Mild and Selective α-Fluorination of Carbonyl Compounds (ketones, 1,3-diketones, β-ketoesters, α-nitroketones, and β-ketonitriles) with *Selectfluor* (F-TEDA-BF_4) in Imidazolium ILs [BMIM/PF_6 or BMIM/NTf_2] with Brønsted-acidic IL [PMIM(SO_3H)/OTf] as Promoter

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Revised

Mild and Selective α-Fluorination of Carbonyl Compounds (ketones, 1,3-diketones, β-ketoesters, α-nitroketones, and β-ketonitriles) with *Selectfluor* (F-TEDA-BF_4) in Imidazolium ILs [BMIM/PF_6 or BMIM/NTf_2] with Brønsted-acidic IL [PMIM(SO_3H)/OTf] as Promoter

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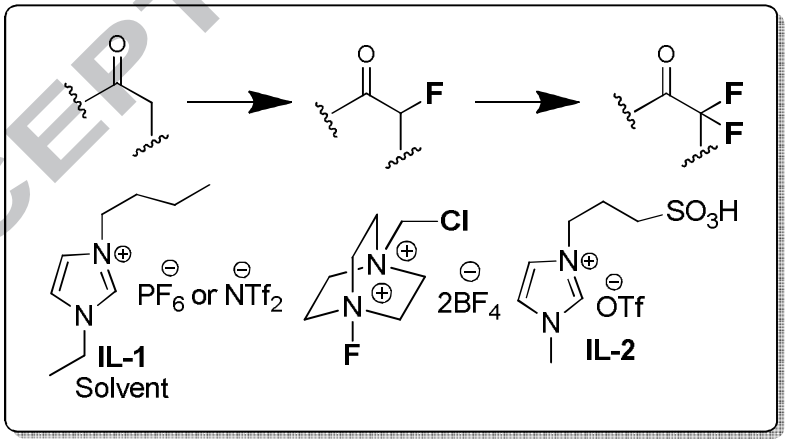
Abstract: Structurally diverse ketones, 1,3-diketones, and β-ketoesters, were selectively monofluorinated with *Selectfluor* (F-TEDA-BF_4) (1 equiv) in [BMIM][PF_6] as solvent and [PMIM(SO_3H)][OTf] as promoter under mild conditions. In selected cases, the monofluorinated products were transformed to the gem-difluoro derivatives by employing an additional equivalent of *Selectfluor,* and gem-difluoro-derivatives were synthesized directly from the substrates by employing 2 equivalents of *Selectfluor.* The method was extended to monofluorination of representative α-nitroketones and β-ketonitriles using [BMIM][NTf_2] without the need for promoter. The described method offers the added advantage of recycling and reuse of the IL solvent.



Keywords: α-fluorination of carbonyls; 1,3-diketones; β-ketoesters; α-nitroketones; Selectfluor; imidazolium-IL; Brønsted-acidic IL

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The ever increasing recognition of the importance of fluorinated organics as building blocks of pharmaceuticals, agrochemicals and functional materials has spurred rapidly growing interest in the development of mild and efficient synthetic methods for fluorine introduction. Strategic introduction of fluorine into organic compounds brings about dramatic changes in physical, chemicals and biological properties including increased metabolic stability, lipophilicity, bio-availability, and increased binding affinity to biological targets.[1-4]

The α-fluorinated carbonyl compounds are valuable building blocks of bioactive molecules, and development of fluorination methods for carbonyl compounds has been continuously evolving since the early 1980's starting with the use of XeF_2[5], $CsSO_4F$,[6] elemental fluorine[7-8], and HF/PhIO.[9] A number of two-step approaches have been reported involving deprotonation (with NaHMDS or LDA) followed by electrophilic fluorination with NFSi and NFOBS,[10] or by TBAH/NF_3O.[11]

