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Indium-catalyzed C–F Bond Transformation through Oxymetalation/β-fluorine Elimination to Access Fluorinated Isocoumarins

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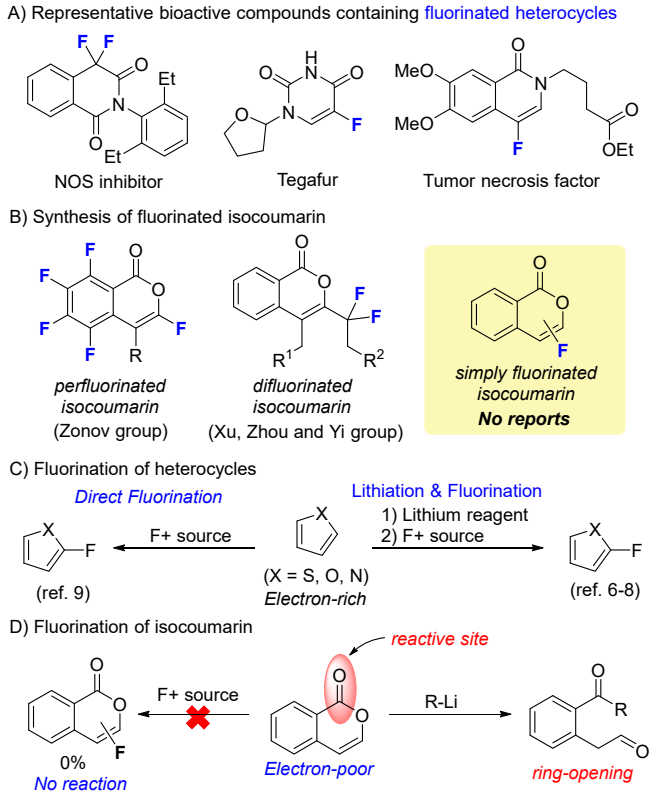
Abstract: Fluorinated heterocycles have attracted much attention in the pharmaceutical and agrochemical industries. Many strategies have already been developed to achieve the synthesis of fluorinated heterocycles. Formidable challenges remain, however, in the synthesis of fluorinated isocoumarin derivatives that are among the most alluring structural motifs. Herein, we report the indium-catalyzed C–F bond transformation of 2-(2,2-difluorovinyl) benzoates, which are readily accessible compounds, to give a diverse array of fluorinated isocoumarins. The present reaction proceeds smoothly using inexpensive reagents: catalytic amount of indium salt in the presence of zinc salt. A theoretical calculation of potential energy profiles showed that the reaction consists of oxymetalation with the elimination of alkyl halide and the β-fluorine elimination.

