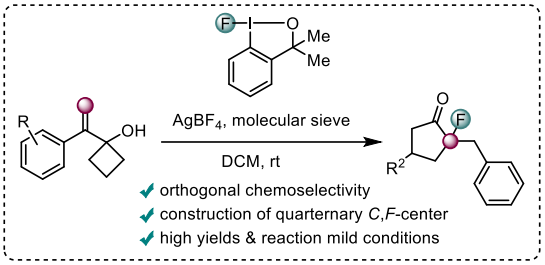
Hypervalent λ^3-Fluoro Iodane Triggered Semipinacol Rearrangements: Efficient Synthesis of Quaternary α-Fluoro Ketones

Pengyuan Zhao,[a][b]‡ Wanying Wang,[a]‡ Tanja Gulder*[a][b]

[a]Biomimetic Catalysis, Department of Chemistry, Technical University Munich, Lichtenbergstrasse 4, 85748 Garching, Germany

[b]Institute of Organic Chemistry, Faculty of Chemistry and Mineralogy, Leipzig University, Johannisallee 29, 04103 Leipzig, Germany

Supporting Information Placeholder

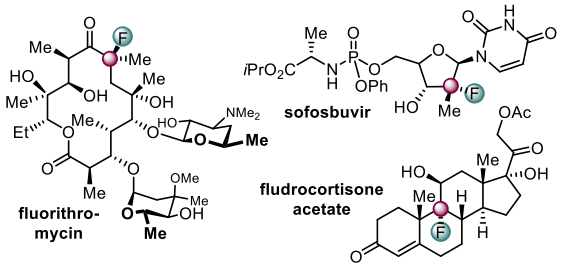


ABSTRACT: Hypervalent λ^3-fluoro iodanes have emerged as versatile reagents as they provide unusual fluorination selectivities under mild reaction conditions. Here, we report on adding a semipinacol rearrangement to the fluorination, aryl migration cascade reaction of styrene derivatives. Thus, various cyclopentanones became accessible in up to 96% yield all bearing quaternary *C,F*-carbon center adjacent to the ketone group. Such fluorinated structural motifs are difficult to build with previously established methods. Preliminary experiments on enantioselective processes validated that asymmetric transformations are likewise feasible.

Although fluorine and hydrogen atoms are similar in size the chemical and physical properties of fluorinated compounds differ significantly from those of their H analogs.[1] Fluorine-containing compounds exhibit superior and often unique chemical, physical, and pharmacological properties, such as high lipophilicity, bioavailability, and stability.[2] This makes organic molecules containing carbon-fluorine bonds so important for multiple disciplines, including materials science,[3] diagnostics,[3b, 4] drug development,[5] and agrochemistry.[6] The demand for fluorinated compounds is thus rapidly growing due to their significant impact on the progress in science and technology and as a consequence even in our daily lives.[7]

The carbon-fluorine quaternary center constitutes a particularly crucial structural feature in bioactive compounds,[8] as illustrated in Figure 1.[9] Despite significant efforts in the past decade, its construction, especially asymmetrically, remains a synthetic challenge to organic chemists.[8] This methodological deficit has resulted in less than 1% of all fluorine-containing medicines currently on the market or in clinical trials featuring carbon-fluorine quaternary centers.[10] Therefore, innovative approaches to forging such fluorine-containing structural motifs are urgently needed to fully realize the pharmaceutical potential of fluorine-containing compounds.

Figure 1. Examples of bioactive compounds containing quaternary *C,F*- center next to oxygenated carbon atoms.



