Doctoral Dissertation

Studies on Formation of Heterocycles and Functionalization of C–F Bonds via Carbo- or Oxymetalation

Tetsuji Yata

January 2022

Department of Applied Chemistry

Graduate School of Engineering

Osaka University

Preface and Acknowledgements

The study of this doctoral dissertation was carried out under the guidance of Prof. Dr. Makoto Yasuda at the Department of Applied Chemistry, Graduated School of Engineering, Osaka University from April 2016 to March 2022. The thesis describes the development of synthetic methodologies using carbometalation and oxymetalation for the synthesis of heterocycles and the functionalization of C–F bonds.

I would like to express my deepest appreciation to Prof. Dr. Makoto Yasuda for his precise guidance, helpful suggestions and hearty encouragements throughout this work. His enthusiasm for chemistry has always motivated me. He also gave me a lot of invaluable experience. I really appreciate him for supervising me. I would also like to thank Professors Dr. Naoto Chatani and Dr. Ikuya Shibata for their helpful advice and kind assistance. I gratefully express acknowledgement to Associate Prof. Dr. Yoshihiro Nishimoto for his great assistance, helpful suggestion and stimulating discussion. I really wish to make a grateful acknowledgement to Assistant Prof. Dr. Akihito Konishi for his sharp comments and kind encouragement. I am grateful to Assistant Prof. Dr. Shuntaro Tsubaki for helpful discussions.

I am deeply thankful to Ms. Yoshimi Shinomiya and Ms. Tomoko Shimizu for giving me her grateful support and heartwarming kindness.

I express my appreciation to the all members of the Yasuda Group. I am deeply indebted to my seniors since I joined Yasuda group in 2016. I would like to express special thanks to my mentor Dr. Yuji Kita for his kind encouragement and great suggestion. I gratefully with to thank Dr. Esumi Naoto, Dr. Yohei Minami, Dr. Kyoungmin Kang, Dr. Kensuke Suzuki, Dr. Shuichi Nakao, Mr. Daiki Tanaka, Mr. Koki Horii, Mr. Fei Wang, Mr. Masaki Fujie, Mr. Naoki Sugihara, Mr. Takehiro Inoue and others for their worthwhile advice and active discussion. I would also wish to thank the kind members, Mr. Junki Hara, Mr. Daiki Tanaka, Mr. Kazuma Tomita, Ms. Haruna Iwasa, Mr. Kazuki Kido, Ms. Miki Saikai, and Mr. Shota Sasaya for listening my silly talking.

I have had the great support of Mr. Hiroshi Moriguchi, Dr. Nobuko Kanehisa, Dr. Kyoko Inoue, and Dr. Hiroaki Tanaka with analytic assistance at the analytical instrumentation facility.

Professor Yasuda also assisted me to visit University of Texas at Dallas, USA. Prof. Dr. Vladimir Gevorgyan willingly accepted me to his group as a visiting researcher for four months from November 2019. Special thanks to him for his kind support and stimulating discussions. I am also grateful for his lab members, especially Mr. Kelvin Pak Shing Cheung, Dr. Daria Kurandina, and Dr. Maxim Ratushnyy.

I wish to thank the JSPS Fellowship for Young Scientists for the financial support.

Finally, I would like to express my gratitude to my parents, Shinji Yata and Eiko Yata, and my sister Sakiko Hashiba for their understanding to my work, constant assistance and financial support.

January, 2022

Tetsuji Yata

List of Publications

1) **Regioselective Synthesis of 5-Metalated 2-Pyrones by Intramolecular Oxymetalation of Carbonyl-ene-yne Compounds Using Indium Trihalide**
T. Yata, Y. Kita, Y. Nishimoto, M. Yasuda
J. Org. Chem. **2019**, *84*, 14330–14341.

2) **Indium-Catalyzed C–F Bond Transformation through Oxymetalation/β-fluorine Elimination to Access Fluorinated Isocoumarins**
T. Yata, Y. Nishimoto, K. Chiba, M. Yasuda
Chem. Eur. J. **2021**, *27*, 8288–8294.

3) **Carboboration-Driven Generation of a Silylium Ion for Vinylic C–F Bond Functionalization by $B(C_6F_5)_3$ Catalysis**
T. Yata, Y. Nishimoto, M. Yasuda
Chem. Eur. J. DOI: 10.1002/chem.202103852

<Supplementary Publications>

1) **Indium Catalyzed Hydrofunctionalization of Styrene Derivatives Bearing a Hydroxy Group with Organosilicon Nucleophiles**
Y. Kita, T. Yata, Y. Nishimoto, M. Yasuda
J. Org. Chem. **2018**, *83*, 740–753.

2) **Selective Oxymetalation of Terminal Alkynes via 6-*Endo* Cyclization: Mechanistic Investigation and Application to the Efficient Synthesis of 4-Substituted Isocoumarins**
Y. Kita, T. Yata, Y. Nishimoto, K. Chiba, M. Yasuda
Chem. Sci. **2018***, 9,* 6041–6052.

3) **Photoinduced Palladium-Catalyzed Carbofunctionalization of Conjugated Dienes Proceeding via Radical-Polar Crossover Scenario: 1,2-Aminoalkylation and Beyond**
K. P. S. Cheung, D. Kurandina, T. Yata, V. Gevorgyan
J. Am. Chem. Soc. **2020**, *142*, 9932–9937.

Contents

General Introduction **5**

Chapter 1: Regioselective Synthesis of 5-Metalated 2-Pyrones by Intramolecular Oxymetalation of Carbonyl-Ene-Yne Compounds Using Indium Trihalide **11**

1-1. Introduction 11

1-2. Results and Discussion 13

1-3. Conclusion 19

1-4. Experimental Section 20

1-5. Reference 36

Chapter 2: Indium-catalyzed C–F bond transformation through oxymetalation/*β*-fluorine elimination to access fluorinated isocoumarins **38**

2-1. Introduction 38

2-2. Results and Discussion 40

2-3. Conclusions 47

2-4. Experimental Section 47

2-5. Reference 75

Chapter 3: Carboboration-Driven Generation of a Silylium Ion for Vinylic C–F Bond Functionalization by $B(C_6F_5)_3$ Catalysis **78**

3-1. Introduction 78

3-2. Results and Discussion 80

3-3. Conclusion 86

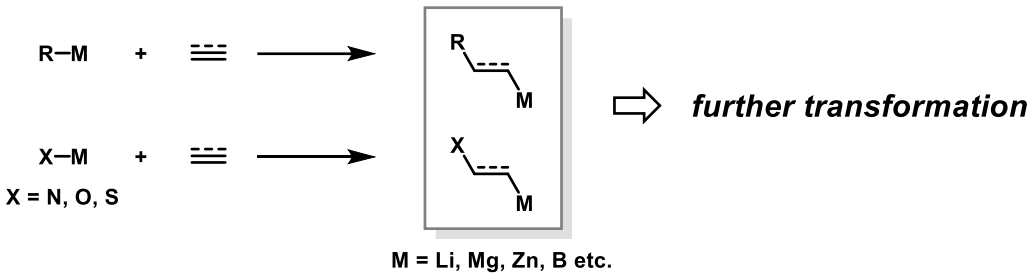
3-4. Experimental Section 86

3-5. References 106

Conclusion **110**

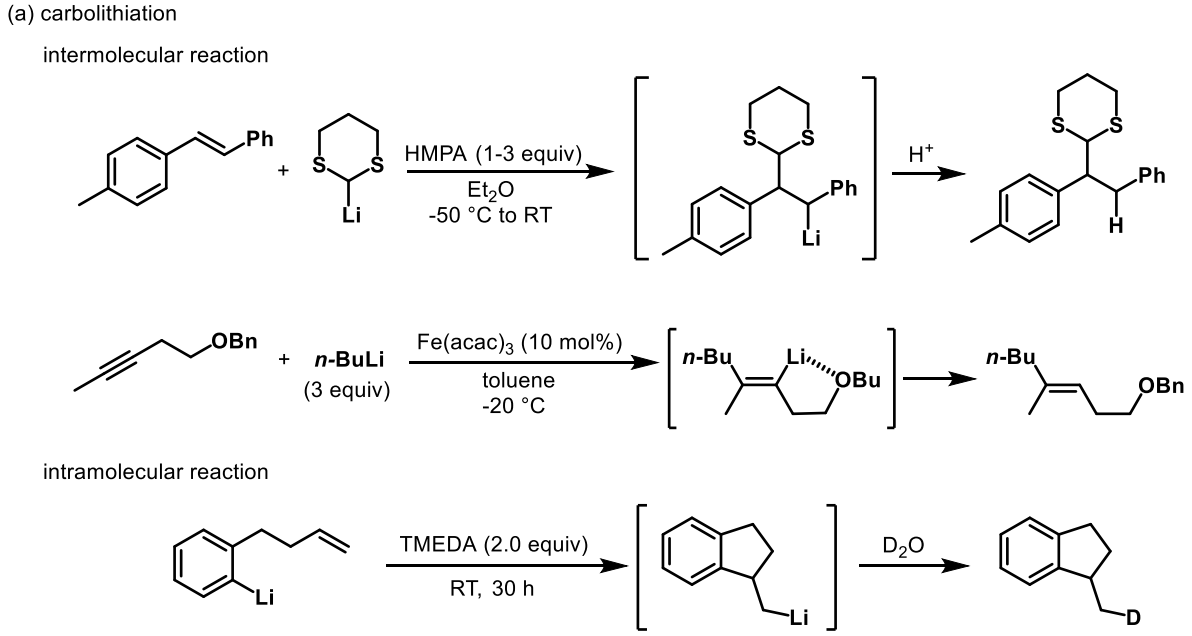
General Introduction

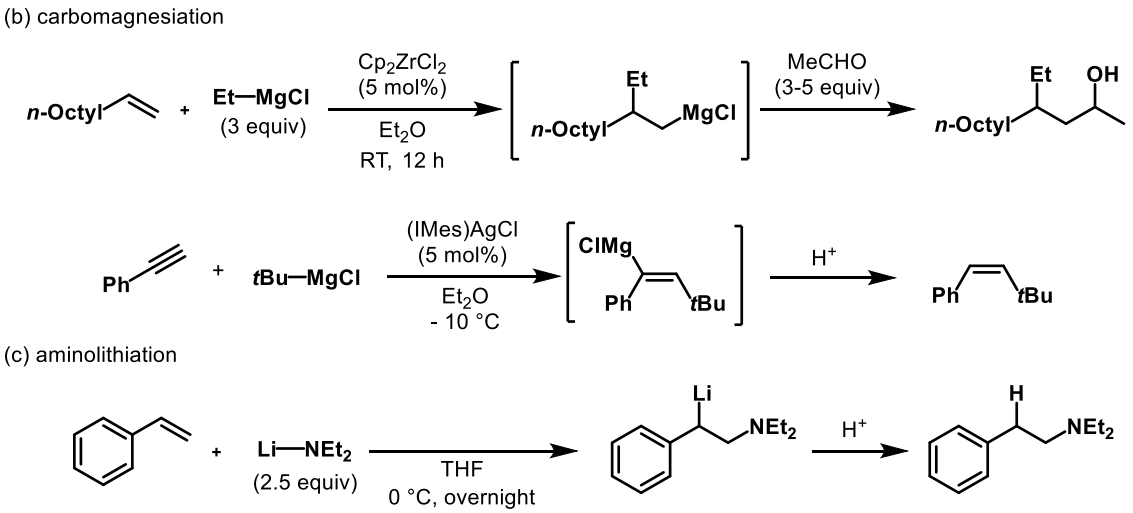
Organometallic compounds have played an important role in organic chemistry because they often bring about more efficient reactions, less use of energy and higher yields of targeted products. Especially, main-group organometallic compounds are the attractive reagents for new bond formations, and new synthetic strategies of the main-group organometallic compounds have received considerable attention.[1] Carbometalation and heterometalation reaction of an unsaturated C–C bond for main-group organometallic compounds is one of the important and efficient reaction because a new C–C/hetero–C bond and a new C–metal bond can be generated simultaneously.[2] The obtained main-group organometallic compound can be further used for subsequent transformations (Scheme 1).



Scheme 1. Carbometalation and heterometalation of carbon–carbon multiple bonds.

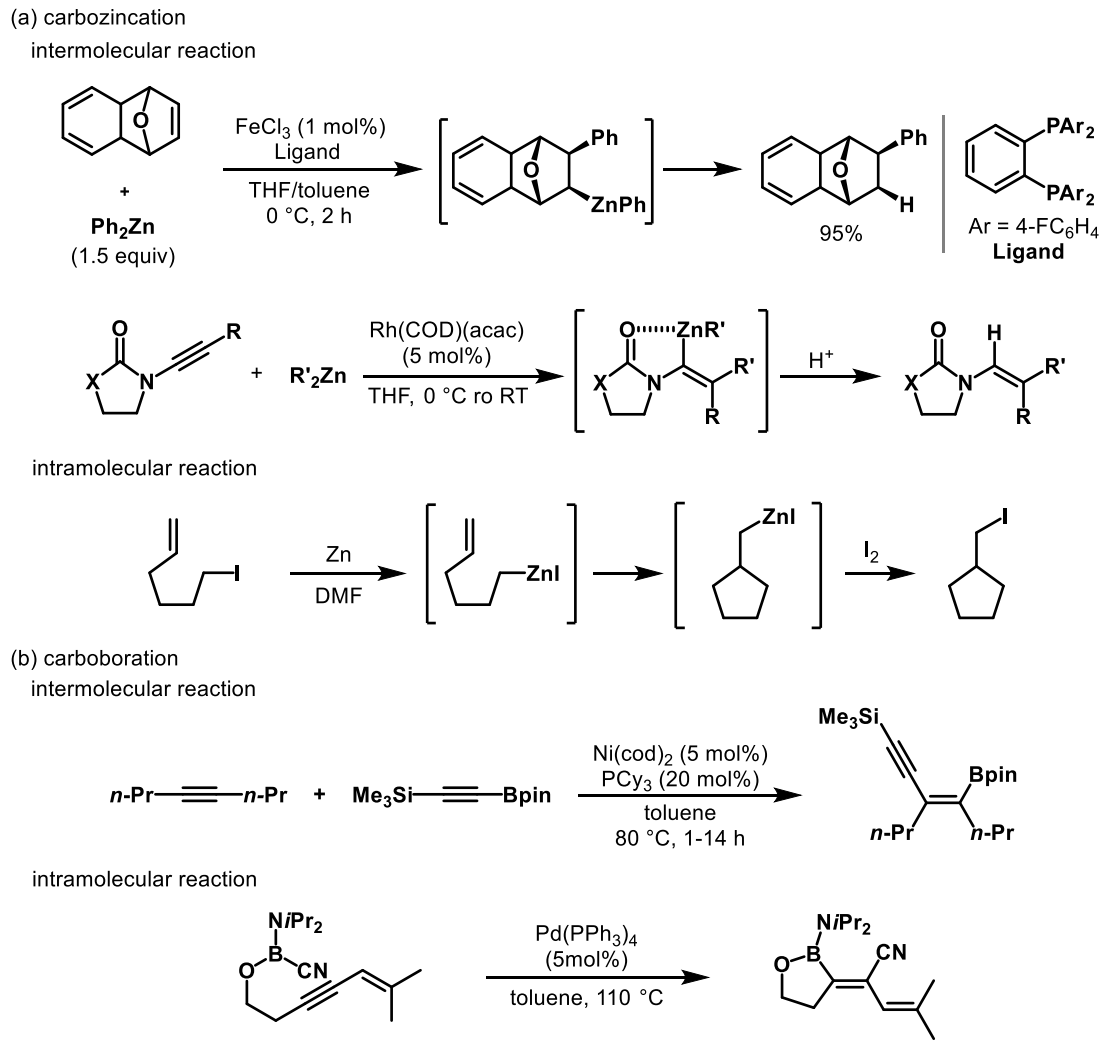
A lot of strategies of the synthesis of organolithium and organomagnesium reagents synthesized by carbometalation or heterometalation pathway were reported (Scheme 2).[3] These organometallic reagents, however, have a low compatibility with functional groups due to their high reactivity.



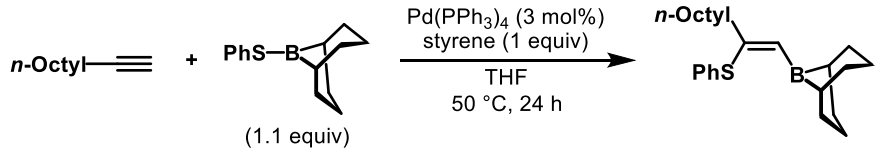


Scheme 2. The synthesis of organolithium and organomagnesium reagents via carbo- or heterometalation: (a) intramolecular carbolithiation (b) intermolecular carbomagnesiation (c) interemolecular aminolithiation.

Organozinc or organoborane reagents are suitable compounds from a point of view of functional-group-tolerance (Scheme 3).[4] However, the transition metals are required for the carbometalation or heterometalation step.



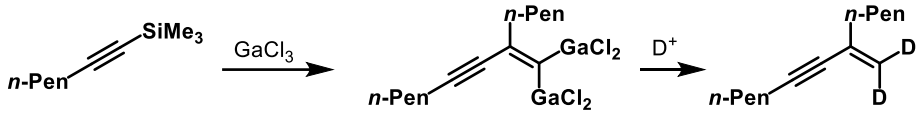
(c) thioboration



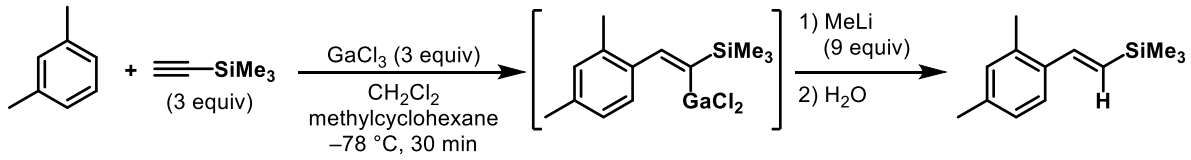
Scheme 3. The synthesis of organozinc and organoborane reagents via carbo- or heterometalation: (a) Fe-catalyzed carbozincation (b) Ni-catalyzed carboboration (c) Pd-catalyzed thioboration.

On the other hand, heavier main-group metal salts such as gallium and indium salts have a moderate Lewis acidity and an affinity to C–C multiple bonds, thus the metals are able to activate a C–C multiple bonds without transition metals to give the corresponding main-group organometallic compounds bearing high functional group tolerance.[5] As pioneering examples for gallium-mediated transformation, Yamaguchi and co-workers established the synthesis of alkenyldichlorogallium species or Friedel-Crafts type alkenylation via activation of trimethylsilylacetylene via carbogallation reaction (Scheme 4).[6]

(a) synthesis of alkenyldichlorogalliums via carbogallation



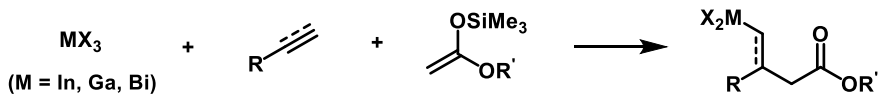
(b) Friedel-Crafts type alkenylation reaction



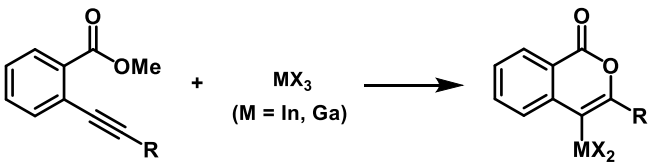
Scheme 4. The earlier works of carbometalation using main-group metal salts

Our group has also reported regio- and stereoselective carbometalation of alkenes or alkynes with silyl ketene acetals using indium or gallium salts.[7] In addition, our group has reported the 6-*endo* selective intramolecular oxymetalation reaction of alkynes with an ester moiety to give isocoumarins (Scheme 5).[8]

(a) regio- and stereoselective carbometalation using heavier main-group metal salts

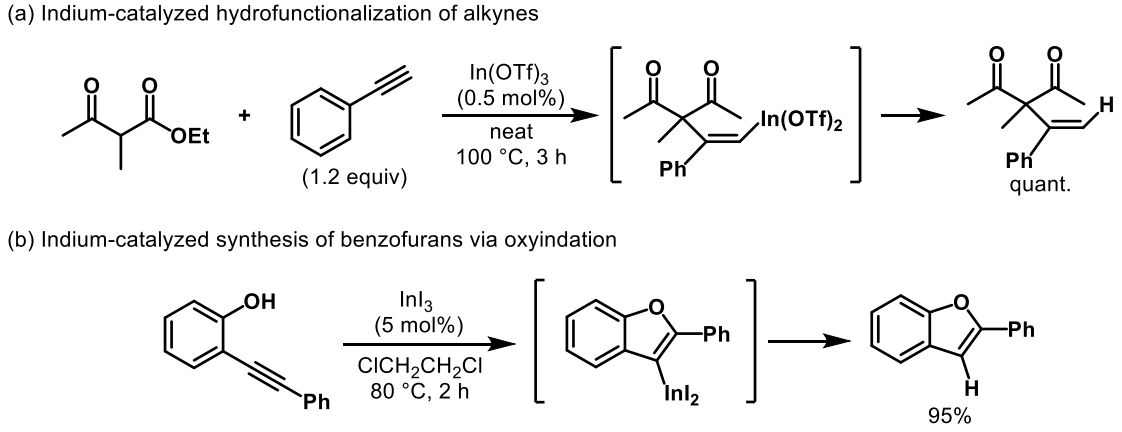


(b) regioselective oxymetalation for the synthesis of metalated isocoumarins



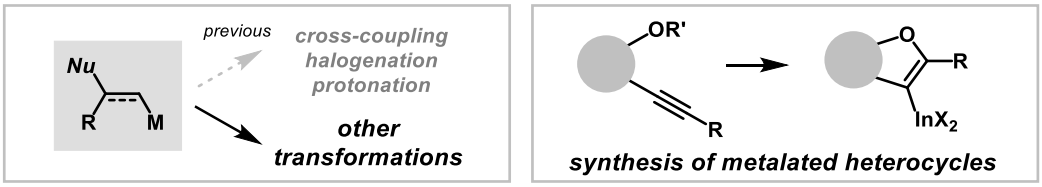
Scheme 5. Our works: (a) three-component carbometalation using heavier main-group metal salts (b) intramolecular oxymetalation for the synthesis of metalated isocoumarins.

The carbometalation or heterometalation reactions by main-group metal salts are also important method for catalytic C–C bond or C–O bond formation (Scheme 6).[9] In these catalytic reactions, however, the generated organometals are confined to the protonation reaction.



Scheme 6. Catalytic reaction via carbo- or heterometalation using main-group metal salts: (a) carboindation-driven hydrofunctionalization reaction (b) intramolecular oxyindation for the synthesis of benzofurans.

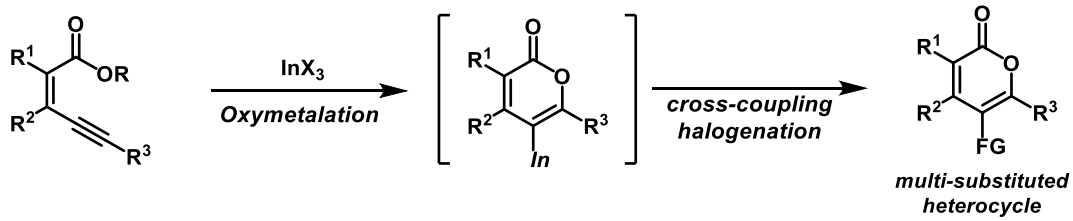
In the case of stoichiometric reactions, transformations of the carbon-metal bond generated from main-group metal salts have been limited by halogenation or cross-coupling reaction with transition metal salts, and there has been little effort to establish other transformation strategies. Furthermore, studies of efficient synthesis of heterocycles bearing a carbon-metal bond are sparse (Scheme 7).



