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Towards Greener Fluorine Organic Chemistry: Direct Electrophilic Fluorination of Carbonyl Compounds in Water and Under Solvent-Free Reaction Conditions

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Abstract: Selective and efficient fluorination of organic 1,3-dicarbonyl compounds was achieved using the electrophilic fluorinating reagents *Selectfluor™ F-TEDA-BF$_4$* (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-tetrafluoroborate) in aqueous medium or *Accufluor™ NFSi* (*N*-fluorobenzenesulfonimide) under solvent-free reaction conditions (SFRC). Under both reaction conditions cyclic 1,3-dicarbonyl compounds were transformed into 2-fluoro-substituted derivatives and acyclic analogues into 2,2-difluoro-substituted compounds, while the reactions of 1-trifluoromethyl-substituted 1,3-dicarbonyls in water resulted in the formation of 2,2-difluoro-3,3-dihydroxy-1-one derivatives. The reactivity of the starting material in water was found to be dependent on its enolizability, hydrophobic interactions and aggregate state at the reaction temperature. Reactions under SFRC proceeded in the molten eutectic phase of the reactants. The technique of competitive reactivity was used in order to evaluate and better understand the effects of reaction conditions on the course of these reactions.

Keywords: fluorine; green chemistry; Selectfluor; solvent-free reactions; water

Introduction

In the development of new synthetic approaches, ecological points of view must be seriously taken into consideration since the emergence of *green and sustainable chemistry* represent a continuous pressing challenge for chemists to develop advanced processes that are not only highly efficient and selective but also environmentally friendly. In the development of environmentally benign synthetic pathways there is a requirement to reduce the number of steps and consequently minimize toxic waste and by-products, produce simpler and safer experimental procedures and design energy efficient syntheses.[1] However, these greener approaches should still exhibit high atom efficiency, selectivity and enable efficient transformations in larger-scale experiments which are of crucial importance for industrial applications. Green chemistry has also developed "green" parameters to describe the sustainability of chemical reactions in order to quantify their impact on the environment.[2a,b] Of these alternative sustainable chemical parameters, the most influential are Trost's atom economy (AE = relative molecular mass of desired product/relative molecular masses of all reactants)[2c,d] and Sheldon's *E* factor (mass of total waste/mass of final product),[2e,f] which quantify the "greenness" of a reaction and mathematically predict or estimate how green each chemical process is. The largest contributors to high values of the *E* factor are organic solvents; many of them are hazardous, volatile and ecologically harmful, especially when used in the large volumes typical of industry. Their use for performing organic reactions should therefore be minimized or even avoided if this can be accomplished with high efficiency, and this approach represents one of the major strategies to reduce *E* factors of reactions and their impact on the environment. It is worth mentioning that steps toward sustainability can also be accomplished by recycling the solvents used in chemical processes and thus contributing to reducing undesirable waste.

In line with this approach, organic reactions can be performed in alternative reaction media including ionic liquids,[3a,b] supercritical fluids, in particular $scCO_2$,[3c] polyethers,[3d] perfluorinated hydrocarbons,[3e] "bio-solvents" like ethyl lactate or polyhy-

droxyalkanoates[3f,g] and water.[4h,i] The use of water as the reaction medium represents the most promising option in the search for cheaper, cleaner and yet efficient technologies. However, in many cases the incompatibility of organic substrates and intermediates with water represents a potential obstacle to efficient transformations in such a medium. In order to overcome this problem, which is a result of the hydrophobic interactions between apolar parts of organic substrates and water,[4a,b] usually organic co-solvents for increasing the homogeneity of the reaction systems are used,[4c] but these consequently contribute to forming additional waste. On the other hand, some organic reactions can be performed by vigorous stirring of neat reactants in an aqueous emulsion or suspension without using any organic additives under so-called "on water" conditions, but no attention has yet been focused on work-up processes, where organic solvents are used almost exclusively.[5]

Another approach to reduce the impact on the environment is to perform organic reactions under solvent-free reaction conditions (SFRC). The advantages of using SRFC are cost savings, lower energy consumption in view of the mild reaction conditions, satisfactory purity of the products, while usually derivatization of the starting compounds can be avoided. Examples show that these reactions can even proceed with higher efficiency, higher regio- and stereoselectivity and, in many cases, because of the higher concentration and better interaction between the reactants, with greater rapidity.[6] When performing organic reactions under SFRC, all of these parameters strongly depend on the aggregate state of the substrates and reagents and on their efficient homogenization, resulting in a significant impact on the change in the aggregate state of the reactants and consequently on the molecular mobility. Improved interactions between the reactants on the macroscopic level can be well established in the case of liquid-liquid or liquid-solid systems, while solid-phase systems usually need additional activation energy.[7a,b] Activation can be accomplished using catalysts, immobilization of reagents on supports,[7c] or by photochemical,[7d] microwave,[7e] mechanochemical[7f] or simple thermal activation of the reaction systems leading to the formation of a liquid phase from the occurrence of an eutectic molten phase system.[7g]

