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Synthesis of acyl fluorides *via* photocatalytic fluorination of aldehydic C–H bonds†

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Acyl fluorides are versatile acylating agents owing to their unique stability. Their synthesis, however, can present challenges and is typically accomplished through deoxyfluorination of carboxylic acids. Here, we demonstrate that acyl fluorides can be prepared directly from aldehydes *via* a C(sp^2)–H fluorination reaction involving the inexpensive photocatalyst sodium decatungstate and electrophilic fluorinating agent *N*-fluorobenzenesulfonimide. This convenient fluorination strategy enables direct conversion of aliphatic and aromatic aldehydes into acylating agents.

Late-stage C–H halogenation has become an enabling tool with a wide range of applications relevant to both natural product synthesis[1] and medicinal chemistry.[2] In particular, C–H fluorination reactions provide unique opportunities to optimize the physicochemical properties and metabolic stability of drug leads[3] or access ^{18}F radiotracers for positron emission tomography (PET) imaging.[3a,4] Among the many C(sp^3)–H fluorination strategies,[4] a growing family of late-stage transformations involve the generation of a carbon-centered radical followed by fluorine atom transfer from reagents such as *N*-fluorobenzenesulfonimide (NFSI) or Selectfluor, a process first demonstrated by Paquin and Sammis.[5] For example, Lectka,[6a] Tan,[6b] and others[7] have described both aliphatic[6] and benzylic[7] C(sp^3)–H fluorination reactions using Selectfluor as the fluorine atom source. In addition, we have reported the decatungstate-catalyzed[8] fluorination of both aliphatic[9a,9b] and benzylic[9c] C(sp^3)–H bonds by exploiting the fluorine atom transfer capacity of NFSI. In a single example, we also demonstrated the utility of this system for the fluorination of aldehydic C(sp^2)–H bonds[10] in the conversion of benzaldehyde into benzoyl fluoride.[9a]

While the conversion of aldehydes into acyl fluorides has been described,[11] the typically harsh reaction conditions (*e.g.*, $CsSO_4F$,[11a] UF_6,[11b] difluoro(aryl)-λ^3-bromane,[11e] F_2 gas[11d,11f]) have limited the widespread adoption of these strategies. As a notable exception, Banks and Lawrence reported that refluxing a solution of 4-chlorobenzaldehyde and Selectfluor in MeCN afforded the corresponding acyl fluoride after 70 hours.[11c] In general, however, acyl fluorides are prepared *via* nucleophilic addition to activated carboxylic acids (deoxyfluorination)[12] or through halide exchange reactions with acyl chlorides (Fig. 1).[13] Importantly, some acyl fluorides are stable to chromatographic purification and thus represent attractive alternatives to acid chlorides or anhydrides for the preparation of amides,[14] esters,[15] and thioesters.[15] Moreover, acyl fluorides are the smallest acyl transfer group, providing certain advantages in systems where traditional coupling strategies are unsuccessful.[16] Finally, while acyl fluorides are generally reacted in organic solvents,[17] their stability in water has inspired investigations of their use as electrophilic tags for bioconjugation.[18] Here, we describe the optimization and scope of a direct aldehyde C(sp^2)–H fluorination and contrast the stability of benzoyl fluoride to a sulfonyl fluoride, a commonly used functional group for bioconjugation studies.

Previously, we have reported that photoactivated tetra-*n*-butylammonium decatungstate (TBADT) catalyzes the conversion of

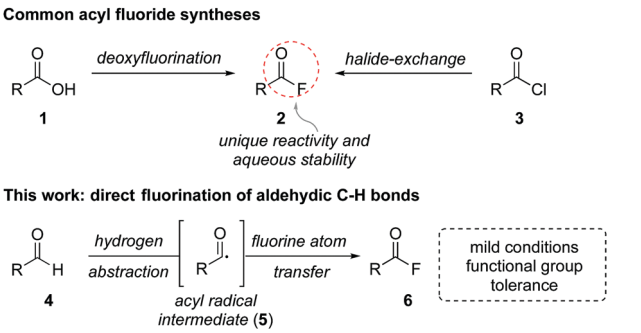

Fig. 1 Synthesis of acyl fluorides from carboxylic acids and the direct conversion of aldehydes to acyl fluorides *via* acyl radical intermediates.