Scheme 7. Points to be improved in the carbometalation or heterometalation

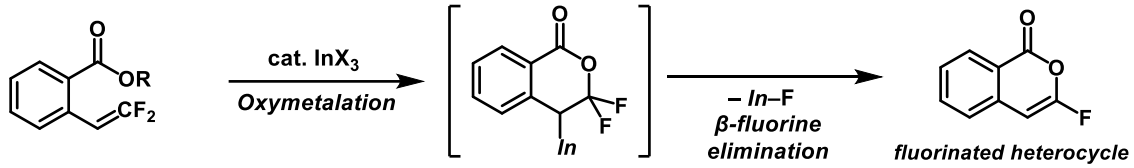
Based on the strategy of carbometalation or heterometalation using main-group metal salts, I developed new synthetic methods using alkynes or fluoroalkenes to form heterocycles and to activate C–F bonds.

In chapter 1, the synthesis of multi-substituted 2-pyrones bearing a carbon–indium bond via oxyindation of carbonyl-ene-yne compounds with indium trihalides was accomplished (Scheme 8). This strategy is a novel selective synthetic method for multi-substituted 2-pyrones. The metalated 2-pyrones intermediate was fully characterized by X-ray crystallographic analysis and NMR spectroscopy. The synthesized tetrasubstituted 2-pyrones showed aggregation-induced emission.



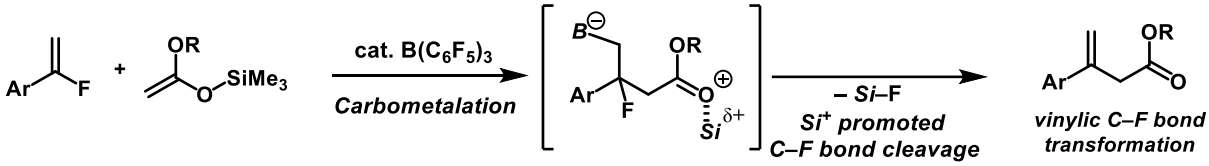
Scheme 8. Synthesis of multi-substituted 2-pyrones via oxyindation

In chapter 2, I developed the indium-catalyzed C–F bond transformation of *gem*-difluoroalkenes bearing ester moieties, which are easily accessible compounds from formyl derivatives, to give a wide variety of fluorinated isocoumarins (Scheme 9). This is the first comprehensive and efficient method for the synthesis of fluorinated isocoumarins. The present reaction proceeds smoothly using main-group metal salts: a catalytic amount of an indium salt in the presence of a zinc salt. A DFT calculation of potential energy surfaces showed that this reaction consisted of oxyindation with the elimination of an alkyl halide and *β*-fluorine elimination.



Scheme 9. Synthesis of fluorinated heterocycles via oxyindation

In chapter 3, I developed a novel strategy for the vinylic C(sp^2)–F bond transformation that was enabled by oxygen-stabilized silylium ions, which were generated by carboboration with silyl ketene acetals and $B(C_6F_5)_3$ catalysis (Scheme 10). A theoretical calculation showed that a cooperation of the silylium ion generated from silyl ketene acetals and $B(C_6F_5)_3$ was essential for C–F bond cleavage. A comparison study of *α*-chloro- or *α*-bromostyrenes demonstrated that this reaction was specifically effective to *α*-fluorostyrenes because of the strong silicon-fluorine affinity.



Scheme 10. Vinylic C–F bond transformation via carboboration

References

[1] For selected reviews, see: (a) M. Wills, *Contemp. Org. Synth.*, **1996**, *3*, 201. (b) I. Coldham, *J. Chem. Soc., Parkin Trans. 1*, **1998**, 1343. (c) K. Afarinkia, *J. Chem. Soc., Perkin Trans. 1*, **1999**, 2025.

[2] For selected textbook and reviews, see: (a) J. F. Normant, A. Alexakis, *Synthesis* **1981**, *11*, 841. (b) E. Negishi, *Acc. Chem. Res*. **1987**, *20*, 65. (c) A. Naoki, Y. Yoshinori, *Bull. Chem. Soc. Jpn.*, **2000**, *73*, 1071. (d) A. G. Fallis, P. Forgione, *Tetrahedron* **2001**, *57*, 5899. (e) A. B. Flynn, W. W. Ogilvie, *Chem. Rev*. **2007**, *107*, 4698. (f) A. Ding, H. Guo, In *Comprehensive Organic Synthesis II*, 2nd ed. (Eds.: P. Knochel, G. A. Molander), Elsevier, Amsterdam, **2014,** pp 891-938.

[3] (a) G. A. Ross, M. D. Koppang, D. E. Bartak, N. F. Woolsey, *J. Am. Chem. Soc.* **1985**, *107*, 6742. (b) A. H. Hoveyda, Z. Xu, *J. Am. Chem. Soc.* **1991**, *113*, 5079. (c) J. A. Seijas, M. P. Vázquez-Tato, C. Entenza, M. M. Martínez, M. G. Ònega, S. Veiga, *Tetrahedron Lett.* **1998**, *39*, 6261. (d) M. Hojo, Y. Murakami, H. Aihara, R. Sakuragi, Y. Baba, A. Hosomi, *Angew. Chem. Int. Ed*. **2001**, *40*, 621. (e) S. Tang, J. Han, J. He, J. Zheng, Y. He, X. Pan, X. She, *Tetrahedron Lett*. **2008**, *49*, 1348. (f) Y. Fujii, J. Terao, N. Kambe, *Chem. Commun*. **2009**, 1115.

[4] (a) T. Ishiyama, K. Nishijima, N. Miyaura, A. Suzuki, *J. Am. Chem. Soc.* **1993**, *115*, 7219. (b) C. Meyer, I. Marek, G. Courtemanche, J.-F. Normant, *Tetrahedron*, **1994**, *50*, 11665. (c) M. Suginome, A. Yamamoto, M. Murakami, *J. Am. Chem. Soc*. **2003**, *125*, 6358. (d) M. Suginome, A. Yamamoto, M. Murakami, *J. Organomet. Chem*. **2005**, *690*, 5300. (e) M. Suginome, M. Shirakura, A. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 14438. (f) B. Gourdet, H. W. Lam, *J. Am. Chem. Soc*. **2009**, *131*, 3802. (g) B. Gourdet, M. E. Rudkin, C. A. Watts, H. W. Lam, *J. Org. Chem*. **2009**, *74*, 7849. (h) S. Ito, T. Itoh, M. Nakamura, *Angew. Chem. Int. Ed.* **2011**, *50*, 454.

[5] Selected reviews: (a) J. P. Sestelo, L. A. Sarandeses, M. M. Martínez, L. Aonso-Marañón, *Org. Biomol. Chem.* **2018**, *16*, 5733. (b) Y. Nishimoto, M. Yasuda, *Chem. Asian J.* **2020**, *15*, 636.

[6] (a) M. Yamaguchi, A. Hayashi, M. Hirama, *Chem. Lett.* **1995**, *24*, 1093. (b) M. Yamaguchi, Y. Kido, A. Hayashi, M. Hirama, *Angew. Chem. Int. Ed.* **1997**, *36*, 1313.

[7] (a) Y. Nishimoto, R. Moritoh, M. Yasuda, A. Baba, *Angew. Chem. Int. Ed.* **2009**, *48*, 4577. (b) Y. Nishimoto, H. Ueda, Y. Inamoto, M. Yasuda, A. Baba, *Org. Lett.* **2010**, *12*, 3390. (c) Y. Nishimoto, H. Ueda, M. Yasuda, A. Baba, *Chem. Eur. J.* **2011**, *17*, 11135. (d) Y. Nishimoto, J. Yi, T. Takata, A. Baba, M. Yasuda, *Molecules* **2018**, *23*, 1884.

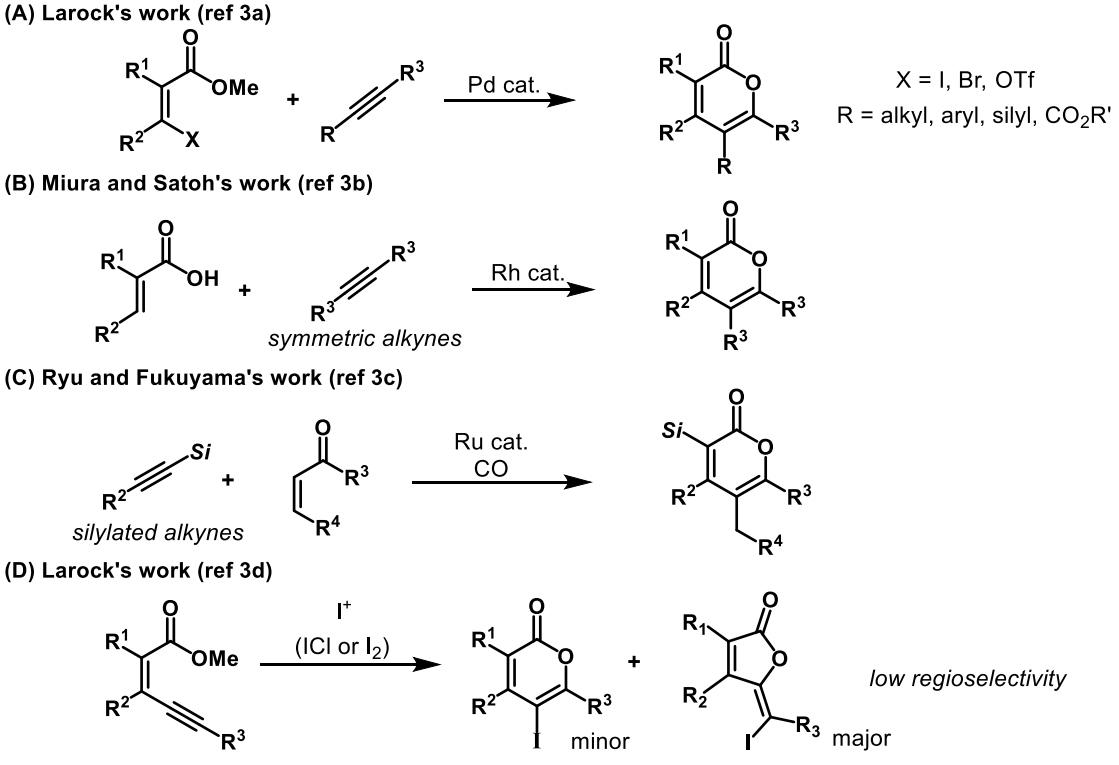
[8] Y. Kita, T. Yata, Y. Nishimoto, K. Chiba, M. Yasuda, *Chem. Sci.* **2018**, *9*, 6041.

[9] (a) M. Nakamura, K. Endo, E. Nakamura, *J. Am. Chem. Soc.* **2003**, *125*, 13002. (b) L. Alonso-Marañón, M. M. Martínez, L. A. Sarandeses, E. Gómez-Bengoa, J. P. Sestelo, *J. Org. Chem.* **2018**, *83*, 7970.

Chapter 1: Regioselective Synthesis of 5-Metalated 2-Pyrones by Intramolecular Oxymetalation of Carbonyl-Ene-Yne Compounds Using Indium Trihalide

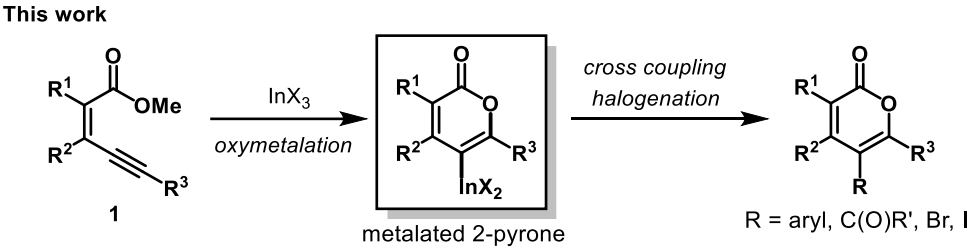
1-1. Introduction

2-Pyrones are an important class of oxygen-containing heterocycles with a broad range of biological activities and are versatile building blocks in organic synthesis.[1] Therefore, the development of general and selective synthetic methods for highly substituted 2-pyrones, particularly tetra-substituted versions, holds great significance. Intramolecular or intermolecular ring-forming reactions catalyzed by transition metals have been recognized as typical methods for the construction of 2-pyrone frameworks. Established general procedures are sufficient for the synthesis of di- and trisubstiututed 2-pyrones.[2] In contrast, only a few studies have focused on the synthesis of tetrasubstituted 2-pyrones.[3] Larock reported a palladium-catalyzed intermolecular [2+4] cyclization between internal alkynes and α,β-unsaturated esters.[3a] This reaction system is an efficient methodology to achieve regioselective synthesis of di-, tri-, and tetrasubstituted 2-pyrones containing aryl, alkyl, silyl, and ester groups (Scheme 1A). Miura and Satoh reported a rhodium-catalyzed oxidative coupling of substituted acrylic acids with alkynes, in which only symmetric alkynes were used for tetrasubstituted 2-pyrones (Scheme 1B).[3b] Ryu and Fukuyama accomplished a Ru-catalyzed [3+2+1] cycloaddition of α,β-unsaturated ketones with silylated alkynes and CO toward the synthesis of tetrasubstituted 2-pyrones. Alkynes other than silylacetylenes were not applicable to this three-compornet reaction (Scheme 1C).[3c] The Larock group established a transition-metal-catalyst-free iodolactonization of carbonyl-ene-ynes with I_2. In this case, tetrasubstituted 2-pyrones were synthesized, but the regioselectivity in the cyclization was low (Scheme 1D).[3d]



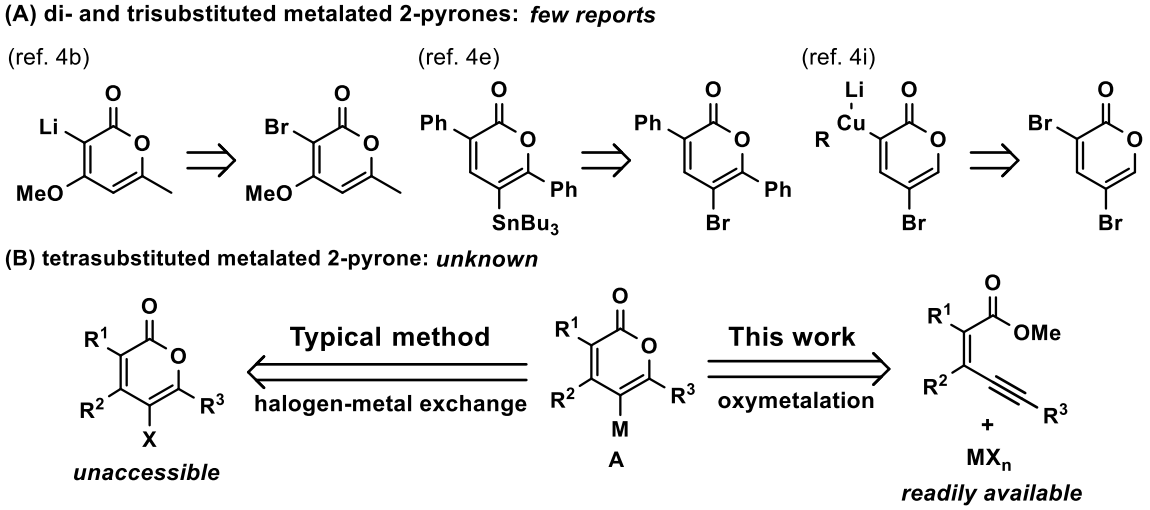
Scheme 1. Reported work: the synthesis of tetrasubstituted 2-pyrones

In this context, we envisioned a strategy employing 2-pyrones with a carbon-metal bond (metalated 2-pyrones) after receiving a hint from our developed oxyindation to afford metalated isocoumarins.[6,7] Transformations of the metal-carbon bond selectively gives multi-substituted pyrones.[4] Herein, we describe a novel selective synthetic method for highly substituted 2-pyrones, including tetrasubstituted versions, by using metalated 2-pyrones synthesized via the intramolecular oxyindation carbonyl-ene-yne compounds **1** with InI_3 (Scheme 2). With this method, it is possible to obtain tetrasubstituted 2-pyrones containing bromine, iodine, and ketone moieties, which have not been prepared by previous methods.



Scheme 2. Oxyindation of carbonyl-ene-yne compound to access multisubstituted metalated 2-pyrones

A metalated 2-pyrone is the key compound in our stratey. Almost all reported syntheses of metalated 2-pyrones depend on a halogen-metal exchange of halogenated 2-pyrones. Therefore, the lack of a facile synthetic procedure for di- or trisubstituted halogenated 2-pyrones[5] has led to an underdevelopment in the synthesis of highly substituted metalated 2-pyrones (Scheme 3A).[4] In addition, a synthesis of tetrasubstituted 2-pyrones has not been achieved (Scheme 3B). With the present synthetic method, the establishment of an oxymetalation of fully substituted carbonyl-ene-ynes **1**, which are easily synthesized from iodoacrylate derivatives and acetylene derivatives, achieves the preparation of 5-metalated 2-pyrones **A**, which includes di-, tri-, and tetrasubstituted versions. This is the first report of the synthesis of tetrasubstituted metalated 2-pyrones.

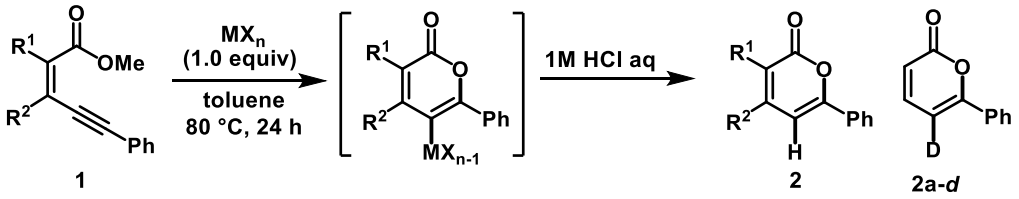


Scheme 3. Retrosynthesis of metalated 2-pyrones: (A) di- and trisubstituted metalated 2-pyrones, (B) tetrasubstituted metalated 2-pyrones

1-2. Results and Discussion

First, various metal salts were surveyed in an intramolecular oxymetalation of carbonyl-ene-yne **1a** (Table 1). Recently, we reported an indium salt-mediated oxymetalation of 2-alkynylbenzoates to synthesize metalated isocoumarins.[6] Therefore, oxyindations of **1a** were conducted using indium halides. A solution of **1a** and InX_3 (X = Cl, Br, and I) in toluene was heated at 80 °C, and then the reaction mixture was quenched using 1 M HCl aq. The use of $InCl_3$ resulted in no reaction (Table 1, entry 1). On the other hand, $InBr_3$ and InI_3 gave the desired product **2a** in 88 and 100% yields, respectively (Table 1, entries 2 and 3). When the reaction using InI_3 was quenched by DCl in D_2O, product **2a**-*d* deuterated at the 5-position was obtained. Typical Lewis acids such as BBr_3, $ZnBr_2$, $AlBr_3$ and $GaBr_3$ were unsuitable (Table 1, entries 4-7). Subjecting the other alkynophilic Lewis acids such as $PdCl_2$, AuCl, and AgOTf to the present oxymetalation resulted in decomposition or recovery of the starting material **1a** (Table 1, entries 8-10). To our delight, a more substituted carbonyl-ene-yne **1b** or **1c** afforded the highly substituted 2-pyrones **2b** or **2c**, respectively (Table 1, entries 11 and 13). Blum and co-workers reported an oxyboration of carbonyl-ene-yne **1a** using *B*-chlorocatecholborane (ClBcat) to afford borylated 2-pyrone,[8] but the oxyboration system was not applicable to multi-substituted substrates such as **1b** (Table 1, entry 12).

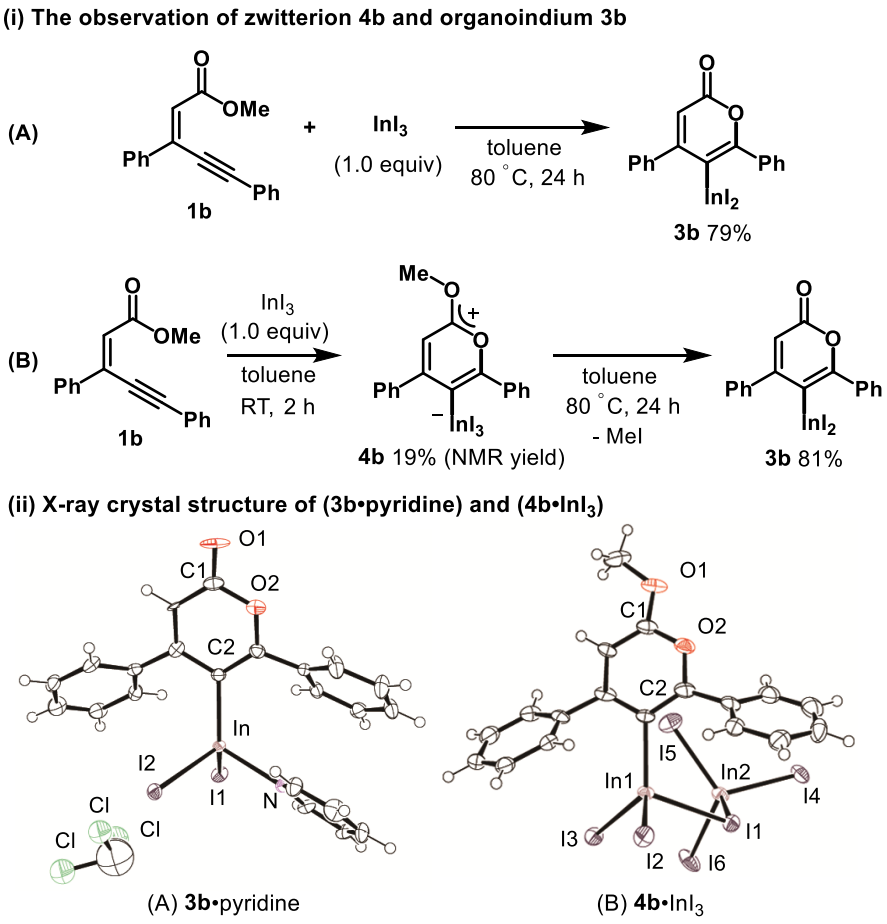
Table 1. Effect of Lewis acids on the oxymetalation of **1a**, **1b**, and **1c**[a].



entry	**1** (R^1, R^2)	MX_n	yield of **2** /%[b]
1	**1a** (H, H)	$InCl_3$	**2a**:0
2	**1a** (H, H)	$InBr_3$	**2a**:88
3[c]	**1a** (H, H)	InI_3	**2a**:100 (2a-*d*:82% D)
4	**1a** (H, H)	BBr_3	**2a**:0
5	**1a** (H, H)	$ZnBr_2$	**2a**:14
6	**1a** (H, H)	$AlBr_3$	**2a**:0
7	**1a** (H, H)	$GaBr_3$	**2a**:45
8	**1a** (H, H)	$PdCl_2$	**2a**:0
9	**1a** (H, H)	AuCl	**2a**:6
10	**1a** (H, H)	AgOTf	**2a**:0
11	**1b** (H, Ph)	InI_3	**2b**:92
12[d]	**1b** (H, Ph)	ClBcat	**2b**:0
13	**1c** (Et, Ph)	InI_3	**2c**:95

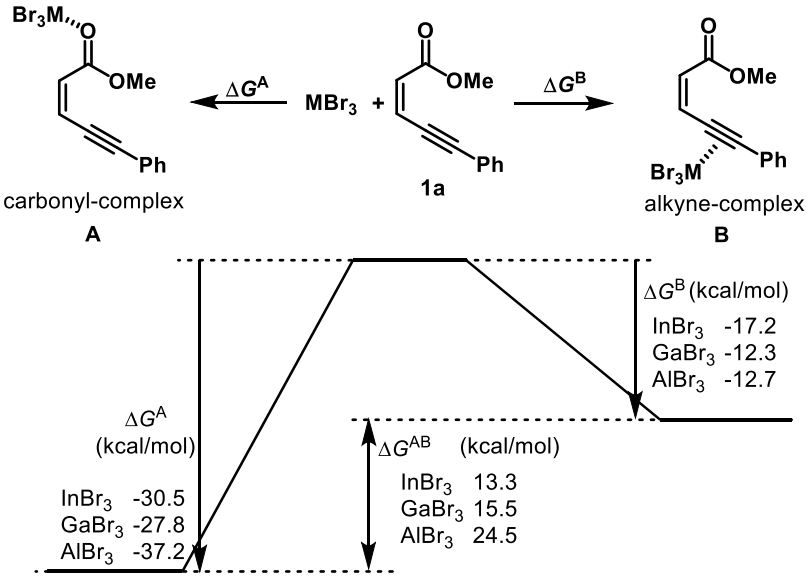
[a]**1** (0.5 mmol), MX_n (0.5 mmol), toluene (1 mL) [b]The yield of **2** was determined by ^{1}H NMR. [c]The reaction mixture was quenched by 1 M DCl in D_2O (1 mL) and a subsequent addition of H_2O (10 mL).[d]**1b** (0.5 mmol), ClBcat (1.4 eq.), toluene (1 mL) 24 h, 100 °C, and then quenched by pinacol (3 eq.) and NEt_3 (1 mL).