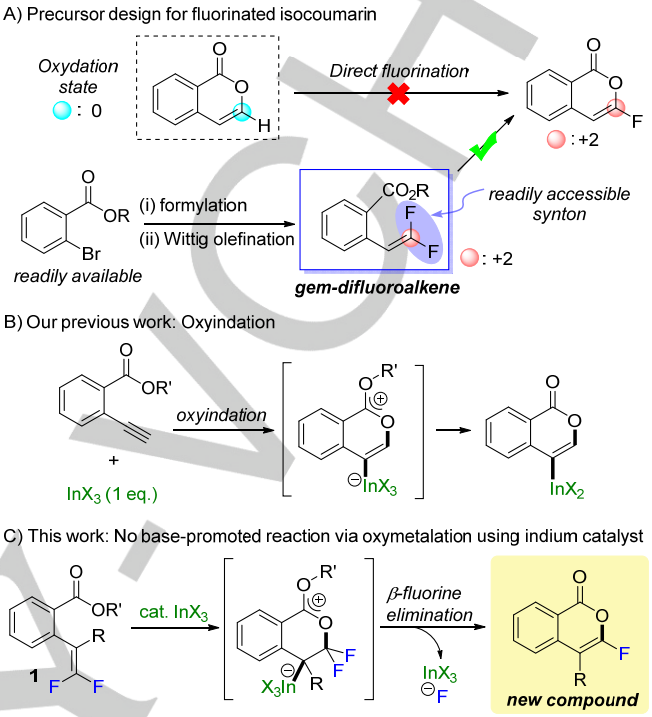
Introduction

Fluorine has played an important role in many fields of science due to inherent properties such as a small size and electronegativity that surpasses that of other halogens.[1] The introduction of fluorine or fluorine-containing structural motifs into organic molecules often brings about desirable bioactivity and provides unique chemical and physical properties. Such attributes have resulted in widespread strategic incorporation of fluorine in the field of medicinal chemistry (Scheme 1A).[2] Although the assembly of fluorinated heterocycles has been an ongoing topic of interest,[3] formidable challenges remain for the synthesis of fluorinated isocoumarin derivatives, yet they possess one of the most alluring structural motifs.[4] Several methods for fluorinated isocoumarins have been reported. Zonov et al. have developed the synthesis of fluorinated isocoumarins using superacids from highly electron-deficient compounds. Xu, Zhou, and Yi et al. have achieved the synthesis of difluorinated isocoumarins using iridium catalyst. However, these reported methods are limited to the synthesis of perfluorinated isocoumarin or difluorinated isocoumarin so the selective introduction of only one fluorine atom to the heterocyclic moiety has never been accomplished (Scheme 1B).[5] Many groups have developed methodologies for the direct incorporation of fluorine into heterocycles. Two approaches are the most reliable (Scheme 1C). The first approach involves a regiospecific lithiation of the starting heterocycle followed by treatment of the fluorine source (Scheme 1C, right). Using this method, a wide variety of fluorinated heterocycles has been synthesized: thiophenes,[6] pyrroles,[6b] furans,[6b, 7] and so forth.[8] The second method involves direct fluorination using electrophilic fluorinating reagents (Scheme 1C, left). Badland et al. reported this strategy for the fluorination of thiophene to synthesize additional matrix metalloproteinase 12 inhibitors.[9a] Sandford et al. has achieved the synthesis of fluorinated pyrrole derivatives using Selectfluor™.[9b] Zhu and Sun et al. have developed an efficient one-pot method for the synthesis of fluorinated benzofuran with high regioselectivity using Selectfluor™.[9c] However, these methodologies are not applicable to the fluorination of isocoumarin. In the case of the lithiation method, a ring-opening reaction would proceed instead of lithiation because of the presence of carbonyl group (Scheme 1D, right). In addition, a direct fluorination of isocoumarins has never been reported due to the lack of their reactivity to common fluorination reagents. In fact, we investigated the electrophilic fluorination of isocoumarin with a Selectfluor™ reagent,[10] but no fluorinated products were obtained (Scheme 1D, left, See Supporting Information). Therefore, a comprehensive and efficient strategy for the synthesis of fluorinated isocoumarin remains in great demand.



Scheme 1. Bioactive compounds containing fluorinated heterocycles and synthesis of fluorinated heterocycles.

The *gem*-difluoroalkenes have gained much attention as versatile fluorinated building blocks for the synthesis of pharmaceuticals, agrochemicals, and functional materials.[11] In recent years, significant progress has been made in the development of useful reactions involving cleavage of the C–F bonds in *gem*-difluoroalkenes.[12] We envisioned the introduction of *gem*-difluoroalkene as starting materials for the synthesis of fluorinated isocoumarin to overcome the difficulties in the fluorination of isocoumarin (Scheme 2A). In the case of direct fluorination, an oxidation state of the carbon atoms at the 3-position of isocoumarin changes from 0 to +2. We thought the installation of a *gem*-difluoroalkene moiety increases the oxidation state of the corresponding carbon atom from 0 to +2 to facilitate the synthesis of fluorinated isocoumarin via a cyclization reaction. Moreover, the *gem*-difluoroalkenes are easily accessible from readily available bromobenzoates via formylation and Wittig difluoroolefination. Thus, the introduction of a difluoro moiety in advance can overcome the difficulties associated with direct electrophilic fluorination. Recently, we developed a process for the oxymetalation of 2-alkynylbenzoic esters using stoichiometric amounts of indium salts without activation of the nucleophilic ester moiety to access metalated isocumarins (Scheme 2B).[13] Also, our group has been developing the carboindation of alkenes using indium salts and organosilicon nucleophiles via the activation of alkene moiety by indium salts.[14] Thus, we suspected that the oxyindation of a *gem*-difluoroalkene unit in benzoic esters **1** followed by *β*-fluorine elimination would achieve the synthesis of fluorinated isocumarins. Moreover, though C–F bond transformation is well known for transition metals, the application of this synthesis to main-group metal catalysis has remained a challenge.[15, 16] Herein, we present a C–F bond transformation strategy for the synthesis of fluorinated isocoumarin using an indium catalyst (Scheme 2C).



Scheme 2. Related work and This work.

