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Direct Photocatalytic Fluorination of Benzylic C-H Bonds with *N*-Fluorobenzenesulfonimide

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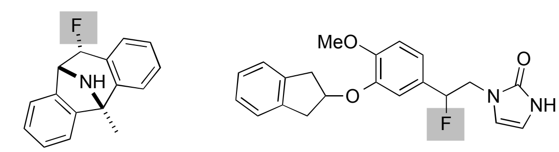
The late-stage fluorination of common synthetic building blocks and drug leads is an appealing reaction for medicinal chemistry. In particular, fluorination of benzylic C-H bonds provides a means to attenuate drug metabolism at this metabolically labile position. Here we report two complimentary strategies for the direct fluorination of benzylic C-H bonds using *N*-fluorobenzenesulfonimide and either a decatungstate photocatalyst or AIBN-initiation.

The incorporation of one or more fluorine atoms into a small molecule is of great interest to medicinal chemistry.[1] For example, replacement of a hydroxyl group or hydrogen atom with a fluorine is a common tactic used to improve metabolic stability, cell permeability, or ligand-target interactions (Figure 1).[2] Consequently, fluorine is present in a large and growing number of approved drugs.[3] Owing to the unfavorable properties of F_2 gas, however, the wide spread incorporation of organofluorines in medicinal chemistry campaigns has relied on the development of electrophilic and nucleophilic fluorination reagents and reactions.[4] To compliment these processes, there has recently been considerable interest in the direct fluorination of unactivated C-H bonds.[5,6] Such late-stage fluorination strategies are especially attractive to drug discovery programs, where the direct fluorination of metabolically labile C-H bonds would obviate extensive re-synthesis campaigns. In particular, the fluorination of benzylic C-H[7-11] bonds provides a means to attenuate metabolic degradation at these so-called "hot spots".[12]

Recently, Lectka described the mechanism of C-H fluorination with Selectfluor[13] and proposed that fluorine transfer from Selectfluor (BDE_{NF} ~260 kJ/mol[14a]) to a carbon radical generates a cationic nitrogen-centered radical that is



1: NMDA antagonist[15]
fluorination improves potency and log P

2: phosphodiesterase-4 inhibitor[16]
10 fold improvement in potency vs alcohol

Figure 1. Beneficial properties of benzylfluorides in lead optimization

responsible for hydrogen abstraction. Curiously, the related fluorine transfer reagent[14] *N*-fluorobenzenesulfonimide (**7**) (NFSI, BDE_{NF} ~267 kJ/mol)[14a] was unable to propagate aliphatic C-H fluorination. Moreover, among the growing number of C-H fluorination reactions, few are operative[7,9,11d] and only our recently reported decatungstate-catalyzed C-H fluorination[17] is optimal with NFSI. This unique photocatalytic fluorination reaction presumably involves C-H abstraction by the photoexcited decatungstate[18] followed by fluorine transfer[14] from NFSI (**7**) (see inset, Scheme 1). Here, we describe the development of a complimentary benzylic C-H fluorination reaction using decatungstate photocatalysis. Moreover, we demonstrate that NFSI is capable of propagating the radical fluorination of benzylic C-H bonds and that benzylic fluorination with NFSI can be initiated by AIBN. Notably, these unique NFSI-based C-H fluorination reactions provide differing selectivities in the fluorination of substrates with multiple benzylic C-H bonds, and thus provide new opportunities for site-specific fluorination.

As depicted in Scheme 1, we first investigated the fluorination of ethyl benzene (**10**) and the *p*-acetoxy derivative **11** using conditions developed previously by us for aliphatic C-H fluorinations.[17] We were surprised that a major product of both reactions were the acetamides **12** and **13**. While decatungstate oxidation of an intermediate benzylic radical to

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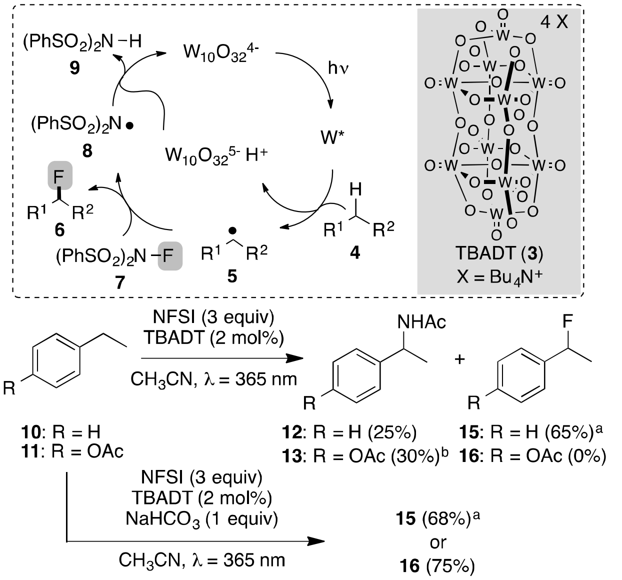


