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Tricomponent Catalytic α,α-Difluorination of Acid Chlorides

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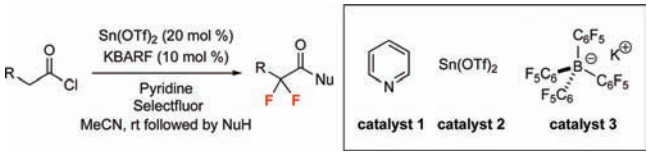
ABSTRACT



The selective α,α-difluorination of carbonyl compounds remains a challenge in modern organic synthesis; current methods often incorporate stepwise processes and/or harsh conditions, providing unsatisfactory mixtures of mono- and difluorinated products. In this communication, a practical, mild, and one-pot method for the selective α,α-difluorination of readily available acid chlorides is reported in which three separate catalysts act synergistically to form products in outstanding selectivity and fair to excellent yields.

Strategic fluorination has become an ever more important weapon in the armamentarium of medicinal chemistry.[1] Substitution of drug molecules with fluorine has been shown to affect the activity of the drug *in vivo*.[2] As a result, the inclusion of fluorine into a host of organic substrates has resulted in a large number of viable drug candidates for the treatment of disease.[1,2] In many cases, fluorine is chosen to replace hydrogen at metabolically labile sites in a biologically active molecule.[3] Along these lines, the positions α to a carbonyl group are often targeted for fluorination.[3] If two α-hydrogens are present, the requirement may be to replace each hydrogen with fluorine. Thus, synthetic methods by which two fluorine atoms can be installed simultaneously α to the carbonyl would be highly useful.

Unfortunately, monocarbonyl compounds have proven to be very difficult substrates for difluorination.[4] In this sense, highly acidic compounds including 1,3-diketones and β-ketoesters are often targeted as substrates for difluorination employing Selectfluor,[5] *N*-fluoro pyridinium salts,[6] and *N*-fluorosulphonimides.[7] Additionally, electrochemical methods have gained popularity among techniques for accessing a variety of α-fluorinated products.[8] Although notable, such efforts often provide unsatisfactory mixtures of mono- and difluorinated adducts. On the other hand, monocarbonyl enolates have been shown to undergo selective mono- and difluorination in the presence of an *N*-F-sultam.[9] However, these methods are generally limited in substrate scope and their need for noncommercial sources of electrophilic fluorine. Instead, we envisaged the use of acid chlorides **1** as ideal substrates for one-pot, selective difluorination. They are inexpensive and readily available, and their α-positions are suitably acidic. In this

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communication, we report a unique "tricomponent" catalytic system for α,α-difluorination that involves a main group Lewis acid ($Sn(OTf)_2$), a catalytic nucleophile that also serves as a reagent (pyridine), and an anionic phase transfer catalyst (KBARF)[10] (potassium tetrakis-(pentafluorophenyl)borate).

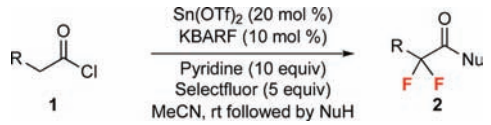


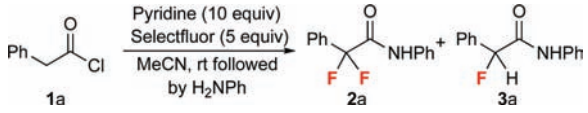
Figure 1. Reaction conditions for selective α,α-difluorination.

These three catalysts work synergistically to effect the efficient α,α-difluorination of a variety of acid chlorides employing Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)[11] as a fluorinating agent and MeCN as solvent (Figure 1). This new method illustrates the power of catalysts acting cooperatively to produce a positive outcome; in this case, the combination of three catalysts is especially notable.

Our screening began by the treatment of phenylacetylchloride (PAC) **1a** with Selectfluor in MeCN. Not surprisingly, no reaction occurred. When several equivalents of pyridine were added as a nucleophilic catalyst and dehydrohalogenating agent (followed by a quench with H_2NPh) only a trace amount of the desired difluorinated amide was present. Unfortunately, raising the temperature of the reaction produced a complex mixture of undesired byproducts. At this point, we decided to introduce a second catalyst in order to enhance the yield of difluorinated product. A number of metal salts were screened for this purpose, although the large majority proved ineffective; Table 1 illustrates the futility of these early attempts. Fortunately, $Zn(OTf)_2$ and $Sn(OTf)_2$ produced a significant increase in both yield and selectivity; $Sn(OTf)_2$ proved to be especially efficacious, and further screening centered on its use.

