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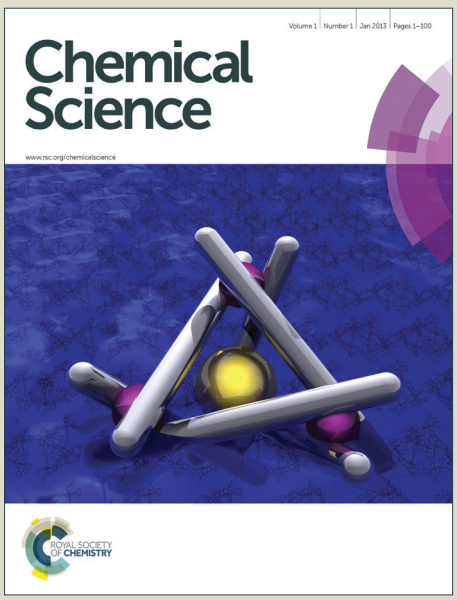

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Edge ARTICLE

Iodoarene-catalyzed fluorination and aminofluorination by Ar-I/HF·pyridine/*m*CPBA system†

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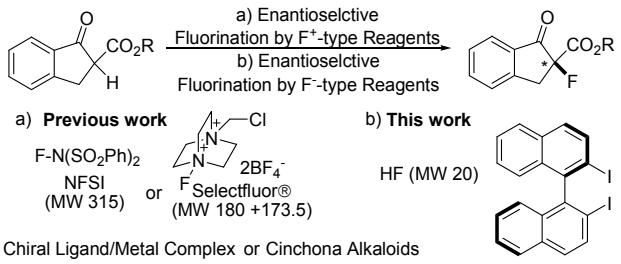
We have developed iodoarene-catalyzed nucleophilic fluorination of β-dicarbonyl compounds and intramolecular aminofluorination of ω-amino-alkenes using the same reaction condition. The key for this reaction is the *in situ* generation of a hypervalent iodine compound $ArIF_2$ by hydrogen fluoride, *m*CPBA and a catalytic amount of iodoarene. Preliminary trials of catalytic asymmetric nucleophilic fluorination were conducted.

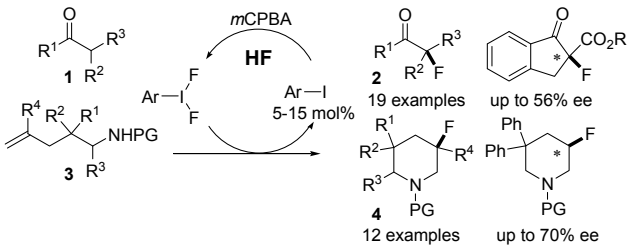
Introduction

During the last few decades, fluoro-pharmaceuticals have achieved great success in the drug market, with top-ten drugs such as Lipitor® and Seretide® being representative examples.[1] Natural products have been extensively used as drugs and as leads to drugs, while fluorine-containing natural products are extremely rare.[2] Organic synthesis is thus the main way to access new organofluorine compounds in medicinal chemistry. Direct fluorination is one of the most powerful synthetic methods for this purpose.[3] Among the fluorinating reagents, hydrogen fluoride or hydrofluoric acid (HF),[4] is economical and is the smallest reagent (MW=20) for direct fluorination. However, recent big progress in this field is mainly due to the success of electrophilic fluorination using F^+-type reagents, *N*-fluorobenzenesulfonimide (NFSI) (MW 315) and Selectfluor® (180+173.5), in particular, enantioselective electrophilic fluorination of β-ketoesters, for example (Scheme 1a).[3] Hence, the development of novel and efficient protocols for the fluorination of organic molecules using HF is of prime importance.[5,6]



Scheme 1. F^+- *vs* F^--reagents: Enantioselective fluorination of *β*-ketoesters.