The halogenation-triggered semipinacol rearrangement of allylic alcohols **1** is widely recognized as a straightforward and efficient method for assembling all-carbon quaternary carbon centers α to a carbonyl group **3** (Figure 2a).[11] In this process, a 1,2 migration of the axial substituent R in **1** is initiated by the formation of the electrophilic haliranium ion **2** (X = I, Br, Cl).[12] As a result, both the construction of the all-carbon quaternary center and ß-halogenation can be achieved simultaneously. Fluorination-induced semipinacol rearrangements have been reported by Kim et al. employing selectfluor. Here, a radical pathway was observed likewise producing the ß-fluorinated products **11** (Figure 2c, left).[13]

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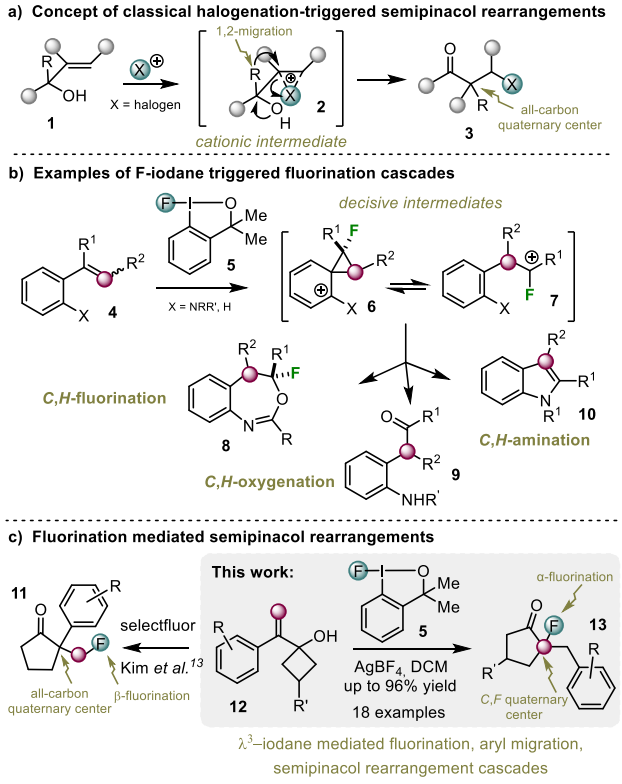
Recently, we[14] and others[15] discovered that hypervalent λ^3-fluoro iodane **5** offers access to novel reactivities and selectivities[16] compared to other popular fluorinating reagents, such as selectfluor, NFSI, and NFPy in various fluorination and fluorination-triggered transformations.[17] This includes for example direct *C,H*-fluorinations, *C,H*-oxygenations, and *C,H*-aminations (Figure 2b).[14a-c] Key to this orthogonal chemoselectivity and thus to structurally novel (fluorinated) scaffolds when employing **5** is the formation of the phenonium ion **6**. Depending on the reaction conditions in combination with the electronic properties of X, **6** can either be directly processed via the nucleophilic opening of the cyclopropyl moiety or rearrange to the more stable α-fluoro carbenium ion **7** followed by the trapping of the positive charge by a nucleophile. The latter reaction pathway leads exclusively to 1,2-aryl migration products such as **8** – **10**.

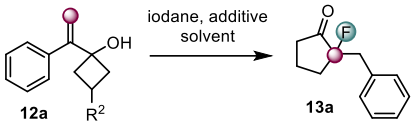
Figure 2. Concepts of a) halogenation-induced semipinacol rearrangement, b) chemodivergent hypervalent iodane fluorinations, and c) their combination for the synthesis of quaternary α-fluor ketones 12.



Inspired by this mechanism, we were eager to explore if fluorocation **7** can be further processed by other transformations than the direct addition of intra- and intermolecular nucleophiles. Considering the versatility of λ^3-iodane **5** triggered fluorinations of styrene derivatives **4**, we were drawn by the possibility of combining this method with the powerful semipinacol rearrangement. Based on the mechanistic scenario described above (Figure 1b), an atypical fluoro-induced semipinacol rearrangement cascade reaction would be accessible leading to cyclic fluoro ketones **13**. The transient electrophile **7** here would undergo *C,C*-migration in the neighboring carbinol under ring expansion (cf. Scheme 6) simultaneously forging the *C,F*-quaternary center. In this article, we report on a new approach involving a twofold rearrangement process of styrene derivatives **12** through a fluorination/1,2-aryl migration/semipinacol rearrangement. These reactions provide access to the challenging but versatile α-quaternary fluoro ketones **13** under mild conditions (Figure 1c, right). In addition, the first steps toward an enantioselective variant of this transformation have been explored.