When the reaction of **1b** with InI_3 was performed under the optimal conditions (Table 1, entry 11) without acid-quenching, metalated 2-pyrone **3b** bearing an InI_2 group at the 5-position was obtained as a white solid (Scheme 4(i), (A)) and protonated product **2b** was hardly observed. This result suggested the oxyindation proceeded. The structure of a **3b**·pyridine complex was identified by X-ray crystallographic analysis (Scheme 4(ii), (A)). (See Supporting Information (SI) for details of the experiments). Oxyindation at room temperature also afforded a white solid (Scheme 4(i), (B)), and, interestingly, it was not **3b.** ^{1}H NMR spectroscopic and X-ray crystallographic analysis clarified the formation as that of zwitterion **4b** (Scheme 4(ii), (B)). An indium atom (In1) of **4b** in the solid state was bound to three iodine atoms (I1, I2, and I3) and a carbon atom (C2), and displayed a distorted tetrahedral geometry. One of the iodine atoms on In1 coordinated to InI_3 in a crystal structure. The bond lengths of the two carbon-oxygen bonds (C1-O1 = 1.300(10) Å, C1-O2 = 1.327(11) Å) in **4b** showed values that fell between that of a typical C-O double bond (1.233 Å) and a single bond (1.401 Å) of the **3b**·pyridine complex. Thus, the positive charge was delocalized in the ester moiety.[9] Subjecting zwitterion **4b** to heating conditions gave metalated 2-pyrone **3b** via the elimination of MeI.



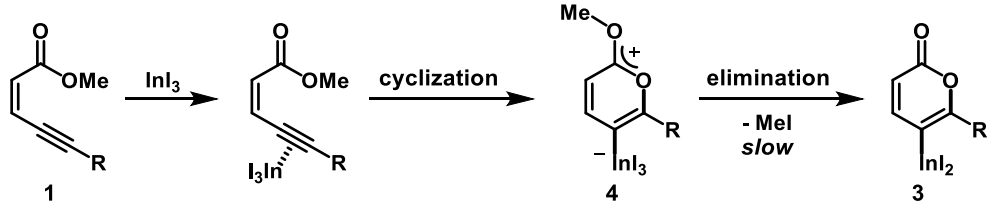
Scheme 4. The observation of intermediates for mechanistic studies.

To gain insight into the reaction mechanism, the coordination mode of carbonyl-ene-yne **1a** to a Lewis acid was investigated by DFT calculation (Scheme 5). In the coordination of either the alkyne moiety (**B**) or the carbonyl oxygen (**A**) in **1a** to $InBr_3$, the Gibbs energy changes were -17.2 kcal mol^{-1} and -30.5 kcal mol^{-1}, respectively. Therefore, both complexations were thermodynamically stable, but carbonyl coordination was more favorable. The energy gap between carbonyl complex **A** and alkyne complex **B** of $AlBr_3$ was very large ($\Delta G^{A\ to\ B}$ = 24.5 kcal mol^{-1}), but $InBr_3$ showed a relatively small value ($\Delta G^{A\ to\ B}$ = 13.3 kcal mol^{-1}). Consequently, $InBr_3$ was more susceptible to the subsequent alkyne coordination compared with $AlBr_3$ after dissociation of the carbonyl coordination.



Scheme 5. Computed binding gibbs free energy for complexation to alkyne vs oxygen (B3LYP/6-31+G(d,p) for H, C, DGDZVP for Al, Ga, In and Br.).

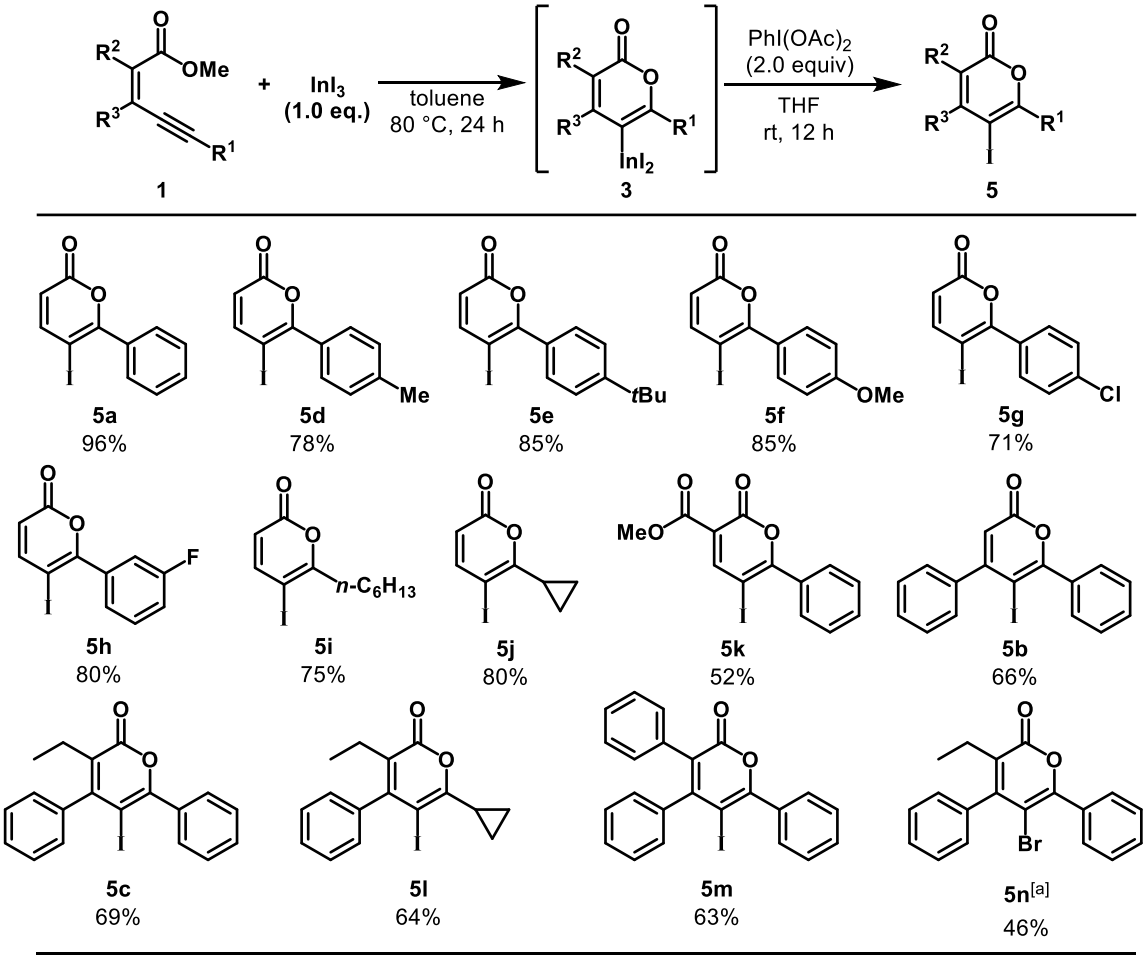
A possible reaction mechanism is depicted in Scheme 6. First, InI_3 acts as an efficient π-electrophilic Lewis acid for the activation of the alkyne moiety of carbonyl-ene-yne **1**[7], and then the intramolecular nucleophilic attack of a carbonyl oxygen atom occurs to generate zwitterion **4**. Then, the elimination of MeI gives metalated 2-pyrone **3**. The elimination is a rate-determinig step.



Scheme 6. A proposed reaction mechanism

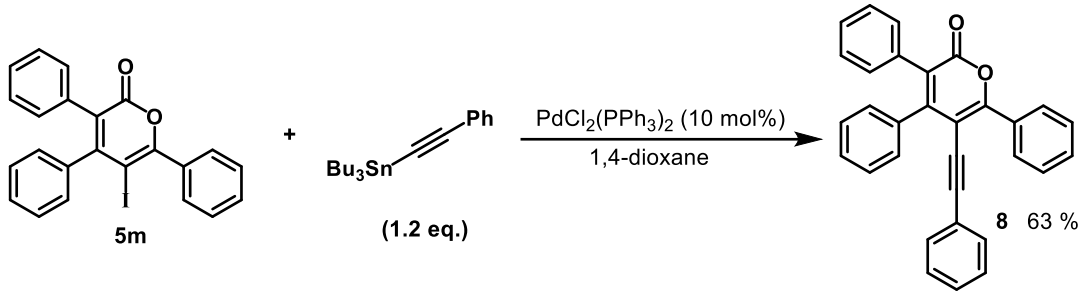
Various types of carbonyl-ene-ynes **1** were applied to the synthesis of 2-pyrone derivatives via the present oxyindation (Scheme 7). Oxyindation of **1a** using InI_3 followed by oxidation of **3a** with $PhI(OAc)_2$ was carried out in a one-pot procedure to afford 5-iodo-2-pyrone **5a** in a 96% yield.[6] Substrates **1** with substituents such as Me, *tert*-Bu, MeO, Cl, and F groups on the aromatic ring bindng to an alkyne moiety

gave the target products **5d**, **5e**, **5f**, **5g**, and **5h**, respectively. The substrates bearing aliphatic alkyne moieties **1i** and **1j** also worked well. Dicarbonyl-ene-yne compound **1k** provided the desired trisubstituted 2-pyrone **5k** in a moderate yield. Subjecting **1b** to halogenation yielded 5-iodo-4,6-diphenyl-2-pyrone **5b**. α,β-Disubstituted substrate **1c** was surveyed in the sequential oxyindation/halogenation process to afford tetrasubstituted 2-pyrone **5c**. Gratifyingly, 2-pyrone **5l** bearing four different substituents on the ring was produced by the reaction using **1l**. The oxyindation of **1m** proceeded in 6-*endo* cyclization to exclusively give 2-pyrone **5m** in contrast to Larock's iodocyclization of **1m** with ICl giving a 5-membered oxacycle as a major product.[3d] Therefore, this result shows our developed method is more effective for the synthesis of multisubstituted 2-pyrones. To our delight, subjecting $InBr_3$ instead of InI_3 to the oxyindation reaction provided fully substituted brominated 2-pyrones **5n** in a moderate yield. Therefore, our approach accomplished the synthesis of tetrasubstituted brominated 2-pyrones as well as iodinated ones.



Scheme 7. Sequential oxymetalation/halogenation of various types of carbonyl-ene-yne [First step: **1** (0.5 mmol), InI_3 (0.5 mmol), toluene (1 mL), 80 °C, 24 h. Second step: $PhI(OAc)_2$ (1.0 mmol), THF (2 mL), rt, 12 h. The isolated yields are shown. [a]$InBr_3$ was used instead of InI_3.]

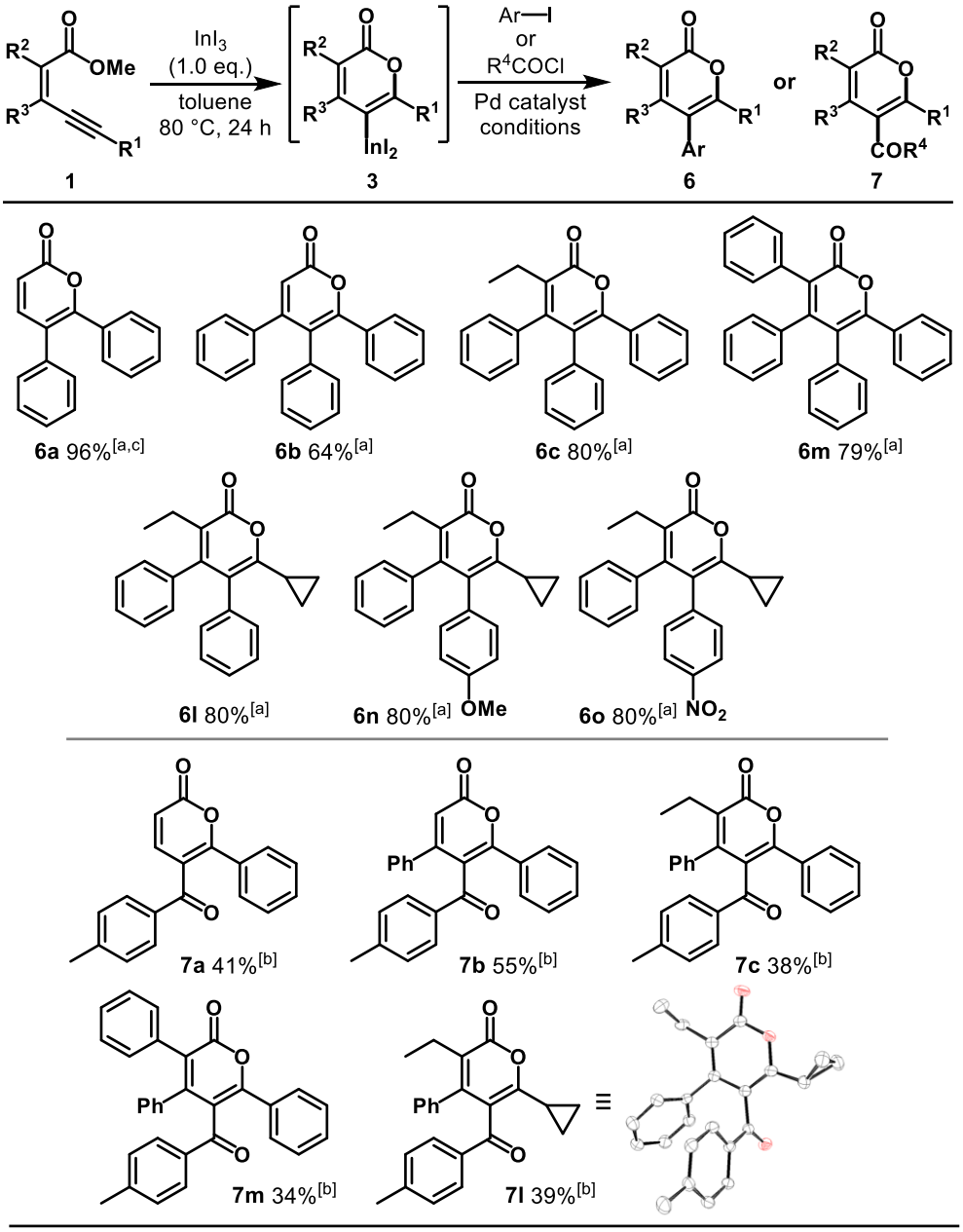
Iodinated 2-pyrone **5m** was used for further transformations with Migita-Kosugi-Stille coupling to give tetra-carbon-substitued 2-pyrones (Scheme 8).[10]



Scheme 8. Synthesis of tetrasubstituted 2-pyrones using still coupling.

Palladium-catalyzed, cross-coupling syntheses of metalated 2-pyrones **3** with aryl iodides or acid chlorides were performed (Scheme 9).[11] After the oxyindation of **1a** with InI_3, iodobenzene, $Pd_2(dba)_3$ catalyst, NaOMe, and DMF were added to the reaction mixture involving InI_2-substituted 2-pyrone **3a**. The Pd-catalyzed coupling reaction between **3a** and iodobenzene smoothly proceeded to produce 5,6-diphenyl-2-pyrone **6a** in a 96% yield. The trisubstituted metalated 2-pyrone derived from **1b** also underwent coupling to afford 4,5,6-triphenyl-2*H*-pyran-2-one **6b**. Various types of tetrasubstituted metalated 2-pyrones derived from **1c**, and **1l-1o** were employed to produce tetra-carbon-substitued 2-pyrones **6c** and **6l-6o**, respectively. Both electron-rich and -poor aryl iodides worked as feasible coupling partners to afford 2-pyrones **6n** and **6o** bearing four different carbon substitutents. Furthermore, the Pd-catalyzed cross coupling of InI_2-substituted 2-pyrones **3** with an acid chloride also proceeded under condition B to give multi-functionalized 2-pyrones **7a**-**7c**, **7l**, and **7m**. The structure of 2-pyrone **7l** was confirmed by X-ray crystallographic analysis. The present oxyindation/cross-coupling sequential process established a modular synthesis of multi-functionalized 2-pyrones.

Tetrasubstituted 2-pyrones **6m** and **7m** had no fluorescence properties in the solution, but an aggregation-induced emission (AIE) was observed in the solid state. Triphenylated 2-pyrone **2c** is known to possess AIE properties and exhibit a higher quantum yield than Alq_3, which is generally used in electroluminescence devices.[12] However, tetrasubstituted 2-pyrones have not been investigated in detail because relatively little is known about a facile synthetic method. We expected to improve the light emission properties by installing a substituent at the 5-position, and thus **6m** and **7m** exhibited greater quantum yields than **2c** (Figure 1A). This result can be ascribed to the fact that the installation of either a phenyl- or an aloyl group changed the intermolecular interactions in the solid state. Figure 1B shows the molecular packing diagrams of compound **6m**, **7m** and **2c**[12]. In the crystal structure of these compounds, there are C-H···π interactions and/or hydrogen bonds among molecules. These interactions limited the molecular motions, giving rise to the emission enhancement in the solid state. A quenching effect is caused by the stacking interactions between 2-pyrone structures in **6m** and **2c**, but not in **7m**. Inhibition of the stacking by the steric hindrance of benzoyl group at the 5-position achieved the strongest light emission of **7m**. The distance between the 2-pyrone skeleton of **6m** is longer than that of **2c** due to the Ph group at the 5-position, so **6m** shows stronger light emission than **2c**.



Scheme 9. One-pot formation of highly substituted 2-pyrones by palladium-catalyzed cross-coupling.

[a]Oxyindation conditions: **1** (0.5 mmol), InI_3 (0.5 mmol), toluene (1 mL), 80 °C, 24 h. Second step conditions: Pd_2dba_3 (0.025 mmol), NaOMe (1.0 mmol), ArI (Ar = 0.35 mmol), DMF (2.5 mL), 110 °C, 24 h. [b]Oxyindation conditions: **1** (0.5 mmol), InI_3 (0.5 mmol), toluene (1 mL), 80 °C, 24 h. Second step conditions: Pd_2dba_3 (0.025 mmol), R^4COCl (1.0 mmol), 1,3-dimethyl-2-imidazolidinone (2.5 mL), 80 °C, 24 h. The isolated yields are shown. [c]The cross coupling was run at 80 °C and KCl was used instead of NaOMe.

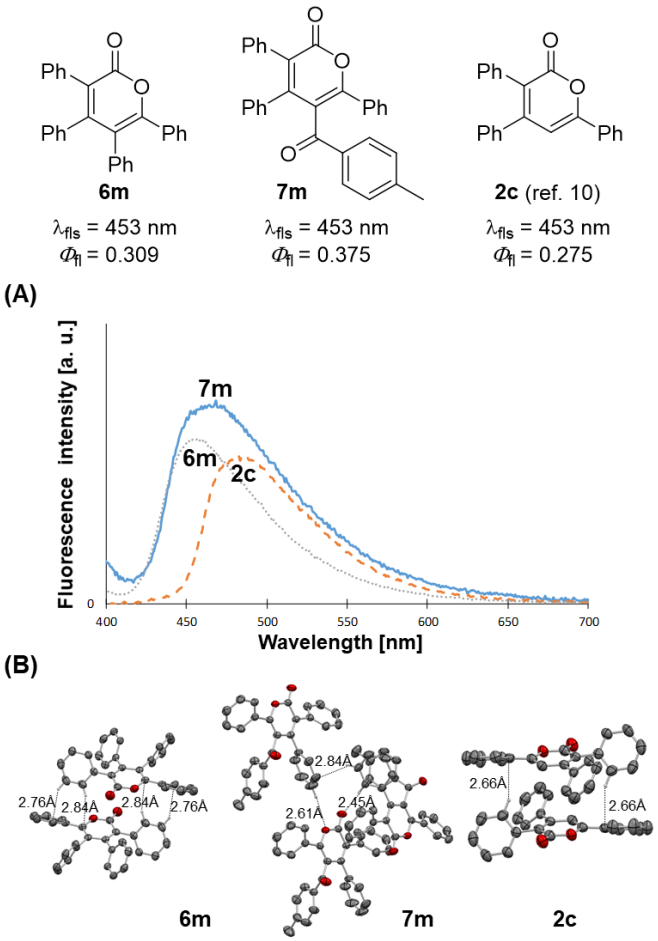


Figure 1. (A) Fluorescence spectra of **6m** and **7m** and **2c** in the solid state upon excitation at 365 nm. The fluorescence intensities of their compounds were calculated based on quantum yield. (B) Packing mode and multiple interactions of compound **6m** and **7m** and **2c**.

1-3. Conclusion

We developed a process for the oxyindation of carbonyl-ene-yne compounds to give 2-pyrones bearing a carbon-indium bond at the 5-position. Metalated 2-pyrones **3** and zwitterion intermediate **4** were fully characterized by X-ray crystallographic analysis and NMR spectroscopy. These results supported a reaction mechanism that is composed of two steps: an indium trihalide-mediated cyclic oxymetalation and the sequential elimination of MeI from **4**. The bromination or iodination of **3** provided 5-halo-2-pyrones **5** which are quite useful as synthetic precursors to multi-substituted 2-pyrones. We developed a general synthesis method for highly substituted 2-pyrones via a cross-coupling reaction using **3**. The synthesized tetrasubstituted 2-pyrones showed aggregation-induced emission (AIE). The oxyindation chemistry described herein could contribute to a modular synthesis of multi-functionalized 2-pyrones.

1-4. Experimental Section

General Information

NMR spectra were recorded on a JEOL JNM-400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) spectrometer. Chemical shifts were reported in ppm on the δ scale relative to tetramethylsilane (δ = 0 for ^{1}H NMR) and residual $CHCl_3$ (δ = 77.0 for ^{13}C NMR) as an internal reference. New compounds were characterized by ^{1}H, ^{13}C, ^{13}C off-resonance techniques, COSY, HMQC, and HMBC. Infrared (IR) spectra were recorded on a JASCO FT/IR-6200 Fourier transform infrared spectrophotometer. Column chromatographies were performed with silica gel. Purification by recycle HPLC was performed using the SHIMADZU recycle HPLC system (SPD-20A, RID-10A, DGU-20A, LC-6AD, and FCV-20H2) from the Japan Analytical Industry Co. (NEXT recycling preparative HPLC). High-resolution mass spectra were obtained using a magnetic sector type mass spectrometer. Reactions were carried out in dry solvents under a nitrogen atmosphere, unless otherwise stated. Reagents were purchased from Aldrich or Tokyo Chemical Industry Co., Ltd. (TCI), FUJIFILM Wako Pure Chemical Corporation and used either after purification by distillation or without purification for solid substrates. X-ray diffraction analysis was carried out via Rigaku XtaLAB Synergy with a Hypix-6000HE. Steady-state emission spectra were recorded on a HAMAMATSU C11347-01 spectrometer with an integrating sphere.