(Difluoroiodo)arenes ($Ar\text{-}IF_2$) are hypervalent iodine compounds prepared from HF with iodosoarenes (Ar-I=O), and they can be widely used as fluorinating reagents without requiring organometallic reagents.[7,8] Hara and co-workers reported the fluorination of β-ketoesters using an HF/amine complex and *p*-tol-IF_2.[9] The method was extended by Kitamura and co-workers for performing *in situ* generated $Ar\text{-}IF_2$ from Ar-I=O and HF/H_2O.[10] Recently, Stuart and co-workers reported cyclic type fluoroiodane which can use fluorination of β-dicarbonyl compounds.[11] Meng and co-workers succeeded in the intramolecular aminofluorination of unsaturated amines using $Ph\text{-}I(OPiv)_2$ and HF/pyridine.[12] Moreover, the asymmetric version of this transformation was disclosed by Nevado and co-workers using chiral $Ar\text{-}IF_2$ reagents.[13] Although $Ar\text{-}IF_2$ reagents are attractive for fluorination, most of the protocols using $Ar\text{-}IF_2$ require a stoichiometric amount of hypervalent iodine reagents, an exception being the electrochemical fluorination reaction by Hara and Fuchigami.[14] Recently, Wang and co-workers partially overcame this catalytic problem in which intramolecular aminofluorination proceeded with a catalytic amount of NaI when pre-oxidized ω-*N*-chloroamino alkenes were used as substrates.[15] We report herein the iodoarene (Ar-I) catalyzed nucleophilic fluorination of β-dicarbonyl compounds with HF/pyridine in the presence of *m*CPBA to furnish α-fluorinated β-ketoesters, β-ketosulfones and β-ketoamides having a tertiary or quaternary fluorinated stereogenic center in good to high yields. The catalytic system is also applicable for the catalytic nucleophilic aminofluorination of ω-amino-alkenes to provide cyclic amines having a tertiary or quaternary fluorinated stereogenic center (Scheme 2). Preliminary results for catalytic asymmetric nucleophilic fluorination reactions of **1** and **3** are also discussed (Scheme 2, Scheme 1b). It should be noted that our method is the first example of enantioselective fluorination of β-ketoesters without using electrophilic fluorinating reagents such as Selectfluor® and *N*-fluorobenzenesulfonimide (NFSI) (Scheme 1).

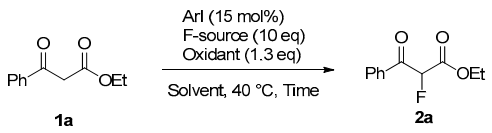


Scheme 2. Nucleophilic fluorination reaction using a catalytic amount of iodine reagent (5-15 mol%) and oxidant.

Results and discussion

We first investigated the catalytic fluorination of β-ketoesters **1** under a modified condition based on reported stoichiometric protocols.[9,10] The fluorination of β-ketoester **1a** with 3HF/Et_3N and *m*CPBA in the presence of 15 mol% of Ph-I in DCE at room temperature was examined. However, α-fluorinated β-ketoester **2a** was obtained in only 5% yield (Table 1, entry 1). Using aqueous HF (46%) or nHF·pyridine as a fluorine source significantly increased the yield to 52% or 66% (entries 2-3). Further improvement was observed by the portion-wise addition of *m*CPBA to a stirred solution to furnish **2a** in 79-94% yield within 2 h (entries 4-5). The iodoarene substituent had influenced the reaction (entries 6-8). While the yields decreased for electron-withdrawing groups on the aromatic ring such as CF_3 and CO_2H (entries 7-8), it improved for an electron-donating group such as 4-iodotoluene (99%, entry 6). The choice of solvent and oxidant are also important for the transformation (entries 9-17). It should be noted that the reaction proceeded even by the use of 5 mol% of 4-MeC_6H_4I, although the chemical yields were 64-67% (entries 18 and 19). The amount of nHF·pyridine could be reduced to 5 equivalents without major loss of chemical yield (80%, entry 20), while two equivalents of nHF·pyridine was not enough for the completion of the reaction even 24 h stirring (39%, entry 21). If iodoarene and oxidant were lacking, the reaction did not proceed (entries 22 and 23).

