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Direct Esterification of Carboxylic Acids with Perfluorinated Alcohols Mediated by XtalFluor-E

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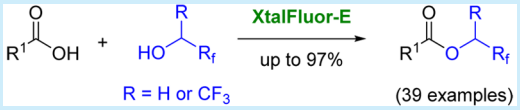
Supporting Information

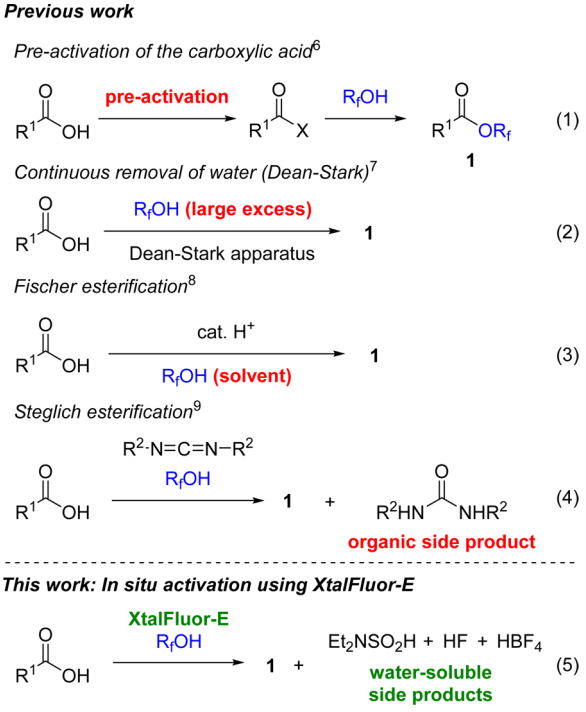
ABSTRACT: The direct esterification of carboxylic acids with perfluorinated alcohols mediated by XtalFluor-E is reported. The corresponding polyfluorinated esters are obtained in moderate to excellent yields with a broad range of carboxylic acids, including aromatic, heteroaromatic, aliphatic, and nonracemic chiral substrates, using only a slight excess (2 equiv) of the perfluorinated alcohol. Control experiments indicate that the reaction does not proceed through the formation of an acyl fluoride but most likely through a (diethylamino)difluoro-λ^4-sulfanyl carboxylate intermediate.



Perfluorination of an organic compound can profoundly modify its physicochemical properties.[1] Within the large family of perfluorinated molecules, polyfluorinated esters with the fluorine located on the alkoxy chain (e.g., **1** in Scheme 1) have found applications in medicinal chemistry,[2] as monomers for the synthesis of perfluorinated polymers,[3] and in organic chemistry as substrates and/or reagents[4] as well as for other usages.[5]

They are generally prepared through preactivation of the carboxylic acid (mostly as the acyl chloride, i.e., X = Cl) prior to the reaction with the polyfluorinated alcohol (Scheme 1, eq 1).[6]

Scheme 1. Previous Work and the Current Method



From a practical aspect, a method that would obviate this preactivation step would be highly desirable. In that regard, the use of a Dean−Stark apparatus (Scheme 1, eq 2)[7] and synthesis through a Fischer esterification reaction (Scheme 1, eq 3)[8] have been described occasionally. However, in the former case, the perfluorinated alcohol is used in large excess, while in the latter, it is used as the solvent, which limits the utility of this approach to low-molecular-weight perfluoroalcohols. Finally, a Steglich esterification using carbodiimide reagents has been explored (Scheme 1, eq 4).[9] Although this approach is more straightforward, the use of carbodiimide reagents leads to the formation of urea byproducts that are sometimes difficult to separate from the desired product.