In recent years, halogenation of various organic compounds with emphasis on green and sustainable development has attracted considerable attention, especially when introduction of halogen atoms is performed under mild reaction conditions in water, ionic liquids or even under SFRC.[8] Efficient and selective fluorinations of organic compounds in aqueous medium and under SFRC, however, have not been a topic of much research interest, obviously due to the high reactivity of molecular fluorine, potentially dangerous interactions of fluorinating agents with water, or simply the incompatibility of reagents in such reaction conditions. We have recently demonstrated that efficient electrophilic fluorofunctionalizations of various organic compounds can be performed efficiently under mild conditions in aqueous medium[9a] and in solvent-less reaction systems[9b] using N–F reagents as mild and alternative F sources to hazardous molecular fluorine. To date only a few other attempts at fluorination of some selected test substrates in pure aqueous medium have been reported utilizing highly diluted molecular fluorine techniques,[10a,b] using potassium bifluoride as a fluorinating agent,[10c] and some scarce examples of electrophilic fluorination of uracil, timin, 1,3,5-trimethoxybenzene and 2,4,6-trimethoxytoluene with *Selectfluor* F-TEDA-BF_4.[10d,e] In the case of solvent-free reactions, research has been mainly focused on nucleophilic fluorination including fluorofunctionalization of epoxides and acetylenes using an excess of $Bu_4N^+H_2F_3^-$ or a combination of KHF_2/$Bu_4N^+H_2F_3^-$ at 100–130 °C,[11a,b] nucleophilic aromatic substitution of chlorodiazenes with the KF/18-crown-6 reagent system under microwave irradiation,[11c] electrochemical anodic fluorination of lactones and cyclic ethers in neat fluoro-substituted electrolytes,[11d] and some less efficient and selective examples of flurotransformation of 1,3-dioxalane-2-one, γ-butyrolactone and toluene with highly diluted molecular fluorine (10–30% F_2/N_2) or gas-liquid micro-reactor technology.[11e–g]

As a response to these challenges and in view of our continuing efforts in developing new greener synthetic methods for efficient and selective halogenation of organic molecules,[12] we now report further investigations on water-based and solvent-free fluorination systems for direct electrophilic fluorination of 1,3-dicarbonyl compounds and solvent-free fluorination of ketones in the molten phase using the SDS catalytic system. These studies allowed a closer insight into the formation of the C–F bond in water and under SFRC on the basis of relative kinetic studies. Special attention was also devoted to development of comprehensive "green" work-ups where at every stage of the process no organic solvents were used.

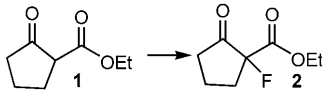
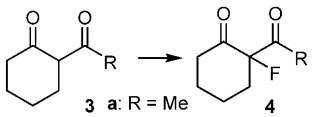
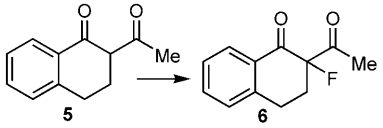
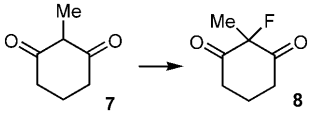
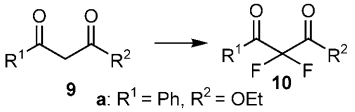
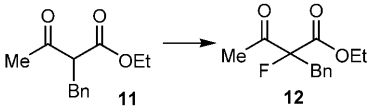
Results and Discussion

The keto-enol tautomerism is one of the main factors regulating the reactivity of carbonyl compounds. Due to the high acidity of protons on the carbon atom between two carbonyls and the possibility of additional stabilization of the enol form by an intramolecular hydrogen bond, values for keto-enol equilibrium constants (K_E) are ordinarily much higher for 1,3-dicarbonyls than those for ketones.[13] The reactivity of 1,3-dicarbonyl compounds towards electrophilic function-

alization is therefore usually high enough for their direct transformation to 2-halo- or 2,2-dihalo-substituted derivatives. When these transformations are performed in aqueous media very important factors regulating the efficiency of the reactions are the hydrophobicity of reactants and their aggregate state at the reaction temperature.