Table 1. Optimization of reaction conditions for fluorination **1a**.

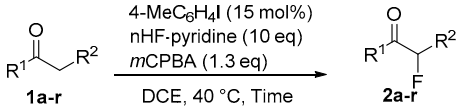


1a **2a**

Entry	ArI	F source (eq)	Solvent	Oxidant	Time (h)	Yield (%)[a]
1[b]	PhI	3HF·Et_3N	DCE	*m*CPBA	24	5
2[b]	PhI	46% HF aq.[c]	DCE	*m*CPBA	15	52
3[b]	PhI	nHF·pyridine	DCE	*m*CPBA	15	66
4[d]	PhI	46% HF aq.	DCE	*m*CPBA	2	79
5[d]	PhI	nHF·pyridine	DCE	*m*CPBA	2	94
6[d]	4-MeC_6H_4I	nHF·pyridine	DCE	*m*CPBA	1	99
7[d]	4-$CF_3C_6H_4I$	nHF·pyridine	DCE	*m*CPBA	24	62
8[d]	4-$CO_2HC_6H_4I$	nHF·pyridine	DCE	*m*CPBA	24	86
9[d]	4-MeC_6H_4I	nHF·pyridine	THF	*m*CPBA	-	NR
10[d]	4-MeC_6H_4I	nHF·pyridine	EtOAc	*m*CPBA	-	NR
11[d]	4-MeC_6H_4I	nHF·pyridine	CH_3Ph	*m*CPBA	0.5	56
12[d]	4-MeC_6H_4I	nHF·pyridine	CF_3Ph	*m*CPBA	1	67
13[d]	4-MeC_6H_4I	nHF·pyridine	DCE	$NaIO_4$	-	NR
14[d]	4-MeC_6H_4I	nHF·pyridine	DCE	TBHP	24	0
15[d]	4-MeC_6H_4I	nHF·pyridine	DCE	$Na_2S_2O_8$	24	25
16[d]	4-MeC_6H_4I	nHF·pyridine	DCE	Oxone®	24	12
17[d]	4-MeC_6H_4I	nHF·pyridine	DCE	50% H_2O_2	-	NR
18[d]	4-MeC_6H_4I[e]	nHF·pyridine	DCE	*m*CPBA	5	64
19[f]	4-MeC_6H_4I[e]	nHF·pyridine	DCE	*m*CPBA	2	67
20[d]	4-MeC_6H_4I	nHF·pyridine[g]	DCE	*m*CPBA	2	80
21[d]	4-MeC_6H_4I	nHF·pyridine[h]	DCE	*m*CPBA	24	39
22[d]	none	nHF·pyridine	DCE	*m*CPBA	-	NR
23	4-MeC_6H_4I	nHF·pyridine	DCE	none	-	NR

[a] Yield was determined by GC analysis. [b] The reaction was carried out at room temperature. [c] HF aq. (80 eq) was used. [d] Oxidant was divided into 2 aliquots, and then added. [e] 4-MeC_6H_4I (5 mol%) was used. [f] Oxidant was divided into 5 aliquots, and then added. [g] nHF·pyridine (5.0 eq) was used. [h] nHF·pyridine (2.0 eq) was used.

Table 2. Scope of the transformation of **1** to **2**.