Materials

Dehydrated solvents, such as toluene, THF, 1,4-dioxane, DMF, and DMI were purchased from FUJIFILM Wako Pure Chemical Corporation and used as obtained. $PhI(OAc)_2$ was purchased from Tokyo Chemical Industry Co., Ltd., and used without further purification. Carbonyl-ene-yne compounds, **1a**, **1b**, **1d-1k**, and **1m** were synthesized by reported procedures, and the spectral data for these compounds are provided in the Supporting Information. Carbonyl-ene-ynes **1c** and **1l** are new compounds, and the synthetic methods and spectral data for these compounds are shown below. InI_3 (Indium Triiodide 99.99%) was purchased from Kojundo Chemical Laboratory. All other reagents were commercially available.

General Procedure for the synthesis of carbonyl-ene-yne 1a[3d], 1b[13], 1d[14], 1e[14], 1f[14], 1g[14], 1h[14], 1i[15], 1[8], 1k[16], and 1m.[3d]

To a solution of methyl (*Z*)-3-iodoacrylate (5 mmol, 1 equiv) in Et_3N (20 mL) were added $PdCl_2(PPh_3)_2$ (0.1 mmol, 0.02 equiv), CuI (0.1 mmol, 0.02 equiv) and acetylene (6.5 mmol, 1.3 equiv). The resulting mixture was heated under nitrogen atmosphere at 55 °C by oil bath. The reaction was monitored by TLC to establish completion. When the reaction was complete, the mixture was quenched by NH_4Cl aq (30 mL). The solution was extracted by Et_2O (3 x 30 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography. Product-containing fractions were combined and concentrated in vacuo to afford **1**.

methyl (*Z*)-2-ethyl-3,5-diphenylpent-2-en-4-ynoate (1c)

The 3-Phenyl-2-propyn-1-ol (20.2 mmol, 2.67 g), dry Et_2O (30 mL), and CuI (2.35 mmol, 0.448 g) were

added to a three-necked flask. To the cooled, stirred mixture at 0 °C was added a 3.0M EtMgBr in diethyl ether (17 mL). Upon complete addition of the Grignard reagent, the mixture was allowed to warm up to room temperature and stirred for 20 h. The dark green mixture was then cooled to 0 °C and I_2 (22.2 mmol, 5.63 g) was added. After warming up to room temperature and stirring at room temperature for 1 h, the reaction mixture was cooled to 0 °C and quenched with sat. NH_4Cl aq (20 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 x 50 mL). The combined ether layers were dried over $MgSO_4$, filtered, and concentrated in vacuo and then the crude (*Z*)-2-{iodo(phenyl)methylene}butan-1-ol (12.3 mmol, 3.56 g) was obtained. The crude (*Z*)-2-{iodo(phenyl)methylene}butan-1-ol was used without further purification.

To a solution of (*Z*)-2-{iodo(phenyl)methylene}butan-1-ol (12.3 mmol, 3.56 g), CH_2Cl_2 (123 mL), and MnO_2 (247 mmol, 21.8 g) were added to a three-necked flask. The reaction mixture was stirred at room temperature for 2 h. The black precipitate was filtered off and the filtrate was concentrated in vacuo and then the crude (*Z*)-2-{iodo(phenyl)methylene}butanal (11.7 mmol, 3.34 g) was obtained. The crude (*Z*)-2-{iodo(phenyl)methylene}butanal was used without further purification.

The (*Z*)-2-{iodo(phenyl)methylene}butanal (11.7 mmol, 3.34 g), MeOH (150 mL), NaCN (47.7 mmol, 2.34 g), AcOH (17.5 mmol, 1.05 g), and MnO_2 (238 mmol, 20.7 g) were added to a three-necked flask. The mixture was stirred at room temperature for 12 h under N_2 atm. The black precipitate was filtered off and the filtrate was concentrated under vacuo. The resulting residue was partitioned between 80 mL of H_2O and 80 mL of Et_2O. The organic layer was separated and the aqueous layer was extracted with ether (3 x 50 mL). The combined ether layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 5:95, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the methyl (*Z*)-2-{iodo(phenyl)methylene}butanoate (**9**) as a yellow oil (3.45 g, 54%).

IR: (neat) 1733 (C=O) cm^{-1}, ^1H NMR: (400 MHz, $CDCl_3$) 7.38-7.32 (m, 2H), 7.30-7.24 (m, 3H), 3.88 (s, 3H), 2.25 (q, J = 7.4 Hz, 2H), 0.98 (t, J = 7.4 Hz, 3H), $^{13}C\{^1H\}$ NMR: (100 MHz, $CDCl_3$) 169.6 (s), 144.7 (s), 142.5 (s), 128.3 (d), 127.7 (d), 96.8 (s), 52.3 (q), 26.2 (t), 13.1 (q), HRMS: (EI, 70 eV) Calculated ($C_{12}H_{13}O_2I$) 315.9960 (M^+) Found 315.9962

To a solution of methyl (*Z*)-2-{iodo(phenyl)methylene}butanoate (5.43 mmol, 1.72 g) in Et_3N (20 mL) were added $PdCl_2(PPh_3)_2$ (0.114 mmol, 0.0800 g), CuI (0.105 mmol, 0.0200 g) and phenylacetylene (6.51 mmol, 0.665 g). The resulting mixture was heated under nitrogen atmosphere at 55 °C. The reaction was monitored by TLC to establish completion. When the reaction was complete, the mixture was quenched by NH_4Cl aq (30 mL). The solution was extracted by Et_2O (3 x 30 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm, diameter 26 nm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the product as a yellow oil (1.24 g, 78%). IR: (neat) 2196 (C≡C), 1721 (C=O) cm^{-1}, ^1H NMR: (400 MHz, $CDCl_3$) 7.43-7.26 (m, 10H), 3.90 (s, 3H), 2.40 (q, J = 7.4 Hz, 2H), 1.04 (t, J = 7.4 Hz, 3H), ^{13}C NMR: (100 MHz, $CDCl_3$) 168.8 (s), 141.4 (s), 138.2 (s), 131.6 (d), 128.5 (d), 128.4 (d), 128.3 (d), 128.2 (d), 128.0 (s), 128.0 (s), 123.1 (s), 96.8 (s), 89.1 (s), 51.9 (q), 24.0 (t), 13.4 (q), HRMS: (EI,

70 eV) Calculated ($C_{20}H_{18}O_2$) 290.1307 (M^+) Found 290.1306

methyl (*Z*)-5-cyclopropyl-2-ethyl-3-phenylpent-2-en-4-ynoate (1l)

To a solution of methyl (*Z*)-2-{iodo(phenyl)methylene}butanoate (**9**) (2.91 mmol, 0.921 g) (The experimental procedure and characterization of this compound (**9**) were described in experimental procedure of methyl (*Z*)-2-ethyl-3,5-diphenylpent-2-en-4-ynoate (**1c**)) in Et_3N (12 mL) were added $PdCl_2(PPh_3)_2$ (0.0329 mmol, 0.0231 g), CuI (0.0735 mmol, 0.0140 g) and phenylacetylene (3.49 mmol, 0.230 g). The resulting mixture was heated under an N_2 atmosphere at 55 °C. The reaction was monitored by TLC to establish completion. When the reaction was complete, the mixture was quenched by NH_4Cl aq (10 mL). The solution was extracted by Et_2O (3 x 10 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm, diameter 26 nm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the product as a yellow oil (0.443 g, 60%). IR: (KBr) 2212 (C≡C), 1722 (C=O) cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) 7.38-7.27 (m, 5H), 3.84 (s, 3H), 2.30 (q, *J* = 7.5 Hz, 2H), 1.43-1.36 (m, 1H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.86-0.82 (m, 2H), 0.76-0.72 (m, 2H), $^{13}C\{^1H\}$ NMR: (100 MHz, $CDCl_3$) 169.0 (s), 139.9 (s), 138.8 (s), 128.7 (s), 128.2 (d), 128.1 (d), 127.8 (d), 102.5 (s), 75.8 (s), 51.7 (q), 23.7 (t), 13.5 (q), 9.1 (t), 0.7 (d), HRMS: (CI, 70 eV) Calculated ($C_{17}H_{19}O_2$): 255.1385 $[M+H]^+$Found 255.1387

General Procedure for oxymetalation of methyl (*Z*)-5-phenylpent-2-en-4-ynoate followed by protonolysis (Table 1)

In a glove box filled for nitrogen, to a sealed vial, InI_3 (0.5 mmol, 1 equiv), toluene (1 mL) and methyl (*Z*)-5-phenylpent-2-en-4-ynoate **1a** (0.5 mmol, 1 equiv) were added. The solution was stirred at 80 °C for 24 h in a heated aluminum block and the reaction mixture was quenched by 1 M HCl aq (1 mL). After addition of water (10 mL), the solution was extracted with CH_2Cl_2 (5 mL x 3). The collected organic layer was dried over $MgSO_4$. The solvent was evaporated and the yield of 6-phenyl-2*H*-pyran-2-one **2** was determined by ^1H NMR using internal standards (1,1,2,2-tetrachloroethane)

Oxymetalation of a carbonyl-ene-yne using InI_3 (1.0 mmol Scale)

To a 10 mL vial filled with InI_3 (0.999 mmol, 0.495 g) in toluene (2 mL) was added methyl (*Z*)-5-phenylpent-2-en-4-ynoate **1a** (1.01mmol, 0.187 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h in a heated aluminum block and the reaction mixture was quenched by water (10 mL) and 1 M HCl aq (2 mL). The solution was extracted by dichloromethane (3 x 10 mL) and the combined organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm, diameter 26 mm, spherical silica gel). Fractions containing the desired product were combines and concentrated in vacuo to give the product **2a** as a pale yellow solid (0.115 g, 67%). (The experimental procedure at 0.5 mmol scale and characterization of **2a** were shown below)

Observation of Zwitterion Intermediate 4b by ^{1}H NMR spectroscopy and X-ray Crystallographic Analysis (Scheme 4)

Oxyindation of methyl (*Z*)-3,5-diphenylpent-2-en-4-ynoate **1b** (0.501 mmol, 0.131 g) with InI_3 (0.505 mmol, 0.250 g) was carried out in toluene (1 mL) at room temperature for 2 h to give a white solid, and then the toluene was evaporated and the residual solid was dissolved in $CDCl_3$. ^{1}H NMR spectroscopy measurements showed that the solid was mixture of two compounds, which were neither the metalated pyrone **3b** nor the starting material **1b**. Recrystallization of the mixture from $CHCl_3$ and heptane provided a crystal and X-ray crystallographic analysis revealed that the one of the two components was the zwitterion intermediate **4b** (CCDC 1910563).

Isolation of Organoindium Compounds 3b and 3b· pyridine (Scheme 4-ii-A and Scheme 4-ii-B)

All operations were carried out in a nitrogen-filled glove box. To a 10 mL vial filled with InI_3 (0.502 mmol, 0.249 g) in toluene (1 mL) was added methyl (*Z*)-3,5-diphenylpent-2-en-4-ynoate (0.493 mmol, 0.129 g). The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, the solvent was removed by decantation to obtain a white solid and the solid was washed by $CHCl_3$ (3 mL x 6). The residue was dried under vacuum to give the product **3b** as a white solid (0.297 g, 81%). **3b** was added to pyridine (0.399 mmol, 0.0316 g) and recrystallized from $CHCl_3$ and heptane to give a single crystal of **3b·pyridine**. The structure was determined by X-ray crystallographic analysis (CCDC 1910738). Characterization by NMR study was also carried out. ^{1}H NMR: (400 MHz, $CDCl_3$) 8.27 (d, J = 4.8 Hz, 2H, 15-H x 2), 7.77-7.72 (m, 3H), 7.54-7.48 (m, 2H, 8-H x 2), 7.36-7.34 (m, 6H), 7.28-7.26 (m, 2H, 16-H x 2), 6.35 (s, 1H, 3-H), ^{13}C NMR: (100 MHz, $CDCl_3$) 167.2 (s, C-6), 162.7 (s), 162.6 (s), 148.0 (d, C-15), 141.1 (s, C-7), 139.1 (d, C-17), 136.0 (s, C-11), 131.2 (d), 130.1 (d), 129.6 (d), 129.09 (d), 129.06 (d), 127.7 (d, C-8), 124.9 (d, C-16), 118.9 (s, C-5), 111.8 (d, C-3).

General Procedure for oxymetalation of carbonyl-ene-yne compounds followed by halogenation (Scheme 7)

In a glove box filled with nitrogen, to a sealed vial, InI_3 (0.5 mmol, 1 equiv), toluene (1 mL) and carbonyl-ene-yne compound **1** (0.5 mmol, 1 equiv) were added. After stirring at 80 °C for 24 h in a heated aluminum block, the suspension was diluted by THF (2.5 mL) and $PhI(OAc)_2$ (1.0 mmol, 1 equiv) was added to the solution in the glove box. The reaction mixture was stirred at rt for 24 h and then quenched by water (5 mL) and 1 M HCl aq (1 mL). The solution was extracted with CH_2Cl_2 (30 mL x 2) and the collected organic layer was dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography.

General Procedure for oxymetalation of carbonyl-ene-yne compounds followed by palladium catalyzed cross coupling with iodoarenes (Scheme 9)

In a glove box filled with nitrogen, to a sealed vial, InI_3 (0.5 mmol, 1.4 equiv), toluene (1 mL) and carbonyl-ene-yne compound **1** (0.5 mmol, 1.4 equiv) were added, and the solution was stirred at 80 °C for 24 h in a heated aluminum block. $Pd_2(dba)_3$ (0.025 mmol, 0.071 equiv), a base such as KCl and NaOMe (2.9 equiv or

none), ArI (0.35 mmol, 1 equiv) and DMF (2.5 mL) was added to the reaction mixture in the glove box and the mixture was stirred at 110 °C for 24 h. The reaction mixture was quenched by water (5 mL) and 1 M HCl aq (1 mL). The solution was extracted with dichloromethane (3 x 30 mL) and the collected organic layer was dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography.

General Procedure for oxymetalation of carbonyl-ene-yne compounds followed by palladium catalyzed cross coupling with acid chlorides (Scheme 9)

In a glove box filled with nitrogen, to a sealed vial, InI_3 (0.5 mmol, 1 equiv), toluene (1 mL) and carbonyl-ene-yne compound **1** (0.5 mmol, 1 equiv) were added, and the solution was stirred at 80 °C for 24 h in a heated aluminum block. $Pd_2(dba)_3$ (0.025 mmol, 0.05 equiv), 4-methylbenzoyl chloride (1.0 mmol, 2 equiv) and 1,3-dimethyl-2-imidazolidinone (2.5 mL) was added to the reaction mixture in the glove box and the mixture was stirred at 80 °C for 24 h in a heated aluminum block. The reaction mixture was quenched by water (5 mL) and 1 M HCl aq (1 mL). The solution was extracted with dichloromethane (3 x 30 mL) and the collected organic layer was dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography.

6-phenyl-2*H*-pyran-2-one (2a)

To a 10 mL vial filled with InI_3 (0.503 mmol, 0.249 g) in toluene (1 mL) was added methyl (*Z*)-5-phenylpent-2-en-4-ynoate (0.500mmol, 0.0931 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h and the reaction mixture was quenched by water (5 mL), 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (2 x 30 mL) and the combined organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm, diameter 26 mm, spherical silica gel) Product-containing fractions were combines and concentrated in vacuo to give the product as a yellow solid (0.0797 g, 93%). The NMR date was agreement with the literature[17].

4,6-diphenyl-2*H*-pyran-2-one (2b)

To a 10 mL vial filled with InI_3 (0.503 mmol, 0.249 g) in toluene (1 mL) was added methyl (*Z*)-3,5-diphenylpent-2-en-4-ynoate (0.500mmol, 0.131 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h and the reaction mixture was quenched by water (5 mL), 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (2 x 30 mL) and the combined organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm, diameter 26 mm, spherical silica gel) Product-containing fractions were combines and concentrated in vacuo to give the product as a white solid (0.100 g, 81%). The NMR date was agreement with the literature[2a].

3-ethyl-4,6-diphenyl-2*H*-pyran-2-one (2c)

To a 10 mL vial filled with InI_3 (0.504 mmol, 0.248 g) in toluene (1 mL) was added methyl (*Z*)-2-ethyl-3,5-

diphenylpent-2-en-4-ynoate (0.502 mmol, 0.146 g) in a nitrogen-filled glove box. The vial was sealed and the mixture was stirred at 80 °C for 24 h and the mixture was quenched by water (3 mL) and 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (2 x 30 mL) and combined organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the product as a white solid (0.126 g, 90%). IR: (KBr) 1716 (C=O) cm^{-1}, mp: 59-61 °C, ^1H NMR: (400 MHz, $CDCl_3$) 7.82 (d, J = 5.1 Hz, 2H), 7.51-7.41 (m, 6H), 7.35 (d, J = 7.4 Hz, 2H), 6.62 (s, 1H), 2.50 (q, J = 7.4 Hz, 2H), 1.16 (t, J = 7.4 Hz, 3H), $^{13}C\{^1H\}$ NMR: (100 MHz, $CDCl_3$) 163.2 (s), 156.3 (s), 152.2 (s), 137.9 (s), 131.4 (s), 130.2 (d), 128.7 (d), 128.6 (d), 127.4 (d), 125.5 (s), 125.2 (d), 104.6 (d), 21.2 (t), 13.3 (q), HRMS:(EI, 70 eV) Calculated ($C_{19}H_{16}O_2$) 276.1150 (M^+) Found 276.1151.

5-iodo-6-phenyl-2*H*-pyran-2-one (5a)

To a 10 mL vial filled with InI_3 (0.503 mmol, 0.249 g) in toluene (1 mL) was added methyl (*Z*)-5-phenylpent-2-en-4-ynoate (0.500 mmol, 0.931 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, iodobenzene diacetate (0.331 g, 1.03 mmol) in THF (2.5 mL) was added to the reaction mixture at room temperature. After stirring for 24 h, the mixture was quenched by water (5 mL), 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (2 x 30 mL) and the combined organic solution was washed by sat. $Na_2S_2O_3$ aq. (1 x 25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm, diameter 26 mm, spherical silica gel) Product-containing fractions were combines and concentrated in vacuo to give the product as a yellow solid (0.143 g, 96%). The NMR date was agreement with the literature[3d].

5-iodo-4,6-diphenyl-2*H*-pyran-2-one (5b)

To a 10 mL vial filled with InI_3 (0.500 mmol, 0.248 g) in toluene (1 mL) was added methyl (*Z*)-5-phenylpent-2-en-4-ynoate (0.500 mmol, 0.931 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, iodobenzene diacetate (0.331 g, 1.03 mmol) in THF (2.5 mL) was added to the reaction mixture at room temperature. After stirring for 24 h, the mixture was quenched by water (5 mL), 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (2 x 30 mL) and the combined organic solution was washed by sat. $Na_2S_2O_3$ aq. (1 x 25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm, diameter 26 mm, spherical silica gel) Product-containing fractions were combines and concentrated in vacuo to give the product as a yellow solid (0.123 g, 66%). The NMR date was agreement with the literature[16].

3-ethyl-5-iodo-4,6-diphenyl-2*H*-pyran-2-one (5c)

To a 10 mL vial filled with InI_3 (0.518 mmol, 0.257 g) in toluene (1 mL) was added methyl (*Z*)-2-ethyl-3,5-

diphenylpent-2-en-4-ynoate (0.502 mmol, 0.146 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, iodobenzene diacetate (0.195 g, 0.604 mmol) in THF (2.5 mL) was added to the reaction mixture at room temperature. After stirring for 24 h, the mixture was quenched by water (3 mL) and 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (2 x 30 mL) and combined organic solution was washed by sat. $Na_2S_2O_3$ aq (1 x 25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the product as a yellow solid (0.139 g, 69%). IR: (KBr) 1714 (C=O) cm^{-1}, mp: 143-144 °C, ^1H NMR: (400 MHz, $CDCl_3$) 7.71-7.69 (m, 2H), 7.50-7.46 (m, 6H), 7.16 (d, J = 6.8 Hz, 2H), 2.35 (q, J = 7.4 Hz, 2H), 1.04 (t, J = 7.4 Hz, 3H), $^{13}C\{^1H\}$ NMR: (100 MHz, $CDCl_3$) 162.1 (s), 157.9 (s), 155.7 (s), 140.8 (s), 134.9 (s), 130.3 (d), 129.6 (d), 128.6 (d), 128.5 (d), 128.0 (d), 127.5 (d), 127.3 (s), 77.5 (s), 23.4 (t), 13.1 (q), HRMS: (EI, 70 eV) Calculated ($C_{19}H_{15}O_2I$) 402.0122 (M^+) Found 402.0117.

5-iodo-6-(p-tolyl)-2*H*-pyran-2-one (5d)

To a 10 mL vial filled with InI_3 (0.503 mmol, 0.249 g) in toluene (1 mL) was added methyl (*Z*)-5-(*p*-tolyl)pent-2-en-4-ynoate (0.510 mmol, 0.102 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, iodobenzene diacetate (0.324 g, 1.01 mmol) in THF (2.5 mL) was added to the reaction mixture at room temperature. After stirring for 24 h, the mixture was quenched by water (5 mL), 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (2 x 30 mL) and the combined organic solution was washed by sat. $Na_2S_2O_3$ aq. (1 x 25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm, diameter 26 mm, spherical silica gel) Product-containing fractions were combines and concentrated in vacuo to give the product as a yellow solid (0.131 g, 84%). IR: (KBr) 1715 (C=O) cm^{-1}, mp: 83-84 °C, ^1H NMR: (400 MHz, $CDCl_3$) 7.68-7.61 (m, 3H), 7.27 (d, J = 7.7 Hz, 2H), 6.09 (d, J = 9.7 Hz, 1H), 2.42 (s, 3H), $^{13}C\{^1H\}$ NMR: (100 MHz, $CDCl_3$) 161.05 (s), 160.98 (s), 153.2 (d), 141.4 (s), 130.5 (s), 129.2 (d), 128.9 (d), 115.2 (d), 66.2 (s), 21.6 (q), HRMS : (EI, 70 eV) Calculated ($C_{12}H_9O_2I$) 311.9647 (M^+) Found 311.9649.

6-{4-(tert-butyl)phenyl}-5-iodo-2*H*-pyran-2-one (5e)

To a 10 mL vial filled with InI_3 (0.503 mmol, 0.249 g) in toluene (1 mL) was added methyl (*Z*)-5-{4-(*tert*-butyl)phenyl}pent-2-en-4-ynoate (0.499 mmol, 0.121 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, iodobenzene diacetate (0.331 g, 1.03 mmol) in THF (2.5 mL) was added to the reaction mixture at room temperature. After stirring for 24 h, the mixture was quenched by water (5 mL), 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (2 x 30 mL) and the combined organic solution was washed by sat. $Na_2S_2O_3$ aq (1 x 25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethel acetate = 95:5, column length 11 cm, diameter 26 mm, spherical silica gel) Product-containing fractions were

combines and concentrated in vacuo to give the product as a yellow solid (0.150 g, 84%). IR: (KBr) 1731 (C=O) cm^{-1},mp: 107-109 °C, ^{1}H NMR: (400 MHz, $CDCl_3$) 7.71 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 9.2 Hz, 1H), 7.47 (d, *J* = 8.7 Hz, 2H), 6.08 (d, *J* = 9.2 Hz, 1H), 1.35 (s, 9H), $^{13}C\{^{1}H\}$ NMR: (100 MHz, $CDCl_3$) 160.92 (s), 160.88 (s), 154.3 (s), 153.2 (d), 130.4 (s), 129.0 (d), 125.1 (d), 115.1 (d), 66.0 (s), 35.0 (s), 31.1 (q), HRMS : (EI, 70 eV) Calculated ($C_{15}H_{15}O_2I$) 354.0117 (M^+) Found 354.0111.