We have already shown that *Selectfluor*^{TM} F-TEDA-BF_4 (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis-tetrafluoroborate), one of the most commonly used electrophilic fluorinating reagents,[14] could also be efficiently used for direct fluorination of organic compounds in aqueous medium.[9a] F-TEDA-BF_4 is soluble and relatively stable in water,[15] making it a very convenient reagent for reactions in such an environment. We started our further investigations with cyclic 1,3-dicarbonyls, known to be more reactive for electrophilic functionalizations than their acyclic analogues, since their degree of enolization is very high.[13] In a typical experiment a dispersion of 1,3-diketone (1 mmol of **3**, **5**, **7**, Table 1) or β-keto ester (**1**) in 5 mL of water was magnetically stirred (700 rpm) at 60–80 °C, and after consumption of the reagent (KI starch paper test), the reaction mixture was cooled to room temperature. In order to reduce the environmental impact of the overall pro-

Table 1. Fluorination of 1,3-dicarbonyl compounds with N–F reagents in water or under solvent-free reaction conditions.

Entry	Fluorofunctionalization	Reaction conditions			
		Water[a]		SFRC[b]	
		Work-up	Yield [%]	Work-up	Yield [%]
1		A	82	A	82
2	 **3** **a**: R = Me **4**	A	84	A	78
3	**b**: R = Ph	B[c]	74	D[c]	83
4		C	91	C[c,d]	93
5		A	80	/	/
6	 **9** **a**: R^1 = Ph, R^2 = OEt **10**	A	89	/	/
7	**b**: R^1 = Ph, R^2 = Me	B	82	D	90
8	**c**: R^1 = R^2 = Ph	C	78	D	75
9	**d**: R^1 = Ph, R^2 = NHPh	C	87	D	80
10	**e**: R^1 = Me, R^2 = OEt	/	/	D	85
11	 **11** **12**		40		40

[a] *Reaction conditions:* 1,3-dicarbonyl compound (1 mmol), F-TEDA-BF_4 (1.1 mmol or 2.2 mmol in the case of **9**), H_2O (5 mL), magnetic stirring (700 rpm), T = 70 °C, reaction time 4–10 h; procedures for isolation of products (work-up): A: extraction with *tert*-butyl methyl ether; B: gently separated from water and removing its traces from liquid products in a dry atmosphere; C: filtering-off crude solid product and drying.

[b] *Reaction conditions:* 1,3-dicarbonyl compound (1 mmol), NFSi (1.1 mmol), homogenization of reactants and heating at 90 °C for 1–4 h; procedures for isolation of crude products (work-up): A: extraction with *tert*-butyl methyl ether; D: distillation under reduce pressure.

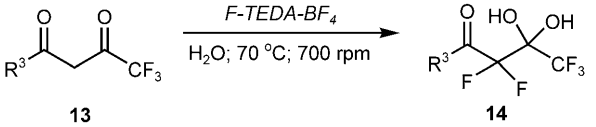
[c] Synthesis also performed on the 5–20 mmol scale.

[d] F-TEDA-BF_4 used as the fluorinating reagent; after completion of the reaction, water was added to the crude reaction mixture and the solid product filtered-off.

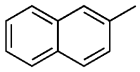
cess as much as possible, special attention was paid to procedures for isolation of the products. If possible the use of organic solvents was avoided and the isolation protocol was chosen depending on the aggregate state of the products and their compatibility with water. In the case of products partly soluble in water, an extraction with *tert*-butyl methyl ether, often applied as a substitute for environmentally unacceptable halogenated solvents, was used as a work-up procedure (A), hydrophobic liquid products were gently separated from water and dried under reduced pressure (B), while solid products were simply filtered-off and dried (C). Following these protocols a variety of cyclic 1,3-dicarbonyl compounds (entries 1–5, Table 1) were selectively and efficiently transformed to their 2-fluoro derivatives **2**, **4**, **6**, and **8** with high isolated yields. Selective mono-fluorofunctionalization of acyclic 1,3-dicarbonyls bearing a methylene carbon atom between two carbonyl functional groups is not an easy task and often strict control of the reaction conditions is necessary in order to diminish over-fluorination to 2,2-difluoro-substituted products, while for complete difluorination the presence at least equivalent amounts of a strong base was reported to be necessary.[16] In our case, the fluorination of a group of acyclic 1,3- dicarbonyl compounds (**9a–d**, Table 1) with F-TEDA-BF_4 in water could also not be selectively stopped at the monofluorination stage, but by using a two-fold excess of the reagent efficient formation of the 2,2-difluoro-substituted products **10a–d** was established without any additional activation of the starting material. We also tested two examples of less active 1,3-dicarbonyl compounds 3-oxobutyric acid ethyl ester (**9e**, entry 10, Table 1) and diethyl malonate, and found that fluorination of **9e** with F-TEDA-BF_4 in water gave a complex reaction mixture of mono- and difluoro products, hydrolyzed products and hydrates, while the reaction under SFRC with NFSi selectively and efficiently yielded 2,2-difluoro-3-oxobutyric acid ethyl ester **10e**. Diethyl malonate was found to be resistant under both reaction conditions. On the other hand, 2-benzyl-3-oxobutyric acid ethyl ester **11** could not be transformed to its 2-fluoro-substituted product **12** with more than 60% yield under these reaction conditions.