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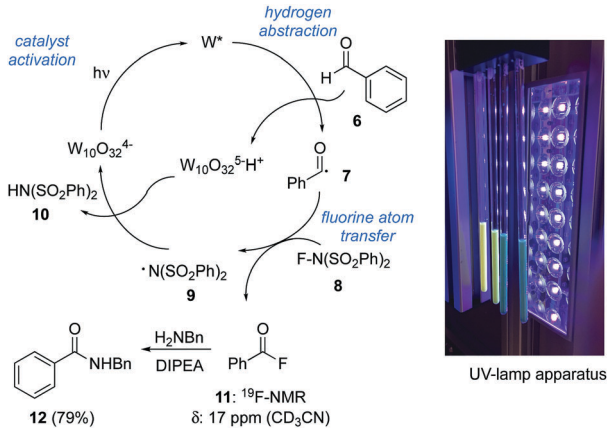


Scheme 1 NaDT-catalyzed C(sp^2)–H fluorination of benzaldehyde.

benzaldehyde into benzoyl fluoride under UV irradiation (λ = 365 nm) in the presence of NFSI (Scheme 1).[9a] Here, fluorine atom transfer[5] from NFSI to the intermediate acyl radical 7 generated from C–H abstraction by photoactivated decatungstate (W*)[8] provides a direct route to benzoyl fluoride (**11**). While the crude acyl fluoride could be characterized by a diagnostic resonance (δ = 17 ppm, CD_3CN) in the ^{19}F NMR spectrum, it was directly reacted with benzylamine to provide *N*-benzylbenzamide (**12**) in good yield (Table 1, entry 1).[9a] It is notable that Fagnoni[8b,8d] and Orfanopoulos[8c] have also exploited decatungstate catalysis in the generation of acyl radicals for the purpose of C–C bond formation. Our interest in further exploring this route to acyl fluorides prompted us to reexamine this reaction. As summarized in Table 1, sodium decatungstate (NaDT)[8h] proved equally efficient (entry 2) for the formation of benzoyl fluoride, while the addition of $NaHCO_3$ (entry 3) or other additives commonly used in decatungstate-catalyzed C–H fluorination reactions[9] failed to further improve the yield of **11**. The use of radical initiators under thermal conditions (*e.g.*, AIBN or ^{t}BuOOH, entries 4 and 5) resulted in markedly decreased yields of **11**. In the interest of exploring other bench stable fluorinating reagents capable of radical chain propagation, we also examined the use of XeF_2[19] alone, which afforded benzoyl fluoride (**11**) albeit in a modest yield of 38% (entry 6). Considering radical chain propagation is operative in the fluorination of benzaldehyde

Table 1 Conversion of benzaldehyde into benzoylfluoride

Entry	Catalyst or initiator	Additive	Fluorine source	Yield[a] (%)
1[b]	TBADT	—	NFSI	79
2[b]	NaDT	—	NFSI	79
3[b]	NaDT	$NaHCO_3$	NFSI	78
4[c]	AIBN	—	NFSI	<2
5[d]	^{t}BuOOH	—	NFSI	10
6[e]	—	—	XeF_2	38
7[f]	—	—	NFSI	<2

[a] Yields determined using quantitative ^{19}F NMR spectroscopic analysis and 1,3,5-tris(trifluoro)methylbenzene (TTMB) as an internal standard. [b] NFSI (1.1 equiv.), decatungstate salt (2 mol%), CH_3CN, 365 nm LED lamp, 2 h. [c] NFSI (1.1 equiv.), AIBN (20 mol%), CH_3CN, 80 °C. [d] NFSI (1.1 equiv.), ^{t}BuOOH (4 equiv.), CH_3CN, 80 °C. [e] XeF_2 (1 equiv.), CH_3CN. [f] NFSI (1.1 equiv.), CH_3CN, 365 nm lamp or 80 °C, 2 h.