A few years ago, the research team of Cossy and our group independently reported the synthesis of amides from carboxylic acids mediated by $(Et_2NSF_2)BF_4$ (XtalFluor-E).[10−13] In this reaction, XtalFluor-E served to activate the carboxylic acid in situ prior to the attack by the amine. Although XtalFluor-E was primarily developed for the deoxofluorination of alcohols, we hypothesized that because of the low nucleophilicity of perfluorinated alcohols,[14,15] selective activation of the carboxylic acid over the perfluorinated alcohol with XtalFluor-E could be possible, thus leading to a direct synthesis of **1** (Scheme 1, eq 5).[13e] Herein we report the direct esterification, mediated by XtalFluor-E, of a broad range of carboxylic acids using only a slight excess of various perfluorinated alcohols. Notably, and as opposed to the use of diimide reagents, this system generates water-soluble side products, which facilitates purification.

Selected optimization data using 5-phenylvaleric acid (**2**) with 2,2,2-trifluoroethanol (TFE) are reported in Table 1. The use of a slight excess of XtalFluor-E with Et_3N (2.5 equiv) and TFE as the solvent provided the desired ester **3** in 68% yield (Table 1, entry 1). Product **3** was obtained in 75% yield with a 1:1 TFE/CH_2Cl_2 mixture (Table 1, entry 2). Further dilution to 1:9 provided an improved yield of 88% (Table 1, entry 3).

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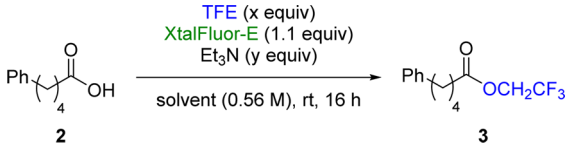
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization Results for the Esterification of 5-Phenylvaleric acid (2) with TFE Using XtalFluor-E[a]



entry	y	solvent	yield (%)[b]
1	2.5	TFE	68
2	2.5	TFE/CH_2Cl_2 (1:1)	75
3	2.5	TFE/CH_2Cl_2 (1:9)	88
4	2.5	TFE/THF (1:9)	80
5	2.5	TFE/toluene (1:9)	60
6	2.5	TFE/EtOAc (1:9)	74
7	2.5	TFE/CH_3CN (1:9)	58
8	0	TFE/CH_2Cl_2 (1:9)	60[c]
9	1	TFE/CH_2Cl_2 (1:9)	89
10	1.5	TFE/CH_2Cl_2 (1:9)	90
11	**1.5**	**TFE (2 equiv) in CH_2Cl_2**	**84**
12	1.5	TFE (1.2 equiv) in CH_2Cl_2	55

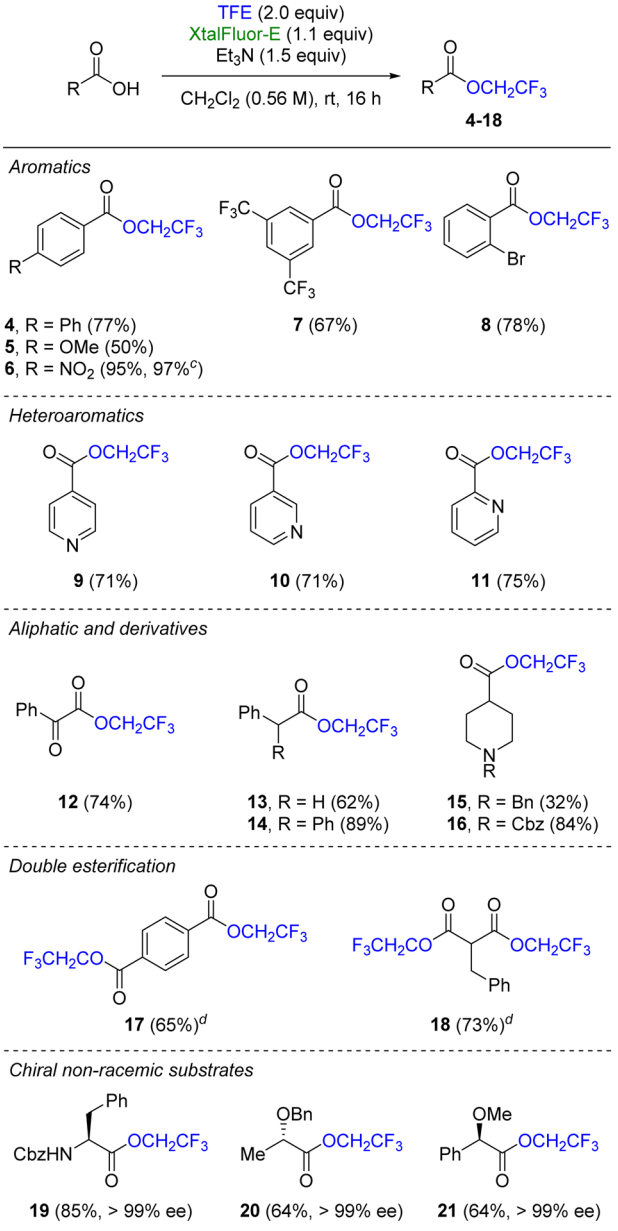
[a]See the Supporting Information for the detailed experimental procedures. The optimized conditions are shown in bold. [b]Isolated yields. [c]Estimated by NMR analysis of the crude reaction mixture.