With the ready availability of *Selectfluor* (F-TEDA-BF_4) as an inexpensive, stable, non-hydroscopic, and mild electrophilic fluorinating agent with broad-based application,[12,13] a new chapter in α-carbonyl fluorination opened up. Microwave assisted fluorination of 1-arylethanone in MeOH gave α-fluoroketones along with dimethyl acetals, which on hydrolysis could be converted to the α-fluoroketones in 65-85% yields.[14] However, competing ring fluorination occurred in this method with electron rich aryl groups.[14] Representative α-fluoroketones were prepared by employing *Selectfluor* with sulfuric acid as catalyst in MeOH or MeCN as solvent.[15] Microwave-assisted monofluorination of representative 1,3-dicarbonyl derivatives were reported with *Selectfluor* in MeCN, and difluorination could be effected by adding 2 equivalents of tetrabutylammonium hydroxide (TBDH) in MeOH /MeCN.[16] The natural progression of research

in this area has been to move toward "greener" methods that avoid the use of volatile organics and would preferably employ no base or additives. Along these lines representative 1,3-dicarbonyl compounds were fluorinated with *Selectfluor* in water by using surfactant[17] or under solvent-free conditions employing Accufluor™ or NFSi.[17b]

In 2002 we reported the first application of room temperature ionic liquids (RTILs) in electrophilic fluorination of arenes employing *Selectfluor*.[18] Our continuing interest in the application of imidazolium ILs as solvent and catalysts for electrophilic/onium ion chemistry,[19] and in electrophilic fluorination with the N-F reagents, provided the ímpetus for the present study to develop mild/selective fluorination protocols for a wide range of carbonyl compounds by using ILs as solvent/promoter without employing other additives, and with recycling and reuse of the IL. Given the importance of α-nitroketones and β-ketonitriles as highly versatile moieties in organic synthesis and limited previous work aimed at developing direct mild fluorination protocols for these compounds,[20] they were also included in our study.

A series of structurally diverse cyclic, acyclic and aromatic ketones were selectively monofluorinated by using 1.0 equivalent of *Selectfluor* in [BMIM][PF_6] as solvent and the Brønsted-acidic IL [PMIM(SO_3H)][OTf] as promoter (Fig.1),[21] in yields ranging from 89% to 56%.[22] Table 1 summarizes the outcomes along with the reaction conditions and the isolated yields.

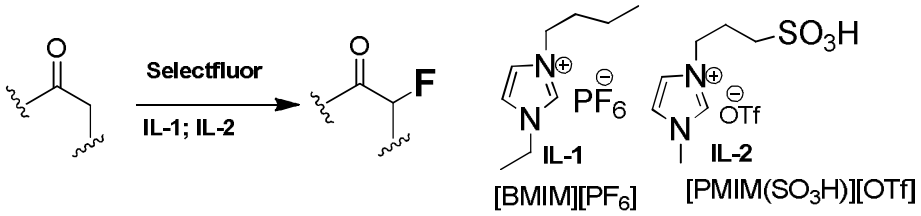
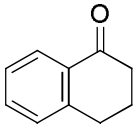
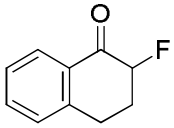
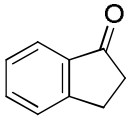
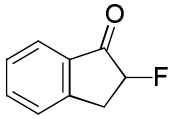
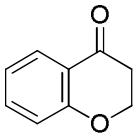
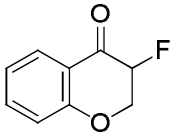
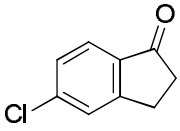
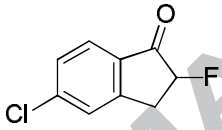
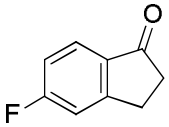
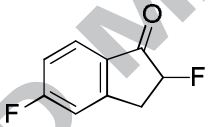
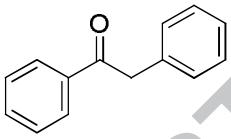
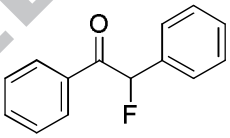
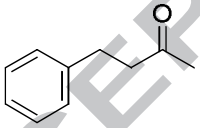
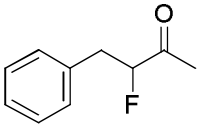
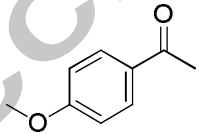
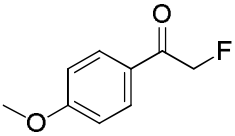
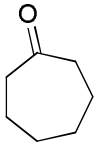
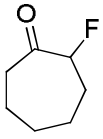


