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Fluorinated Organic Molecules |*Hot Paper*|

A Fluorination/Aryl Migration/Cyclization Cascade for the Metal-Free Synthesis of Fluoro-Benzoxazepines

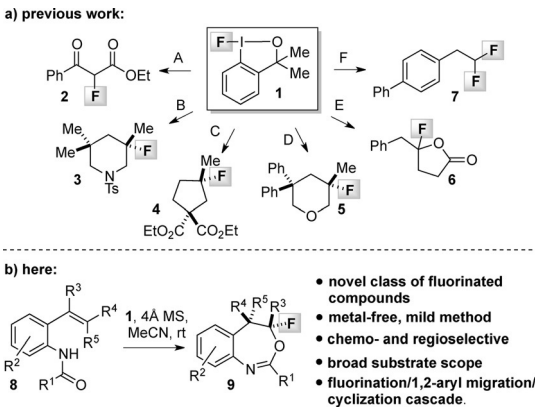
Anna Ulmer, Christoph Brunner, Andreas M. Arnold, Alexander Pöthig, and Tanja Gulder*[a]

Dedicated to Prof. Dr. Dr. h.c. mult. Gerhard Bringmann on the occasion of his 65th birthday

Abstract: Fluorinated organic molecules are of high interest for many applications across chemical and medical disciplines. Efficient methods for the synthesis of such compounds are thus needed. Within this work, application of the bench-stable cyclic hypervalent iodine(III) fluoro reagent **1** facilitated the development of an efficient, metal-free method for the preparation of the novel class of 4-fluoro-1,3-benzoxazepines starting from readily available styrenes. The efficacy and broad applicability of this concept is demonstrated by the synthesis of 20 structurally diverse congeners in high yields, regio-, and diastereoselectivities. The presented method provides complementary chemoselectivity when compared to the common, commercially available electrophilic fluorination reagents, such as selectfluor. First mechanistic investigations with isotopically labeled substrates reveal a complex reaction mechanism, proceeding via an unusual fluorination/1,2-aryl migration/cyclization cascade.

Although the first organofluoro compound was already described in 1835,[1] the knowledge associated with fluorine chemistry—and thus its application—limped behind that of the other halogens. It was not until the turn of the millennium that fluorination reactions have experienced a big boost, fueled by the introduction of well manageable reagents, and the development of the first selective fluorinations, etc. Since then, the field has rapidly evolved.[2] The enormous interest in C–F bonds goes far beyond organic chemistry and is due to the unique nature of this structural motif. With its small size and high electronegativity, a fluorine substituent influences the character of a molecule like no other element. Already a single fluorine atom can significantly alter solubility, bioavailability, and metabolic stability and thus often improves the chemical and pharmacokinetic properties, when compared to the corresponding C–H analogue.[2b,d,3] It is therefore not surprising that fluorine compounds play a key role in the pharmaceutical and agrochemical industry today.[2b,d,3,4] Organofluoro compounds have even found their way into newly developing fields, like, for example, non-invasive diagnostic techniques such as positron emission tomography (PET),[2b,5] or the development of 'intelligent' materials.[6] The tremendous benefit of the C–F structural scaffold is certainly accompanied with a huge demand for effective, generally applicable, and selective strategies to generate such bonds. This not only includes the development of new transformations in general, but also providing a tool box of mild, sustainable, and efficient protocols and reagents. In particular, the discovery of the robust fluoro aza reagents, such as selectfluor (**11**, see Table 1),[7] extensively inspired the field of electrophilic fluorinations, unlocking synthetic pathways to a large number of novel molecules.[2k] These fluorination agents, with most of them being commercially available today, suffer, for example, from high costs which is due to the employment of F_2 gas during their production.

Hypervalent (λ^3)-iodine-fluoro compounds constitute a rewarding alternative to such *N*-fluoro transfer agents. However, the high reactivity and chemical instability of the linear difluoro aryl compounds[8] have hampered their broad application. In 2013, Togni[9] and Stuart[10] reported on the preparation of the bench-stable, crystalline fluoro benziodoxole **1**[11] using easily accessible and cheap fluorides. In contrast to the structurally analogous Togni reagent,[12] which is successfully applied in trifluoromethylations, only a handful of applications of



Scheme 1. Applications of fluoro iodane **1**.