Using other cosolvents (THF, toluene, EtOAc, and CH_3CN) instead of CH_2Cl_2 provided lower yields (58−80%) (Table 1, entries 4−7). Running the reaction in the absence of Et_3N provided a considerably lower yield as estimated by NMR analysis of the crude reaction mixture (Table 1, entry 8), but 1.5 equiv seemed to be the optimal amount (Table 1, entries 9 and 10). Finally, the amount of TFE could be reduced to 2 equiv without a major effect on the outcome (Table 1, entry 11), although further reducing it to 1.2 equiv resulted in a lower yield (Table 1, entry 12). The conditions shown in Table 1, entry 11 were chosen as the optimized ones.

With those conditions in hand, the esterification of other carboxylic acids was investigated, and the results are shown in Scheme 2. Various aromatic carboxylic acids provided the desired esters **4**−**8** in moderate to excellent yields. The reaction could also be performed on a gram scale, as illustrated by the esterification of 1.00 g of 4-nitrobenzoic acid in 97% yield. Interestingly, the TFE esters of all regioisomers of picolinic acid (**9**−**11**) could be obtained in good yields (71−75%). A *β*-keto carboxylic acid such as phenylglyoxylic acid reacted well, providing ester **12** in 74% yield. Aliphatic carboxylic acids could also be used as substrates for this transformation, as illustrated by the use of derivatives of phenylacetic acid and isonipecotic acid. In the latter case, a Cbz protecting group is preferred over a benzyl group, probably because of the reduced basicity of the nitrogen. Phthalic acid and a benzylmalonic acid could both be bisesterified to provide **17** and **18**, respectively, in good yields when the stoichiometry of the reagents was adjusted accordingly. The reaction could be extended to nonracemic chiral carboxylic acids. For instance, Cbz-protected L-phenylalanine could be esterified with TFE to provide ester **19** in 85% yield. Likewise, the reactions of *O*-benzyl-(*S*)-lactic acid and *O*-methyl-(*R*)-mandelic acid provided esters **20** and **21**, respectively, in good yields. In all cases, chiral HPLC analyses showed no loss of enantiopurity.

To further extend the utility of this transformation, esterification with other perfluorinated alcohols was explored, as shown in Scheme 3. For that purpose, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP, **22**), 2,2,3,3,3-pentafluoro-1-propanol (PFPOH, **23**), 2,2,3,3,4,4,4-heptafluoro-1-butanol (**24**), 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro-1-octanol (**25**), and 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptadecafluoro-1-nonanol (**26**) were used. A wide range of carboxylic acids could be esterified (or bisesterified in the case of phthalic acid) to provide the corresponding esters **27**−**46** in moderate to excellent yields (45−96%).