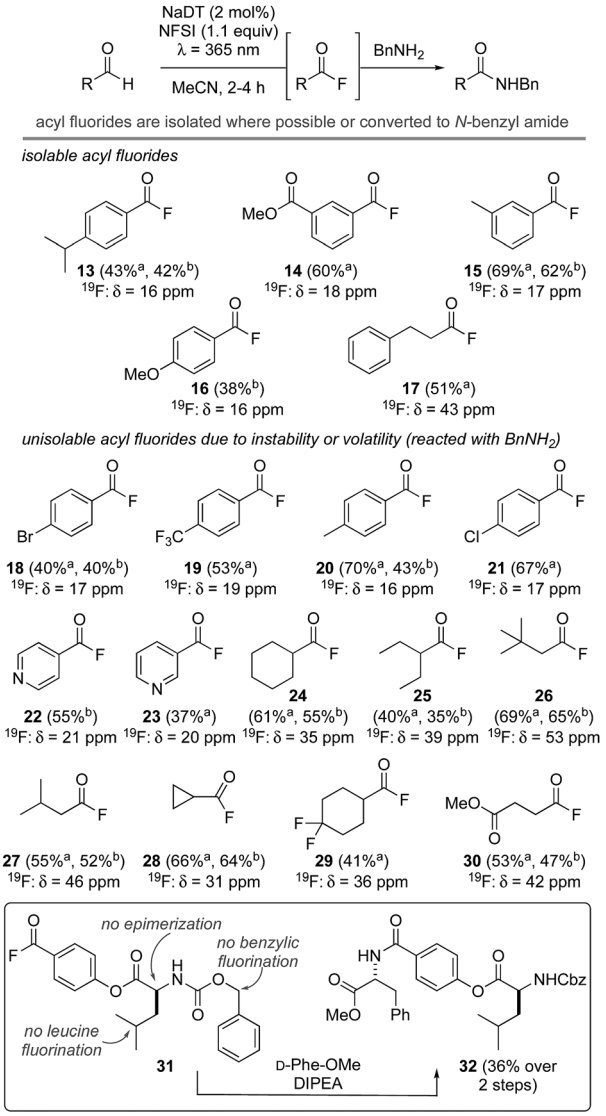


Fig. 2 Synthesis of (hetero)aromatic and aliphatic acyl fluorides. [a] Yields of acyl fluorides determined using quantitative ^{19}F NMR and 1,3,5-tris(trifluoro)-methylbenzene (TTMB) as an internal standard; [b] isolated yield of *N*-benzyl amide over two steps from aldehyde.

with Selectfluor,[11c] we examined the equivalent fluorination using NFSI alone. As highlighted in entry 7, without the photocatalyst NaDT no benzoyl fluoride was observed under UV-irradiation or thermal conditions (80 °C). These results indicate that the NFSI-derived nitrogen-centered radical **9** (Scheme 1) is incapable of chain propagation[9c] in the fluorination of aldehydes, and that decatungstate catalysis plays a key role in this process.

As depicted in Fig. 2, we further examined the conversion of a collection of aliphatic and aromatic aldehydes into acyl fluorides. Surprisingly, in only a small number of cases were we able to isolate and purify the acyl fluoride by flash column chromatography. While the isolation of acyl fluorides **13–17** highlight the unique stability of these acyl halides, the majority of acyl fluorides decomposed during isolation and/or purification, or proved challenging to isolate owing to their volatility. Instead, the

crude acyl fluorides were characterized by ^{19}F NMR spectroscopy then directly converted into amides by reaction with benzylamine (see ESI† for details). Following this strategy, variously substituted benzaldehydes could be directly transformed into acyl fluorides **13–16** and **18–21**. Likewise, several aliphatic aldehydes were directly converted into the corresponding acyl fluorides including the unusual cyclopropanecarbonyl fluoride **28**. Interestingly, here the major product **28** derives from trapping of the acyl radical intermediate with NFSI rather than fragmentation.[20] It is notable that the generation of acyl radicals from aliphatic aldehydes is often accompanied by varying amounts of decarbonylation.[8b] Consequently, the acyl fluorides **24** and **29** were produced along with small amounts (<10%) of the corresponding decarbonylative fluorination products (*i.e.*, aliphatic fluorides), while production of the acyl fluoride **25** was accompanied by 24% of 3-fluoropentane. Given that we have previously described the decatungstate catalyzed fluorination of aliphatic C(sp^3)–H bonds, we were pleased to observe no off-site fluorination of aliphatic aldehydes[9a,b] and no competing benzylic fluorination[9c] or aldehyde α-fluorination in any of the aldehydes explored. Unsurprisingly, the general incompatibility of NFSI with nitrogen nucleophiles[21] complicated fluorination of heteroaryl aldehydes (*e.g.*, indole, pyrimidine, imidazole, indazole), however, the pyridine-containing acyl fluorides **22** and **23** could be accessed in modest yield using this process. Finally, we explored fluorination of an *N*-Cbz leucine-containing benzaldehyde ester. While we have previously reported rapid fluorination of leucine at the branched position,[9b] we observed no leucine fluorination or other off-site fluorination (*e.g.*, benzylic), and clean conversion to the corresponding acyl fluoride **31**, which was subsequently reacted with phenyl alanine methyl ester to afford the amide **32**. Overall, these mild reaction conditions represent a convenient alternative to existing strategies for aldehyde fluorination that rely on strong oxidants such as F_2 gas[11f] or the highly electrophilic fluorinating reagents BrF_3[11i] and $CsSO_4F$.[11a]

