

# Fluorine-Directed Diastereoselective Iodocyclizations\*\*

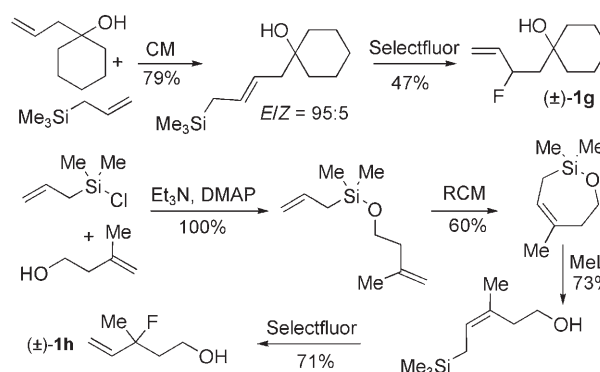
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In memory of Charles Mioskowski

The imposing number of known fluorinated  $\gamma$ -lactones and tetrahydrofurans, along with their derivatives, clearly reflects the importance of these molecules, especially in medicinal chemistry. For example, fluorinated nucleosides are prevalent among inhibitors of human immunodeficiency viruses.<sup>[1]</sup> The electrophile-induced cyclization of fluorinated precursors has emerged as a suitable route to prepare these heterocycles. This strategy was applied successfully to homoallylic fluorides for the preparation of diverse  $\alpha$ -fluoro-iodolactones.<sup>[2]</sup> In contrast, no iodolactonization and only two examples of iodoetherification of allylic fluorides have been reported, despite the undoubted value of the resulting products.<sup>[3]</sup> The lack of information in this area is due to the difficulties associated with the preparation of starting allylic fluorides featuring the strategically positioned carboxylic acid or alcohol group. Recently, we developed a robust route to allylic fluorides from allylsilanes which tolerates a large range of functional groups.<sup>[4]</sup> This led us to study the reactivity of allylic fluorides in iodine-induced cyclizations. Herein, we document that the iodolactonization and iodoetherification of allylic fluorides enable the streamlined synthesis of a diverse collection of  $\beta$ -fluoro- $\gamma$ -lactones and fluorinated tetrahydrofurans, respectively. The experimental results combined with theoretical studies provide evidence in support of an “inside fluoro effect” to account for the sense and high level of stereocontrol of these reactions.

The allylic fluorides **1a–i** were prepared to probe the effect of various substituents on the reaction feasibility and the stereoselectivity of a number of iodocyclizations

(Table 1). Compounds **1a–g** were prepared by using a cross-metathesis reaction followed by a fluorodesilylation of the resulting functionalized allylsilanes by using selectfluor.<sup>[4,5]</sup> The synthesis of **1h** and **1i** was more challenging and relied on a multistep ring-closing metathesis and ring-opening approach to access the allylsilanes required for subsequent electrophilic fluorinations.<sup>[5,6]</sup> The synthesis of the allylic fluorides ( $\pm$ )-**1g** and ( $\pm$ )-**1h** is shown in Scheme 1.



**Scheme 1.** Synthesis of allylic fluorides ( $\pm$ )-**1g** and ( $\pm$ )-**1h**.

CM = cross-metathesis, DMAP = 4-dimethylaminopyridine, RCM = ring-closing metathesis.