[a] *A. Ulmer, C. Brunner, A. M. Arnold, Dr. A. Pöthig, Dr. T. Gulder*
Department Chemie and Catalysis Research Center (CRC)
Technische Universität München
Lichtenbergstrasse 4, 85747 Garching (Germany)
E-mail: tanja.gulder@tum.de
Homepage: http://www.halogene.ch.tum.de

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the electrophilic F-source **1** are known to date (Scheme 1 a). Besides the monofluorination of 1,3-dicarbonyls reported by Stuart (reaction A),[10,13] the group of Szabó recently described the use of fluoro iodane **1** in geminal difluorinations[14] and fluorocyclizations[15a] of alkenes. In both cases, the addition of transition metal tetrafluoroborates, such as $AgBF_4$ (reaction F), $Zn(BF_4)_2{\cdot}xH_2O$ (reaction B and D), and $[Cu(MeCN)_4]BF_4$ (reaction C) was necessary to obtain the fluorinated products in good yields. These reports were complemented a few weeks ago by fluorolactonizations (reaction E).[15b] Also in this case, activation of **1** was needed to obtain product **6** in good yields.

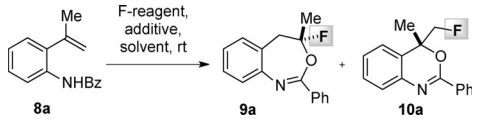
With our research focusing on the development and application of novel halogenation concepts, especially in the field of iodine(III)-mediated halofunctionalizations,[16] we were intrigued by the straightforward access to **1** and the opportunities thereby provided to the synthetic community. Despite the tremendous progress in fluorine chemistry and the utility of fluorinated (hetero)cycles, the electrophilic fluoroaddition to C–C double bonds is still problematic. This results from the reduced reactivity of the well-established fluoro electrophiles compared to their corresponding chloro, bromo, and iodo derivatives.

We now report on the development of a metal-free, mild, and easy-to-handle method for the generation of 4-fluoro-1,3-benzoxazepines **9** (Scheme 1 b). Using the obtained protocol, various structurally diverse derivatives of the pharmacologically interesting heterocycles **9** are accessible in a highly selective manner. Starting from *o*-styryl benzamides **8**, products **9** are formed via a complex fluorination/aryl migration/cyclization cascade, which is evident from our first studies on the reaction mechanism. This sequence proceeds with high efficiency and permits, for the first time, the direct synthesis of fluorinated 1,3-benzoxazepines.

Our studies on the fluoro iodoxole triggered generation of *F*-heterocycles commenced by treating benzamide **8a** with **1**, initially expecting a 6-*exo* cyclization with concomitant formation of an exocyclic fluoromethylene unit to give benzoxazine **10a** (Table 1).[17] As an entry point, we tested the optimized conditions for the electrophilic addition of **1** to olefins reported by Szabó et al.[14,15a] While the addition of $AgBF_4$ did not yield any fluorinated product (entry 1), the use of catalytic amounts of $Zn(BF)_4$ gave a single product. However, this was not the expected benzoxazine **10a**, but the fluorinated 1,3-benzoxazepine **9a** obtained in very good 89% (entry 2). Benzoxazepines are per se a class of highly bioactive compounds.[18] Nevertheless, efficient strategies to the 1,3-derivatives are generally rare[19] and do not exist at all for fluorinated analogues **9** obtained here. We thus embarked on the optimization and application of our observed reactivity to provide an efficient synthetic method to these exciting fluorinated scaffolds.