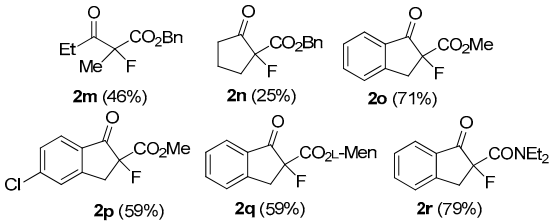


1a-r **2a-r**

Entry	1	R^1	R^2	2	Time (h)	Yield (%)[a]
1[b]	**1a**	Ph	CO_2Et	**2a**	0.5	98
2[b]	**1b**	2-MeC_6H_4	CO_2Me	**2b**	0.5	74
3[b]	**1c**	3-MeC_6H_4	CO_2Me	**2c**	0.5	62
4[b]	**1d**	4-MeC_6H_4	CO_2Me	**2d**	0.5	53
5[b]	**1e**	3-$MeOC_6H_4$	CO_2Me	**2e**	0.5	61
6[b]	**1f**	4-$MeOC_6H_4$	CO_2Me	**2f**	0.5	72
7[b]	**1g**	4-ClC_6H_4	CO_2Me	**2g**	0.5	59
8[b]	**1h**	4-BrC_6H_4	CO_2Me	**2h**	0.5	78
9[b]	**1i**	Cyclohexyl	CO_2Me	**2i**	1	91
10[b]	**1j**	3-Furanyl	CO_2Et	**2j**	0.5	64
11[b]	**1k**	Ph	$CONEt_2$	**2k**	0.5	66
12[c]	**1l**	Ph	SO_2Ph	**2l**	24	71

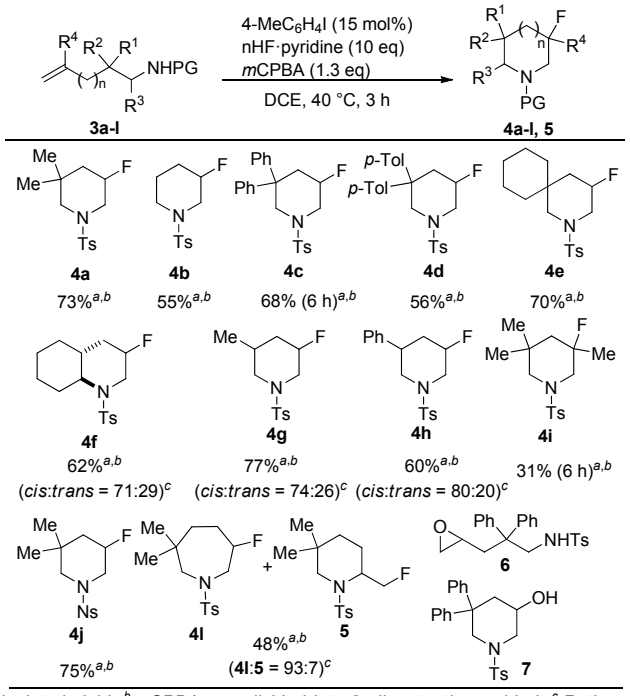
[a] Isolated yield. [b] *m*CPBA was divided into 2 aliquots, then added. [c] *m*CPBA (1.95 eq) was divided into 3 aliquots, then added.

With the optimized conditions in hand, we next evaluated the scope of β-ketoesters **1** (Table 2). The reaction condition was broadly adapted to a series of β-ketoesters **1a-j**, and the target compounds **2a-j** were obtained in good to excellent yields within 1 h (entries 1-10). Products with electron-donating (entries 2-6) and electron-withdrawing groups (entries 7 and 8) at the *ortho*, *meta* or *para* position of the benzene ring were obtained in good yields. The substrates having aliphatic (entry 9) and heterocyclic (entry 10) moieties were also nicely fluorinated under the same condition to provide **2i** and **2j** in good yields. Moreover, the reaction of β-ketoamide **1k** and β-ketosulfone **1l** gave desired products **2k** and **2l** in high yields (entries 11 and 12). Fluorination of cyclic and acyclic tertiary β-ketoesters **1m-q** was nicely converted to α-fluorinated-β-ketoesters **2m-q** having a quaternary stereogenic center in moderate to high yields. Tertiary β-ketoamide **1r** was also fluorinated in this condition to furnish **2r** in high yield (Scheme 3). Very recently, Kitamura and co-workers reported similar results of catalytic fluorination of α-methylene β-dicarbonyl compounds using 2-substrated-ArI(cat)/HF(aq.)/*m*CPBA system.[10d] However, they did not examine the fluorination reaction of α-methine β-dicarbonyl compounds providing fluorinated compounds having a quaternary carbon stereocenter, which is indispensable for the application to the asymmetric variants of this fluorination reaction discussed in the later part of this manuscript.