These compounds were subjected to iodocyclizations (Table 1). Most reactions were conducted at room temperature in the presence of  $I_2$  in  $CH_2Cl_2$  and aqueous  $NaHCO_3$  (conditions A) or in  $CH_3CN$  in the absence of base (conditions B). *N*-Iodosuccinimide (NIS) was used in  $CH_3CN$  (conditions C) for the ring closure of ( $\pm$ )-**1e** only. The iodolactonizations of **1a–d** led to the  $\beta$ -fluorinated iodolactones **2a–d** in high yields, with the exception of **1c**, which has the propensity to decompose (entries 1–4). Conditions A and B allowed for similar reaction efficiency and a high level of diastereocontrol, although the use of  $I_2$  in  $CH_3CN$  gave a cleaner crude mixture for the iodolactonization of **1d** (entry 4). The *syn* and *anti* fluorinated acids (+)-**1a** and (+)-**1b** gave the enantiopure  $\beta$ -fluoro- $\gamma$ -lactones (–)-**2a** and (–)-**2b**, respectively, with d.r. > 20:1 (entries 1 and 2). Compounds ( $\pm$ )-**1c** and ( $\pm$ )-**1d** with the fluorinated carbon atom as the single stereocenter were also converted into the desired lactones ( $\pm$ )-**2c** and ( $\pm$ )-**2d**, respectively, with excellent diastereoselectivity (> 20:1; entries 3 and 4). The iodoetherifications of the structurally related alcohols ( $\pm$ )-**1e** and ( $\pm$ )-**1f** were equally successful in delivering the fluorinated tetrahydrofurans ( $\pm$ )-**2e** and ( $\pm$ )-**2f** in high yields. The level

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[\*\*] We are grateful to the EPSRC (M.T.), the National Foundation of South Africa (K.T.), the EU (MEIF CT 2006 03970 (M.S.)), the National Institute of General Medical Sciences, and the National Institutes of Health (GM 36700 to K.N.H.) for financial support. We also thank the NSF-PACI and UCLA-ATS for computing sources.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

**Table 1:** Iodocyclization of **1a–j** and bromocyclization of **1e**.

Entry	Substrate	Product <sup>[a]</sup>	Conditions <sup>[b]</sup>	Yield [%] <sup>[c]</sup>	d.r. <sup>[d]</sup>
1			A B	86 94	> 20:1 > 20:1
2			A B	95 74	> 20:1 > 20:1
3			A B	24 25	> 20:1 <sup>[e]</sup> > 20:1 <sup>[e]</sup>
4			A B	48 72	> 20:1 > 20:1
5			A C	52 81	12:1 5:1
6			A	92	> 20:1
7			D	80	7:1
8			A	69	12:1
9			A	88	9:1
10			A	69	9:1
11			A B	100 100	2:1 2:1

[a] Major isomer. [b] A:  $I_2$ ,  $CH_2Cl_2$ /aqueous  $NaHCO_3$ ; B:  $I_2$ ,  $CH_3CN$ ; C: *N*-Iodosuccinimide,  $CH_3CN$ ; D: *N*-Bromosuccinimide,  $CH_3CN$ . [c] Yields of isolated products. [d] Determined by  $^1H$  or  $^{19}F$  NMR analysis of the crude reaction mixture. [e] Determined by  $^1H$  or  $^{19}F$  NMR analysis after purification.

of stereocontrol remained excellent for **2f** (d.r. > 20:1) but was slightly decreased for **2e** (d.r. = 12:1; entries 5 and 6). (±)-**2e** and (±)-**2k** were formed, respectively, in high yields but with more modest diastereoselectivity by using NIS or *N*-bromosuccinimide (NBS), (entries 5 and 7). The method was extended to the preparation of the fluorinated spiro derivative (±)-**2g** and of (±)-**2h** and (±)-**2i**, each of which possesses a methylated quaternary center (conditions A). The d.r. values were equal or superior to 9:1 (entries 8–10). The relative stereochemistry was assigned by NOE experiments for **2a–i** and by X-ray diffraction analysis for (±)-**2d**.<sup>[5]</sup> Both the relative and the absolute configuration of (–)-**2b** was confirmed by X-ray crystallography.<sup>[5]</sup> Compounds **2a–i** all featured a *syn*relationship between the fluorinated and the newly formed stereogenic centers. A control experiment served to support the role of the fluorine substituent, which appears to be a very effective *syn*stereodirector for these reactions. Cyclization of (–)-**1j** afforded (+)-**2j** in quantita-

tive yield but with a significant loss of stereoselectivity (entry 11). The selectivities summarized in Table 1 are either similar to or an improvement on those reported in the literature for the iodocyclizations of allylic alcohols, ethers, or amines.<sup>[7]</sup>