5-iodo-6-(4-methoxyphenyl)-2*H*-pyran-2-one (5f)

To a 10 mL vial filled with InI_3 (0.500 mmol, 0.248 g) in toluene (1 mL) was added methyl (*Z*)-5-(4-methoxyphenyl)pent-2-en-4-ynoate (0.513 mmol, 0.111 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, iodobenzene diacetate (0.330 g, 1.02 mmol) in THF (2.5 mL) was added to the reaction mixture at room temperature. After stirring for 24 h, the mixture was quenched by water (5 mL) and 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (2 x 30 mL) and the combined organic solution was washed by sat. $Na_2S_2O_3$ aq (25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the product as a yellow solid (0.139 g, 85%). IR: (KBr) 1748 (C=O) cm^{-1}, mp: 117-118 °C, ^{1}H NMR: (400 MHz, $CDCl_3$) 7.74 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 9.7 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 2H), 6.05 (d, *J* = 9.7 Hz, 1H), 3.85 (s, 3H), $^{13}C\{^{1}H\}$ NMR: (100 MHz, $CDCl_3$) 161.3 (s), 160.9 (s), 160.5 (s), 153.3 (d), 130.9 (d), 125.4 (s), 114.5 (d), 113.4 (d), 65.5 (s), 55.3 (q), HRMS : (EI, 70 eV) Calculated ($C_{12}H_9O_3I$) 327.9596 (M^+) Found 327.9601.

6-(4-chlorophenyl)-5-iodo-2*H*-pyran-2-one (5g)

To a 10 mL vial filled with InI_3 (0.500 mmol, 0.248 g) in toluene (1 mL) was added methyl (*Z*)-5-(4-chlorophenyl)pent-2-en-4-ynoate (0.499 mmol, 0.110 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, iodobenzene diacetate (0.324 g, 1.01 mmol) in THF (2.5 mL) was added to the reaction mixture at room temperature. After stirring for 24 h, the mixture was quenched by water (5 mL) and 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (2 x 30 mL) and the combined organic solution was washed by sat. $Na_2S_2O_3$ aq (25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm, diameter 26 mm, spherical silica gel) Product-containing fractions were combined and concentrated in vacuo to give the product as a yellow solid (0.115 g, 71%). IR: (KBr) 1715 (C=O) cm^{-1}, mp: 129-130 °C, ^{1}H NMR: (400 MHz, $CDCl_3$) 7.70 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 9.7 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 6.12 (d, *J* = 9.7 Hz, 1H), $^{13}C\{^{1}H\}$ NMR: (100 MHz, $CDCl_3$) 160.3 (s), 159.4 (s), 152.8 (d), 136.8 (s), 131.6 (s), 130.5 (d), 128.4 (d), 115.6 (d), 66.8 (s), HRMS: (EI, 70 eV) Calculated ($C_{11}H_6ClO_2I$) 331.9101 (M^+) Found 331.9098.

6-(3-fluorophenyl)-5-iodo-2*H*-pyran-2-one (5h)

To a 10 mL vial filled with InI_3 (0.507 mmol, 0.251 g) in toluene (1 mL) was added methyl (*Z*)-5-(3-

fluorophenyl)pent-2-en-4-ynoate (0.509 mmol, 0.104 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, iodobenzene diacetate (0.195 g, 0.604 mmol) in THF (2.5 mL) was added to the reaction mixture at room temperature. After stirring for 24 h, the mixture was quenched by water (3 mL) and 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (2 x 30 mL) and combined organic solution was washed by sat. $Na_2S_2O_3$ aq (25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the product as a yellow solid (0.126 g, 80%). IR: (KBr) 1724 (C=O) cm^{-1}, mp: 82-83 °C, ^1H NMR: (400 MHz, $CDCl_3$) 7.64 (d, J = 9.7 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.46-7.43 (m, 2H), 7.20 (m, 1H), 6.14 (d, J = 9.7 Hz, 1H), $^{13}C\{^1H\}$ NMR: (100 MHz, $CDCl_3$) 162.1 (d, $^1J_{CF}$ = 247.4 Hz), 160.3 (s), 159.2 (s), 152.9 (d), 135.1 (d, $^3J_{CF}$ = 8.2 Hz), 130.0 (dd, $^3J_{CF}$ = 8.2 Hz), 125.1 (dd, $^4J_{CF}$ = 3.3 Hz), 117.9 (dd, $^2J_{CF}$ = 21.3 Hz), 116.5 (dd, $^2J_{CF}$ = 23.8 Hz), 116.0 (d), 67.0 (s), HRMS : (EI, 70 eV) Calculated ($C_{11}H_6FO_2I$) 315.9397 (M^+) Found 315.9397.

6-hexyl-5-iodo-2*H*-pyran-2-one (5i)

To a 10 mL vial filled with InI_3 (0.500 mmol, 0.248 g) in toluene (1 mL) was added methyl (*Z*)-undec-2-en-4-ynoate (0.500 mmol, 0.0971 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, iodobenzene diacetate (0.331 g, 1.03 mmol) in THF (2.5 mL) was added to the reaction mixture at room temperature. After stirring for 24 h, the mixture was quenched by water (5 mL), 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (2 x 30 mL) and the combined organic solution was washed by sat. $Na_2S_2O_3$ aq. (1 x 25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combines and concentrated in vacuo to give the product as a yellow oil (0.115 g, 75%). The NMR date was agreement with the literature[15].

6-cyclopropyl-5-iodo-2*H*-pyran-2-one (5j)

To a 10 mL vial filled with InI_3 (0.501 mmol, 0.248 g) in toluene (1 mL) was added methyl (*Z*)-5-cyclopropylpent-2-en-4-ynoate (0.507 mmol, 0.0762 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, iodobenzene diacetate (0.334 g, 1.04 mmol) in THF (2.5 mL) was added to the reaction mixture at room temperature. After stirring for 24 h, the mixture was quenched by water (3 mL) and 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (2 x 30 mL) and combined organic solution was washed by sat. $Na_2S_2O_3$ aq (1 x 25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combines and concentrated in vacuo to give the product as a yellow solid (0.105 g, 64%). IR: (KBr) 1714 (C=O) cm^{-1}, mp: 87-88 °C, ^1H NMR: (400 MHz, $CDCl_3$) 7.44 (d, J = 9.2 Hz, 1H), 5.92 (d, J = 9.2 Hz, 1H), 2.24-2.17 (m, 1H), 1.21-1.20 (m, 2H), 1.07-1.05 (m, 2H), $^{13}C\{^1H\}$ NMR: (100 MHz, $CDCl_3$) 165.3 (s),

160.7 (s), 151.9 (d), 113.1 (d), 66.2 (s), 17.5 (d), 9.8 (t), HRMS: (EI, 70 eV) Calculated ($C_8H_7O_2I$) 261.9491 (M^+) Found 261.9490.

methyl 5-iodo-2-oxo-6-phenyl-2*H*-pyran-3-carboxylate (5k)

To a 10 mL vial filled with InI_3 (0.500 mmol, 0.248 g) in toluene (1 mL) was added dimethyl 2-(3-phenylprop-2-yn-1-ylidene)malonate (0.501 mmol, 0.122 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, iodobenzene diacetate (0.318 g, 0.987 mmol) in THF (2.5 mL) was added to the reaction mixture at room temperature. After stirring for 24 h, the mixture was quenched by water (5 mL), 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (2 x 30 mL) and combined organic solution was washed by sat. $Na_2S_2O_3$ aq (1 x 25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm, diameter 26 mm, spherical silica gel) Product-containing fractions were combines and concentrated in vacuo to give the product as a yellow solid (0.0920 g, 52%). IR: (KBr) 1757 (C=O) cm^{-1}, mp: 144-146 °C, ^1H NMR: (400 MHz, $CDCl_3$) 8.53 (s, 1H), 7.82 (d, J = 7.2 Hz, 2H), 7.58-7.47 (m, 3H), 3.94 (s, 3H), $^{13}C\{^1H\}$ NMR: (100 MHz, $CDCl_3$) 165.5 (s), 162.7 (s), 158.9 (d), 156.6 (s), 132.5 (s), 131.8 (d), 129.4 (d), 128.3 (d), 115.7 (s), 64.8 (s), 53.0 (q), HRMS: (EI, 70 eV) Calculated ($C_{13}H_9O_4I$) 355.9546 (M^+) Found 355.9550.

6-cyclopropyl-3-ethyl-5-iodo-4-phenyl-2*H*-pyran-2-one (5l)

To a 10 mL vial filled with InI_3 (0.301 mmol, 0.149 g) in toluene (1 mL) was added methyl (*Z*)-5-cyclopropyl-2-ethyl-3-phenylpent-2-en-4-ynoate (0.30 mmol, 0.0765 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, iodobenzene diacetate (0.195 g, 0.604 mmol) in THF (2.5 mL) was added to the reaction mixture at room temperature. After stirring for 24 h, the mixture was quenched by water (3 mL), 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (2 x 30 mL) and combined organic solution was washed by sat. $Na_2S_2O_3$ aq (1 x 25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combines and concentrated in vacuo to give the product as a yellow solid (0.0701 g, 64%). IR: (KBr) 1714 (C=O) cm^{-1}, mp: 83-84 °C, ^1H NMR: (400 MHz, $CDCl_3$) 7.49-7.40 (m, 3H), 7.08-7.05 (m, 2H), 2.40-2.38 (m, 1H), 2.24 (q, J = 7.5 Hz, 2H), 1.28-1.16 (m, 2H), 1.05-1.00 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H), $^{13}C\{^1H\}$ NMR: (100 MHz, $CDCl_3$) 161.9 (s), 161.1 (s), 155.6 (s), 140.7 (s), 128.40 (d), 128.36 (d), 127.3 (s), 125.0 (s), 76.5 (s), 23.1 (t), 18.3 (d, C-13), 13.1 (q, C-8), 9.4 (t, C-14), HRMS: (EI, 70 eV) Calculated ($C_{16}H_{15}O_2I$) 366.0117 (M^+) Found 366.0113.

5-iodo-3,4,6-triphenyl-2*H*-pyran-2-one (5m)

To a 10 mL vial filled with InI_3 (0.503 mmol, 0.249 g) in toluene (1 mL) was added methyl (*Z*)-2,3,5-triphenylpent-2-en-4-ynoate (0.499 mmol, 0.1691 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, iodobenzene diacetate (0.331 g, 1.03 mmol) in THF (2.5

mL) was added to the reaction mixture at room temperature. After stirring for 24 h, the mixture was quenched by water (5 mL), 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (2 x 30 mL) and the combined organic solution was washed by sat. $Na_2S_2O_3$ aq (1 x 25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm, diameter 26 mm, spherical silica gel) Product-containing fractions were combines and concentrated in vacuo to give the product as a yellow solid (0.1424 g, 63%). The NMR date was agreement with the literature[3d].

5-bromo-3-ethyl-4,6-diphenyl-2*H*-pyran-2-one (5n)

To a 10 mL vial filled with $InBr_3$ (0.499 mmol, 0.177 g) in toluene (1 mL) was added methyl (*Z*)-2-ethyl-3,5-diphenylpent-2-en-4-ynoate (0.496 mmol, 0.144 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, iodobenzene diacetate (0.324 g, 1.01 mmol) in THF (2.5 mL) was added to the reaction mixture at room temperature. After stirring for 24 h, the mixture was quenched by water (3 mL) and 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (3 x 20 mL) and combined organic solution was washed by sat. $Na_2S_2O_3$ aq (1 x 25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the product as a yellow solid (0.0812 g, 46%). IR: (KBr) 1714 (C=O) cm^{-1}, mp: 114-116 °C, ^1H NMR: (400 MHz, $CDCl_3$) 7.79-7.78 (m, 2H), 7.50-7.46 (m, 6H), 7.20 (d, J = 6.8 Hz, 2H), 2.33 (q, J = 7.2 Hz, 2H), 1.05 (t, J = 7.2 Hz, 3H), $^{13}C\{^1H\}$ NMR: (100 MHz, $CDCl_3$) 161.7 (s), 155.0 (s), 153.6 (s), 137.3 (s), 132.6 (s), 130.3 (d), 129.3 (d), 128.5 (d), 128.4 (d), 128.2 (s), 128.1 (d), 127.6 (d), 102.7 (s), 22.9 (t), 13.0 (q), HRMS: (EI, 70 eV) Calculated ($C_{19}H_{15}O_2Br$) 354.0255 (M^+) Found 354.0253

5,6-diphenyl-2*H*-pyran-2-one (6a)

To a 10 mL vial filled with InI_3 (0.507 mmol, 0.251 g) in toluene (1 mL) was added methyl (*Z*)-5-phenylpent-2-en-4-ynoate (0.499 mmol, 0.0930 g) in a nitrogen-filled glove box. The vial was sealed and the mixture was stirred at 80 °C for 24 h. Then, Pd_2dba_3 (0.0317 mmol, 0.0290 g), NaOMe (1.02 mmol, 0.0551 g), iodobenzene (0. 350 mmol, 0.0715 g), DMF (2.5 mL) were added to the reaction mixture at room temperature. After stirring at 110 °C for 24 h, the mixture was quenched by water (5 mL), and 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (3 x 30 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the product as a pale yellow solid (0.0834 g, 96%). The NMR date was agreement with the literature[3b].

4,5,6-triphenyl-2*H*-pyran-2-one (6b)

To a 10 mL vial filled with InI_3 (0.505 mmol, 0.250 g) in toluene (1 mL) was added methyl (*Z*)-3,5-

diphenylpent-2-en-4-ynoate (0.499 mmol, 0.131 g) in a nitrogen-filled glove box. The vial was sealed and the mixture was stirred at 80 °C for 24 h. Then, Pd_2dba_3 (0.0317 mmol, 0.0290 g), NaOMe (1.02 mmol, 0.0551 g), iodobenzene (0. 350 mmol, 0.0715 g), DMF (2.5 mL) were added to the reaction mixture at room temperature. After stirring at 110 °C for 24 h, the mixture was quenched by water (5 mL), and 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (3 x 30 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the product as a pale yellow solid (0.0727 g, 64%). The NMR date was agreement with the literature[18].

3-ethyl-4,5,6-triphenyl-2*H*-pyran-2-one (6c)

To a 10 mL vial filled with InI_3 (0.507 mmol, 0.251 g) in toluene (1 mL) was added methyl (*Z*)-2-ethyl-3,5-diphenylpent-2-en-4-ynoate (0.503 mmol, 0.146 g) in a nitrogen-filled glove box. The vial was sealed and the mixture was stirred at 80 °C for 24 h. Then, Pd_2dba_3 (0.0317 mmol, 0.0290 g), NaOMe (1.02 mmol, 0.0551 g), iodobenzene (0. 350 mmol, 0.0715 g), DMF (2.5 mL) were added to the reaction mixture at room temperature. After stirring at 110 °C for 24 h, the mixture was quenched by water (5 mL), and 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (3 x 30 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 80 : 20, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the product as a pale yellow solid (0.0987 g, 80%). IR: (KBr) 1706 (C=O) cm^{-1}, mp: 159-161 °C, ^1H NMR: (400 MHz, $CDCl_3$) 7.28 (d, J = 8.7 Hz, 2H), 7.22-7.14 (m, 6H), 7.04-6.99 (m, 3H), 6.95-6.92 (m, 2H), 6.86-6.82 (m, 2H), 2.37 (q, J = 7.4 Hz, 2H), 1.09 (t, J = 7.4 Hz, 3H), $^{13}C\{^1H\}$ NMR: (100 MHz, $CDCl_3$) 162.8 (s), 154.7 (s), 154.5 (s), 136.3 (s), 135.1 (s), 132.7 (s), 131.1 (d), 129.1 (d), 128.1 (d), 127.9 (d), 127.81 (d), 127.78 (d), 127.4 (d), 127.0 (d), 126.7 (s), 119.4 (s), 22.0 (t), 13.3 (q), HRMS: (EI, 70 eV) Calculated ($C_{25}H_{20}O_2$) 352.1463 (M^+) Found 352.1465.

6-cyclopropyl-3-ethyl-4,5-diphenyl-2*H*-pyran-2-one (6l)

To a 10 mL vial filled with InI_3 (0.300 mmol, 0.148 g) in toluene (0.6 mL) was added methyl (*Z*)-5-cyclopropyl-2-ethyl-3-phenylpent-2-en-4-ynoate (0.300 mmol, 0.0763 g) in a nitrogen-filled glove box. The vial was sealed and the mixture was stirred at 80 °C for 24 h. Then, Pd_2dba_3 (0.0165mmol, 0.0151 g), NaOMe (0.583 mmol, 0.0315 g), iodobenzene (0.225 mmol, 0.046 g), DMF (1.5 mL) were added to the reaction mixture at room temperature. After stirring at 110 °C for 24 h, the mixture was quenched by water (5 mL), and 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (3 x 30 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the product as a pale yellow solid (0.0605 g, 85%). IR: (KBr) 1699 (C=O) cm^{-1}, mp: 138-140 °C, ^1H NMR: (400 MHz, $CDCl_3$) 7.18-7.10 (m, 6H), 7.00 (d, J = 7.7 Hz, 2H), 6.90 (d, J = 7.2 Hz, 2H), 2.28 (q, J = 7.4 Hz, 2H), 1.62-1.57 (m, 1H), 1.23-

1.19 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H), 0.83-0.78 (m, 2H), $^{13}C\{^{1}H\}$ NMR: (100 MHz, $CDCl_3$) 162.9 (s), 159.2 (s), 154.1 (s), 136.6 (s), 135.1 (s), 131.0 (d), 128.0 (d), 127.9 (d), 127.7 (d), 127.3 (d), 126.9 (d), 123.7 (s), 118.3 (s), 21.7 (t), 13.4 (q), 12.4 (d), 8.5 (t), HRMS: (EI, 70 eV) Calculated ($C_{22}H_{20}O_2$) 316.1463 (M^+) Found 316.1460.

3,4,5,6-tetraphenyl-2*H*-pyran-2-one (6m)

To a 10 mL vial filled with InI_3 (0.300 mmol, 0.148 g) in toluene (0.6 mL) was added methyl (*Z*)-2,3,5-triphenylpent-2-en-4-ynoate (0.300 mmol, 0.0763 g) in a nitrogen-filled glove box. The vial was sealed and the mixture was stirred at 80 °C for 24 h. Then, Pd_2dba_3 (0.0165mmol, 0.0151 g), NaOMe (0.583 mmol, 0.0315 g), iodobenzene (0.225 mmol, 0.046 g), DMF (1.5 mL) were added to the reaction mixture at room temperature. After stirring at 110 °C for 24 h, the mixture was quenched by water (5 mL), and 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (3 x 30 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the product as a white solid (0.0712 g, 79%). The NMR date was agreement with the literature[3b]. This compound was identified by X-ray crystallographic analysis (CCDC 1910558).

6-cyclopropyl-3-ethyl-5-(4-methoxyphenyl)-4-phenyl-2*H*-pyran-2-one (6n)

To a 10 mL vial filled with InI_3 (0.520 mmol, 0.258 g) in toluene (1 mL) was added methyl (*Z*)-5-cyclopropyl-2-ethyl-3-phenylpent-2-en-4-ynoate (0.500 mmol, 0.127 g) in a nitrogen-filled glove box. The vial was sealed and the mixture was stirred at 80 °C for 24 h. Then, Pd_2dba_3 (0.0285 mmol, 0.0261 g), NaOMe (0.102 mmol, 0.0551 g), 4-iodoanisole (0.0351 mmol, 0.0821 g), and DMF (2.5 mL) were added to the reaction mixture at room temperature. After stirring at 110 °C for 24 h, the mixture was quenched by water (5 mL), and 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (3 x 30 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the product as a yellow solid (0.101 g, 80%). IR: (KBr) 1698 (C=O) cm^{-1}, mp: 109-111 °C, ^{1}H NMR: (400 MHz, $CDCl_3$) 7.16-7.06 (m, 6H), 6.80-6.78 (m, 2H), 6.60 (d, J = 8.2 Hz, 1H), 3.58 (s, 3H), 2.32-2.22 (m, 2H), 1.56-1.51 (m, 1H), 1.20-1.18 (m, 2H), 1.02 (t, J = 7.5 Hz, 3H), 0.81-0.76 (m, 2H), $^{13}C\{^{1}H\}$ NMR: (100 MHz, $CDCl_3$) 163.3 (s), 159.1 (s), 157.0 (s), 154.8 (s), 136.7 (s), 132.5 (d), 129.2 (d), 127.8 (d), 127.6 (d), 127.2, 127.15, 127.10, 124.0 (s), 123.5 (d), 120.0 (d), 114.7 (s), 110.2 (d), 54.9 (q), 21.7 (t), 13.4 (q), 12.2 (d), 8.13 (t), 8.06 (t), HRMS: (EI, 70 eV) Calculated ($C_{23}H_{22}O_3$) 346.1569 (M^+) Found 346.1570.

6-cyclopropyl-3-ethyl-5-(4-nitrophenyl)-4-phenyl-2*H*-pyran-2-one (6o)

To a 10 mL vial filled with InI_3 (0.520 mmol, 0.258 g) in toluene (1 mL) was added methyl (*Z*)-5-cyclopropyl-2-ethyl-3-phenylpent-2-en-4-ynoate (0.500 mmol, 0.127 g) in a nitrogen-filled glove box. The

vial was sealed and the mixture was stirred at 80 °C for 24 h. Then, Pd_2dba_3 (0.0263 mmol, 0.0241 g), NaOMe (0.990 mmol, 0.0540 g), 1-iodo-4-nitrobenzene (0.354 mmol, 0.0881 g), and DMF (2.5 mL) were added to the reaction mixture at room temperature. After stirring at 110 °C for 24 h, the mixture was quenched by water (5 mL) and 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (3 x 30 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the product as a yellow solid (0.102 g, 80%). IR: (KBr) 1714 (C=O) cm^{-1}, mp: 167-169 °C, ^1H NMR: (400 MHz, $CDCl_3$) 8.01 (d, *J* = 8.2 Hz, 2H), 7.24-7.15 (m, 5H), 6.93-6.86 (m, 2H), 2.29 (q, *J* = 7.4 Hz, 2H), 1.52-1.46 (m, 1H), 1.30-1.24 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.90-0.83 (m, 2H), $^{13}C\{^1H\}$ NMR: (100 MHz, $CDCl_3$) 162.2 (s), 159.6 (s), 152.8 (s), 146.7 (s), 142.6 (s), 135.8 (d), 132.1 (d), 128.2 (s), 128.0 (s), 127.8 (s), 124.5 (s), 123.1 (d), 116.6 (s), 21.7 (t), 13.3 (q), 12.6 (d), 8.9 (t), HRMS: (EI, 70 eV) Calculated ($C_{22}H_{19}NO_4$) 361.1314 (M^+) Found 361.1312.