Results and Discussion

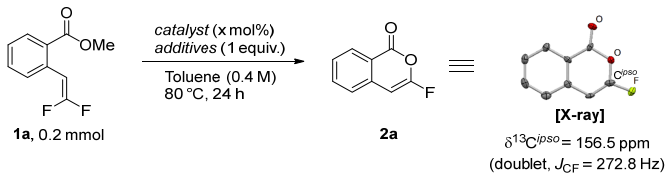
Reaction optimization for the synthesis of fluorinated isocoumarin

For optimization of the reaction conditions, 2-(2,2-difluoroethenyl)benzoate **1a** was selected as a standard substrate (Table 1). Heating a mixture of **1a** and 0.5 equivalent of InI_3 in toluene at 80 °C for 24 h afforded annulated product **2a** bearing a fluorine at the C-3 position in an excellent yield (Table 1, entry 1). The structure of **2a** was confirmed by NMR spectroscopy and X-ray crystallography (CCDC 2051246 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures). Employment of other transition metals was less efficient (Table 1, entries 2-6). The use of other main group metal salts was inefficient (Table 1, entries 7-11). Reducing the amount of the loading catalyst resulted in a low yield of **2a** (Table 1, entries 12 and 13), which revealed that InI_3 is a fluoride anion acceptor that changes into InF_xI_{3-x} to weaken the catalytic activity. The use of InF_3 was less efficient due to the lack of solubility to solvent (Table 1, entry 14)[17]. In the cases of using catalytic amount of InI_3 (Table 1, entries 12 and 13), the turnover number is about 2.5, which means that InI_3 and InI_2F

work well as a catalyst, but $InIF_2$ is a moderate active catalyst and InF_3 does not work as shown in entry 14.

We envisioned that the addition of a scavenger for fluoride anions could regenerate InI_3 as a catalyst. The use of ZnI_2 as an additive promoted the expected catalytic reaction in the presence of a catalytic amount of InI_3 to give **2a** in a good yield (Table 1, entry 18), whereas the use of other fluorine-trapping reagents was ineffective (Table 1, entries 15-17). Finally, the use of $InCl_3$ instead of InI_3 in the catalytic system provided **2a** quantitatively (Table 1, entry 19) (See Supporting Information in detail). The loading of $InCl_3$ was successfully lowered to 1 mol% and returned a good yield of **2a** (Table 1, entries 19-21).

Table 1. Reaction optimization of the synthesis of fluorinated isocoumarin.



1a, 0.2 mmol

2a

$\delta^{13}C^{ipso}$ = 156.5 ppm (doublet, J_{CF} = 272.8 Hz)