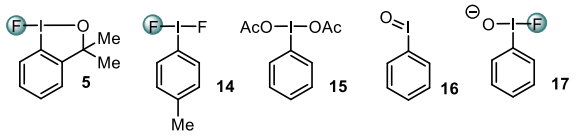
The initial focus of our study was on finding the optimal conditions for the fluorination, aryl migration, semipinacol rearrangement cascade by utilizing cyclobutanol **12a** as the model substrate (Table 1). All attempts to convert **12a** directly with F-iodane **5**, regardless of the solvent used, were unsuccessful (not shown). Only by adding Lewis acids in DCM in equimolar amounts to activate **5**,[18] the α-fluoro cyclobutanol **13a** was detected in the reaction mixture (Table 1, entries 2-3 and SI). $AgBF_4$ gave the best results (50% yield, Table 1, entry 2, and SI).[14c] The tetrafluoroborate played a crucial role in these transformations as only tetrafluoroborate salts delivered **13a** and other silver(I) salts, such as $AgNO_3$, did not give any product **12a** at all (entry 4). Employing the more reactive linear difluoroiodo toluene (**14**) with or without $AgBF_4$ resulted in a complete decomposition of **12a** or only the formation of traces of **13a** (entries 5 – 6). As BF_4^- can act as a fluoride source[15b] we also investigated other non-fluorinated iodanes, like e.g., PIDA (**15**) and **16** (entries 7-8).

Table 1. Optimization of the reaction conditions



entry	iodane	additive	solvent	yield[a]
1	**5**	-	DCM	-
2	**5**	$AgBF_4$	DCM	50%
3	**5**	$[Cu(CH_3CN)_4]BF_4$	DCM	34%
4	**5**	$AgNO_3$	DCM	-
5	**14**	$AgBF_4$	DCM	-
6	**14**	-	DCM	traces
7	**15**	$AgBF_4$	DCM	-
8	**16**	$AgBF_4$	DCM	45%
9	**5**	$AgBF_4$	DMF	13%
10	**5**	$AgBF_4$	MeCN	-
11	**5**	$AgBF_4$	$CHCl_3$	22%
12[b]	**5**	$AgBF_4$	DCM	90%[c]

All reactions were performed using **12a** (17.4 mg, 0.1 mmol, 1.0 eq.), iodane (0.1 mmol, 1.0 eq.), additive (0.1 mmol, 1.0 eq.), 4Å MS (25 mg) in 1 mL solvent for 8 h unless otherwise stated; [a]yields were determined by ^{1}H-NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard; [b]**12a** (84 mg, 0.3 mmol, 3.0 eq.), $AgBF_4$ (58.4 mg, 0.3 mmol, 3.0 eq.) were applied; [c]isolated yield.