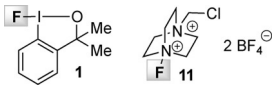
In-depth studies to improve the reaction conditions showed that the conversion of **8a** with **1** also occurred without a Lewis acidic additive. In this case, the reaction time slightly increased from 5 min to 15 min, but the heterocycle **9a** was obtained in similar yields (83%, entry 3). A screening of different solvents revealed that the transformation tolerates nonpolar as well as polar aprotic solvents (entries 4–6). Lewis basic and thus cation-stabilizing solvents dramatically accelerated the reaction rate (< 5 min; entry 5 and 6). To avoid possible hydrolysis of **1** under our reaction conditions, different desiccants were added to the reaction mixture (entries 7–9). The best results were achieved using 4 Å molecular sieves, which raised the yield of 4-fluoro-4,5-dihydro-benz[*d*][1,3]-oxazepine (**9a**) to 90% (77% isolated yield). Interestingly, the change of the electrophilic fluorine source from **1** to the fluoro aza compound selectfluor (**11**) was accompanied with a completely altered chemoselectivity. Now the oxazine **10a** was formed solely in 61% yield after 24 h (entry 10).[20,21] This result impressively shows that the fluoro iodine(III) reagent **1** is not only significantly more reactive but also provides a completely different chemoselectivity when compared to the common electrophiles such as **11**. With the application of **1**, novel paths in electrophilic fluorinations are now available, leading to unprecedented fluorinated scaffolds.

Table 1. Optimization of the reaction conditions for the synthesis of 4-fluoro-4,5-dihydro-benz[*d*][1,3]-oxazepine (**9a**).



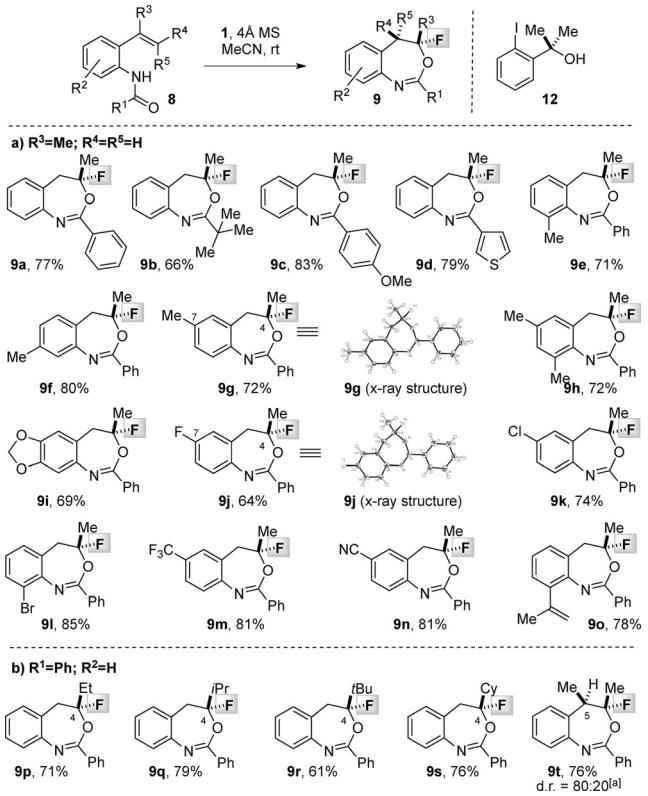
8a **9a** **10a**

	F reagent	Solvent	Additive	*t*	Yield [%][a]	**9a/10a**
1[b]	**1**	DCM	$AgBF_4$[c]	18 h	–[d]	–
2	**1**	DCM	$Zn(BF_4)_2{\cdot}xH_2O$[e]	5 min	89 (74)[f]	1:0
3	**1**	DCM	–	15 min	83	1:0
4	**1**	toluene	–	15 min	76	1:0
5	**1**	HFIP	–	< 5 min	81	1:0
6	**1**	MeCN	–	< 5 min	82	1:0
7	**1**	MeCN	Na_2SO_4	< 5 min	86	1:0
8	**1**	MeCN	$MgSO_4$	< 5 min	83	1:0
9	**1**	**MeCN**	**4 Å MS**	**< 5 min**	**90 (77)**[f]	**1:0**
10	**11**[g]	MeCN	–	24 h	61	0:1



[a] The yield was determined by ^{1}H NMR spectroscopy of the crude product using an internal standard. [b] The reaction was conducted at 40 °C. [c] 10 mol% $AgBF_4$. [d] 15% **8a** was re-isolated. [e] 5 mol% $Zn(BF_4)_2{\cdot}xH_2O$. [f] Isolated yield. [g] 2.4 equiv **11** were used.