The remarkable diastereoselectivity of the iodolactonizations prompted us to carry out theoretical studies to determine the origin of the stereoselectivity in these fluorine-directed cyclizations.<sup>[8]</sup> The preferential conformations of starting materials **1a** and **1b** as well as the relative energies of the stereoisomeric lactones **2a–c** and **2j** are given in the Supporting Information. The products observed experimentally are the most stable, but the relative energies between stereoisomers are within 1 kcal mol<sup>–1</sup> of each other and do not explain the high diastereoselectivity for the iodolactonizations. The reactions are likely to be under kinetic control as the product ratios do not change over time under conditions A or B. Optimization of the geometry of an unsubstituted iodonium ion was carried out and showed that the iodonium complex lies between an iodonium ion and an iodonium– $\pi$  complex. The calculated bond lengths (1.44 Å for C–C and 2.29 Å for C–I) agree with previous experimental results and are an improvement on earlier theoretical studies.<sup>[9]</sup> Rotamers of iodonium complexes **3–5** substituted with an ethyl, a fluoromethyl, and a fluoroethyl group, respectively, were considered. For the ethyl-substituted iodonium **3**, rotamers that place the methyl group *anti* or *outside* are equally stable. The rotamer with the methyl group *inside* is higher in energy, since this conformer is more sterically hindered. For the fluoromethyl-substituted iodonium complex **4**, the fluorine substituent prefers to reside *inside* by 3 kcal mol<sup>–1</sup> with respect to the *outside*, and 5 kcal mol<sup>–1</sup> with respect to the *anti* arrangements. In the fluoroethyl iodonium complex **5**, the most stable rotamers **5<sub>inside, outside</sub>** and **5<sub>inside, anti</sub>** are equal in energy (Figure 1).

Transition structures necessary for the attack of a carboxylate or alkoxide on an  $I_2$ –alkene complex were located. The  $I_2$ – $\pi$  complex is loosely associated, with the C–C bond length being the same as an uncoordinated alkene (1.34 Å); the C–I bonds are longer (3.14 Å) than those of the iodonium ion. Attack of a formate ion ( $HCOO^-$ ) on an  $I_2$ –ethylene complex was examined. Transition state **6** leads to an

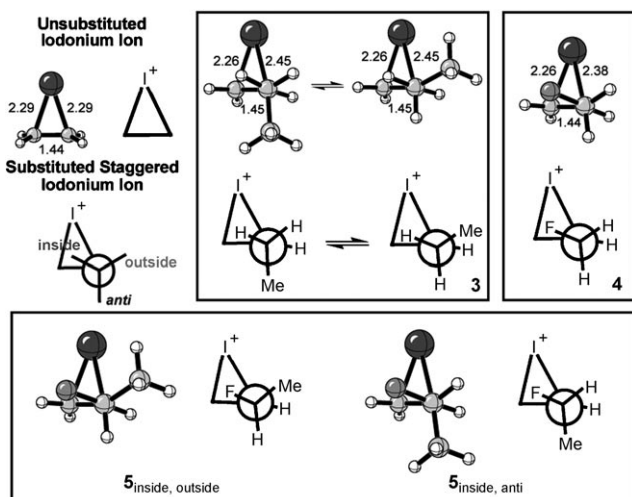


Figure 1. Most stable rotamers for substituted iodonium ions, 3–5.

iodide ion complexed with the iodoformate product. The two iodoformates can interconvert via TS **7** (Figure 2).

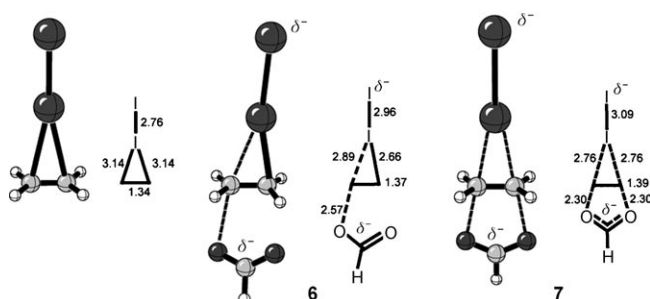


Figure 2. Transition state located for  $\text{HCOO}^-$  addition to an  $\text{I}_2$ -ethylene  $\pi$  complex.