One of the most notable limitations on the use of Selectfluor is its relative insolubility in commonly used organic solvents. Even in MeCN, the solvent of choice for many reactions with Selectfluor, its solubility is undesirably low and presents a limitation in its overall use as a fluorinating agent.[12] In our reaction, increased ratios of difluorinated product were achieved utilizing a minimal amount of solvent; however, substantial quantities of ketene dimer were likewise prevalent. In an effort to minimize dimer formation, lower reaction temperatures and slower addition times of acid chloride were examined. Unfortunately, these attempts resulted in unsatisfactory yields of difluorinated product. At this point, we sought a means to increase Selectfluor solubility – namely, we imagined that the addition of an anionic phase transfer catalyst (anionic-PTC) could act to bring Selectfluor into solution more effectively.

Table 1. Screening of Lewis Acid Catalysts



entry	Lewis acid	**2a:3a**	yield %
1[a]	BF_3-Et_20	–	0
2[a]	Sc(0Tf)3	–	0
3[a]	$ln(OTf)_3$	–	0
4[a]	$(PPh_3)_2PdCl_2$	–	trace
5[a]	$(dppp)NiCl_2$	–	trace
6[a]	$LiClO_4$	–	trace
7[a]	$TiCl_4$	1:1	12%
8[a]	$Zn(OTf)_2$	2:1	23%
9[a]	$Sn(OTf)_2$	11:1	57%
10[b]	$Sn(OTf)_2$	50:1	82%

[a] Reactions perfomed with 20 mol % catalyst loading; product ratios and yields determined after 3 h. [b] Run with 10 mol % KBARF as cocatalyst.

Consequently, we screened KBARF[8] as a *third* catalyst and found a notable increase in reaction rate, cleanliness, and yield; the role of the KBARF cocatalyst is therefore suggestive of a solubilizing agent for Selectfluor. Such tricomponent catalytic systems are fairly rare in synthetic chemistry,[13] a fact stemming from their inherent complexity, difficulty of study, and potential for deleterious intercatalyst interactions.[14] In the present method, it is apparent that the anionic-PTC is unlikely to engage detrimentally with the Lewis acid $Sn(OTf)_2$ and pyridine and, thus, makes an ideal complement to a polycatalytic system.

Early on, it was found that shorter reaction times resulted in *increased* difluorination; in general, reaction times of 1 to 3 h were found to be optimal for most substrates. The necessity for brief reaction times may be attributed to putative degradation of the highly reactive acylpyridinium salt following initial difluorination. A representative comparison of reaction time to yield of difluorinated product is illustrated for PAC following a quench with aniline (Table 2). We also sought to assess the

(10) For a review of fluorinated tetraarylborates as anionic phase-transfer catalysts, see: Ichikawa, J.; Kobayashi, H.; Sonada, T. *Rep. Inst. Adv. Mater. Study* **1988**, *2*, 189–207.

(11) For a review of Selectfluor, see: Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192–212.

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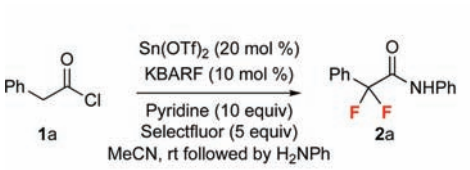
Table 2. Effect of Reaction Time on Yield

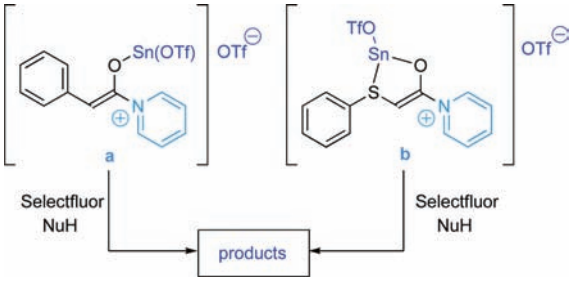


time h	yield %
1	47
3	82
5	71
9	59
12	52

scope of this reaction through a screening of acid chloride substrates (Table 3) employing aniline as a quenching agent. Substitution of the aromatic ring with electron-rich substituents was found to give unsatisfactory yields of difluorinated product (as opposed to more electron-deficient aromatics). Upon further analysis, steric effects were also found to influence the selectivity of difluorination. Substrates possessing bulky substituents near the α-center afforded predominantly monofluorinated products, and those whose α-protons lack significant acidity were likewise found to be ineffective candidates for difluorination.