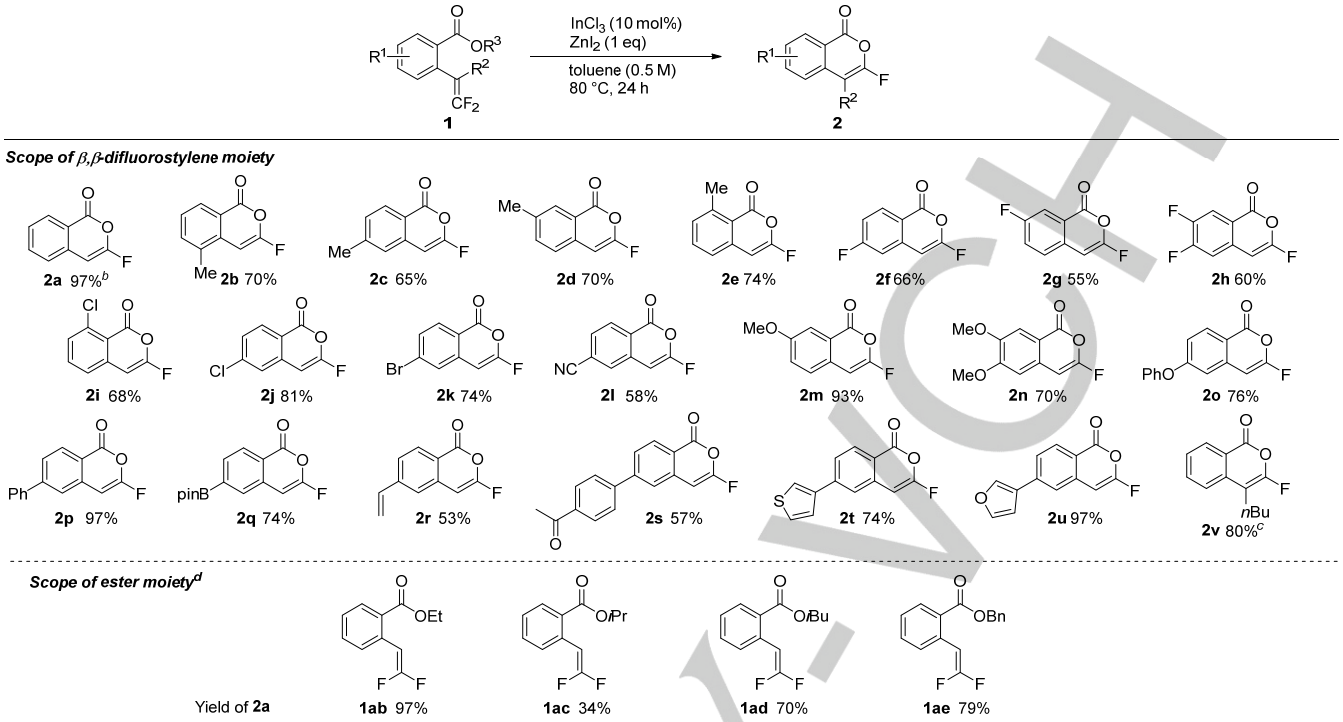
Entry	Catalyst (x mol%)	Additive	Yield %[a]
1	InI_3 (50)	-	>97
2	$PdCl_2$ (50)	-	0
3	$CuBr_2$ (50)	-	0
4	$FeBr_3$ (50)	-	0
5	AgOTf (50)	-	0
6	$AgSbF_6$ (50)	-	29
7	ClBcat (50)	-	0
8	AlI_3 (50)	-	0
9	GaI_3 (50)	-	33
10	ZnI_2 (50)	-	6
11	$BiBr_3$ (50)	-	33
12	InI_3 (10)	-	23
13	InI_3 (20)	-	48
14	InF_3 (20)	-	0
15	InI_3 (20)	Me_3SiI	40
16	InI_3 (20)	$BF_3 \cdot OEt_2$	58
17	InI_3 (20)	Bu_4NI	0
18	InI_3 (10)	ZnI_2	72
19	$InCl_3$ (10)	ZnI_2	>97
20	$InCl_3$ (5)	ZnI_2	95
21	$InCl_3$ (1)	ZnI_2	75[b]

[a] Reaction conditions: x mol% catalyst, 1 equiv additives, **1a** (0.3 mmol, 1 equiv) in 0.6 mL of toluene at 80 °C for 24 h under nitrogen. Yields were determined by ^1H NMR. [b] 3 days

Scope of the *gem*-difluoroalkenes

The substrate generality of the present synthetic method was investigated via the use of a wide variety of substituted *gem*-difluoroalkenes (Table 2). Fluorinated isocoumarin **2a** was isolated in 97% yield. Substrates with methyl groups at different positions in the benzene ring were also applicable to afford the desired products **2b**-**2e** in high yields. Commonly encountered functional groups such as fluoro (**2f–2g**), chloro (**2i** and **2j**), bromo (**2k**), cyano (**2l**), methoxy (**2m**), phenoxy (**2o**), and phenyl (**2p**) were well tolerated, giving the corresponding products in 55–86% yields regardless of their electronic properties. Gratifyingly, the substrate bearing a Bpin (pinacolatoboronyl) group furnished the desired product **2q** in 74% yield. Notably, vinyl (**2r**) and acetyl (**2s**) groups, which could poison $InCl_3$ and ZnI_2 also survived. Heterocyclic groups were amenable to this reaction process and afforded the corresponding products in good yields (**2t** and **2u**). Furthermore, a substrate with a n-butyl substituted difluoroalkene moiety, which should retard the reaction based on steric reasoning, also proceeded to afford the desired product (**2v**). Next, the scope of ester moieties was evaluated. A substoichiometric amount of InI_3 in the reaction of substrates bearing a bulky ester moiety (**1ab**, **1ad**, and **1ae**) was required to achieve reasonable yields. In particular, the annulation of **1ac** gave diminished yields, presumably due to the competitive substrate decomposition via 1,5-migration.[18]

Table 2. Substrate scope of 2-(2,2-difluorovinyl)benzoates for the synthesis of fluorinated isocoumarins



[a] Reaction conditions: **1** (0.2 mmol, 1 equiv), $InCl_3$ (0.02 mmol, 10 mol%), ZnI_2 (0.2 mmol, 1 equiv), in toluene (0.5 M, 0.4 mL), 80 °C, 24 h. Isolated yields are shown. [b] 2 mmol scale. [c] 20 mol% $InCl_3$ was used. [d] **1** (0.2 mmol, 1 equiv), InI_3 (0.1 mmol, 50 mol%), in toluene (0.5 M, 0.4 mL), 80 °C, 1 h