The preferential conformations of transition states substituted with ethyl, fluoromethyl, or fluoroethyl groups were investigated. The attack of one of the formate oxygen atoms on the more substituted carbon atom occurs with the forming bond lengths consistently between 2.6 and 2.8 Å. The formate ion approaches the alkene at an angle of around  $110^\circ$ , thus indicating attack on the backside of the  $\sigma_{\text{C-I}}^*$  bond.<sup>[10]</sup> As shown in Figure 3 for the ethyl-substituted  $\text{I}_2$ - $\pi$  complex, the second oxygen atom may be either proximal or distal to the alkene. A proximal orientation provides a stabilizing electrostatic interaction between the negatively charged oxygen atom and the positively charged carbon atoms of the  $\text{I}_2$ - $\pi$  complex. The resulting transition state is at least 4 kcal mol $^{-1}$  more stable than those with the second oxygen atom located distal.

The transition states for *inside*, *outside*, and *anti* conformations of Me and F<sup>[11]</sup> were considered. The relative enthalpies are given in the Supporting Information, and the most stable conformers are shown in Figure 4.

The fluorine substituent in **8** prefers to reside *inside* rather than *outside* by 1 kcal mol $^{-1}$ . An allylic methyl group shows a

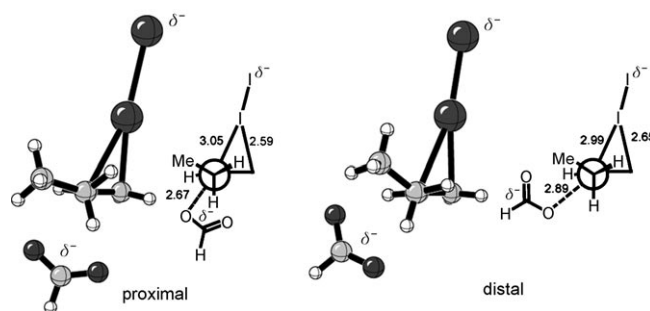


Figure 3. Transition state for  $\text{HCOO}^-$  attack on an ethyl-substituted  $\text{I}_2$ - $\pi$  complex.

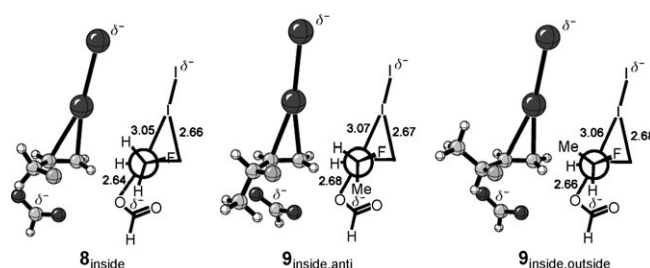


Figure 4. Most stable rotamers for TS **8** and **9**.

slight preference for *anti* versus *outside*. When fluoro and methyl groups are present, rotamers **9**<sub>inside,anti</sub> and **9**<sub>inside,outside</sub> are equal in energy because both feature the fluorine substituent *inside*, and the methyl group has little conformational preference for the *anti* versus *outside* arrangement. These isomers are preferred over those with the fluorine substituent *outside* by 1 kcal mol $^{-1}$  and over the fluorine substituent *anti* by 3 kcal mol $^{-1}$ .

Transition structures for intramolecular etherification of **1e** were located (Figure 5). Although less symmetric transition structures were located, these were higher in energy than **10** and **11**. The reaction path is likely to involve a two-step no-intermediate mechanism as proposed by Singleton et al. for reactions of singlet oxygen.<sup>[12]</sup> In transition structures **10** and **11**, the fluorine substituent prefers to reside *inside* by 2.1 kcal mol $^{-1}$ .