Scheme 1. Decatungstate-catalyzed fluorination of unactivated C-H bonds and the fluorination of ethyl benzenes **10** and **11**. [a] Yield of the volatile benzyl fluoride **15** based on analysis of ^{1}H NMR spectra with internal standard. [b] Accompanied by 42% recovered **11**.

a carbocation[19] followed by reaction with acetonitrile would explain the formation of these Ritter-type products, Brønsted acid activation[20] of initially formed benzylic C-F bonds by dibenzenesulfonamide (**9**, NHSI) may also be operative. Thus, we evaluated the effect of various bases as additives to the fluorination of **10**. Unsurprisingly, soluble amine bases such as pyridine and Et_3N were not compatible with this process, neither were a small collection of inorganic bases (e.g., Cs_2CO_3, Na_2CO_3, K_2CO_3, LiOH). Fortunately, when either $NaHCO_3$ or Li_2CO_3 was added to the reaction mixture the desired benzyl fluoride **15** was formed as the exclusive product in good yield. Likewise, employing these reaction conditions with the ethyl benzene **11**, the fluoroethyl benzene **16** was produced in 75% yield. To gain further insight into the formation of acetamides **12** and **13**, the benzyl fluorides **15** and **16** were treated independently with a catalytic amount of NHSI (**9**) in CH_3CN, which led to mixtures containing predominantly the acetamides **12** and **13** at temperatures as low as 35 °C. When these reactions were repeated without NHSI, the benzyl fluorides were recovered unreacted. This NHSI-promoted fluoride substitution reaction represents a unique example of Brønsted acid catalyzed C-F activation and may prove itself to be a useful transformation with further examination.

In order to gain insight into the scope of the decatungstate-catalyzed benzylic C-H fluorination reaction, we evaluated its effectiveness on a range of substrates with differing electronic and steric features. As summarized in Figure 2 (conditions A), we were pleased to find that this reaction is general and cleanly provides a range of benzyl fluorides **17**-**30** in modest to

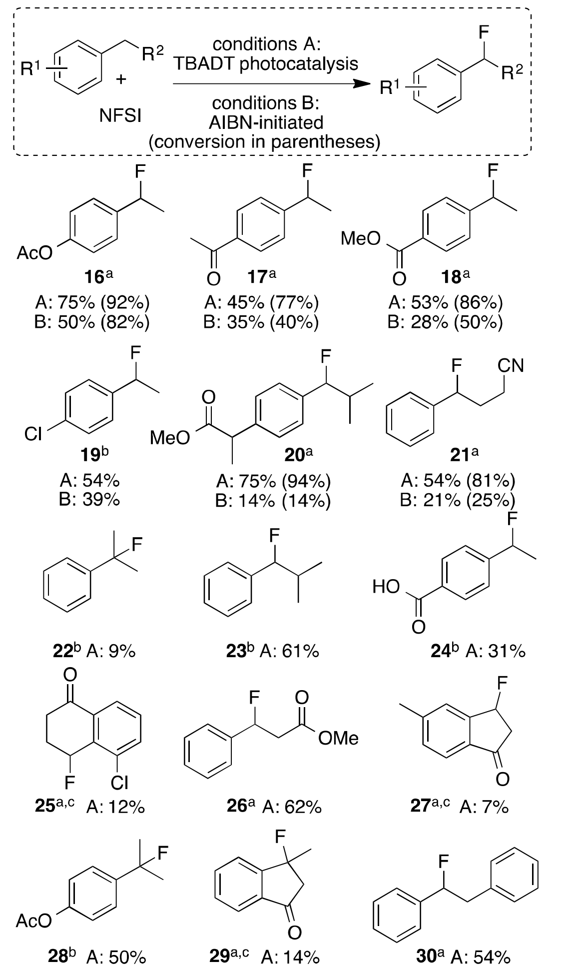
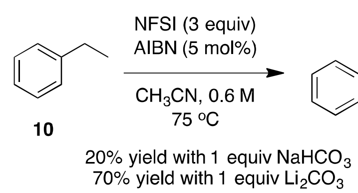


Figure 2. Decatungstate-catalyzed and AIBN-initiated fluorination of benzylic C-H bonds. Conditions A: NFSI (3 equiv), TBADT (2 mol%), CH_3CN (0.6 M), $NaHCO_3$ (1 equiv), 365 nm lamp, 16-48 h. Conditions B: NFSI (3.0 equiv), AIBN (5 mol%), CH_3CN (0.6 M), Li_2CO_3 (1 equiv), 75 °C, 16 h. [a] Isolated yield. [b] Yield based on analysis of ^{1}H NMR spectra recorded on the crude reaction mixture with an internal standard. [c] Accompanied by the isomeric α-fluoroketone.