Experimental and DFT investigation of the reaction mechanism

Based on our developed oxyindation[13a] and other groups' proposed mechanisms,[19] we propose two plausible reaction mechanisms, as outlined in Figure 1. In catalytic cycle B, intermediate **II** is generated from the 2-(2,2-difluoroethenyl)benzoate **1a** with InX_3 (**I**) via oxyindation.[20] The elimination of an alkyl halide (R–X) from **II** leads to organoindium species **III,**[21] which then undergoes *β*-fluorine elimination to give product **2a** and InX_2F (**IV**). Lastly, a halide exchange between InX_2F and ZnI_2 occurs to give catalytically active InX_3 (**I**) and zinc fluoride salt. In catalytic cycle A, a nucleophilic addition of the ester moiety to the *gem*-difluoroalkene moiety proceeds to form zwitterionic species **V**, and subsequently the abstraction of a fluoride anion by InX_3 produces product **2a**.

At first, the reaction mixture was monitored by ^1H NMR spectroscopy to investigate the reaction mechanism (Scheme 3). When starting material **1a** was reacted with InI_3 (1 equiv) in $CDCl_3$ at 80 °C for 30min in sealed tube, MeI (12%) was observed at 2.18 ppm with the same amount of fluorinated isocoumarin **2a** (13%). However, no intermediates were observed except for the starting material **1a** and MeI and the final product **2a**.

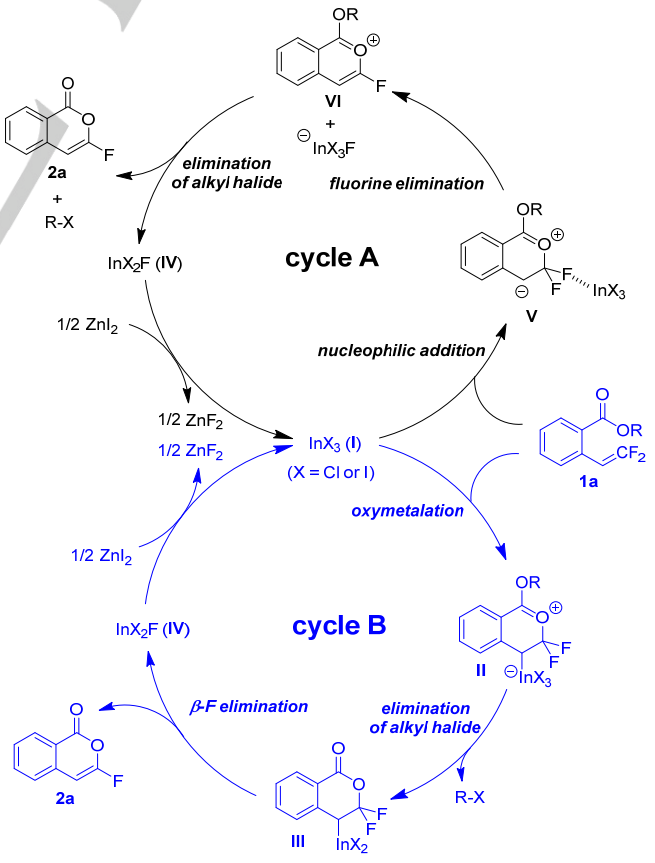
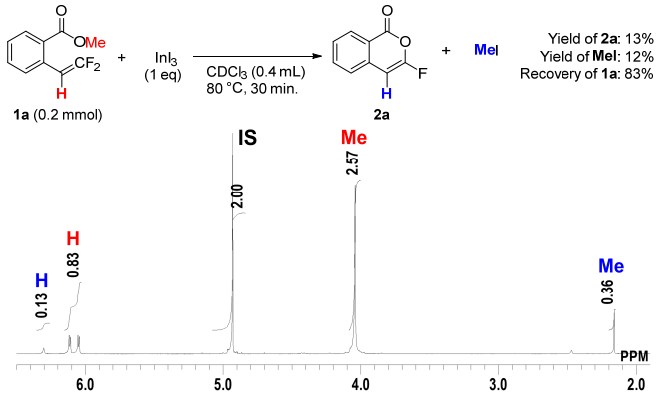


Figure 1. Proposed catalytic cycle: (A) nucleophilic addition-elimination pathway (B) The pathway via an oxymetalation step.