The trifluoromethyl functional group, due to its strong negative inductive effect, regulates to a considerable extent the reactivity of trifluoromethyl-substituted organic molecules. Enolization of CF_3-substituted 1,3-dicarbonyl compounds is very high and stabilization of the enol form is additionally supported by involvement of the trifluoromethyl group in the intramolecular hydrogen bond,[13] and therefore its reactivity towards electrophilic transformation is expected to be enhanced. Fluorination of trifluoromethyl-substituted 1,3-diketones (**13**, Table 2) with F-TEDA-BF_4 in pure water was found to be very efficient, but contrary to our previous observations in the case of halogenation of these kind of compounds with N–X succinimides,[12e] the fluorotransformation again could not be stopped at the monofluorination stage and completing reactions leading to the formation of 2,2-difluoro derivatives seemed to be the best choice. The introduction of fluorine atoms obviously enhanced water addition to the carbonyl group next to the electron-withdrawing trifluoromethyl group, so that 2,2-difluoro-3,3-dihydroxy-1-one derivatives **14** were the final products isolated following organic solvent-less isolation protocols.

Table 2. Fluorination of trifluoromethyl substituted 1,3-dicarbonyl compounds with F-TEDA-BF_4 in water.[a]



13 14

Entry	Substrate **13**	Work-up	Yield [%]
1	**a**: R^3 = 	A	83
2		C	61
3	**b**: R^3 = Ph	C	82
4	**c**: R^3 = 	C	92

[a] *Reaction conditions:* 1,3-dicarbonyl compound (1 mmol), F-TEDA-BF_4 (2.2 mmol), H_2O (5 mL), magnetic stirring (700 rpm), $T = 70\,°C$, reaction time 4–6 h; procedures for isolation of crude products (work-up): A: extraction with *tert*-butyl methyl ether; C: filtering off crude solid product and drying.

Direct transformation of a carbon-hydrogen bond to a carbon-fluorine bond under solvent-free reaction conditions (SFRC) remains a challenging task. The formation of a C–F bond, the strongest single bond in organic molecules, is an energy releasing process often causing stability problems in such reaction systems. The migration of reactants and the consequent possibilities of their efficient contact for successful exchange of electrons are considerably different from those taking place in solution. The aggregate state of the reactants at the reaction temperature is a very important factor regulating the course of reactions. Liquid-liquid reaction systems represent the simplest situation, while solid-liquid systems and especially solid-solid systems are more complex, which could cause problems, but also opens up new exciting possibilities.[6] Following our preliminary investigations,[9b] fluorotransformation of various types of organic compounds under SFRC could be efficiently performed using Selectfluor™ F-TEDA-BF_4 or Accufluor™ NFSi (*N*-fluorobenzenesulfonimide). Going further as shown in Table 1, a variety of 1,3-dicarbonyl compounds could be selectively and effectively fluorinat-

Table 3. Effect of reaction medium on the relative reactivity of 1,3-dicarbonyl compounds towards fluorination with F-TEDA-BF_4.

	Substrate	Relative rate factors (k_{rel})[a]			
		H_2O	0.05% aqueous SDS	dry MeCN	SFRC
1	**9a** liquid	1.0	1.0	1.0	1.0
2	**9b** mp 54 °C	10.2	15.0	3.5	7.1
3	**9c** mp 77 °C	0.4	1.7	9.5	<0.01
4	**11** liquid	0.2	0.4	<0.001	<0.01
5	**3a** liquid	20.0	>100	>100	>100
6	**5** mp 66 °C	23.0	>100	>100	>100

[a] Relative rate factors were calculated from the equation[18] $k_{rel}=k_A/k_B=\log[(A-X)/A]/\log[(B-Y)/B]$ derived from the Ingold–Show relation,[19] where A and B are the amounts (in mmols) of starting materials and X and Y the amounts of products derived from them and determined from ^{19}F NMR spectra of crude reaction mixtures using octafluoronaphthalene as the internal standard.

ed under SFRC and the results obtained were comparable to those observed after analogous reactions in water medium. The efficiency of a particular transformation was found to be crucially dependent on the aggregate state of the starting material. In the case of liquid compounds, reactions using either reagent gave comparable results, but with F-TEDA-BF_4 the consumption of starting material needed considerably longer reaction times (4–24 h), while reactions with solid substrates gave much better results using NFSi as the reagent. In the first case we were dealing with reactions in a liquid-solid system, where potentially better solubility of the reagent in a particular substrate at the reaction temperature (80–90 °C) could enhance the reaction rate. On the other hand, we observed that formation of a C–F bond using NFSi under SFRC proceeded in a molten phase system which works as a new reaction medium, enabling rapid migration of reactants and efficient interactions between them. Further potential inconveniences derived from reactions performed under SFRC are connected with uneven energy transport, often resulting in the formation of hot-spots with high localized microscopic temperatures.[17] Since these problems become more evident in scaled-up processes, we tackled this challenge and performed larger-scale fluorinations under SFRC, and in both model cases (entry 3: **3b** to **4b**; molten phase system and entry 4: **5** to **6**; liquid-solid system) no uncontrollable exothermicity was observed. Compound **11** was again found to be unsuitable for fluorination, also under SFRC (entry 10).