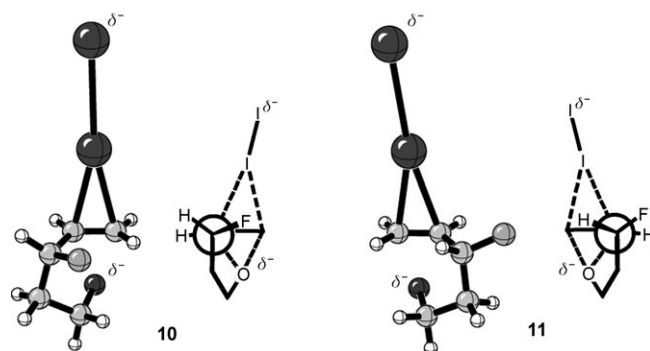
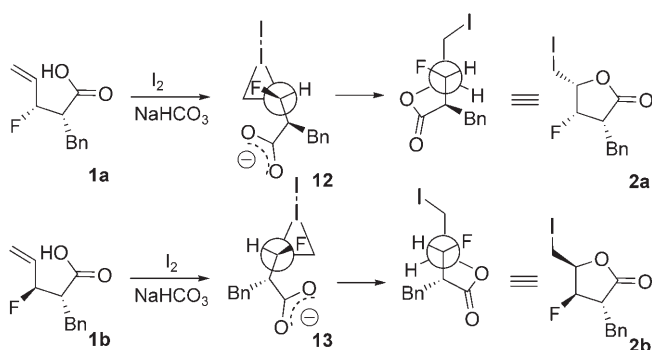


Figure 5. Intramolecular etherification TS **10** and **11**.

An *anti* fluorine substituent aligns the electron-withdrawing  $\sigma_{\text{C-F}}^*$  orbital with one of the C–I bonds, thereby destabilizing the  $\text{I}_2$ – $\pi$  complex. In comparison with the iodonium ions, preference for the fluorine substituent *inside* is lower in the  $\text{I}_2$ – $\pi$  complex as this complex is neutral compared to the positively charged iodonium ion. An *inside* fluorine substituent minimizes the interaction between the  $\sigma_{\text{C-F}}^*$  orbital and the C–I bond. The positioning of the fluorine substituent *inside* also enables its lone pairs of electrons to stabilize the partial positive charge of the  $\text{I}_2$ – $\pi$  complex. Previous studies have shown that the fluorine substituent of the allylic fluorides prefer to reside *inside* in polar cycloaddition transition states with nitrile oxides and prefer *inside* or *outside* positions in nonpolar cycloaddition transition states with butadiene.<sup>[13]</sup> In  $\text{I}_2$ – $\pi$  complex, an *anti* fluorine substituent destabilizes the iodonium ion and is disfavored; an *inside* fluorine substituent is stabilizing and preferred.

The proposed conformers for the diastereomeric  $\text{I}_2$ – $\pi$  complex **12** and **13** feature the fluorine substituent *inside* and the alkyl group *anti*, which may easily form the major fluorinated lactones that are observed experimentally. The internal carboxylate groups that adopt the proximal orientation reside in a nearly ideal position for backside attack on the iodonium ion. These models clarify how the allylic fluoride dictates the stereochemical outcome of these reactions. Without fluoro substitution neither the iodonium ion nor the iodonium– $\pi$  complex shows any preference for *syn* or *anti* products, in agreement with the experimental data for cyclization of (–)-**1j** (Scheme 2).



**Scheme 2.** Most stable rotamers of **12**–**13**. Bn = benzyl.

In conclusion,  $\beta$ -fluorinated  $\gamma$ -lactones and tetrahydrofurans are now accessible by iodocyclization of various allylic fluorides. The fluorine substituent acts as a highly efficient *syn*-stereodirecting group for the ring closure. The “*inside* fluoro effect”, which accounts for the observed selectivity, may prove useful for predicting the stereochemical outcome of a host of electrophilic reactions with allylic fluorides. The results are consistent with the “*inside* alkoxy effect” that

accounts for the iodocyclizations of allylic ethers or alcohols.<sup>[7d]</sup>

Received: July 31, 2007

Published online: November 16, 2007

**Keywords:** density functional calculations · fluorine · lactones · stereoelectronic effect · tetrahydrofurans

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