Scheme 3. Monitoring of the reaction of *gem*-difluoroalkene **1a** with InI_3 in $CDCl_3$ by ^1H NMR spectroscopic analysis. Dibromomethane was used as an internal standard (IS). Reagents and conditions: **1a** (0.2 mmol), InI_3 (1 equiv), $CDCl_3$ (0.4 mL), 80 °C, 30min.

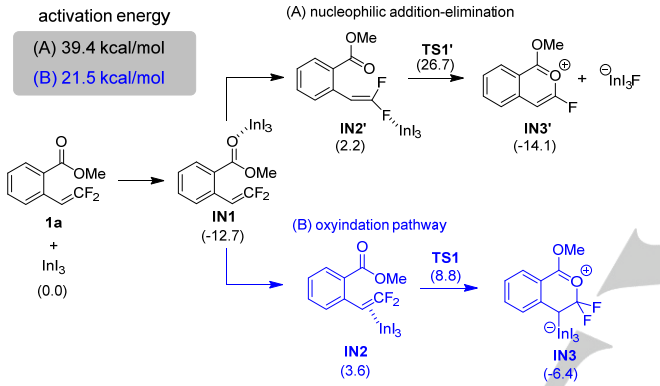


Figure 2. A comparison of plausible mechanisms: (A) nucleophilic addition-elimination pathway and (B) oxymetalation pathway; Free energies (ΔG, 300 K, in kcal mol^{-1}) of intermediates and transition states are given