Figure 1. α-Fluorination of Ketones

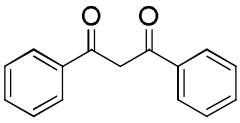
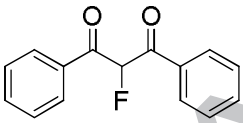
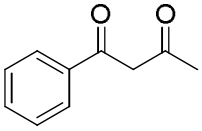
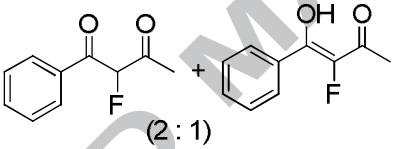
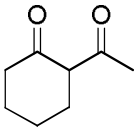
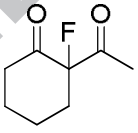
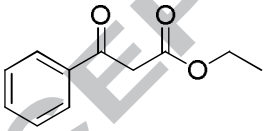
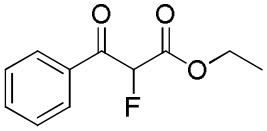
Table 1: Fluorination of Carbonyl Compounds[a]

Entry	Substrate	Product	Time (h)	Temp (°C)	Yield[b] (%)
1			16	80	87
2			16	80	84
3			12	80	83
4			15	80	82
5			15	80	86
6			5	80	89
7			15	80	71
8			16	80	56
9			15	80	69

[a] Carbonyl compound and Selectfluor (0.25 mmol each); [BMIM(SO_3H)][OTf] (0.5 mmol); [BMIM][PF_6] (25 equiv); [b] Isolated yield after chromatographic purification

With this data at hand, the method was then extended to representative 1,3-diketones and β-ketoesters, and the monofluorinated derivatives were obtained in isolated yields ranging from 87% to 72% (see Table 2). In the reaction of 1-phenyl-butane-dione (entry 2) the fluoro-enol-tautomer coexisted with the fluoro-diketone (see NMR data in supplementary information).

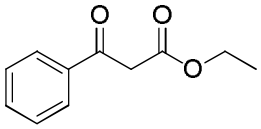
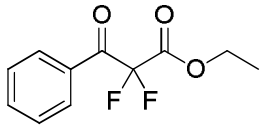
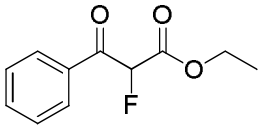
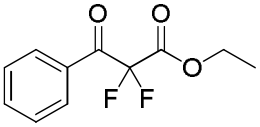
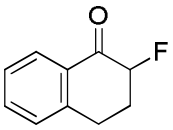
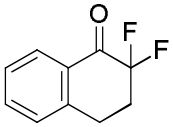
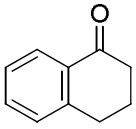
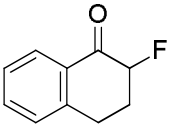
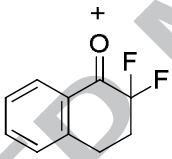
Table 2: Fluorination of 1,3-Dicarbonyl Compounds[a]

Entry	Substrate	Product	Time (h)	Temp (°C)	Yield[b] (%)
1			5	80	85
2		 (2 : 1)	7	80	72
3			7	80	82
4			5	80	87

[a] Carbonyl compound and Selectfluor (0.25 mmol each); [BMIM(SO_3H)][OTf] (0.5 mmol); [BMIM][PF_6] (25 equiv); [b] Isolated yield after chromatographic purification.

Direct difluorination employing 2 equivalents of *Selectfluor* and stepwise mono- to di fluorination were subsequently demonstrated via the examples shown in Table 3. In entry 4, a 2 : 1 mixture of difluoro- to monofluoro derivative was obtained.

Table 3: Direct Difluorination and Stepwise Mono- to Di-fluorination[a]

Entry	Substrate	Product	Time (h)	Temp (°C)	Yield[b] (%)
1			15	80	86
2			15	80	88
3			16	80	85
4		 + 	15	80	29 57

[a] Carbonyl compound (0.25 mmol); Selectfluor (1 equiv, except in runs 1 and 4 where 2 equiv was used); [BMIM(SO_3H)][OTf] (0.5 mmol); [BMIM][PF_6] (25 equiv); [b] Isolated yield after chromatographic purification.