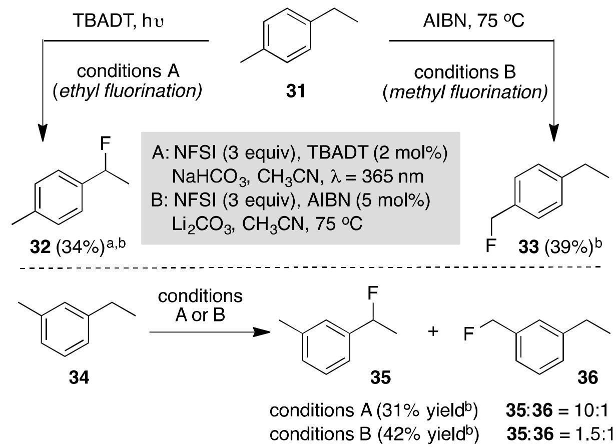
good yield. It is notable that the discrepancies between conversion (in parentheses) and isolated yields reflect the difficulty in isolating and separating the benzyl fluoride products from the parent hydrocarbon, a challenge common to late-stage C-H fluorination strategies.[21] Importantly, both electron rich (e.g., **16** and **28**) and electron poor (e.g., **17**-**19**) alkylbenzenes are competent substrates for this reaction. The fluorination of isobutylbenzenes proceeded smoothly (e.g., **20** and **23**), however, more sterically encumbered isopropyl benzenes proved difficult to fluorinate (e.g., **22**) and proceeded in modest yield only with the electron rich *p*-acetoxy derivative. In this later case, the desired fluoroisopropyl adduct **28** was produced in 50% yield. In all cases, deoxygenation of the acetonitrile solvent was critical to avoid competing decatungstate-catalyzed benzylic oxidation.[19a] In contrast to all other benzylic C-H fluorination reactions,[7-11] replacing NFSI with Selectfluor resulted in significantly lower yields. Interestingly, despite the necessary addition of base to these reactions (*vide supra*), benzylic C-H fluorination is competitive with α-fluorination of ketone-containing substrates, and provides access to the unusual γ-fluorotetralone **25** and β-fluoroindanones **27** and **29**.

In an effort to gain further insight into the mechanism of decatungstate-catalyzed benzylic fluorination, we examined the fluorination of ethyl benzene (i.e., **10** $\rightarrow$ **15**, Scheme 1) without the photocatalyst and observed no formation of the benzylfluoride **15** (with or without irradiation or heating). However, when a catalytic amount of the radical initiator AIBN was added and the reaction mixture was heated (75 °C), we observed clean conversion to the benzylfluoride **15**, albeit in modest yield (~20%, eq 1). We were able to improve the yield of this AIBN-initiated reaction to 70% by simply replacing $NaHCO_3$ with Li_2CO_3. This dramatic base effect may be understood by considering that $NaHCO_3$ slowly decomposes to Na_2CO_3[22] at the elevated temperatures required for the AIBN-initiated reaction, and that Na_2CO_3 is incompatible with the NFSI fluorination reaction (*vide supra*). It is notable that several aliphatic substrates failed to fluorinate using these reaction conditions (i.e., AIBN, NFSI, Li_2CO_3) suggesting that unlike Selectfluor,[11,13] NFSI is only capable of propagating the radical fluorination of relatively weak C-H bonds (BDE_{CH} benzylic ~377 kJ/mol). As summarized in Figure 2 (conditions B), these reaction conditions proved to be less optimal and general than the decatungstate-catalyzed fluorination (conditions A), and several substrates containing benzylic C-H bonds failed to provide any fluorinated products (e.g., **22**-**24**).