5-(4-methylbenzoyl)-6-phenyl-2*H*-pyran-2-one (7a)

To a 10 mL vial filled with InI_3 (0.502 mmol, 0.249 g) in toluene (1 mL) was added methyl (*Z*)-5-phenylpent-2-en-4-ynoate (0.499 mmol, 0.0930 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, Pd_2dba_3 (0.0262 mmol, 0.0240 g), *p*-toluoyl chloride (0.990 mmol, 0.153 g), DMI (2.5 mL) were added to the reaction mixture at room temperature. After stirring at 110 °C for 24 h, the mixture was quenched by water (5 mL), and 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (3 x 30 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the product as a yellow oil (0.0595 g, 41%). IR: (neat) 1743 (C=O), 1651 (C=O) cm^{-1}, ^1H NMR: (400 MHz, $CDCl_3$) 7.60 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 9.4 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.32-7.27 (m, 1H), 7.23 (t, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 6.39 (d, *J* = 9.4 Hz, 1H), 2.31 (s, 3H), $^{13}C\{^1H\}$ NMR: (100 MHz, $CDCl_3$) 193.3 (s), 163.0 (s), 160.7 (s), 144.7 (s), 144.5 (d), 133.5 (s), 131.22 (d), 131.16 (s), 129.8 (d), 129.2 (d), 128.9 (d), 128.4 (d), 116.6 (s), 113.6 (d), 21.6 (q), HRMS: (EI, 70 eV) Calculated ($C_{19}H_{14}O_3$) 290.0943 (M^+) Found 290.0941.

5-(4-methylbenzoyl)-4,6-diphenyl-2*H*-pyran-2-one (7b)

To a 10 mL vial filled with InI_3 (0.507 mmol, 0.251 g) in toluene (1 mL) was added methyl (*Z*)-3,5-diphenylpent-2-en-4-ynoate (0.511 mmol, 0.134 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, Pd_2dba_3 (0.0247 mmol, 0.0226 g), *p*-toluoyl chloride (0.100 mmol, 0.155 g), DMI (2.5 mL) were added to the reaction mixture at room temperature. After stirring at 110 °C for 24 h, the mixture was quenched by water (5 mL), and 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (3 x 30 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length

11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the product as a white solid (0.101 g, 55%). IR: (KBr) 1724 (C=O), 1662 (C=O) cm^{-1}, mp: 199-201 °C, d^{1}H NMR: (400 MHz, $CDCl_3$) 7.58-7.53 (m, 4H), 7.32-7.19 (m, 8H), 7.05 (d, *J* = 8.2 Hz, 2H), 6.36 (s, 1H), 2.29 (s, 3H), $^{13}C\{^1H\}$ NMR: (100 MHz, $CDCl_3$) 193.4 (s), 161.0 (s), 159.9 (s), 157.2 (s), 144.8 (s), 135.9 (s), 134.7 (s), 131.5 (s), 130.9 (d), 129.4 (d), 129.3 (d), 128.6 (d), 128.52 (d), 128.45 (d), 127.5 (d), 118.0 (s), 113.2 (d), 21.7 (q), HRMS : (EI, 70 eV) Calculated ($C_{25}H_{18}O_3$) 366.1256 (M^+) Found 366.1259.

3-ethyl-5-(4-methylbenzoyl)-4,6-diphenyl-2*H*-pyran-2-one (7c)

To a 10 mL vial filled with InI_3 (0.502 mmol, 0.249 g) in toluene (1 mL) was added methyl (*Z*)-2-ethyl-3,5-diphenylpent-2-en-4-ynoate (0.506 mmol, 0.147 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, Pd_2dba_3 (0.0263 mmol, 0.0229 g), *p*-toluoyl chloride (0.996 mmol, 0.154 g), DMI (2.5 mL) were added to the reaction mixture at room temperature. After stirring at 110 °C for 24 h, the mixture was quenched by water (5 mL), and 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (3 x 30 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the product as a white solid (0.0749 g, 38%). IR: (KBr) 1715 (C=O), 1661 (C=O) cm^{-1}, mp: 192-194 °C, ^{1}H NMR: (400 MHz, $CDCl_3$) 7.55 (d, *J* = 7.2 Hz, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.28-7.20 (m, 6H), 7.03 (d, *J* = 8.2 Hz, 4H), 2.36 (q, *J* = 7.2 Hz, 2H), 2.29 (s, 3H), 1.08 (t, *J* = 7.2 Hz, 3H), $^{13}C\{^1H\}$ NMR: (100 MHz, $CDCl_3$) 193.7 (s), 162.2 (s), 155.5 (s), 151.6 (s), 144.6 (s), 134.8 (s), 131.5 (s), 130.4 (d), 129.4 (d), 129.1 (d), 128.4 (d), 128.25 (d), 128.22 (d), 128.1 (d), 127.8 (d), 127.3 (s), 119.0 (s), 21.6 (s), 21.5 (s), 13.2 (s), HRMS: (EI, 70 eV) Calculated ($C_{27}H_{22}O_3$) 394.1569 (M^+) Found 394.1574.

5-(4-methylbenzoyl)-3,4,6-triphenyl-2*H*-pyran-2-one (7m)

To a 10 mL vial filled with InI_3 (0.500 mmol, 0.248 g) in toluene (1 mL) was added methyl (*Z*)-2,3,5-triphenylpent-2-en-4-ynoate (0.501 mmol, 0.169 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, Pd_2dba_3 (0.0263 mmol, 0.0229 g), *p*-toluoyl chloride (1.01 mmol, 0.157 g), DMI (2.5 mL) were added to the reaction mixture at room temperature. After stirring at 110 °C for 24 h, the mixture was quenched by water (5 mL), and 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (3 x 30 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 80:20, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the product as a white solid (0.0750 g, 34%). IR: (KBr) 1722 (C=O), 1663 (C=O) cm^{-1}, mp: 158-159 °C, ^{1}H NMR: (400 MHz, $CDCl_3$) 7.62 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.35-7.26 (m, 3H), 7.21-6.89 (m, 12H), 2.29 (s, 3H), $^{13}C\{^1H\}$ NMR: (100 MHz, $CDCl_3$) 193.5 (s), 161.5 (s), 157.5 (s), 152.7 (s), 144.7 (s), 134.9 (s), 134.8 (s), 133.0 (s), 131.5 (s), 130.8 (d), 130.6 (d), 129.4 (d), 129.2 (d), 128.9 (d), 128.51 (d), 128.50 (d), 128.1 (d), 127.8 (d), 127.7 (d), 125.2 (s), 119.3 (s), 21.7 (q), HRMS : (EI, 70 eV) Calculated ($C_{31}H_{22}O_3$) 442.1569 (M^+) Found 442.1571. This compound was identified by X-ray

crystallographic analysis (CCDC 1910562).

6-cyclopropyl-3-ethyl-5-(4-methylbenzoyl)-4-phenyl-2*H*-pyran-2-one (7l)

To a 10 mL vial filled with InI_3 (0.301 mmol, 0.149 g) in toluene (0.6 mL) was added methyl (*Z*)-5-cyclopropyl-2-ethyl-3-phenylpent-2-en-4-ynoate (0.300 mmol, 0.0763 g) in a nitrogen-filled glove box. The vial was sealed, and the mixture was stirred at 80 °C for 24 h. Then, Pd_2dba_3 (0.0154 mmol, 0.0141 g), *p*-toluoyl chloride (0.598 mmol, 0.0924 g), DMI (1.6 mL) were added to the reaction mixture at room temperature. After stirring at 110 °C for 24 h, the mixture was quenched by water (5 mL), and 1 M HCl aq (1 mL). The solution was extracted by dichloromethane (3 x 30 mL) and dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oily residue was purified by column chromatography (hexane/ethyl acetate = 80 : 20, column length 11 cm, diameter 26 mm, spherical silica gel). Product-containing fractions were combined and concentrated in vacuo to give the product as a white solid (0.0419 g, 39%). IR: (KBr) 1715 (C=O), 1659 (C=O) cm^{-1}, mp: 120-121 °C, ^1H NMR: (400 MHz, $CDCl_3$) 7.60 (d, *J* = 8.2 Hz, 2H), 7.17-7.15 (m, 5H), 6.99-6.98 (m, 2H), 2.37 (s, 3H), 2.29 (q, *J* = 7.4 Hz, 2H), 1.62-1.58 (m, 1H), 1.26-1.25 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H), 0.88-0.86 (m, 2H), $^{13}C\{^1H\}$ NMR: (100 MHz, $CDCl_3$) 194.0 (s), 162.1 (s), 160.5 (s), 151.3 (s), 144.6 (s), 135.2 (s), 135.1 (s), 129.5 (d), 129.2 (d), 128.1 (d), 128.0 (d), 127.7 (d), 124.5 (s), 118.2 (s), 21.7 (q), 21.1 (t), 13.2 (q), 12.9 (d), 8.9 (t), HRMS: (EI, 70 eV) Calculated ($C_{24}H_{22}O_3$) 358.1569 (M^+) Found 358.1567. This compound was identified by X-ray crystallographic analysis (CCDC 1910561).

3,4,6-triphenyl-5-(phenylethynyl)-2*H*-pyran-2-one (8)

To a solution of 5-iodo-3,4,6-triphenyl-2*H*-pyran-2-one (0.206 mmol, 0.0928 g) and $PdCl_2(PPh_3)_2$ (0.0245 mmol, 0.0172 g) in 1,4-dioxane (1 mL) was added tributyl(phenylethynyl)stannane (0.249 mmol, 0.0977 g). The mixture was stirred at 90 °C for 14 h. The mixture was quenched by H_2O (1 mL) and was extracted with dichloromethane (3 x 10 mL). The collected organic layer was dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate = 99:1, column length 10 cm, diameter 26 mm silica gel) to give the product (0.0555 g, 63%) IR: (KBr) 1722 (C=O) cm^{-1}, mp : 208-210 °C, ^1H NMR: (400 MHz, $CDCl_3$) 8.30-8.26 (m, 2H), 7.52-7.50 (m, 3H), 7.28-7.16 (m, 13H), 6.95 (dd, *J* = 8.0, 1.7 Hz, 2H), $^{13}C\{^1H\}$ NMR: (100 MHz, $CDCl_3$) 161.0 (s), 154.9 (s), 136.1 (s), 133.3 (s), 131.8 (s), 131.0 (s), 130.7 (d), 130.5 (d), 129.3 (d), 128.7 (d), 128.3 (d), 128.2 (d), 128.1 (d), 127.7 (d), 127.61 (d), 127.57 (d), 125.5 (d), 124.4 (s), 122.5 (s), 104.9 (d), 102.7 (s), 97.6 (s), 84.4 (s), HRMS: (EI, 70 eV) Calculated ($C_{31}H_{20}O_2$) 424.1463 (M^+) Found 424.1466 This compound was identified by X-ray crystallographic analysis (CCDC 1915263).

1-5. Reference

[1] (a) T. Sunazuka, S. Ōmura, *Chem. Rev.* **2005**, *105*, 4559-4580. (b) A. Goel, V. J. Ram, *Tetrahedron* **2009**, *65*, 7865-7913. (c) J. S. Lee, *Mar. Drugs* **2015**, *13*, 1581-1620. (d) Y. Hoshino, Y. Ikeda, Y. Nakai, K. Honda, *Chem. Lett.* **2017**, *46*, 1743-1746. (e) E. M. C. Chaves, J. E. R. Honório-Júnior, C. N. S. Sousa, V. S. Monteiro, D. T. T. Nonato, L. P. Dantas, A. S. S. C. Lúcio, J. M. Barbosa-Filho, M. C. A. Patrocínio, G. S. B. Viana, S. M. M. Vasconcelos, *Brain Dis.* **2018**, *33*, 139-149.

[2] For selective examples, see.: (a) R. Manikandan, M. Jeganmohan, *Org. Lett.* **2014**, *16*, 652-655. (b) S.-Q. Qiu, T. Ahmad, Y.-H. Xu, T.-P. Loh, *J. Org. Chem*. **2019**, *84*, 6729. (c) J. Preindl, S. Schulthoff, C. Wirtz, J. Lingnau, A. Fürstner, *Angew. Chem. Int. Ed.*, **2017**, *56*, 7525-7530. (d) C. -X. Zhou, A. Fürstner, *J. Am. Chem. Soc.*, **2018**, *140*, 10514-10523. (e) A. Fürstner, *Angew. Chem. Int. Ed.*, **2018**, *57*, 4215-4233. and references cited therein.

[3] (a) R. C. Larock, M. J. Doty, X. Han, *J. Org. Chem.* **1999**, *64*, 8770-8779. (b) S. Mochida, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2009**, *74*, 6295-6298. (c) T. Fukuyama, Y. Higashibeppu, R. Yamaura, I. Ryu, *Org. Lett.* **2007**, *9*, 587-589. (d) T. Yao, R. C. Larock, *J. Org. Chem.* **2003**, *68*, 5936-5942.

[4] (a) K. Hauge, *Acta Chem. Scand.* **1969**, *23*, 1059-1061. (b) T. A. Carpenter, P. J. Jenner, F. J. Leeper, J. Staunton, *J. Chem. Soc., Chem. Commun.*, **1980**, 1227. (c) G. H. Posner, W. Harrison, D. G. Wettlaufer, *J. Org. Chem.* **1985**, *50*, 5041-5044. (d) Z. Liu, J. Meinwald, *J. Org. Chem.* **1996**, *61*, 6693-6699. (e) J. Sauer, D. K. Heldmann, K.-J. Range, M. Zabel, *Tetrahedron* **1998**, *54*, 12807-12822. (f) H. Hagiwara, K. Kobayashi, S. Miya, T. Hoshi, T. Suzuki, M. Ando, T. Okamoto, M. Kobayashi, I. Yamamoto, S. Ohtsubo, M. Kato, H. Uda, *J. Org. Chem.* **2002**, *67*, 5969-5976. (g) Q. Lin, W. K. Leong, *Organometallics* **2003**, *22*, 3639-3648. (h) C. M. Crawforth, I. J. S. Fairlamb, R. J. K. Taylor, *Tetrahedron Lett.* **2004**, *45*, 461-465. (i) X. Yang, P. Knochel, *Synthesis* **2006**, *15*, 2618-2623. (j) N. P. Yahaya, K. M. Appleby, M. Teh, C. Wagner, E. Troschke, J. T. W. Bray, S. B. Duckett, L. A. Hammarback, J. S. Ward, J. Milani, N. E. Pridmore, A. C. Whitwood, J. M. Lynam, I. J. S. Fairlamb, *Angew. Chem. Int. Ed.* **2016**, *55*, 12455-12459.

[5] (a) I. E.-S. El-Kholy, F. K. Rafla, M. M. Mishrikey, *J. Chem. Soc. C* **1969**, 1950-1954. (b) P. d. March, M. Moreno-Mañas, R. Pi, I. Ripoll, F. Sánchez-Ferrando, *J. Heterocyclic Chem.* **1985**, *22*, 1537-1542. (c) T. Shimo, M. Ohe, K. Somekawa, *J. Heterocyclic Chem.* **1991**, *28*, 1831-1833. (d) Y. Wang, D. J. Burton, A Facile, *J. Org. Chem.* **2006**, *71*, 3859-3862. (e) A. Nakhi, Md. S. Rahman, S. Archana, R. Kishore, G. P. K. Seerapu, K. L. Kumar, D. Haldar, M. Pal, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4195-4205. (f) E. Wei, B. Liu, S. Lin, B. Zhao, F. Liang, *Org. Biomol. Chem.* **2013**, *11*, 7212-7217.

[6] Y. Kita, T. Yata, Y. Nishimoto, K. Chiba, M. Yasuda, *Chem. Sci.* **2018**, *9*, 6041-6052.

[7] Indium salts were widely used as carbophilic Lewis acid. For selective review articles, see: (a) J. P. Sestelo, L. A Sarandeses, M. M. Martinez, L. A. Marañón, *Org. Biomol. Chem.*, **2018**, *16*, 5733. (b) S. I. Lee, N. Chatani, *Chem. Commun.*, **2009**, *4*, 371-384. (c) V. Mamane, P. Hannen, A. Fürstner, *Chem. Eur. J.* **2004**, *10*, 4556-4575.

[8] D. J. Faizi, A. Issaian, A. J. Davis, S. A. Blum, *J. Am. Chem. Soc.* **2016**, *138*, 2126–2129.

[9] The bond lengths of two carbon-oxygen bonds (C1-O1 and C1-O2) in **4b** are similar with the reported

cationic 2-pyrone. P. Legzdins, W. S. McNell, E. G. Vessey, *Organometallics* **1992**, *11*, 2718-2723.

[10] (a) M. Kosugi, K. Sasazawa, Y. Shimizu, T. Migita, *Chem. Lett.* **1977**, 301-302. (b) M. Kosugi, Y. Shimizu, T. Migita, *Chem. Lett.* **1977**, 1423-1424. (c) D. Milstein, J. K. Stille, *J. Am. Chem. Soc*. **1987**, *100*, 3636-3638. (d) C. Cordovilla, C. Bartolome, J. Ḿ. Martínez-Ilarduya, P. Espinet, *ACS Catal*. **2015**, *5*, 3040-3053.

[11] Zhao, L. Shen, Z.-L. Shen, T.-P. Loh, *Chem. Soc. Rev.* **2017**, *46*, 586–602

[12] (a) K. Hirano, S. Minakata, M. Komatsu, *Chem. Lett.* **2001**, *30*, 8-9. (b) K. Hirano, S. Minakata, M. Komatsu, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1567-1575. (c) Z. Kin, H. Kajii, Y. Ohmori, M. Komatsu, S. Minakata, M. Tsumura, K. Namura, *J. Phys. Chem. Solids* **2006**, *67*, 2326-2330.

[13] Y. Zhu, and Z. Shen, *Adv. Synth. Cata.*, **2017**, *359*, 3515-3519.

[14] P.-Y. Tseng, S.-C. Chuang, *Adv. Synth. Catal.*, **2013**, *355*, 2165-2171.

[15] F. Bellina, M. Biagetti, A. Carpita, R. Rossi, *Tetrahedron*, **2001**, *57*, 2857-2870.

[16] C.-Z. Zhu, Y.-L. Sun, Y. Wei, M. Shi, *Adv. Synth. Catal.*, **2017**, *359*, 1263-1270.

[17] M. Uchiyama, H. Ozawa, K. Takuma, Y. Matsumoto, M. Yonehara, K. Hiroya, T. Sakamoto, *Org. Lett*., **2016**, *8*, 5517-5520.

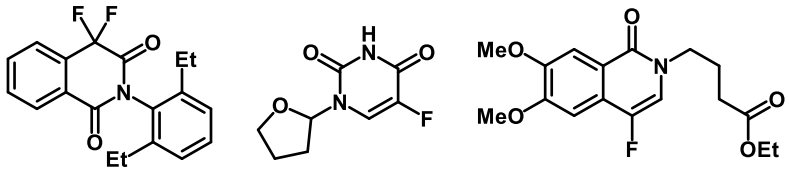
[18] R. Prakash, K. Shekarrao, S. Gogoi, *Org. Lett.*, **2015**, *17*, 5264-5267.

Chapter 2: Indium-catalyzed C–F bond transformation through oxymetalation/*β*-fluorine elimination to access fluorinated isocoumarins

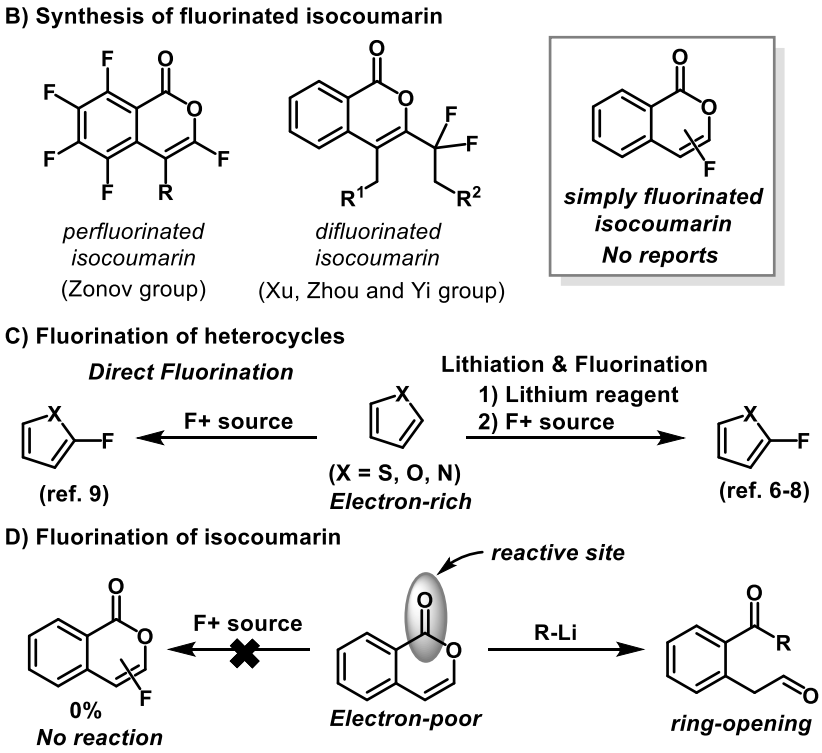
2-1. Introduction

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.

A) Representative bioactive compounds containing fluorinated heterocycles

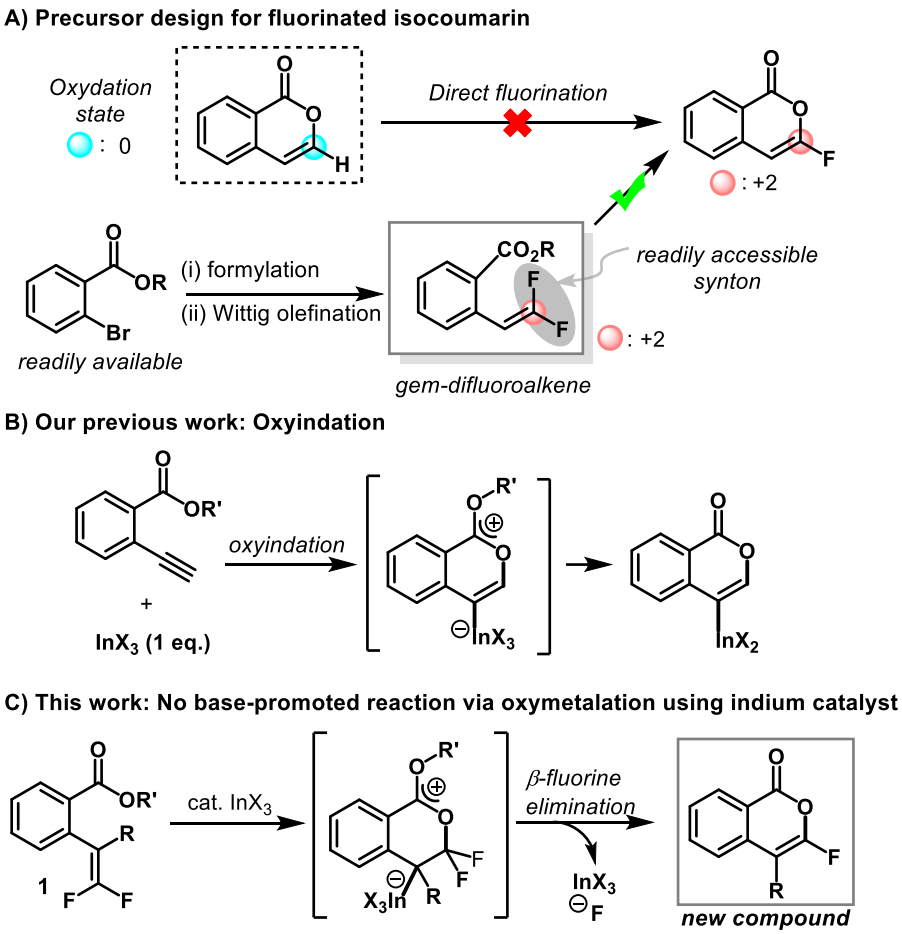


NOS inhibitor Tegafur Tumor necrosis factor



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

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 works and this work.