Scheme 2. Results for the Esterification of Various Carboxylic Acids with TFE Using XtalFluor-E[a,b]



[a]See the Supporting Information for the detailed experimental procedures. [b]Isolated yields are shown. [c]The reaction was performed on a 5.98 mmol scale (i.e., 1.00 g of the acid). [d]TFE (4.0 equiv), XtalFluor-E (2.2 equiv), and Et_3N (3 equiv) were used instead.

To gain insight into the reaction mechanism, a series of control experiments were run. First, we reacted **25** with XtalFluor-E, omitting the carboxylic acid and Et_3N (Scheme 4, eq 1). A moderate conversion of 66% was obtained, and NMR analysis of the crude reaction mixture revealed the formation of

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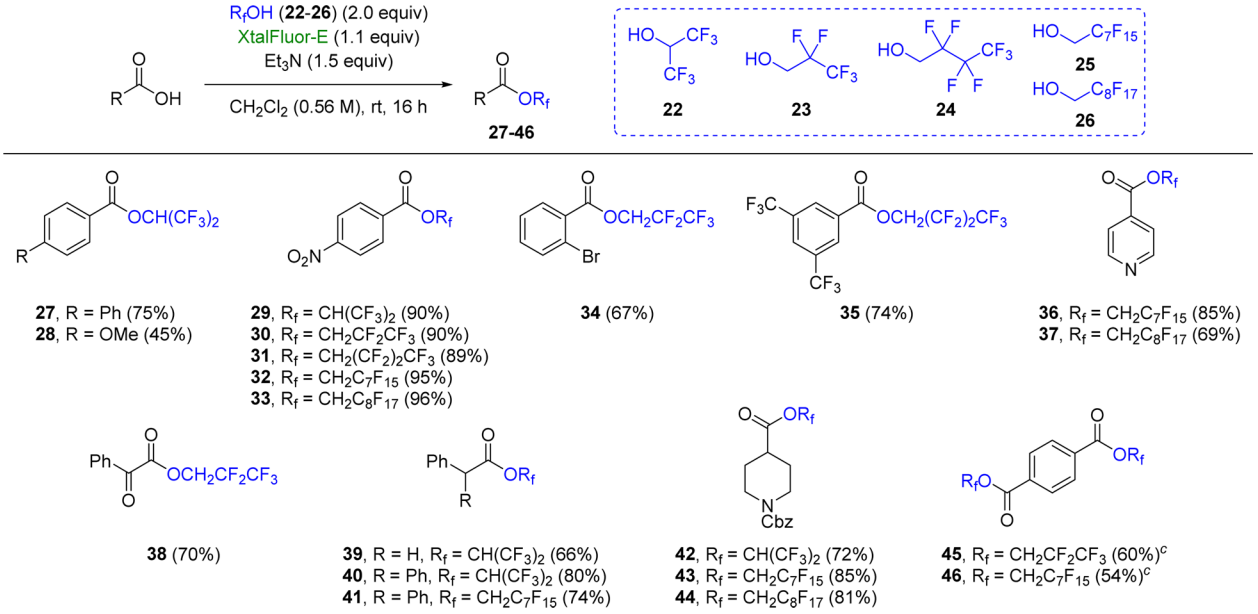
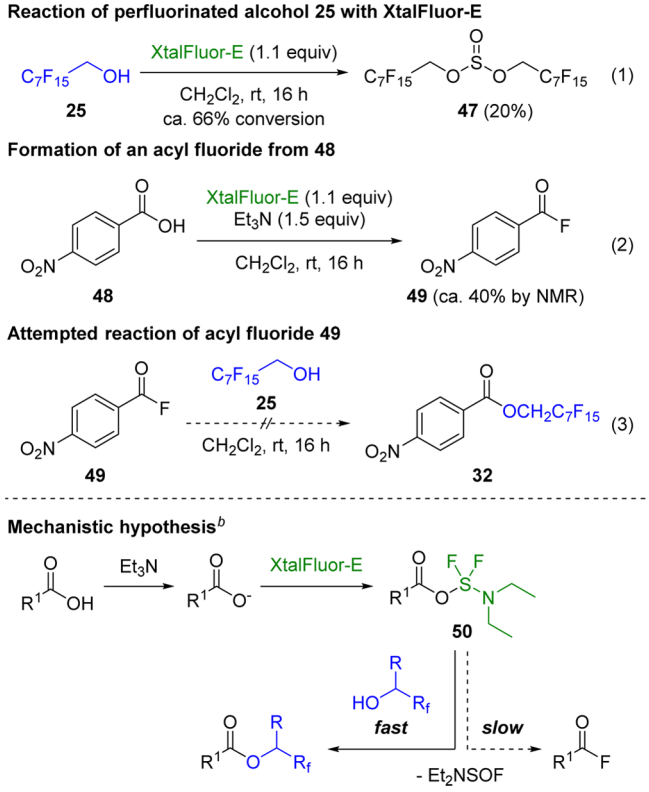
Scheme 3. Selected Results for the Esterification of Various Carboxylic Acids with Perfluorinated Alcohols Using XtalFluor-E[a,b]