In order to evaluate the structural effects of 1,3-dicarbonyls on fluorination with F-TEDA-BF_4 in different reaction media, we measured the relative reactivity of some cyclic and acyclic 1,3-dicarbonyls in pure water, in a 0.05% aqueous solution of the amphiphile sodium dodecyl sulfate (SDS), in dry acetonitrile, and under SFRC using the technique of competitive reactivity and calculated their values as relative rate factors (k_{rel}).[18,19] As evident from Table 3, 1-phenylbutane-1,3-dione **9b** was found to be from 3.5 (in dry MeCN) to 15.0 (in aqueous solution of the amphiphile) fold more reactive than the reference substrate 3-oxo-3-phenylpropionic acid ethyl ester **9a** (entry 2). These results could be explained by the fact that the degree of enolization is ordinarily higher in 1,3-diketones than β-keto esters, while enolization was established as considerably higher in aqueous solutions of amphiphiles, and generally lower in MeCN than in pure water.[13] In the case of 1,3-diphenylpropane-1,3-dione **9c** other factors regulate its reactivity. Although **9c** is even more enolizable than **9b**, its reactivity in pure water was found to be twice as low as that of **9a**. Due its higher hydrophobic character and higher melting point, its incompatibility with water became the main factor decreasing its reactivity. In the presence of catalytic amounts of SDS as an anionic amphiphile the improved homogeneity of the reaction mixture accelerated fluorination, while in the totally homogeneous MeCN system the expected high relative reactivity was established (entry 3). Despite the fact that 2-benzyl-3-oxobutyric acid ethyl ester **11** exhibited a high degree of enolization in water,[12h] hydrophobic interactions and steric hindrance in the enolic tautomeric form played an important role in its low reactivity under all the reaction conditions studied (entry 4). Both the cyclic 1,3-dicarbonyls liquid 2-acetylcyclohexanone (**3a**, entry 5) and solid 2-acetyl-1-tetralone (**5**, entry 6), due to their high degree of enolization, showed the expected relative reactivity; in pure water they were found to be more than twenty fold more reactive than the reference material **9a**, while in the other three reaction media a reactivity more than two decades higher was established.

Direct electrophilic fluorination of ketones has for a long represented a problem, one which was partly resolved a decade ago following direct fluorofunctionalization of various structural types of carbonyl compounds using N–F reagents in MeCN or MeOH

Table 4. Transformation of ketones to corresponding α-fluoro ketones using F-TEDA-BF_4 in the SDS aqueous micelle-based system[21] or NFSi in the molten phase solvent-free reaction system.[a]

	Ketone	Transformation to α-fluoro ketone [%] in aqueous SDS	SFRC
1	1-Indanone	100	58
2	1-Tetralone	100	62
3	Benzosuberone	100	61
4	Propiophenone	90	65
5	5-Nonanone	95	0
6	2-Octanone	95	0

[a] *Reaction conditions:* ketone (1 mmol), NFSi (1 mmol), SDS (0.1 mmol), heating at 90 °C for 24 h.

medium,[20] and very recently, after an unsuccessful attempt in pure water,[9a] the application of the SDS aqueous micelle-based system was shown to be a promising alternative.[21] However, direct transformations of ketones to their α-fluoro derivatives under SFRC still remains a challenging task.[9b] We tried to solve this problem by the addition of Lewis or Brønsted acid catalysts, usually used as enolization promoters. Unfortunately none of acid activators such as *p*-toluensulfonic acid (PTSA), 4-dodecylbenzensulfonic acid (DBSA), sulfuric acid, acetic acid, or niobic acid gave an at least moderate degree of fluorotransformation. Furthermore, we checked the effects of the addition of amphiphiles, and catalytic amounts of SDS (up to 10 mol%), which gave to some extent acceptable results, but the transformation of aryl alkyl ketones to their α-fluoro derivatives (entries 1–4, Table 4) did not reach more than 65%, while dialkyl ketones seemed to be resistant under these reaction conditions.