Scheme 3. Variation of products having a quaternary stereogenic center **2m**-**r** obtained by fluorination.

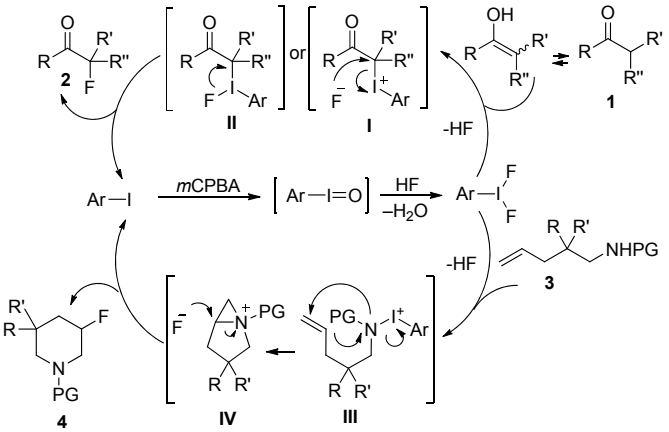
Table 3. Variation of substrates for intramolecular aminofluorination of alkenes.



[a] Isolated yield. [b] *m*CPBA was divided into 2 aliquots, then added. [c] Ratio was determined by ^{19}F NMR spectroscopy.

Our catalytic system consisting of 4-MeC_6H_4I/nHF·pyridine/*m*CPBA was found to be effective for not only the fluorination of 1,3-dicarbonyl compounds, but also for the intramolecular aminofluorination of terminal alkenes[16] (Table 3). 3-Fluoropiperidines **4a-j** and 3-fluoroazepane **4l** were obtained in good to high yields, almost independent of the substituent group of R^1 to R^4 (H, aliphatic, aromatic, and cyclic), under the same reaction conditions as the fluorination to β-dicarbonyl compounds. It should be noted that this aminofluorination reaction has not been performed by N-F-type reagents. The fused-ring compound **4f** was obtained in 62% yield with a 71:29 isomer ratio. The 1,3-disubstituted products **4g** and **4h** with moderate stereoselectivities were obtained in 77% and 60% yields, respectively. Tri-substituted olefin **3i** gave the quaternary alkyl fluoride **4i**, but the yield was 31%. Yield was comparable even if it changed the protecting group of nitrogen at aminoalkene from a tosyl to a nosyl group **4j**. The aminofluorination of 1-hexylamine derivative **3l** provided a mixture of 3-fluoroazepane **4l** and 2-fluoromethylpiperidine **5** in a 93:7 isomer ratio. A small amount of epoxides and 3-hydroxypiperidines such as **6** and **7** were observed as by-products in all cases (confirmed by ^{1}H- and ^{19}F-NMR spectral comparison of crude reaction mixtures to those of authentic samples). Hence, the use of other oxidants instead of *m*CPBA to avoid epoxidation of alkenes and the removable of water generated in situ would be helpful to improve the yields of the aminofluorination.