We speculate that the reaction may proceed via sequential electrophilic addition of fluorine from an activated Sn(II) enolate intermediate (Scheme 1a).[15] Quenching of the reaction with an appropriate nucleophile results in displacement of pyridine and resultant product formation. Sulfur-containing substrates (entries 6 and 8, Table 3) may involve internal chelation of tin through the carbonyl and sulfide groups, illustrated for entry 6 (Scheme 1b).

Scheme 1. Proposed Tin Enolate Intermediates Derived from Acid Chloride Substrates

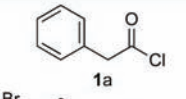
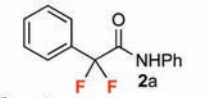
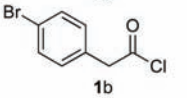
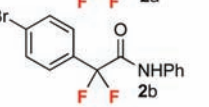
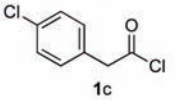
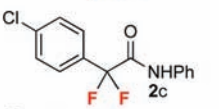
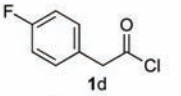
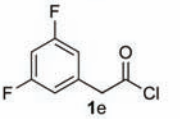
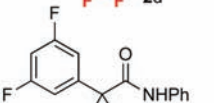
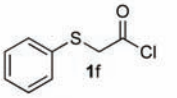
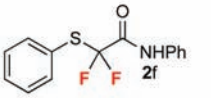
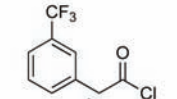
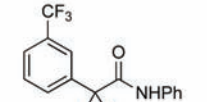
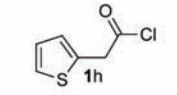
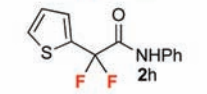
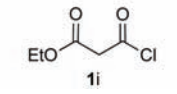
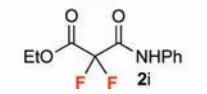


In an advantage over previous methods of difluorination, this reaction also provides accessibility to a host of carboxylic acid derivatives through selection of appropriate quenching agents. This in turn allows for various derivitizations of the acid chloride employed (Table 4). In each case, appropriate functional groups can be synthesized in good to excellent yields from an aryl acetylchloride precursor, thereby eliminating the need for prefunctionalized substrates.

Until now, fluorination of carbonyl compounds using metal enolates and Selectfluor has generally yielded

(15) For a review of tin(II) enolates, see: Mukaiyama, T. *Pure Appl. Chem.* **1986**, *58*, 505–512.

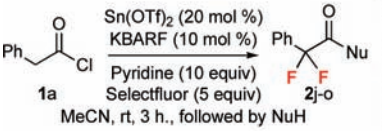
Table 3. Survey of Acid Chloride Substrates

entry	acid chloride	product	yield %
1[c]	 1a	 2a	82
2[c]	 1b	 2b	69
3[c]	 1c	 2c	54
4[b]	 1d	 2d	62
5[a]	 1e	 2e	66
6[c]	 1f	 2f	46
7[c]	 1g	 2g	54
8[d]	 1h	 2h	42
9[c]	 1i	 2i	45

[a] Yields determined after 1 h. [b] Yields after 2 h. [c] Yields determined after 3 h. [d] Yields determined after 24 h. Reactions run using $Sn(OTf)_2$ (20 mol %), KBARF (10 mol %), Pyridine (10 equiv),and Selectfluor (5 equiv) and quenched with H_2NPh (3.5 equiv).

monofluorinated products.[16] However, acid chlorides, being susceptible to sequential enolization, have proven effective substrates for difluorination in combination with an operationally straightforward tricomponent catalyst system.

Table 4. Derivitization of Acid Chlorides through Quenching Agent Selection



entry	NuH	product	yield %
10	EtOH	2j	71
11	$NaBH_4$	2k	73
12	MeOH	2l	79
13	H_2O	2m	60
14	BnOH	2n	74
15	$HNEt_2$	2o	63

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Future work will concentrate on the elucidation of the reaction mechanism, as well as the expansion of the substrate scope to aliphatic acid chlorides and applications to natural product derivitization. Functionalization of common therapeutics will likewise be explored.

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Supporting Information Available. Synthetic procedures and the characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.