Conclusions

To promote efforts for a green chemical approach to selective and efficient fluorination of organic compounds, protocols for fluorination of organic 1,3-dicarbonyl compounds in water using Selectfluor™ F-TEDA-BF_4, or under solvent-free reaction conditions (SFRC) using Accufluor™ NFSi, were developed with additional attention to avoidance of organic solvents also in the phase of isolation of reaction products. A series of cyclic and acyclic 1,3-dicarbonyl compounds were efficiently transformed to their 2-fluoro- or 2,2-difluoro-substituted derivatives without the need for prior activation of the starting compounds or the use of acid activators, while their reactivity in pure water was found to be regulated by their enolizabilities, aggregate state at the reaction temperature and hydrophobic interactions. The effects of aggregate state and hydrophobicity could be diminished by addition of the anionic amphiphile sodium dodecyl sulfate (SDS) to the reaction system, which improved the reactivity. Fluorination under SFRC was found to be faster than in water; reactions proceeded in the molten eutectic phase enabling better homogenization of the reaction system and consequently more rapid migration of reactants, their more efficient contact, and more regular heat transfer. To our satisfaction, we succeeded in the transformation of a C–H into a C–F bond with high selectivity and efficiency and extended the methodology to scaled-up procedures. Direct fluorination of ketones under SFRC was found ineffective, but following the application of the SDS catalytic system moderate yields of α-fluoro ketones were obtained. The use of pure aqueous or solvent-free reaction conditions for direct electrophilic fluorination of carbonyl compounds, including the development of environmentally friendlier work-up procedures, represents a significant step towards greener fluorine organic chemistry.

Experimental Section

Direct Fluorination of 1,3-Dicarbonyl Compounds in Water: General Procedure

A solid or liquid 1,3-dicarbonyl compound (1 mmol) was placed in a glass flask (25 mL) equipped with a magnetic stirrer, 5 mL of deionized water were then added and the reaction system was intensively stirred (700–800 rpm) at 60–80 °C to obtain a well dispersed aqueous system. F-TEDA-BF_4 (1.10–2.10 mmol; 390–744 mg) was added in two portions to the aqueous dispersion and stirred at 60–80 °C until the KI (0.1 M) test showed consumption of the fluorinating reagent. The reaction mixture was cooled to room temperature and the resulting 2-fluoro- or 2,2-difluoro 1,3-dicarbonyls were isolated under the following "green" isolation procedures:

Method A: In the case of less hydrophobic 2-fluoro or 2,2-difluoro products (**2**, **3a**, **8**, **10a**), the reaction system was diluted with water (10 mL) and extracted with *tert*-butyl methyl ether (2 × 5 mL). The combined ether phases were dried over anhydrous Na_2SO_4 and solvent was then removed under reduced pressure.

Method B: In the case of liquid hydrophobic 2-fluoro or 2,2-difluoro products (**4b**, **10b**), the aqueous phase was

gently separated from the heavier dense products collected on the bottom of the reaction vessel. The isolated crude liquid products were then dried under vacuum and distilled to obtain the final pure 2-fluoro- or 2,2-difluoro-1,3-dicarbonyl compounds.

Method C: The reaction mixture was cooled in an ice-bath and solid crystalline 2-fluoro or 2,2-difluoro products (**6**, **10c**, **10d**) which crystallized efficiently from aqueous solution were filtered off under reduced pressure, washed with water (3×10 mL) and dried.

The 2-fluoro- or 2,2-difluoro-1,3-dicarbonyl compounds obtained were characterized by ^{1}H, ^{19}F, ^{13}C NMR and MS analysis and spectroscopic data for known compounds are presented in Supporting Information.

2-Benzoyl-2-fluorocyclohexanone (4b): Distillation under residue pressure; yield: 183 mg (83%); yellow viscous liquid; ^{1}H NMR: δ=1.85–2.16 (m, 5H), 2.52–2.62 (m, 1H), 2.67–2.77 (m, 2H), 7.44 (m, 2H), 7.56 (m, 1H), 8.01 (m, 2H); ^{19}F NMR: δ=- 151.5 (tm, J=17.1 Hz); ^{13}C NMR: δ=21.9 (d, J=7.6 Hz, C-4), 27.2 (C-5), 37.3 (d, J=21.5 Hz, C-3), 40.4 (C-6), 102.1 (d, J=198.5 Hz, C-2), 128.5, 129.9 in 133.7 (C_{ArH}), 134.4 (C_{Ar}), 194.7 (d, J=27.2 Hz, COPh), 204.0 (d, J=18.1 Hz, CO); IR: ν=2950, 2870, 1731, 1686, 1595, 1447, 1273, 1223, 1107, 843, 692, 616 cm^{-1}; MS: m/z=220 (M^+, 1%), 200 (14), 172 (18), 105 (100), 77 (65); HR-MS: m/z=220.0899, calcd. for $C_{13}H_{13}FO_2$: 220.0906; anal. calcd. for $C_{13}H_{13}FO_2$: C 70.90, H 5.95; found: C 70.79, H 6.07.