(eq 1)

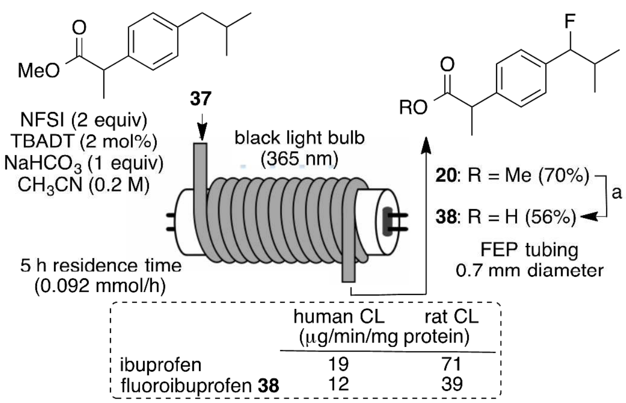
During our examination of both the decatungstate-catalyzed and AIBN-initiated fluorination reactions, we evaluated the fluorination of *p*-ethyl toluene (**31**) (Scheme 2). Surprisingly, the decatungstate-catalyzed reaction selectively fluorinated the ethyl group in **31**, while the AIBN-initiated fluorination provided the fluoromethyl product **33** exclusively. A similar trend was observed in the fluorination of *m*-ethyltoluene (**34**). Ni has reported analogous selectivity in the amination of *p*-ethyltoluene with NFSI, and suggested a preference for hydrogen abstraction from the methyl group in **31** based on steric considerations.[23] In the present case, it is important to note that NFSI is not completely dissolved in the decatungstate-catalyzed reactions at room temperature but is fully solublilized at 75 °C in the AIBN-initiated reactions. Thus, we speculated that the unique fluorination selectivities may in fact result from a higher concentration of NFSI in the heated reactions and the consequent trapping of an initially formed methyl radical. Conversely, at lower concentrations of NFSI (decatungstate-catalyzed reaction), equilibration between benzylic radicals[24] may be responsible for the preferred formation of the fluoroethyl products **32** and **35**. To probe this hypothesis, the AIBN-initiated fluorination of **31** (conditions B) was repeated with decreasing amounts of NFSI to assess the effect of NFSI concentration. When substoichiometric amounts (0.5 equiv) of NFSI were added to this reaction, the fluoroethyl product **32** was also observed as a minor product (**33**:**32** = 1.4:1). This result indicates that the equilibration of benzylic radicals is likely responsible for the differing selectivities in the fluorination of ethyl toluenes, and provides a useful tool for imparting or attenuating selectivity in the fluorination of substrates with multiple benzylic C-H bonds.



Scheme 3. Differing selectivities in the fluorination of ethyltoluenes using AIBN-initiated or decatungstate-catalyzed processes. [a] Accompanied by 7% of **33**. [b] Yield based on analysis of ^{1}H NMR spectra with internal standard.

Finally, in an effort to decrease the reaction time for the decatungstate-catalyzed fluorination, we examined the fluorination of ibuprofen methyl ester (**37**) in flow.[10,25] As depicted in Scheme 3, irradiation of the reaction mixture in FEP tubing (3 m length, 1.4 mL total volume) wrapped around a blacklight blue lamp (BLB lamp, λ = 365 nm) reduced the reaction time from 24 h (batch) to 5 h (flow) without impacting the yield. Considering the potential importance of late-stage fluorination to medicinal chemistry we were also interested in gauging the effect of benzylic fluorination on basic pharmacokinetic properties of ibuprofen. Thus, the ester **20** was hydrolyzed to afford the fluoroibuprofen **38**. Not surprisingly, fluorination of ibuprofen resulted in a modest decrease in pKa (from 4.35 (ibuprofen) to 4.23 (**38**)). Fluorination of ibuprofen also slightly improved metabolic stability in both human and rat microsomes, leading to a decrease in clearance from 19 to 12 µg/min/mg protein in human microsomes and 71 to 39 µg/min/mg protein in rat microsomes.

In summary, we have developed two complimentary methods for benzylic fluorination that rely on the fluorine transfer agent NFSI in combination with either a decatungstate photocatalyst or radical initiator (AIBN). These processes tolerate a range of functional groups in providing benzyl fluorides in modest to excellent yield. Furthermore, the photocatalyic fluorination can be adapted to continuous flow without compromising yield.[26] That this process is uniquely effective with NFSI and not Selectfluor differentiates it from existing and complimentary benzylic fluorination strategies and provides new opportunities for late stage fluorination in drug discovery.



Scheme 3. Photochemical fluorination of ibuprofen methyl ester (**37**) in flow, and synthesis of fluoroibuprofen **38**. a) LiOH, MeOH, THF, H_2O, 24 h

Notes and references

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26 TBADT-catalyzed fluorination of 4-ethylphenyl acetate and 4-ethylacetophenone in continuous flow provided the corresponding benzyl fluorides **16** (66%, 2h) and **17** (34%, 16h) in yields similar to those achieved in batch reactions (see Figure 2).