The reaction mechanism for the catalytic fluorination of β-dicarbonyl compounds and the intramolecular aminofluorination of alkenes are shown in Scheme 4. First, ArI=O is generated by ArI and *m*CPBA, confirmed by ^{1}H-NMR. The reaction of ArI=O with HF provides $ArIF_2$ *in situ*.[10] In the fluorination reaction of β-dicarbonyl compounds, $ArIF_2$ reacts with enolized β-dicarbonyl compounds **1** to provide hypervalent iodonium fluorides **I** with the release of HF. α-Fluorinated-β-dicarbonyl compounds **2** are produced by the nucleophilic attack of the fluoride anion with the re-generation of iodoarene, although a ligand coupling pathway via **II** might be an additional possibility. On the other hand, intramolecular aminofluorination starts with the oxidation of the nitrogen of aminoalkenes **3** by $ArIF_2$ to provide intermediates **III** with the exit of HF. Then, the nucleophilic attack from the olefin moiety to the nitrogen provides aziridinium intermediates **IV**, followed by the nucleophilic fluorination of **IV** affording fluoropiperidine **4**[13,15] with the reproduction of Ar-I. The epoxides such as **6** should not be intermediates, since **6** was not converted into **4c** under the same fluorination condition. The requirement of excess HF could be explained by assuming the following reasons; the formation of Ar-IF_2 from Ar-I=O is possibly reversible under this condition; the competitive hydroxylation reaction providing **7** was also detected in the last nucleophilic fluorination step from **IV** to **4**. Hence the use of excess amount of HF has the advantages of providing good yields.

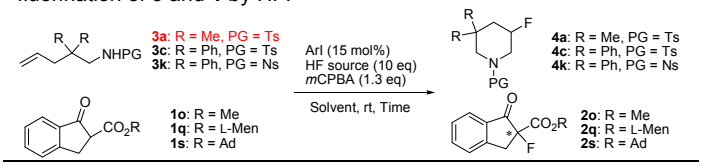


Scheme 4. Proposed reaction mechanism.

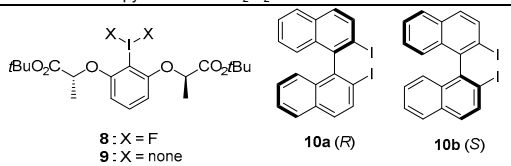
Finally, a preliminary study of enantioselective fluorination was conducted. While Nevado and co-workers reported the first enantioselective intramolecular aminofluorination of **3c** using a stoichiometric amount of chiral of (*R*,*R*)-*tert*-butyl lactate iododifluoride **8** to furnish **4c** with up to 81% ee,[13] catalyst **9** was found to be less efficient under our catalytic condition (43%, 0% ee, Table 4, entry 1).[17] After a brief screening of chiral iodoarene catalysts, (*R*)-binaphthyl diiodide **10a** was found to be effective for asymmetric induction. The desired reaction proceeded in moderate yields with good enantioselectivities of 45-70% ees (entries 2-6). The absolute stereochemistry of **4c** induced by catalyst **10a** was determined to be *R* by the comparison of the optical rotation of the reported one.[13] In the case of β-ketoesters **1o** **1q**, and **1s**, higher

enantioselectivity was observed for the fluorination of **1q** and **1s** having a sterically demanding adamantyl ester with 56-65% selectivities (entries 8-11). The enantioselectivity did not improve by the use of 50 mol% of **10a**, while the reaction time was shorten from 17 h to 3 h (entry 11). The enantioselective electrophilic fluorination of β-ketoesters using Selectfluor® or NFSI has been well-studied with excellent enantioselectivity obtained up to 99% ee,[18] however, these electrophilic fluorinating reagents are not cost-friendly. Less expensive fluorinating reagents such as HF or KF have been desired for a long time in industrial chemistry. Our reaction is the first example of the enantioselective nucleophilic fluorination of β-ketoesters using cost-friendly HF.