2,2-Difluoro-3-oxo-3,*N*-diphenylpropionamide (10d): Crystallization from water and distillation under residue pressure; yield: 239 mg (87%); white solid, mp 97.0–99.0; ^{1}H NMR: δ=7.15–7.20 (m, 1H), 7.31–7.36 (m, 2H), 7.47–7.57 (m, 4H), 7.62–7.67 (m, 1H), 8.13–8.18 (m, ArH+NH, 3H); ^{19}F NMR: δ=- 108.3 (bs); ^{13}C NMR: δ=110.8 (t, J=267.0 Hz, CF_2), 120.4, 126.0 128.9 and 129.3 (C_{ArH}), 130.5 (t, J=3.0 Hz, C_{Ar}), 135.1 (C_{ArH}), 136.4 (C_{Ar}), 159.3 (t, J=27.4 Hz, CONH), 187.3 (t, J=27.4 Hz, COPh); IR: ν=3334, 1721, 1683, 1599, 1537, 1448, 1159, 1123, 745, 685 cm^{-1}; MS: m/z=275 (M^+,15%), 120 (2), 105 (100), 77 (41); HR-MS: m/z=275.0758, calcd.for $C_{15}H_{11}F_2NO_2$: 275.0766; anal. calcd.for $C_{15}H_{11}F_2NO_2$: C 65.45, H 4.04, N 5.09; found: C 65.35, H 4.00, N 5.05.

2,2-Difluoro-4,4,4-trifluoro-3,3-dihydroxy-1-thiophen-2-yl-butan-1-one (14a): Preparative TLC (SiO_2, CH_2Cl_2/EtOH, 9.5:0.5); yield: 229 mg (83%); highly hygroscopic volatile white solid, mp 47.5–49.0 °C; ^{1}H NMR: δ=4.80 (bs, 2H, OH), 7.28 (t, J=4.7 Hz, 1H), 7.96 (d, J=4.7 Hz, 1H), 8.19 (bs, 1H); ^{19}F NMR: δ=- 81.6 (t, J=10.8 Hz, 3F, CF_3), −114.4 (qd, J=10.8 Hz, J=1.7 Hz, 2F); ^{13}C NMR: δ=92.9 (m, J=33.2 Hz, C-3), 111.1 (t, J=266.5 Hz, CF_2), 121.3 (q, J=288.3 Hz, CF_3), 129.8 (C_{ArH}), 137.4 (t, J=3.0 Hz, C_{Ar}), 138.2 (t, J=6.0 Hz, C_{ArH}), 139.2 (C_{ArH}), 183.5 (t, J=28.6 Hz, CO); MS: m/z=276 (M^+, 1%), 258 (4), 183 (3), 162 (3), 111 (100), 83 (9), 69 (5); HR-MS: m/z=275.9890, calcd. for $C_8H_5F_5O_3S$: 275.9879.

2,2-Difluoro-4,4,4-trifluoro-3,3-dihydroxy-1-phenylbutan-1-one (14b): Crystallization from $CHCl_3$/n-hexane 4:1; yield: 221 mg (82%); solid, mp 49.5–51.0 °C; ^{1}H NMR: δ=4.70 (bs, 2H, OH), 7.52–7.57 (m, 2H), 7.72 (d, J=6.1 Hz, 1H), 8.12 (d, J=6.1 Hz, 2H); ^{19}F NMR: δ= −1.6 (t, J=11.1 Hz, 3F, CF_3), −112.4 (qd, J=11.1 Hz, J=1.4 Hz, 2F); ^{13}C NMR: δ=93.3 (m, J=33.0 Hz, C-3), 111.8 (t, J=271.0 Hz, CF_2), 121.3 (q, J=287.5 Hz, CF_3), 129.3 (C_{ArH}), 131.0 (t, J=3.7 Hz, C_{ArH}), 132.2 (t, J=3.7 Hz, C_{Ar}), 135.6 (C_{ArH}), 191.9 (t, J=29.4 Hz, CO); IR: ν=3435, 1682, 1599, 1206, 1076, 960, 844, 723, 672; MS: m/z=270 (M^+, 3), 269 (M^+−1, 100), 253 (18), 233 (20), 155 (15), 147 (45), 121 (83); HR-MS: m/z=269.0237, calcd. for $C_{10}H_7F_5O_3$: 269.0239; anal. calcd. for $C_{10}H_7F_5O_3$: C 44.46, H 2.61; found: C 44.59, H 2.56.