2-2. Results and Discussion

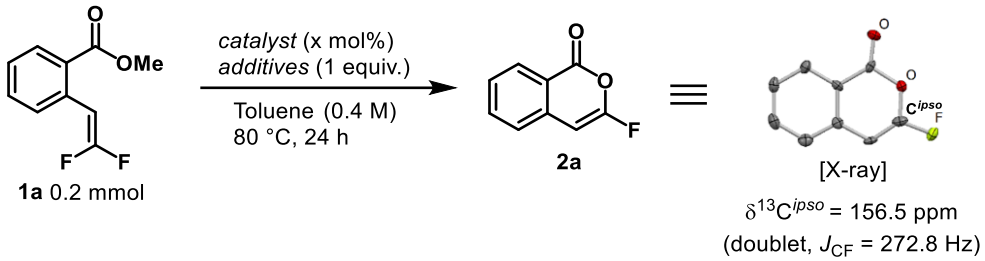
Reaction optimization for the synthesis of fluorinated isocoumarin

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. 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.



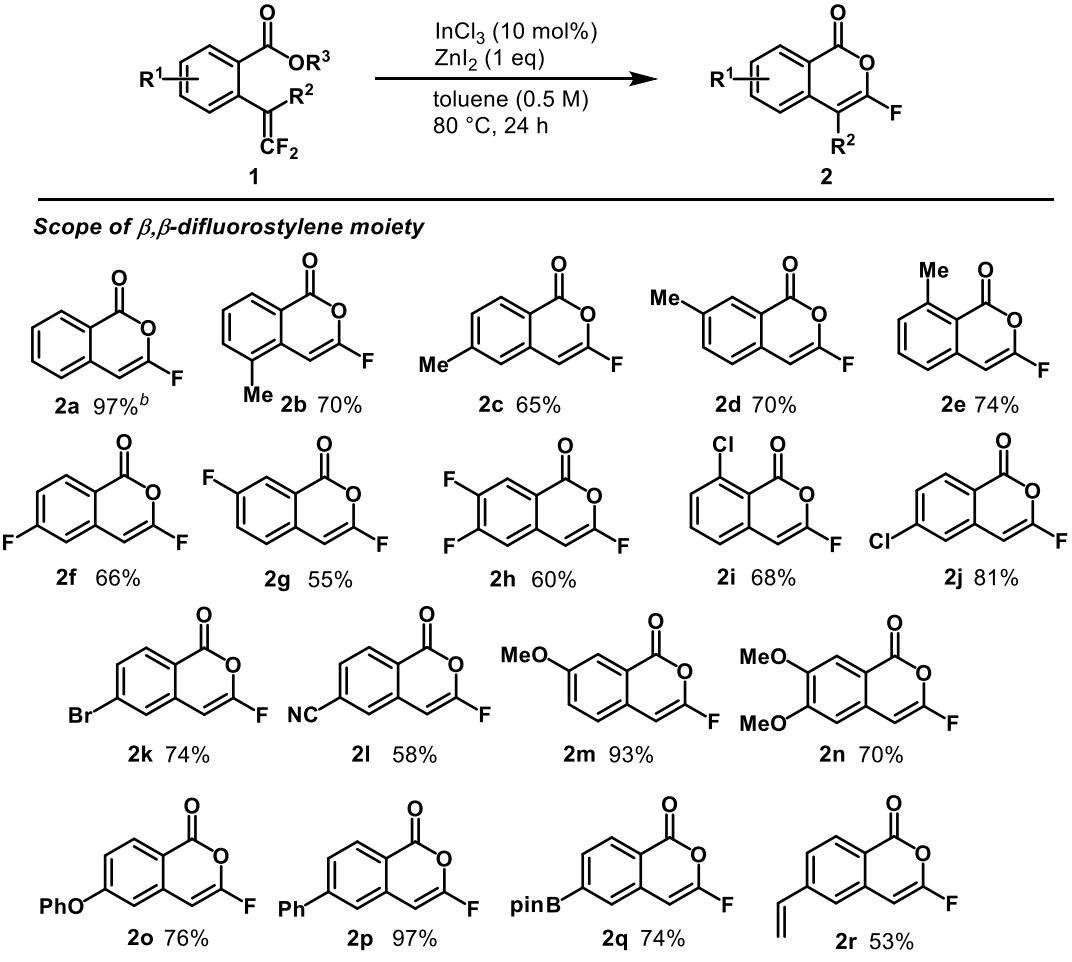
Entry	Catalyst (x mol%)	Additive	Yield %[a]
1	InI_3 (50)	-	>97
2	$PdCl_2$ (50)	-	0
3	$CuBr_2$ (50)	-	0
4	$FeBr_3$ (50)	-	0
5	AgOTf (50)	-	0
6	$AgSbF_6$ (50)	-	29
7	ClBcat (50)	-	0
8	AlI_3 (50)	-	0
9	GaI_3 (50)	-	33
10	ZnI_2 (50)	-	6
11	$BiBr_3$ (50)	-	33
12	InI_3 (10)	-	23
13	InI_3 (20)	-	48
14	InF_3 (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]

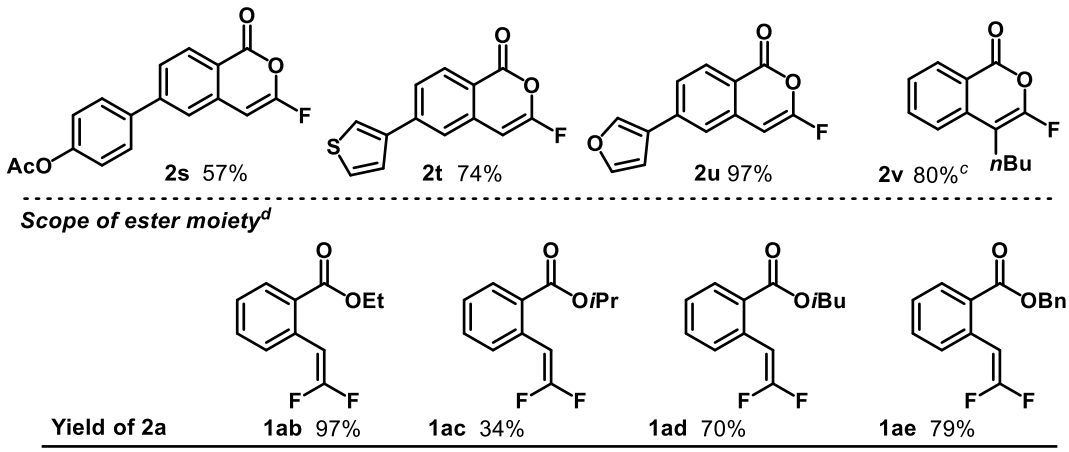
[a] Reaction conditions: x mol% catalyst, 1 equiv additives, **1a** (0.3 mmol, 1 equiv) in 0.6 mL of toluene at 80 °C for 24 h under nitrogen. Yields were determined by ^1H NMR. [b] 3 days

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**.

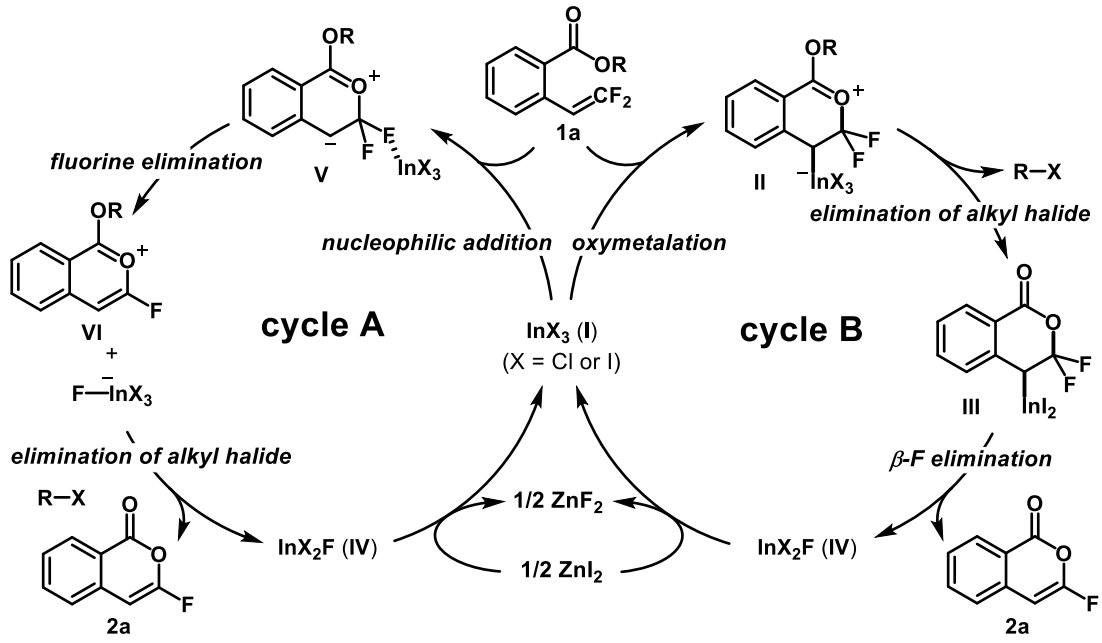
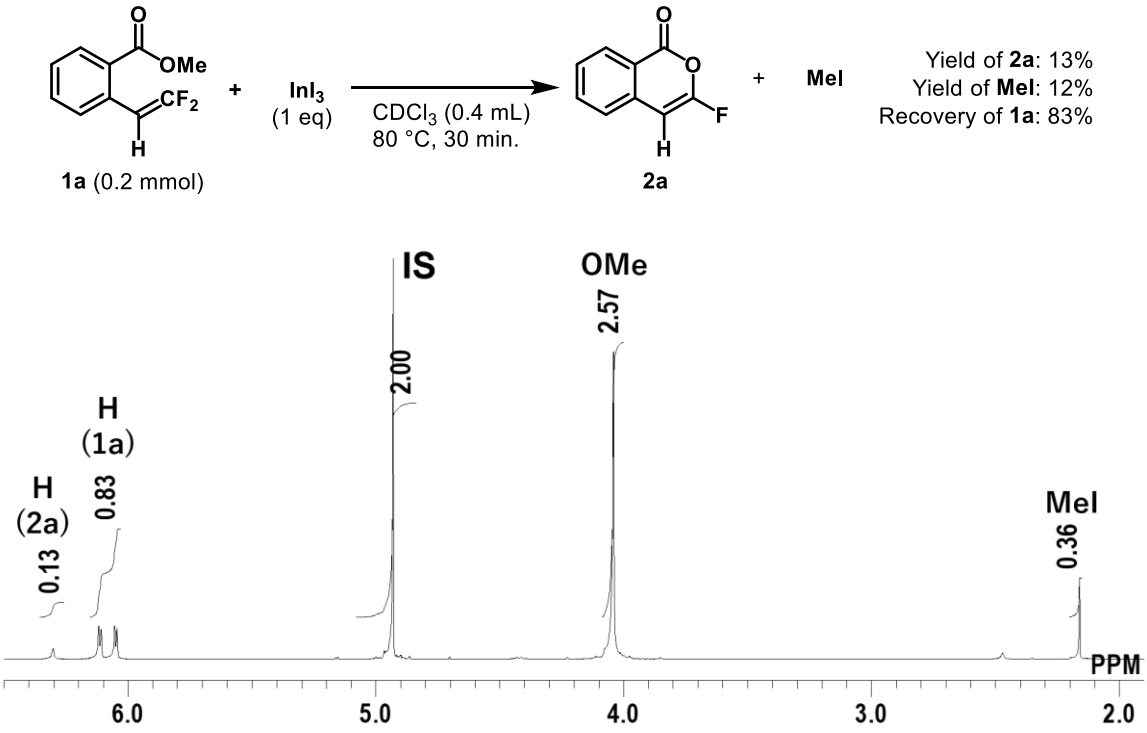


Figure 1. Proposed mechanisms: (A) nucleophilic addition-elimination pathway (B) oxymetalation pathway.

At first, the reaction mixture was monitored by ^{1}H 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**.



Scheme 3. Monitoring of the reaction of *gem*-difluoroalkene **1a** with InI_3 in $CDCl_3$ by ^{1}H 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.

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).

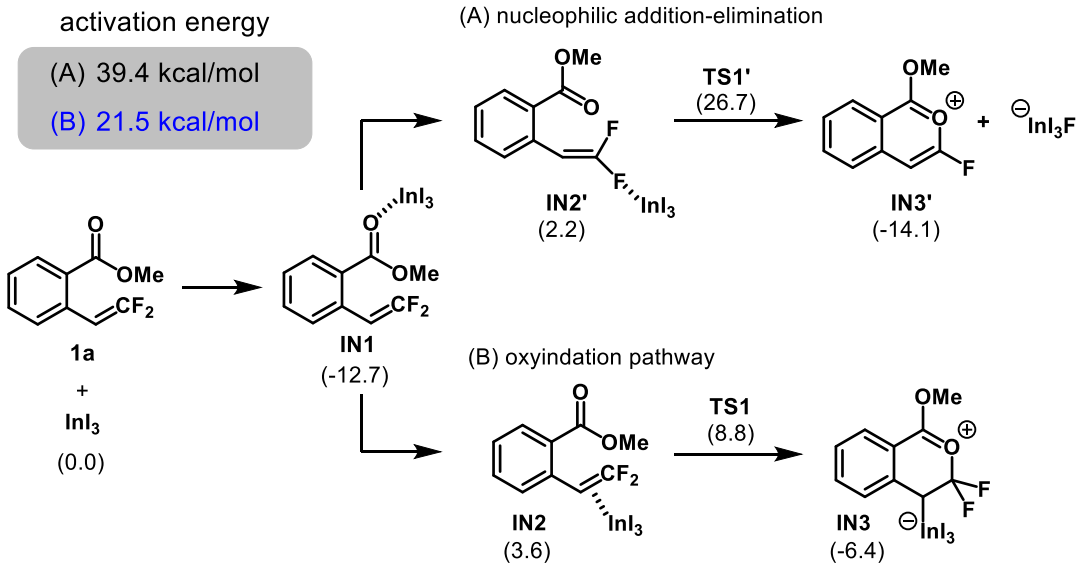


Figure 2. A comparison of plausible mechanisms: (A) nucleophilic addition-elimination pathway and (B) oxymetalation pathway; Free energies (ΔG, 300 K, in kcal mol^{-1}) of intermediates and transition states are given

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**).

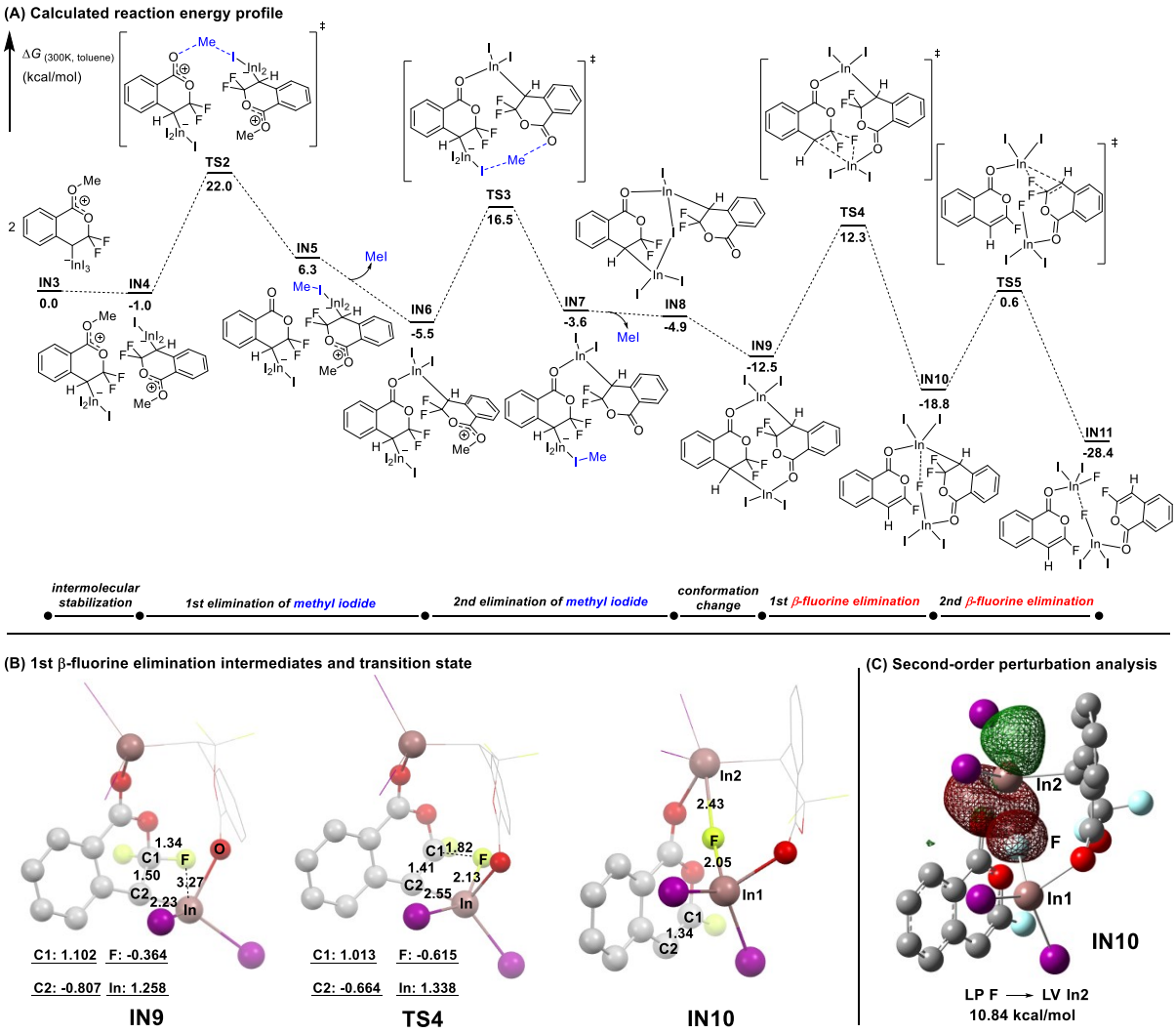


Figure 3. (A) Computed mechanism for the elimination of alkyl halide and the β-fluorine elimination. DFT calculation was performed at ωB97X-D/Def2-SVPD. The solvation effect was introduced using the IEF-PCM model, and toluene was used as a solvent. (B) Optimized structures of the 1st β-fluorine elimination 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**.

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).

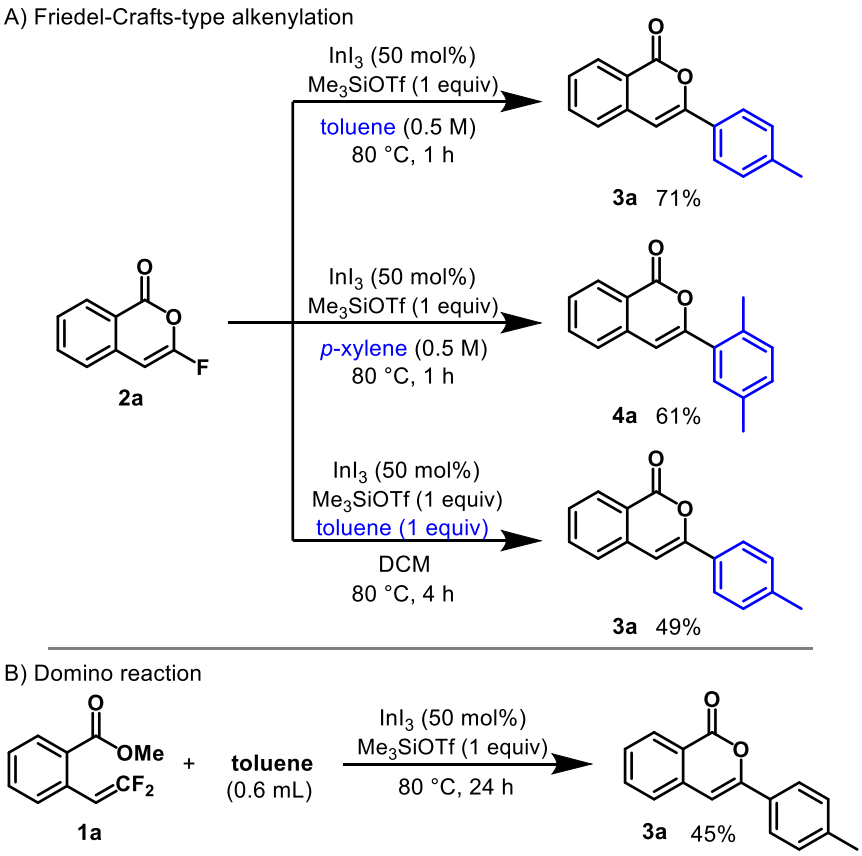


Figure 4. Further investigations: (A) Friedel-Crafts-type alkenylation (B) Domino reaction of cyclization via oxymetalation and Friedel-Crafts-type alkenylation; Isolated yield.

2-3. 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.

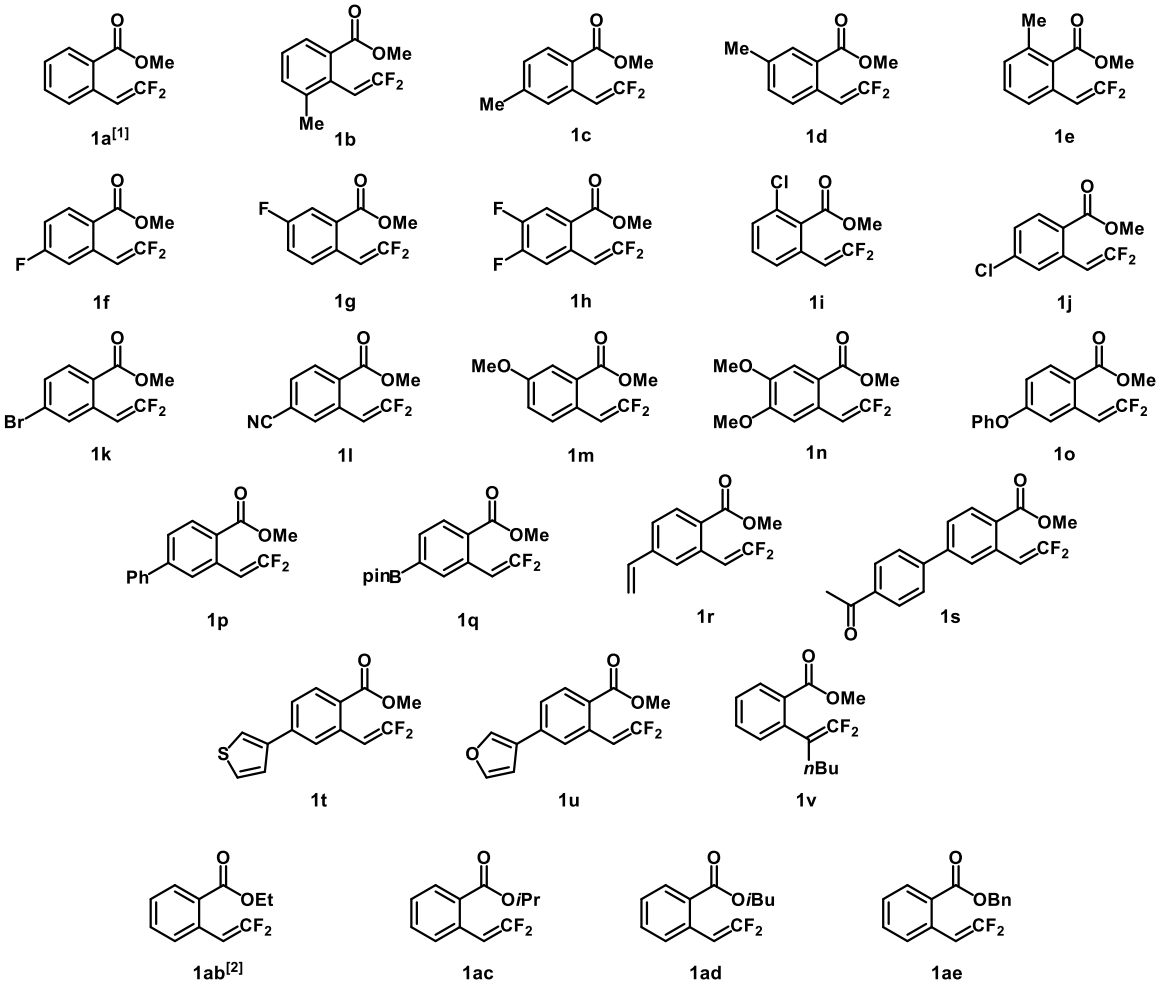
2-4. Experimental Section

General Information

NMR spectra were recorded on JEOL-AL400, JEOL-ECS400 (400 MHz for ^{1}H, 100 MHz for ^{13}C, 376 MHz for ^{19}F) and Bruker AVANCE III spectrometers (600 MHz for ^{1}H, and 150 MHz for ^{13}C). Chemical shifts were reported in ppm on the δ scale relative to tetramethylsilane (δ = 0 for ^{1}H NMR) and residual $CHCl_3$ (δ = 77.0 for ^{13}C NMR) as an internal reference, and boron trifluoride – ethyl ether complex (δ = -158.3 for ^{19}F NMR) as an external reference. High-resolution mass spectra were recorded on a JEOL JMS-700. Column chromatography was performed on silica gel (MERK C60 or Fuji Silysia FL100DX). All reactions were

carried out under nitrogen. Yields were determined by ^{1}H NMR using internal standards (CH_2Br_2). Data collection for X-ray crystal analysis was performed on Rigaku/XtaLAB Synergy-S/Mo ($MoK_\alpha\lambda$ = 0.71075 Å) and Rigaku/XtaLAB Synergy-S/Cu ($CuK_\alpha\lambda$ = 1.54187 Å) diffractometers. All dry solvent and metal salts were purchased from Aldrich or Tokyo Chemical Industry Co., Ltd. (TCI), FUJIFILM Wako Pure Chemical Corporation and used after purification by distillation or used without purification for solid substrates.