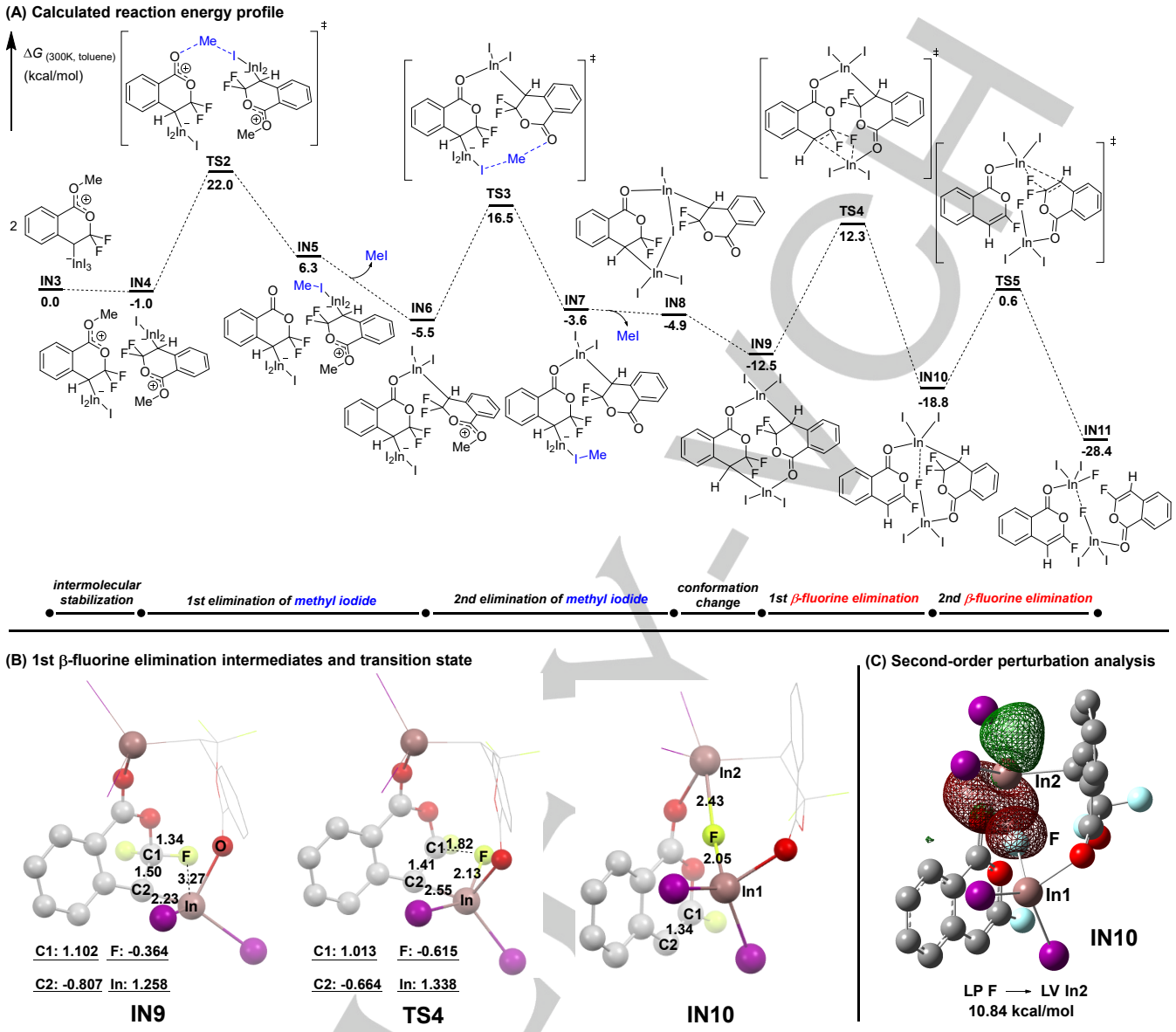


Figure 3. (A) Computed mechanism for the elimination of alkyl halide and the β-fluorine elimination. DFT calculation was performed at ωB97XD/Def2SVPD. The solvation effect was introduced using the IEFPCM model, and toluene was used as a solvent. (B) Optimized structures of the 1st β-fluorine elimination step. The values denoted in the structures are the bond lengths in Å. Values underlined are the relevant natural charges for the selected atoms. (C) Second-order perturbation theory analysis of **IN10**.

We performed density functional theory (DFT) calculations to investigate the possibilities of the two proposed paths. Figure 2 shows the computational results for cyclization steps via nucleophilic addition-elimination (Figure 2, A) and via oxymetalation (Figure 2, B) (See the supporting information for computational details). Indium complex **IN1** is initially formed by the coordination of a carbonyl moiety of **1a**. In the addition-elimination mechanism, the coordination of the fluorine group to InI_3 activates the fluoroalkene moiety. The resulting species (**IN2'**) undergo cyclization via **TS1'** (26.7 kcal/mol) to form intermediate **IN3'**. In the oxymetalation path, InI_3 acts as a *π*-electrophilic Lewis acid to activate the *gem*-difluoroalkene (**IN2**), thereby facilitating intramolecular cyclization to give zwitterionic intermediate **IN3** via **TS1** with free energy of only 8.8 kcal/mol.[13a] Cyclization via nucleophilic addition-elimination is accompanied by an activation energy of 39.4 kcal/mol, which is much higher than that in the oxymetalation path (21.5 kcal/mol). Therefore, the oxymetalation mechanism is an operative reaction path (See Supporting Information in detail).

The computed mechanism for the generation of **IN3** by oxyindation is shown in Figure 3. The intramolecular elimination of MeI in a single molecule does not proceed (See Supporting Information). Initially, the association between two **IN3**s leads to complex **IN4** with slight stabilization. Subsequently, abstraction

of the Me group by the iodine atom of the anionic indium moiety occurs via the transition state **TS2** with an activation energy of 24.0 kcal/mol and yields intermediate **IN5**. The dissociation of MeI from **IN5** then gives intermediate **IN6**. The second elimination of MeI occurs through a mechanism similar to the first elimination to give symmetric indium complex **IN9** via metastable intermediates **IN7** and **IN8**. The *β*-fluorine elimination from **IN9** occurs via transition state **TS4** ($\Delta G^{\ddagger}$ = 24.8 kcal/mol) to give **IN10**. In transition state **TS4**, the cleavage of C1–F and C2–In and the bonding of In–F occur synchronously at distances of 1.82 and 2.55 and 2.13 Å, respectively (Figure 3, B). The In–F bond is significantly shortened from 3.27 Å to 2.13 Å, and the C1–F bond is moderately extended from 1.34 Å to 1.82 Å while the C1–C2 and C2–In bonds are changed less compared with the In–F and C1–F bonds. NBO analysis of **TS4** and **In9** indicates an apparent increased negative charge on the fluorine atom. Therefore, abstraction of the fluoride anion with assistance of the indium center as a Lewis acid proceeds preferentially in the *β*-fluorine elimination step. The second-order-perturbation theory analysis for the interaction between the indium and fluorine atoms in **IN10** is depicted in Figure 3C. There is a meaningful interaction between the lone pair on the F atom and the vacant orbital on the In2 atom (10.84 kcal/mol), which indicates that the fluorine atom is stabilized by the two indium atoms in **IN10**. Finally, the second *β*-fluorine elimination process proceeds via **TS5** ($\Delta G^{\ddagger}$ = 19.4 kcal/mol) to produce final product **2a** (**IN11**).