The possibility to replace the IL-promoter for microwave (MW) was explored using the example in Table 1, entry 1. A comparable conversion could be achieved at 120 °C after 30 min irradiation but side-products/tar began to form. Increasing the temperature 150 °C led to more decomposition and lower conversion of the desired product. Based on this assay it was decided to continue to employ the promoter in place of MW.

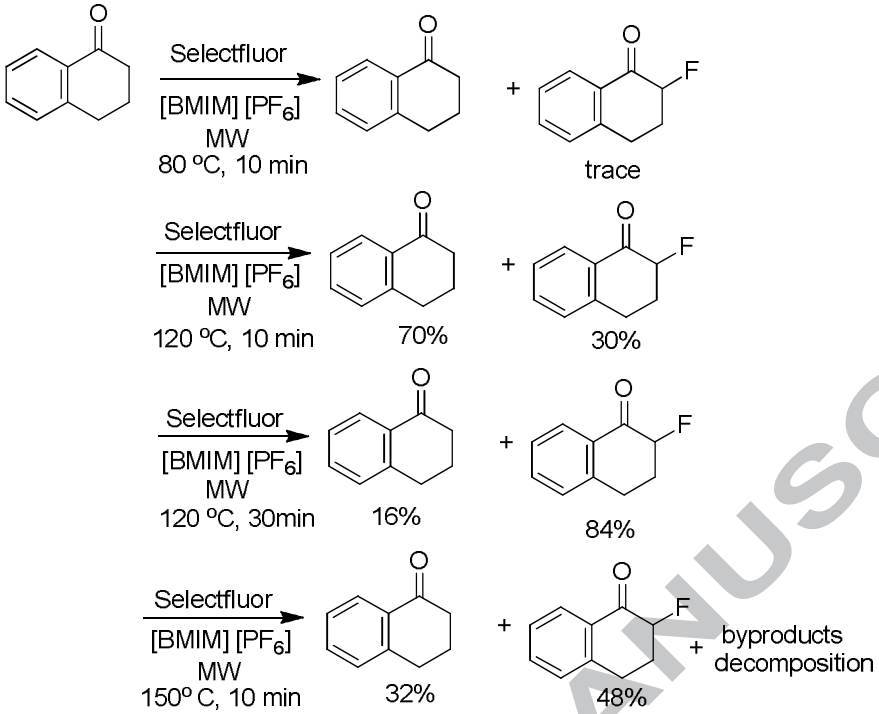


Chart 1. Application of microwave in place of IL promoter

The ability to synthesize the α-fluoro-nitro-carbonyl compounds by direct mild fluorination is highly desirable.

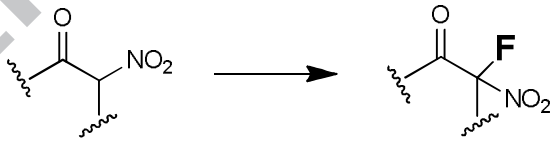
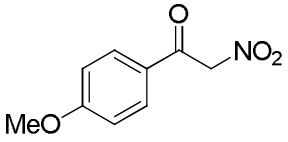
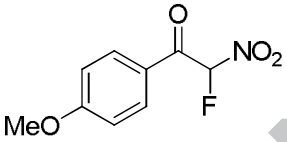
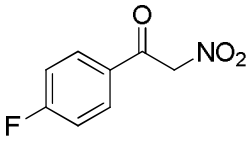
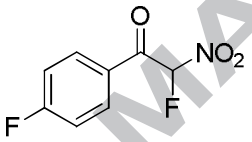
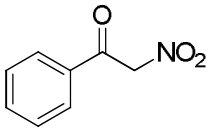
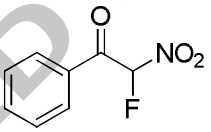
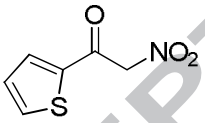
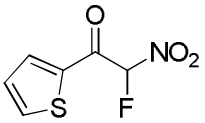
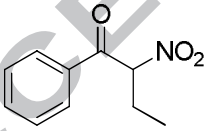
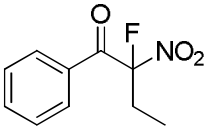