With the optimized reaction conditions in hand, we explored the scope of this transformation by converting a variety of structurally diverse styrenes **8** into the corresponding benzoxazepines **9** (20 examples, Scheme 2). The fluorocyclization generally occurred in very good yields (61%–85%), forming exclusively the seven-ring products **9**. In all cases the carboxyl oxygen atom served as the only intramolecular nucleophile. Attack of the amide aromatic portion and a therewith associated carbocyclization leading to the likewise possible dibenzazepinone derivatives was never observed. In general, the reaction is very robust towards structural changes. Variation of the amide functionality showed that aryl as well as alkyl carbox-

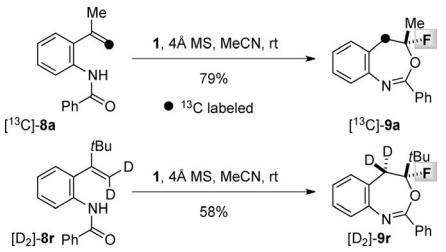


Scheme 2. Substrate scope of the metal-free fluorocyclization. 1.00 mmol (1.0 equiv) **8** together with 336 mg **1** (1.20 mmol, 1.2 equiv) and 4 Å molecular sieve (50 mg) were stirred at room temperature in 10 mL absolute MeCN (0.1 M).[a] d.r. was determined from the crude ^{1}H NMR spectrum.

ylates at the nitrogen are tolerated, leading to the corresponding benzoxazepines **9a**–**9d** in 66%–83% yield. Heteroaromatic moieties, such as 3-thiophene, were likewise accepted in this oxidative transformation (**9d**, 79% yield). Electron-rich as well as electron-poor substituents at the aniline delivered the desired heterocycles **9** in good to excellent yields (64%–85%). Ring closure proceeded smoothly under these mild conditions, even with substrates bearing strongly activated and therefore oxidation sensitive benzene rings, such as the dioxolane substituted styrene **8i**. No fluorination or oxidation of the aromatic system was detectable. The positions of the substituents had, furthermore, no significant impact on product formation. This was probed by treatment of different regioisomeric tolyl compounds **8e**–**8h** (71%–80% yield). The X-ray crystal structures, which were obtained for the tolyl **9g** and the fluoro benzene analogue **9j**, unambiguously verified the formation of an oxazepine ring system with a quaternary carbon center at C-4.

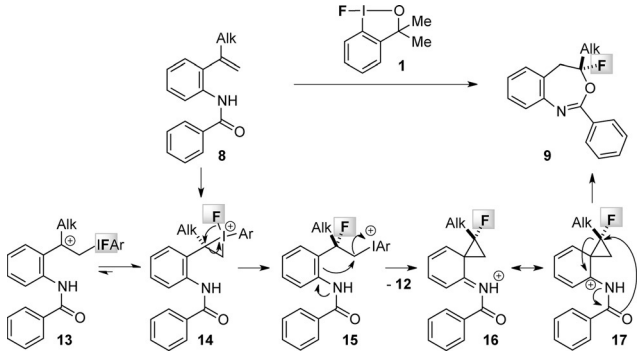
Substrates bearing differently substituted C–C double bonds were tested next (Scheme 2b), giving rise to benzoxazepines **9p**–**9t** in 61%–79%. Here, even the challenging, trisubstituted styrenes, such as the C-4 and C-5 methylated **8t**, were easily converted under the developed conditions (76%). The ring closure proceeded with good diastereoselectivities (80:20), the relative configuration of the methyl groups (*cis*) being conserved in the major diastereomer. To test the practicability of our fluorocyclization method, selected examples (**8a**, **8b**, and **8g**) were transformed on a gram scale, yielding the corresponding products in comparable yields. Besides heterocycles **9**, the only other component identified in the reaction mixture was the benzyl alcohol **12**, which is generated from **1** after fluorine atom transfer. Alcohol **12** was isolated in excellent 91% yield and was then re-subjected to generate reagent **1**. This significantly contributes to the sustainability of the described transformation.