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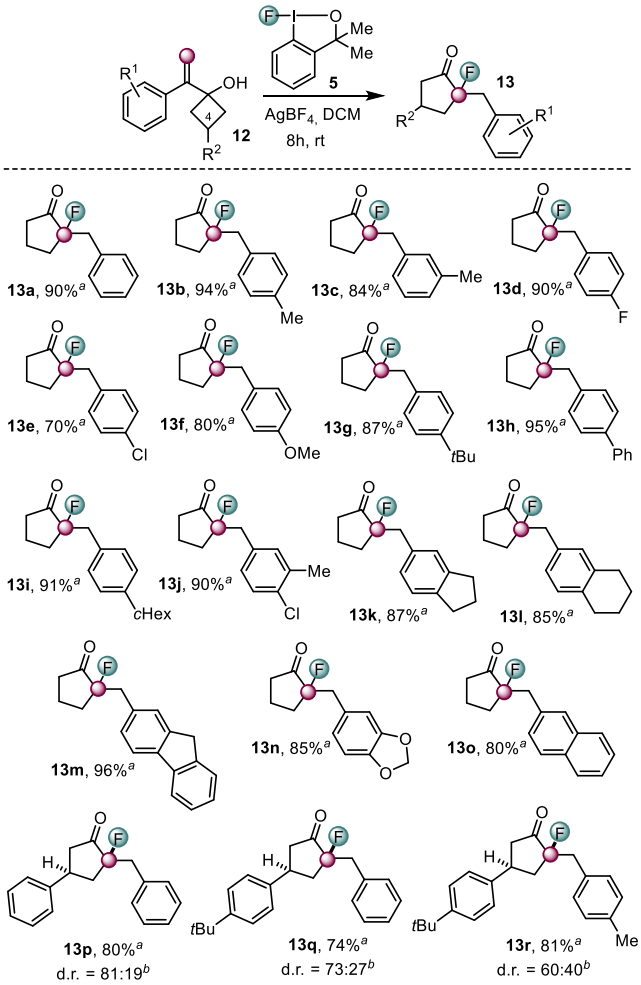
Interestingly, **16** also furnished the cyclobutanol **12a** albeit with a slightly lower yield of 45%. Here, we postulate fluoro oxygen iodane **17** as the actual fluorinating species which is formed in situ by the addition of fluoride to **15** (for the postulated mechanism see SI). To further improve the yield, various solvents, such as DMF, MeCN, and chloroform, were investigated (entries 2, 9-11, and SI). However, no or only poor conversion of cyclobutanol **12a** was detectable. A breakthrough was achieved by changing the equivalents of iodane **5** and the Lewis acid (see SI). By mixing three equivalents of both λ^3-fluoro iodane **5** and $AgBF_4$ with **12a** in DCM at room temperature (Table 1, entry 12) the reaction turned out to be very clean and the yield of the isolated product **12a** was enhanced to 90%.

Scheme 1. Scope of the fluorination, aryl migration, semipinacol rearrangement reaction

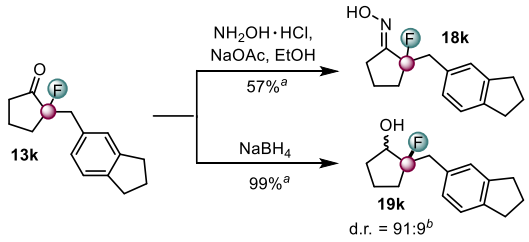


All reactions were performed with **12** (0.1 mmol, 1.0 eq.), **5** (84 mg, 0.3 mmol, 3.0 eq.), $AgBF_4$ (58.4 mg, 0.3 mmol, 3.0 eq.), 4Å MS (25 mg) in DCM (1 mL) at rt for 8 h. [a]isolated yields. [b]the diastereomeric ratio (d.r.) was determined by ^{1}H- and ^{19}F-NMR spectroscopy from the crude reaction mixture.

With the optimized reaction conditions in hand, we next explored the substrate scope of this triple cascade by applying a variety of styrene derivatives **12**. The results are summarized in Scheme 1. Overall, the conversion of the cyclobutanols **12** to the desired *α*-quaternary fluoro ketones **13** proceeded regio- and chemoselectively in good to excellent 70 – 96% yields. Side reactions, such as 1,1- or 1,2-difluorinations of the olefine moiety were not observed. Besides alterations in the aryl part, both electron-withdrawing and electron-donating substituents were equally well accepted, the method tolerated aromatic substituents at *C*-4 of the cyclobutane ring. The products **13p** – **13r** were formed in good yields (74 – 81%) but only as mixtures of diastereomers (up to d.r. = 81:19).

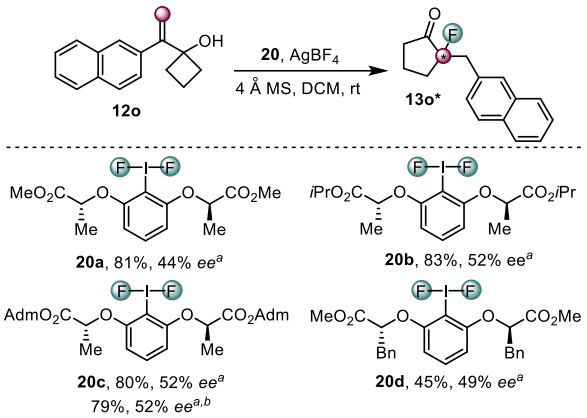
With this straightforward access to α-fluoro cyclopentanones **13**, a first glimpse of their synthetic utility was probed next by exemplarily transforming the carbonyl functionality next to the *C*,*F*-quaternary center (Scheme 2). Conversion of **13k** to the oxime **18k** proceeded smoothly. Likewise, the cyclopentanol derivative **19k** was obtained in almost quantitative yields and a high diastereomeric ratio of 90:10 (conditions have not been optimized) by reducing **13k** with $NaBH_4$.