Orfanopoulous[22] has previously demonstrated that photoactivated decatungstate in combination with various oxidants can effect oxidation of primary alcohols. Based on this precedent, we also examined the direct conversion of primary alcohols into acyl fluorides *via* a one-pot procedure. As indicated in Fig. 3, both benzylic and aliphatic alcohols could be converted directly into acyl fluorides (using 2.5 equiv. of NFSI) and subsequently *N*-benzyl amides *via* decatungstate catalysis in modest to good yield over these three steps. Here, the intermediate vicinal fluorohydrin generated following sequential C–H abstraction

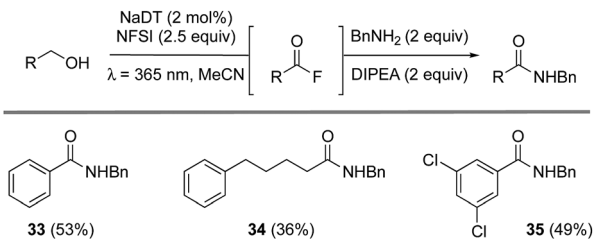
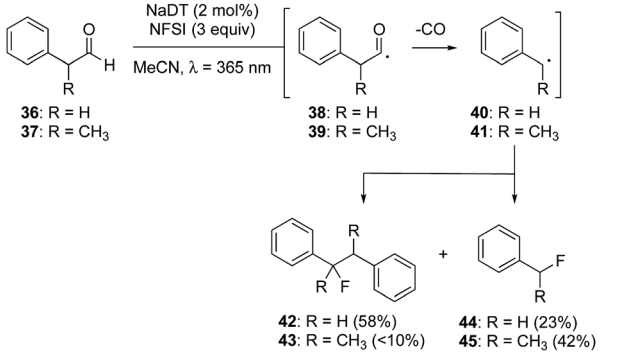


Fig. 3 Direct conversion of benzylic and aliphatic alcohols into amides **33–35**.



Scheme 2 Decatungstate-promoted radical decarbonylation of phenylacetaldehydes.

and fluorine atom transfer quickly looses fluoride to afford an aldehyde *in situ*. A second sequence of C–H abstraction/fluorine atom transfer then provides the intermediate acyl fluoride.

To gain additional mechanistic insight into this process, we considered that decarbonylation of phenylacetaldehydes would provide evidence supporting the intermediacy of acyl radicals.[8b,21] As depicted in Scheme 2, when an MeCN solution of phenylacetaldehyde (**36**) or 2-phenylpropionaldehyde (**37**) were irradiated with catalytic NaDT and excess NFSI, the corresponding benzyl fluorides **44** and **45** were produced directly (Scheme 2). The relatively low yield for fluorotoluene **44** can be attributed to the coincident formation and subsequent fluorination of 1,2-diphenylethane producing benzyl fluoride **42**. Fluoroethylbenzene **45** was the major product derived from the fluorination of phenylpropionaldehyde (**37**).

Considering that acyl fluorides have recently demonstrated utility as electrophilic tags for bioconjugation,[18] we sought to contrast the stability of benzoyl fluorides to sulfonyl fluorides, which are commonly used for selective modification of proteins, target identification and validation, and mapping of enzyme active sites.[23] As detailed in the ESI,† under acidic (pH = 4), neutral (pH = 7), and basic (pH = 9) conditions, benzoyl fluoride proved to be moderately stable with a $t_{1/2} \sim 90$ h for conversion to benzoic acid. Conversely, phenyl sulfonyl fluoride was completely unreactive under these conditions (see ESI†). We also compared the stability of benzoyl fluoride and benzenesulfonyl fluoride in the presence of cysteine methyl ester and found approximately 80% of benzoyl fluoride and 35% of benzenesulfonyl fluoride had reacted after 24 hours. While these data suggest that acyl fluorides do not possess comparable stability to phenylsulfonyl fluorides, they may still prove useful for bioconjugation studies by tuning reactivity through addition of *ortho* substituents or groups that deactivate the carbonyl.

In summary, we describe the direct preparation of acyl fluorides from aldehydes through a process that relies on photoactivated decatungstate catalysis and fluorine atom transfer. Importantly, this straightforward process avoids use of highly reactive reagents typically required for equivalent transformations (*e.g.*, F_2, BrF_3, UF_6 and $CsSO_4F$). We expect that this process should prove complimentary to deoxyfluorination of carboxylic acids typically adopted for acyl fluoride synthesis.

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Conflicts of interest

There are no conflicts to declare.

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