The formation of the C-4 alkylated benzoxazepines **9** from styrenes **8** follows a complex mechanism, which formally involves a 7-*endo* cyclization followed by migration of the alkyl moiety from C-5 to C-4. To get insights into the detailed mechanism of this transformation, stable isotopically labeled starting materials [^{13}C]-**8a** und [D$_2$]-**8r** were treated with fluoro benziodoxole **1** under standard conditions (Scheme 3). Analysis of the products [^{13}C]-**9a** and [D$_2$]-**9r** revealed that the isotopically labeled atoms are exclusively located in the benzylic position of **9**, clearly pointing at a 1,2-shift of the backbone aryl moiety rather than migration of the alkyl group.



Scheme 3. Control experiments with stable isotopically labeled **8**.

Based on the obtained information, we conclude that the formation of benzoxazepines **9** follows a novel fluorination/1,2-aryl migration/cyclization cascade (Scheme 4).[15b] In the first step, the fluoro reagent **1** is nucleophilically attacked by the olefinic double bond, forming the iodo(III)ranium ion **14**. The three-membered heterocycle is then selectively opened at the benzylic position by an intramolecular 1,2-fluoro shift. A mechanism proceeding via the likewise conceivable benzylic carbocation **13** seems unlikely because of the good diastereoselectivity in the formation of **9t**. The 1,2-iodofluorine species



Scheme 4. Postulated mechanism for the formation of **9**.

15 obtained from **14** is stabilized by displacement of the iodobenzene **12** by nucleophilic attack of the aryl ring, furnishing the cyclopropyl compound **16**. The latter is in an equilibrium with phenonium ion[22] **17**.[14,23,24] Ring opening of the spirocyclopropyl ring in **17** takes place intramolecularly via a 6-*endo* cyclization with simultaneous ring expansion to the seven-membered oxazepine **9**. In contrast to previous reports,[23a,e] the nucleophilic attack of the amide oxygen here occurs regioselectively at the higher substituted and thus more electrophilic carbon atom of the cyclopropane unit. This exclusively leads to the C-4 alkylated products **9**.

In summary, we succeeded in developing an effective and transition-metal free pathway for the synthesis of novel 4-fluoro-1,3-benzoxazepines **9** starting from readily available styrenes **8** and the bench-stable, non-toxic, and easily obtainable fluoro iodane **1**. The presented cyclization reaction was conducted with a variety of structurally diverse substrates and proceeded with complete regioselectivity. Because of the mild reaction conditions of this oxidative transformation, even chemically sensitive functionalities, like, for example, electron-rich structural elements with a high susceptibility towards oxidation, were tolerated, giving the desired products **9** in high yields. Furthermore, the execution of this fluorocyclization is experimentally very simple and proceeds with very short reaction times. In contrast to traditional electrophilic fluorinating agents, such as selectfluor (**11**), the hypervalent fluoro iodane **1** dramatically differs in its chemoselectivity. While **11** facilitates the formation of oxazines **10**, the structurally novel seven-membered ring products **9** were obtained as the only product in all cases when **1** was applied. Mechanistically, the reaction follows a fluorination/1,2-aryl migration/cyclization cascade that opens access to a new class of fluorinated heterocycles, whose pharmacological potential needs to be explored in the future. In general, the presented fluorination method using hypervalent iodo-fluoro reagents constitutes a promising new tool, capable of creating unprecedented reactivities, thus pushing the boundaries in organofluorine chemistry.

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Keywords: 1,2-aryl shift · benzoxazepines · fluorination · hypervalent iodine

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