2,2-Difluoro-4,4,4-trifluoro-3,3-dihydroxy-1-naphthalen-2-ylbutan-1-one (14c): Crystallization from $CHCl_3$/*n*-hexane, 4:1; yield: 294 mg (92%); solid, mp 75.5–77.0 °C; ^{1}H NMR: δ=4.91 (bs, 2H, OH), 7.61 (ddd, J=9.0 Hz, J=6.1 Hz, J=0.9 Hz, 1H), 7.69 (ddd, J=9.0 Hz, J=6.2 Hz, J=0.8 Hz, 1H), 7.88–8.07 (m, 4H), 8.73 (bm, 1H); ^{19}F NMR: δ=−81.5 (t, J=11.1 Hz, 3F, CF_3), −111.8 (qt, J=11.1 Hz, J=1.1 Hz, 2F); ^{13}C NMR: δ=92.9 (m, J=27.5 Hz, C-3), 112.4 (t, J=267.4 Hz, CF_2), 121.3 (q, J=288.7 Hz, CF_3), 124.7 (t, J=2.3 Hz, C_{ArH}), 127.3 (C_{ArH}), 127.8 (C_{ArH}), 129.4 (t, J=1.5 Hz, C_{Ar}), 130.0 (C_{ArH}), 130.2 (C_{ArH}), 130.4 (C_{ArH}), 132.1 (C_{Ar}), 133.9 (t, J=4.6 Hz, C_{ArH}), 136.3 (C_{Ar}), 190.8 (t, J=30.5 Hz, CO); IR: ν=3420, 1673, 1626, 1202, 1172, 1109, 1075, 972, 799; MS: m/z=320 (M^+, 20%), 155 (100), 127 (70), 77 (10); HR-MS: m/z=320.0465, calcd for $C_{14}H_9F_5O_3$: 320.0472; anal. calcd. $C_{14}H_9F_5O_3$: C 52.52, H 2.83; found: C 52.30, H 2.73,

Fluorination of 1,3-Dicarbonyl Compounds using N−F Reagents under SFRC; General Procedure

In the case of liquid substrates, 1 mmol of starting material and 1.10–2.10 mmol of finely powdered NFSi were mixed in a 15 mL glass vessel and the reaction mixture formed was then heated at 85 °C for 30–120 min. In the case of solid starting materials, the substrate and NFSi were triturated in a glass mortar to obtain a well homogenized mixture, quantitatively transferred to a glass vessel and heated at 85–95 °C to obtain a reactive molten phase system and the temperature was maintained for 2 h. The course of reaction was monitored by TLC and the resulting 2-fluoro- or 2,2-difluoro-1,3-dicarbonyls were isolated under the following "green" isolation procedures:

Method A: In the case of temperature-sensitive 2-fluoro-1,3-dicarbonyl products (**2**, **4a**) the reaction mixture was diluted with water (10 mL) and extracted with *tert*-butyl methyl ether (2×5 mL). The combined organic phases were then treated with a 40% aqueous solution of Na_2SO_3 (2×10 mL) and afterward dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the crude products obtained were purified by flash column chromatography on silica to yield the final pure fluoro-substituted 1,3-dicarbonyl products.

Method D: Various 2-fluoro- or 2,2-difluoro-1,3-dicarbonyl products (**4b**, **10b–d**) were isolated from the crude reaction mixture following distillation under reduced pressure.

Determination of Relative Rate Factors (k_{rel}) for the Fluorination of 1,3-Dicarbonyls in Various Reaction Media or under Solvent-Free Reaction Conditions; Typical Experimental Procedure

The relative rate factors of the studied 1,3-dicarbonyls (**3a**, **5**, **9a–c**, and **11**) were determined using the technique of competitive reactivity,[13,14] which was carried out as follows: 1 mmol of reference 3-oxo-3-phenylpropionic acid ethyl

ester **9a**, 1 mmol of the comparative 1,3-dicarbonyl compound (**9b, c**, **11**, **3a**, or **5**) and 1 mmol of fluorinating agent F-TEDA-BF_4 were dispersed or dissolved in 5 mL of the reaction media (pure H_2O, 0.05% aqueous SDS, anhydrous MeCN), or mixed when the reactivities were compared under SFRC. The reaction systems were stirred at 70 °C (solvents) or held at 90 °C (SFRC) for 10 h. Thereafter, the reaction mixtures were cooled to room temperature, extracted with *tert*-butyl methyl ether (15 mL) and the organic phases were then washed with 20 mL of water. After removal of the solvent under reduced pressure, the amounts (mmol) of α-fluoro-substituted products were determined from ^{19}F NMR spectra using octafluoronaphthalene as the internal standard. The relative reactivity expressed by the relative rate factor (k_{rel}) was calculated from the equation,[18] derived from the Ingold–Show relation:[19] $k_{rel} = k_A/k_B = \log [(A-X)/A]/\log [(B-Y)/B]$, where A (compared) and B (reference) is the amount (mmol) of starting material and X (compared) and Y (reference) the amounts (mmol) of corresponding products. The relative rate factors obtained shown in Table 3 are the average values of three independent measurements with 2.0% maximum error.

Supporting Information

General remarks, experimental protocols for large-scale synthesis, characterization data of products identified as the known compounds and copies of NMR spectra of new compounds are supplied in the Supporting Information.

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