[a]See the Supporting Information for the detailed experimental procedures. [b]Isolated yields are shown. [c]**23** or **25** (4.0 equiv), XtalFluor-E (2.2 equiv), and Et_3N (3 equiv) were used instead.

Scheme 4. Control Experiments and Mechanistic Hypothesis[a]



[a]See the Supporting Information for the detailed experimental procedures. [b]The counterions have been omitted for clarity.

sulfinate **47** (20%) along with some unidentified XtalFluor-E-related products.[10b] The fluoride[16] corresponding to **25** was not observed. For comparison, complete conversion in less than 5 min was reported with hydrocinnamyl alcohol.[10b] The slower reaction of perfluorinated alcohols with XtalFluor-E likely originates from their impaired nucleophilicity due to the powerful inductive effect of the adjacent fluorine atoms.[14] Next, in two separate experiments, we investigated whether the reaction proceeds through an acyl fluoride, as it has been shown that XtalFluor-E is able to convert a carboxylic acid to an acyl fluoride, albeit slowly in the absence of an external source of fluoride.[10b] To this end, 4-nitrobenzoic acid (**48**)[17] was subjected to the reaction conditions without any perfluorinated alcohol. After 16 h, a low conversion of ca. 40% to the corresponding acyl fluoride **49** was determined by NMR analysis (Scheme 4, eq 2). In addition to this slow formation of the acyl fluoride, which is not compatible with the time required for the completion of the esterification reaction, no transformation was observed when independently synthesized acyl fluoride **49** was allowed to react with perfluorinated alcohol **25** (Scheme 4, eq 3). On the basis of those two observations, we discarded the acyl fluoride pathway. Hence, our current working hypothesis is the following: First, deprotonation of the carboxylic acid by Et_3N would lead to the more nucleophilic carboxylate.[11] Reaction of the latter with XtalFluor-E would generate (diethylamino)difluoro-λ^4-sulfanyl carboxylate **50**.[5,6] Under the reaction conditions, the formation of the acyl fluoride would be slower than the reaction of **50** with the perfluorinated alcohol, which would generate the desired perfluorinated ester in addition to diethylaminosulfinyl fluoride.[18]

In summary, we have reported the use of XtalFluor-E as an effective promoter for the direct esterification of carboxylic acids using perfluorinated alcohols. The corresponding polyfluorinated esters are obtained in moderate to excellent yields with a broad range of carboxylic acids, including aromatic, heteroaromatic, aliphatic, and nonracemic chiral substrates, using only a slight excess (2 equiv) of the perfluorinated alcohol. Control experiments indicated that the reaction does not proceed through the formation of an acyl

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fluoride but most likely through a (diethylamino)difluoro-λ^4-sulfanyl carboxylate intermediate.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03365.

Detailed experimental procedures and full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(6) For example, see refs 2b,c, 3c, and 4c.

(7) For example, see ref 4a.

(8) For example, see refs 2a,e, 4f, and 5b.

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