Table 4. Preliminary study of catalytic enantioselective nucleophilic fluorination of **3** and **1** by HF.[a]



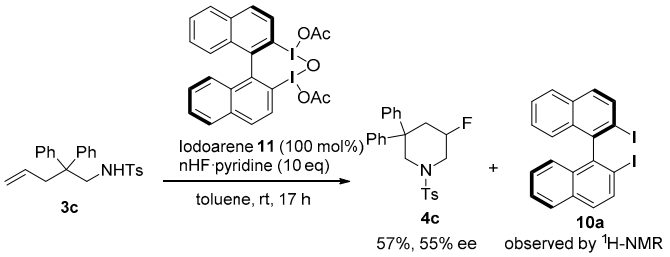
entry	3 or 1	ArI	HF source	Solvent	Time (h)	4 or 2	Yield (%)	Ee (%)[b]
1	**3c**	**9**	nHF·pyridine	toluene	72	**4c**	43	0
2	**3c**	**10a**	nHF·pyridine	CH_2Cl_2	12	**4c**	60	50 (*R*)
3	**3c**	**10a**	nHF·pyridine	toluene	12	**4c**	64	59 (*R*)
4[c]	**3c**	**10a**	46% HF aq.	toluene	24	**4c**	46	70 (*R*)
5[c,d]	**3c**	**10a**	46% HF aq.	toluene	45	**4c**	65	69 (*R*)
6	**3k**	**10a**	nHF·pyridine	toluene	24	**4k**	60	45
7	**1o**	**10b**	nHF·pyridine	toluene	3	**2o**	71	25
8	**1q**	**10a**	nHF·pyridine	toluene	42	**2q**	40	56 (de)[e]
9	**1q**	**10b**	nHF·pyridine	toluene	19	**2q**	63	65 (de)[e]
10	**1s**	**10a**	nHF·pyridine	toluene	17	**2s**	41	56
11[d]	**1s**	**10a**	nHF·pyridine	toluene	3	**2s**	51	56
12	**3a**	**10b**	nHF·pyridine	CH_2Cl_2	12	**4a**	68	3



[a] *m*CPBA was divided into 2 aliquots, then added. [b] Ees were determined by HPLC analysis. [c] The reaction was carried out at 0 °C. [d] Iodoarene **10a** (50 mol%) was used. [e] Des were determined by ^{19}F NMR analysis.

The further experiment was conducted for the elucidation of a reaction mechanism (Scheme 5). Stoichiometric amount (100 mol%) of oxygen-bridged hypervalent I(III)-I(III) reagent **11**[7c,20a] was examined for enantioselective intramolecular aminofluorination of **3c**. The results (57%, 55% ee) are almost the same as the catalytic system using **10a** (64%, 59% ee, Table 4, entry 3). Besides, the I(I)-I(I) reagent **10a** was observed in the end of the reaction. These results indicated that both oxygen-bridged hypervalent I(III)-I(III) compound and corresponding I(I)-I(III) species would be reactive for this transformation. This fact might be one of the reasons of moderate enantioselectivities observed, since two reactive species would responsible for the reaction.

The origins of the stereochemical outcome of the fluorination of **1** and aminofluorination of **3** are not known. However, the π-π interaction of phenyl group in **3** with naphthyl group in **10a** could play a key role for aminofluorinations of **3**, since the enantioselectivity was significantly dropped with the substrate **3a** having methyl group instead (Table 4, entries 2 vs 11). Further studies are surely required for this discussion.



Scheme 5. Enantioselective aminofluorination using a stoichiometric amount of hypervalent diiodine reagent **11**.

Conclusions

In conclusion, we have developed a catalytic fluorination system consisting of Ar-I(cat)/HF/*m*CPBA. The catalytic system is applicable to two kinds of reactions including the fluorination of β-dicarbonyl compounds and the intramolecular aminofluorination of ω-amino-alkenes. α-Fluorinated β-ketoesters, β-ketoamides, β-ketosulfones and cyclic amines having a tertiary or quaternary fluorinated stereogenic center can be nicely constructed by this method. Preliminary trials of catalytic asymmetric variants were also conducted, and promising enantioselectivities of the desired products were obtained, including the first example of enantioselective nucleophilic fluorination[19] of β-ketoesters. Further investigation of asymmetric reactions based on a novel design of iodoarenes[20-21] and application of the current reaction system to other fluorination reactions are in progress.

Acknowledgements

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Notes and references

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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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