Fig 2. Direct fluorination of α-nitroketones

A previously reported attempt to synthesize the monofluoro-analog of benzoylnitromethane by using base/solvent/*Selectfluor* led instead to oxidation to benzoic acid.[20] The present study was extended to fluorination of α-nitroketones with reasonable success via the

examples shown in Table 4. Reactions were carried out in [BMIM][NTf_2] as solvent to improve solubility and lower the viscosity.[23] Control experiments indicated that addition of Brønsted acid IL was unnecessary and that reactions were cleaner without the promoter.

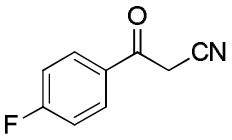
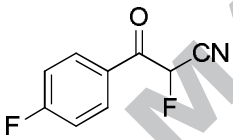
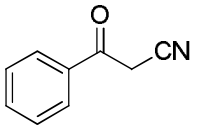
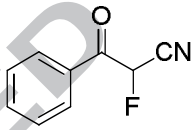
Table 4: Fluorination of alpha-Nitro-ketones[a]

Entry	Substrate	Product	Time (h)	Temp (°C)	Yield[b] (%)
1			15	75	56
2			10	75	63
3			10	75	61
4			10	75	65
5			15	75	49

[a] Carbonyl compound and Selectfluor (0.25 mmol each); [BMIM][NTf_2] (25 equiv); [b] Isolated yield after chromatographic purification.

Extension of the method to β-ketonitriles was less satisfactory and the limited substrates that were tested gave lower isolated yields of the monofluoro-derivative. In a previous study[20] employing a two-step deprotonation/fluorination approach α-benzoylacetonitrile reacted with NaH/THF/*Selectfluor* to give a mixture of mono- and difluoro compounds, and the difluoro-derivative was obtained in 60% yield by using 2.2 equivalents of *Selectfluor*. Clearly further studies are needed to improve on these methods.

Table 5: Fluorination of β-Ketonitriles[a]

Entry	Substrate	Product	Time (h)	Temp (°C)	Yield[b] (%)
1			15	80	32
2			15	80	29

[a] Carbonyl compound and Selectfluor (0.25 mmol each); [BMIM][NTf_2] (25 equiv); [b] Isolated yield after chromatographic purification.

Finally, an attempt to introduce a fluorine alpha to carbonyl in a Mannich base resulted in elimination (Figure 3).

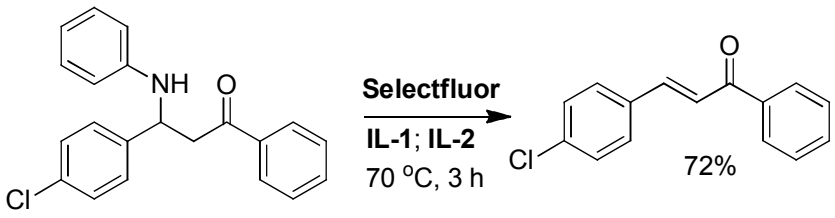


Fig 3. Attempted fluorination of a Mannich base

Focusing on the efficacy of the recycling and reuse of the IL solvent in this method, fluorination of ethyl benzoylacetate (entry 4; Table 2) was selected, and following an initial fresh run, the reaction was repeated for four more cycles.[24] The results sketched in chart 1 shows a gradual decrease in the isolated yields from 87% with the fresh IL down to 69% after a total of 5 consecutive reactions.

