-F. Paquin, G. M. Sammis, *J. Am. Chem. Soc.* **2012**, *134*, 4026 – 4029.
[17] J. C. T. Leung, C. Chatalova-Sazepin, J. G. West, M. Rueda-Becerril, J.-F. Paquin, G. M. Sammis, *Angew. Chem.* **2012**, *124*, 10962 – 10965; *Angew. Chem. Int. Ed.* **2012**, *51*, 10804 – 10807.
[18] H. Teare, E. G. Robins, E. Arstad, S. K. Luthra, V. Gouverneur, *Chem. Commun.* **2007**, 2330 – 2332.
[19] C. L. Hill, *J. Mol. Catal. A* **2007**, *262*, 2 – 6.
[20] M. D. Tzirakis, I. N. Lykakis, M. Orfanopoulos, *Chem. Soc. Rev.* **2009**, *38*, 2609 – 2621.
[21] C. L. Hill, *Synlett* **1995**, 127 – 132.
[22] C. Tanielian, *Coord. Chem. Rev.* **1998**, *178 – 180*, 1165 – 1181.
[23] S. Protti, D. Ravelli, M. Fagnoni, A. Albini, *Chem. Commun.* **2009**, 7351 – 7353.
[24] I. N. Lykakis, C. Tanielian, R. Seghrouchni, M. Orfanopoulos, *J. Mol. Catal. A* **2007**, *262*, 176 – 184.
[25] L. A. Combs-Walker, C. L. Hill, *J. Am. Chem. Soc.* **1992**, *114*, 938 – 946.
[26] B. S. Jaynes, C. L. Hill, *J. Am. Chem. Soc.* **1995**, *117*, 4704 – 4705.
[27] R. F. Renneke, M. Pasquali, C. L. Hill, *J. Am. Chem. Soc.* **1990**, *112*, 6585 – 6594.
[28] D. C. Duncan, T. L. Netzel, C. L. Hill, *Inorg. Chem.* **1995**, *34*, 4640 – 4646.
[29] D. Dondi, M. Fagnoni, A. Albini, *Chem. Eur. J.* **2006**, *12*, 4153 – 4163.
[30] Typical experimental procedure (fluorination of (−)-bornyl acetate): TBADT (0.02 equiv), NFSI (113 mg, 1.2 equiv), and $NaHCO_3$ (3 mg, 0.1 equiv) were added to a 2 M solution of (−)-bornyl acetate (59 mg, 0.3 mmol) in acetonitrile (0.15 mL). The resulting suspension was sparged with N_2 for 5 min. The reaction vessel was then sealed, and the mixture was stirred while being irradiated between two 15 Watt UVB-BLB lamps (centered at $\lambda = 365$ nm) at room temperature for 17 h. After work-up and purification (see the Supporting Information), the major fluorinated isomer **2** was obtained as a colorless oil (26 mg, 40%).
[31] D. Ravelli, M. Zema, M. Mella, M. Fagnoni, A. Albini, *Org. Biomol. Chem.* **2010**, *8*, 4158 – 4164.
[32] M. Ochiai, A. Yoshimura, M. M. Hoque, T. Okubo, M. Saito, K. Miyamoto, *Org. Lett.* **2011**, *13*, 5568 – 5571.
[33] S. Stavber, Z. Planinsek, M. Zupan, *J. Org. Chem.* **1992**, *57*, 5334 – 5337.
[34] X.-L. Qui, F.-L. Qing, *Eur. J. Org. Chem.* **2011**, 3261 – 3278.
[35] P. Laverman, O. C. Boerman, F. H. M. Corstens, W. J. G. Oyen, *Eur. J. Nucl. Med.* **2002**, *29*, 681 – 690.

Communications

C–H Activation

S. D. Halperin, H. Fan, S. Chang, R. E. Martin, R. Britton* ____ ■■■■–■■■■

A Convenient Photocatalytic Fluorination of Unactivated C–H Bonds



The direct fluorination of unactivated C(sp^3)–H bonds is catalyzed by the inexpensive photocatalyst tetrabutylammonium decatungstate (TBADT). This convenient reaction provides direct access to a wide range of fluorinated organic molecules, including structurally complex natural products, acyl fluorides, and fluorinated amino acids.