Scheme 2. Further transformation of the α-fluoro ketones 13



Given the synthetic challenges associated with the formation of fluorinated quaternary carbon centers especially in an enantioselective manner, we conducted preliminary studies on turning this triple cascade into an enantioselective reaction by employing the chiral difluoro iodo recorcinols **20** instead of **5** (Scheme 3). The expected cyclobutanone **13o** was produced with *ee*'s of up to 52% when sterically demanding esters, such as *i*Pr or adamantly esters were present in **20**. Exchanging the substituents in the lactic acid part (**20d** (Bn) vs. **20a** (Me)) resulted in a significant drop in chemical yield. Although hypervalent iodane **20** loading could be reduced to 1.5 equivalents, further attempts to lower, or even to render the reaction catalytic,[19] were yet not successful (for more information see the Supporting Information).

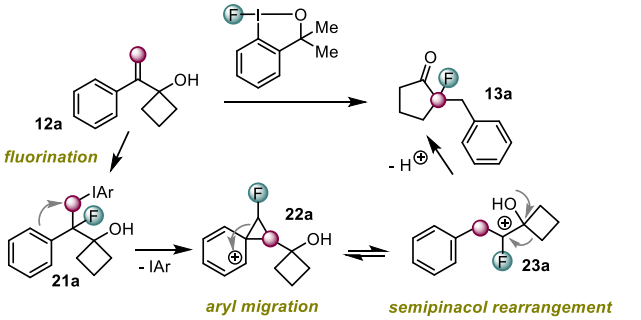
Scheme 3. Preliminary validation of enantioselective cascade reactions to 13



All reactions were performed with **12o** (22.4 mg, 0.1 mmol, 1.0 eq.), **22** (0.15 mmol, 1.5 eq.), $AgBF_4$ (29.2 mg, 0.15 mmol, 1.5 eq.), 4Å MS (25 mg) in DCM (1mL) at rt for 8 h. [a]The enantiomeric excess (*ee*) was determined by HPLC on a chiral phase (IA column) [b]The reaction was performed at 0 °C for 24 h.

In summary, we further demonstrated the power of F-iodanes in addressing orthogonal reactivity to well-established electrophilic fluorination agents, such as selectfluor. Because of the mild reaction conditions, F-iodane-mediated fluorinations can easily be combined with other transformations leading to efficient cascade reactions. Based on previous mechanistic investigations and the above results we hypothesize that after the regioselective addition of F-iodane **5** to the alkene moiety in **12** immediate substitution of the iodine(III) hypernucleofug occurs. Under dearomatization, the spirocyclic phenonium ion **22a** is generated and stabilizes itself by opening the cyclopropyl ring and restoring the benzene ring leading to the α-fluoro carbocation **23**. The transient cation gets finally trapped by *C*,*C*-migrative ring expansion, and with the formation of the carbonyl functionality. This mechanistic scenario led to the generation of **13** as a single regioisomer. Importantly, the first studies on the validation of enantioselectivity by employing chiral difluoro resorcinols **20** have been described and further efforts in this direction are underway in our laboratory.

Scheme 4. The postulated mechanism for the λ³-iodane fluorination triggered semipinacol rearrangement



ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization of all compounds, and further information on the substrate scope are presented in the Supporting Information. The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

* E-mail: Tanja.gulder@uni-leipzig.de

Author Contributions

P.Z. and W.W. conceived the project, designed and carried out the synthetic work, and analysed the data. T.G. conceived the project, provided guidance, and wrote the manuscript. All authors have given approval to the final version of the manuscript. ‡These authors contributed equally.

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