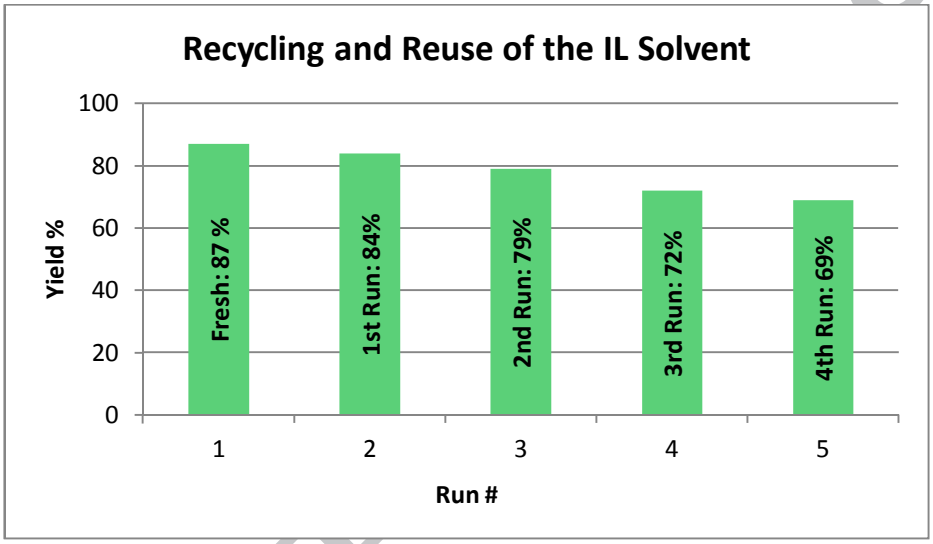


Chart 1.Recycling and reuse of [BMIM][PF_6] for entry 4 in Table 2

In summary a mild and selective fluorination method that is applicable to structurally diverse ketones, 1,3-diketones, and β-ketoesters has been presented that employs [BMIM][PF_6] as recyclable solvent, utilizes the readily available *Selectfluor*, and uses the Brønsted-acidic IL [PMIM(SO_3H)][OTf] as promoter. Selective monofluorination of α-nitroketones was also achieved in acceptable isolated yields by using [BMIM][NTf_2] as solvent without any promoter. Fluorination of β-ketonitriles proved more challenging with lower isolated yields and further studies are called for.

Supplementary Information (see footnote on the first page of this article)**:** experimental procedures, spectral/characterization data, and selected NMR spectra.

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21) The Brønsted acidic IL promotes the reaction via acid-catalyzed enolization

22) **Typical procedure for fluorination of carbonyl compounds:** The carbonyl compound (0. 25 mmol) and Selectfluor (0.25 mmol) were added to [BMIM][PF_6] (25 equiv.) in a Schlenk tube, and [PMIM(SO_3H)][OTf] (~ 0.5 mmol) was introduced at r.t. with stirring under a nitrogen atmosphere. The reaction mixture was stirred at 80 °C for the specified period of time (see Tables). After completion of the reaction (TLC monitoring), the reaction mixture was extracted several times with diethyl ether (4 x 10 mL), and the combined organic extracts was washed with aqueous saturated $NaHCO_3$ followed by water, dried ($MgSO_4$), and the solvent was evaporated under vacuum. The crude product was purified by silica gel column chromatography using 3 to 6% diethyl ether in hexane as eluent.

23) **General procedure for fluorination of *α*-nitro-ketones:** The *α*-nitro-ketone (0.25 mmol) and *Selectfluor* (0.25 mmol) were added to [BMIM][NTf_2] (25 equiv.) in a Schlenk tube at r.t., and the reaction mixture was stirred at 75 ^oC for 10 to 12 h. After

completion of reaction (TLC monitoring), the reaction mixture was extracted several times with 40% ethyl acetate in hexane (4 x10 mL) and the combined organic extract was washed with water, dried over $MgSO_4$, and the solvent was evaporated under vacuum. The crude mixture was purified by silica gel column chromatography using 12 % ethyl acetate in hexane as eluent.

24) **Recycling and re-use of IL (fluorination of ethylbenzoylacetate):** Following the extraction of the product from the IL phase in an earlier run (as described above), the Schlenk tube containing the IL was placed under vacuum for 10 h, at 70 ^{o}C. Upon cooling to r.t. it was re-charged with fresh substrate and *Selectfluor*, along with a small quantity (~ 0.3 mmol) of the fresh Brönsted acidic IL, and the reaction was repeated (control experiments in which additional [PMIM(SO_3H)][OTf] was not introduced resulted in noticeably lower conversions).