Further transformation

Further transformation of the C–F bonds in fluorinated isocoumarins was successful, as shown in Figure 4. Fluoroalkenes readily underwent Friedel-Crafts-type intramolecular cyclization mediated by Brønsted or Lewis acids.[22] In contrast, there have been few reports of intermolecular types of reactions, and those that have been reported require electron-rich arenes.[22a] Gratifyingly, we discovered the C–F bond of **2a** was transformed with alkylbenzenes such as toluene and xylenes in the presence of an indium catalyst and Me_3SiOTf. Finally, the double C–F bond domino transformation from compound **1a** was examined. When **1a** was exposed to an indium catalyst and Me_3SiOTf in toluene, the cyclization via oxymetalation and the Friedel-crafts type alkenylation proceeded sequentially through fluorinated isocoumarin **2a** (Figure 4, B).

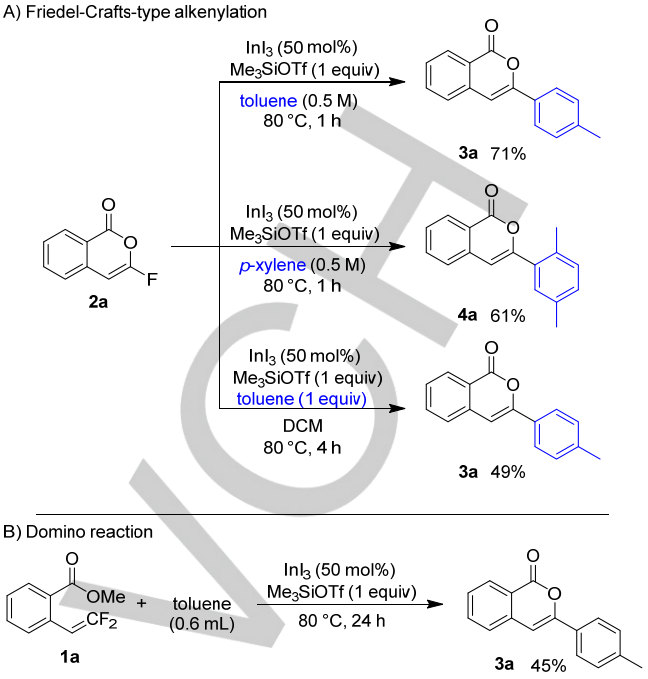


Figure 4. Further investigations: (A) Friedel-Crafts-type alkenylation (B) Domino reaction of cyclization via oxymetalation and Friedel-Crafts-type alkenylation; Isolated yield.

Conclusions

In summary, we have developed an indium-catalyzed system that transforms the C–F bond of 2-(2,2-difluoroethennyl) benzoate derivatives via an oxymetalation process using an indium catalyst to produce various fluorinated isocoumarins. The reactions proceeded under mild conditions without transition metals. The obtained fluorinated compound was transformed via Friedel-Crafts-type alkenylation. Mechanistic studies using a computational approach were conducted to interpret the reaction mechanism. Given the importance of fluorinated heterocyclic compounds in functional molecules, our method may find significant applications.

Acknowledgements

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Keywords: C-F bond transformation • catalysis • *gem*-difluoroalkene • fluorinated heterocycles • Indium

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[17] A certain amount of precipitate was observed in reaction mixture after completing reaction. As the indium salt is fluorinated via β-fluorine elimination, the indium salt become less soluble in toluene, weakening the catalytic activity. In addition, DFT calculation were performed to estimate the interaction between gem-difluorostyrene and InF_3, but the InF_3 complex was not found, whereas InI_3-complex was obtained. Thus, we conclude that InF_3 does not have a π-Lewis acidity enough to proceed the cyclization reaction and not suitable as a catalyst for our reaction system.

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[20] InI_3 could be generated in the presence of $InCl_3$ and ZnI_2 and can act as a gem-difluoroalkene activator (See Supporting Information).

[21] The reaction mixture was monitored by ^{1}H NMR after completing the reaction in a sealed NMR tube to observe the quantitative generation of MeI without MeF.

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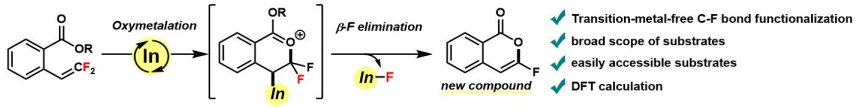

We have developed an indium-catalyzed system that transforms the C–F bond of 2-(2,2-difluoroethenyl)benzoate derivatives via an oxymetalation process using an indium catalyst to produce various fluorinated isocoumarins. The reactions proceeded under mild conditions without transition metals.