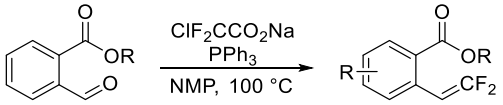
Materials



The known compounds **1a** and **1ab** were prepared according to the literatures[23][24], and the spectral data are in agreement with the reports. The new compounds **1b-1v, 1ac-1ae** were prepared by the methods described in the literature and their spectral data are shown in this supporting information.

Method A

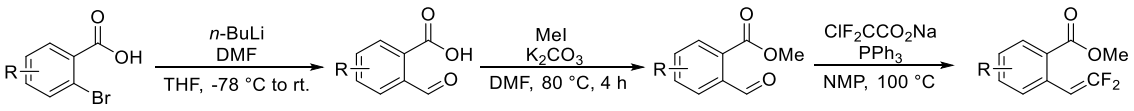
Synthesis of **1ac, 1ad,** and **1ae**



In a 20 mL oven-dried round-bottom flask with a stir bar, the corresponding aldehyde (1.0 equiv, 5.0 mmol), triphenyl phosphine (1.2 eq, 6.0 mmol) were dissolved in NMP (10 mL), then the mixture was heated to 100 °C. To the reaction mixture at 100 °C was added sodium 2-chloro-2,2-difluoroacetate (2.0 equiv, 10 mmol) slowly. After the reaction finished according to the TLC, the reaction mixture was cooled to room temperature, quenched with water and extracted with Et_2O. The combined organic layers were washed with H_2O_2 (30 wt% in water, 2 mL), brine (10 mL x 3) and dried over $MgSO_4$. After solvent was removed under reduced pressure, the crude residue was purified by flash column chromatography on silica gel (hexane only) to afford the title compound.

Method B

Synthesis of **1b-1j**, **1m**, and **1n**



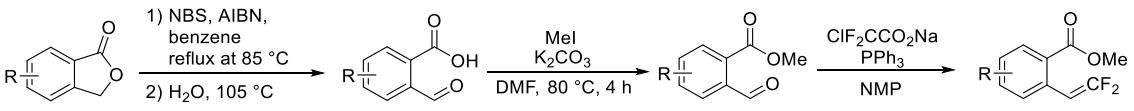
In a 100 mL oven-dried round-bottom flask with a stir bar, the corresponding 2-bromobenzoic acid (1.0 equiv, 5.0 mmol) was dissolved in THF (42 mL), then the mixture was cooled to -78 °C. To the reaction mixture at -78 °C, *n*-BuLi (6.9 mL, 11 mmol, 1.6 mol/L in hexane) was added dropwise over 30 min while the temperature was maintained at -78 °C. After being stirred at -78 °C for 30 min, DMF (4.2 mL) was added dropwise at -78 °C. After this time, the mixture was allowed to stir at room temperature overnight, and then diluted with Et_2O (50 mL) and H_2O (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (30 mL x 3). The combined organic layers were washed with brine (40 mL x 2), dried over $MgSO_4$, filtered, concentrated in vacuo. After removal of the solvent, the crude residue was used for next reaction without further purification.

In a 50 mL oven-dried round-bottom flask with a stir bar, the corresponding 2-formyl benzoic acid (5.0 mmol), K_2CO_3 (0.76 g, 5.5 mmol), and MeI (0.78 mL, 13 mmol) were dissolved in dry DMF (10 mL) and the mixture was stirred at 80 °C, for 4 h. After cooling to room temperature, the mixture was diluted with H_2O and extracted with Et_2O (15 mL x 3). The organic layer was washed with brine (20 mL x 3), and dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was used for the next reaction without further purification.

The target compound **1b-1j**, **1m**, and **1n** were finally prepared by **Method A** from the corresponding 2-formyl benzoic acid.

Method C

Synthesis of **1k,** and **1l.**



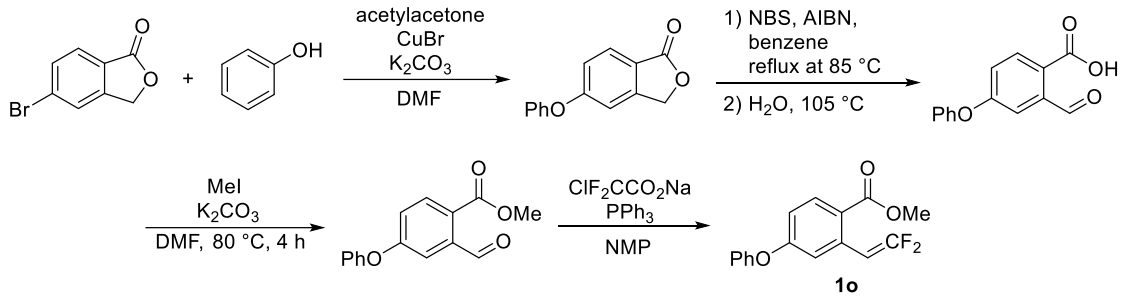
In a 20 mL round-bottom flask with a stir bar, the corresponding phthalide (1.0 equiv, 2.0 mmol), NBS (0.39

g, 1.0 equiv, 2.2 mmol), and AIBN (16 mg, 5.0 mol%, 0.1 mmol), were dissolved in benzene, then the mixture was refluxed for 1h. After completion of the reaction, the round-bottom flask was kept in ice bath for precipitation. Solid precipitate was removed by filtration; filtrate was concentrated in vacuo to afford crude product. Water (30 mL) was added to the crude product and refluxed for 1h. The reaction mixture was then cooled to rt, the compound was extracted with Et_2O, dried over $MgSO_4$ concentrated in vacuo to afford a crude product, which was used without further purification.

The target compound **1k**, **1l,** and **1x** were finally prepared by **Method A** from the corresponding 2-formyl benzoic acid.

Method D

Synthesis of **1o**

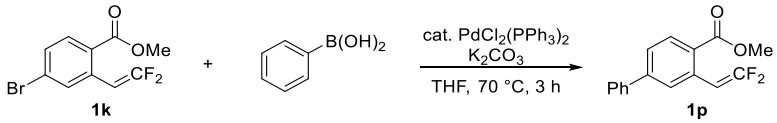


Following the literature method,[25] to an oven-dried 50 mL round-bottom flask with a stir bar were added 5-bromophthalide (2.1 g, 10 mmol), acetylacetone (0.10 g, 1.0 mmol), CuBr (0.14 g, 1.0 mmol), K_2CO_3 (1.4 g, 10 mmol), phenol (1.2 g, 13 mmol), and DMF (10 mL) under nitrogen. Then the mixture was stirred at 90 °C for 12 h. After cooling to the room temperature, water (10 mL) was added and the mixture was extracted with Et_2O (10 mL x 3). The combined organic layers were washed with 1M HCl (15 mL x 1) and brine (20 mL x 3) and dried over $MgSO_4$. After solvent was removed under reduced pressure, the crude residue was purified by column chromatography on silica gel (Hexane/EtOAc = 80:20) to afford the 5-phenoxy phthalide in 30% yield.

The target compound **1o** was finaly prepared by **Method B** from the corresponding phthalide.

Method E

Synthesis of **1p**

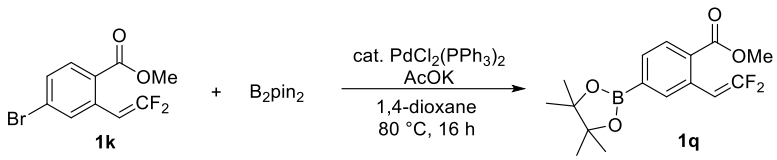


In a 30 mL round-bottom flask with a stir bar, compound **1k** (0.55 g, 1.0 equiv, 2.0 mmol), $PdCl_2(PPh_3)_2$ (0.14 g, 0.1 equiv, 0.2 mmol), $PhB(OH)_2$ (0.49 g, 2.0 equiv, 4.0 mmol), and K_2CO_3 (0.55 g, 2.0 equiv, 4.0 mmol) were dissolved in THF (10 mL), then the mixture was refluxed at 70 °C. After being stirred at 70 °C for 3 h, the mixture was diluted with EtOAc (15 mL) and water (10 mL), the layers was separated, and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered the mixture and the solution was concentrated in vacuo and purified the residue

by chromatography on silica gel (Hexane/EtOAc = 99:1) to afford the compound **1p** in 36% yield.

Method F

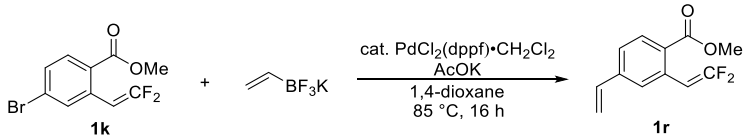
Synthesis of **1q**



In a 50 mL oven-dried round-bottom flask equipped with a stir bar, compound **1k** (0.55 g, 1.0 equiv, 2.0 mmol) and $PdCl_2(PPh_3)_2$ (0.14 g, 0.1 equiv, 0.5 mmol) were dissolved in 1,4-dioxane (24 mL). After stirring for 5 min at 50 °C, to the reaction mixture were added B_2pin_2 (1.0 g, 2.0 equiv, 4.0 mmol) and AcOK (0.39 g, 2.0 equiv, 2.0 mmol). The reaction mixture was stirred at 80 °C for 16 h. After cooling to room temperature, water (15 mL) was added and the mixture was extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered the mixture and the solution was concentrated in vacuo and purified the residue by chromatography on silica gel (Hexane/EtOAc = 98:2) to afford the compound **1q** in 73% yield.

Method G

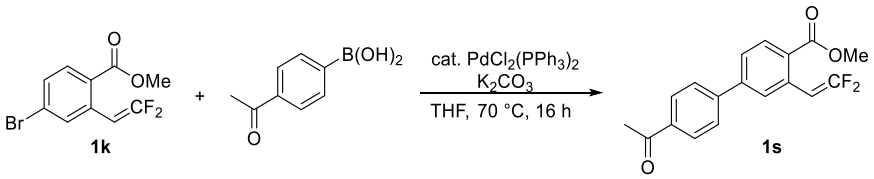
Synthesis of **1r**



In a 30 mL oven-dried round-bottom flask equipped with a stir bar, compound **1k** (0.55 g, 1.0 equiv, 2.0 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.16 g, 0.1 equiv, 0.2 mmol), NEt_3 (0.41 g, 2.0 equiv, 4.0 mmol), and potassium vinyltrifluoroborate (0.40 g, 1.5 equiv, 3.0 mmol) were dissolved in EtOH (5.0 mL), then the mixture was stirred at 85 °C for 16 h. After cooling to room temperature, water (5.0 mL) was added and the mixture was extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered the mixture and the solution was concentrated in vacuo and purified the residue by chromatography on silica gel (Hexane/EtOAc = 85:15) to afford the compound **1r** in 89% yield.

Method H

Synthesis of **1s**

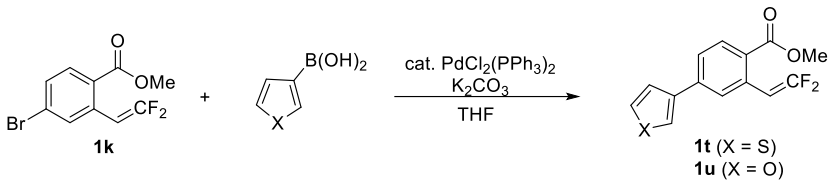


In a 30 mL round-bottom flask with a stir bar, compound **1k** (0.55 g, 1.0 equiv, 2.0 mmol), $PdCl_2(PPh_3)_2$ (0.14 g, 0.1 equiv, 0.2 mmol), 4-acetylphenylboronic acid (0.66 g, 2.0 equiv, 4.0 mmol), and K_2CO_3 (0.55 g,

2.0 equiv, 4.0 mmol) were dissolved in THF (10 mL), then the mixture was refluxed at 70 °C. After being stirred at 70 °C for 16 h, the mixture was diluted with EtOAc (15 mL) and water (10 mL), the layers was separated, and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered the mixture and the solution was concentrated in vacuo and purified the residue by chromatography on silica gel (Hexane/EtOAc = 80:20) to afford the compound **1s** in 62% yield.

Method I

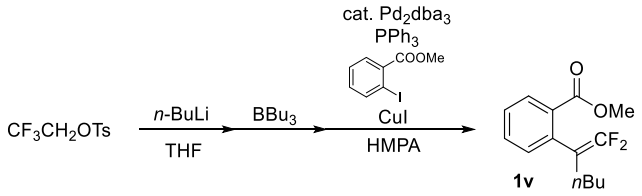
Synthesis of **1t, 1u**



In a 30 mL oven-dried round-bottom flask equipped with a stir bar, compound **1k** (0.55 g, 1.0 equiv, 2.0 mmol), $PdCl_2(PPh_3)_2$ (0.14 g, 0.1 equiv, 0.2 mmol), the corresponding heterocyclic boronic acid (4.0 mmol, 2.0 equiv), and K_2CO_3 (0.55 g, 2.0 equiv, 4.0 mmol) were dissolved in THF (8.0 mL), then the mixture was reluxed at 70 °C. After being stirred at 70 °C for 16 h, the mixture was diluted with EtOAc (15 mL) and water (10 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered the mixture and the solution was concentrated in vacuo and purified the residue by chromatography on silica gel (Hexane/EtOAc = 80:20) to afford the compound **1t** or **1u** in 71% or 44% yield, respectively.

Method J

Synthesis of **1v**



In a 100 mL round-bottom flask with a stir bar, to a solution of 2,2,2-trifluoroethyl *p*-toluenesulfonate (1.3 g, 5.0 mmol) in THF (20 mL), *n*-BuLi (6.9 mL, 11 mmol, 1.6 mol/L in hexane) was added dropwise over 10 min while the temperature was maintained at -78 °C. After addition, the mixture was stirred for 20 min at -78 °C, and then tributylborane (5.5 mL, 1.0 M in THF, 5.0 mmol) was added at -78 °C. After being stirred for 1 h, the reaction mixture was allowed to warm to room temperature and stirred for an additional 3 h. Then to the reaction mixture was added a solution of PPh_3 (0.36 g, 0.40 mmol), $Pd_2(dba)_3$ (34 mg, 0.04 mmol), and methyl 2-iodobenzoate (1.1 g, 4.0 mmol) in HMPA (6.0 mL). After being stirred at room temperature for 5 h, the reaction was quenched with phosphate buffer (pH 7.0). The mixture was filtered, and then organic materials were extracted with EtOAc (20 mL x 3). The combined organic phase was washed

with brine (20 mL), dried over $MgSO_4$, filtered the mixture and the solution was concentrated in vacuo and purified the residue by chromatography on silica gel (Hexane only) to afford the compound **1v** in 65 % yield.

isopropyl 2-(2,2-difluorovinyl)benzoate (1ac).

Prepared according to **Method A** using the corresponding aldehyde (0.96 mg, 5.0 mmol). The crude mixture was purified by chromatography on silica gel (hexane only) to afford the product as a yellow oil (0.53 mg, 47%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 7.7 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.48 (t, J = 7.7 Hz, 1H), 7.30 (t, J = 7.7 Hz, 1H), 6.26 (dd, J_{H-F} = 25.8, 4.1 Hz, 1H), 5.27-5.20 (m, 1H), 1.37 (d, J = 6.3 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 156.3 (dd, J_{CF} = 297.5, 287.1 Hz), 131.9, 131.1 (dd, J_{CF} = 8.1, 5.2 Hz), 130.7, 129.4, 129.3, 126.9, 80.2 (dd, J_{CF} = 32.4, 11.4 Hz), 68.7, 21.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ -88.1 (d, J = 24.4 Hz), -89.8 (t, J = 27.5 Hz).

HRMS: (EI, 70 eV) Calculated ($C_{12}H_{12}F_2O_2$) 226.0805 (M^+) Found 226.0802

isobutyl 2-(2,2-difluorovinyl)benzoate (1ad)

Prepared according to **Method A** using the corresponding aldehyde (1.0 g, 5.0 mmol). The crude mixture was purified by chromatography on silica gel (hexane only) to afford the product as a yellow oil (0.69 g, 57%).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.97 (d, J = 7.9 Hz, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.49 (t, J = 7.9 Hz, 1H), 7.31 (t, J = 7.9 Hz, 1H), 6.28 (dd, J_{H-F} = 26.0, 4.2 Hz, 1H), 4.09 (d, J = 6.6 Hz, 2H), 2.11-2.04 (m, 1H), 1.03 (d, J = 6.8 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ: 167.0, 156.3 (dd, J_{CF} = 298.0, 287.5 Hz), 132.0, 131.3 (dd, J_{CF} = 8.4, 5.5 Hz), 130.8, 129.5 (dd, J_{CF} = 8.7, 1.7 Hz), 128.9 (d, J_{CF} = 4.6 Hz), 126.9, 80.3 (dd, J_{CF} = 32.4, 11.0 Hz), 71.3, 27.8, 19.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ -87.9 (d, J = 24.4 Hz), -89.7 (t, J = 27.5 Hz).

HRMS: (CI, 70 eV) Calculated ($C_{13}H_{15}F_2O_2$) 241.1040 ($[M+H]^+$) Found 241.1041

benzyl 2-(2,2-difluorovinyl)benzoate (1ae)

Prepared according to **Method A** using the corresponding aldehyde (1.2 g, 5.0 mmol). The crude mixture was purified by chromatography on silica gel (hexane only) to afford the product as a yellow oil (0.56 g, 41%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 7.7 Hz, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.45-7.25 (m, 6H), 6.29 (dd, J_{H-F} = 25.8, 4.1 Hz, 1H), 5.34 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 156.4 (dd, J_{CF} = 298.0, 287.5 Hz), 135.7, 132.3, 131.6 (dd, J_{CF} = 8.6, 5.7 Hz), 131.0, 129.5, 129.4, 128.6, 128.3, 128.2, 126.9, 80.2 (dd, J_{CF} = 32.4, 10.5 Hz), 66.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ -87.7 (d, J = 27.5 Hz), -89.5 (t, J = 25.9 Hz).

HRMS: (EI, 70 eV) Calculated ($C_{16}H_{12}F_2O_2$) 274.0805 (M^+) Found 274.0801

methyl 2-(2,2-difluorovinyl)-3-methylbenzoate (1b)

Prepared according to **Method B** using the corresponding 2-bromobenzoic acid (1.1 g, 5.0 mmol). The crude mixture was purified by chromatography on silica gel (hexane only) to afford the product as a yellow oil (0.14 g, 13%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.27 (t, J = 7.8 Hz, 1H), 5.64 (dd, J_{H-F} = 26.8, 2.1 Hz, 1H), 3.88 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 154.9 (dd, J_{CF} = 291.4, 288.5 Hz), 138.8, 134.2, 131.3, 129.4 (dd, J_{CF} = 7.2, 2.4 Hz), 128.4, 127.9, 78.8 (dd, J_{CF} = 30.7, 19.2 Hz), 52.5, 20.7 (d, J_{CF} = 2.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -90.1 (t, J = 30.5 Hz), -91.8 (d, J = 33.6 Hz).

HRMS: (EI, 70 eV) Calculated ($C_{11}H_{10}F_2O_2$) 212.0649 (M^+) Found 212.0648

methyl 2-(2,2-difluorovinyl)-4-methylbenzoate (1c)

Prepared according to **Method B** using the corresponding 2-bromobenzoic acid (1.1 g, 5 mmol). The crude mixture was purified by chromatography on silica gel (hexane only) to afford the product as a yellow oil (0.18 g, 17%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 8.2 Hz, 1H), 7.36 (s, 1H), 7.11 (d, J = 8.2 Hz, 1H), 6.29 (dd, J_{H-F} = 26.3, 4.5 Hz, 1H), 3.88 (s, 3H), 2.39 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 156.3 (dd, J_{CF} = 297.5, 287.1 Hz), 142.8, 131.5 (dd, J_{CF} = 8.1, 5.2 Hz), 131.0, 130.1 (d, J_{CF} = 7.6 Hz), 127.8, 125.6 (d, J_{CF} = 4.8 Hz), 80.2 (dd, J_{CF} = 32.4, 10.5 Hz), 52.0 , 21.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ -88.0 (d, J = 30.5 Hz), -89.7 (t, J = 27.5 Hz).

HRMS: (EI, 70 eV) Calculated ($C_{11}H_{10}F_2O_2$) 212.0649 (M^+) Found 212.0650

methyl 2-(2,2-difluorovinyl)-5-methylbenzoate (1d)

Prepared according to **Method B** using the corresponding 2-bromobenzoic acid (1.1 g, 5.0 mmol). The crude mixture was purified by chromatography on silica gel (hexane only) to afford the product as a yellow oil (0.14 g, 13%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.44 (d, J = 8.2 Hz, 1H), 7.30 (d, J = 8.2 Hz, 1H), 6.22 (dd, J_{H-F} = 26.1, 4.3 Hz, 1H), 3.89 (s, 3H), 2.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 156.2 (dd, J_{CF} = 297.5, 287.1 Hz), 136.8, 133.0, 131.3, 129.3 (d, J_{CF} = 8.6 Hz), 128.4 (dd, J_{CF} = 8.6, 5.7 Hz), 128.3 (d, J_{CF} = 5.7 Hz), 80.0 (dd, J_{CF} = 32.4, 10.5 Hz), 52.1, 20.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ -88.5 (d, J = 30.5 Hz), -90.1 (t, J = 25.9 Hz).

HRMS: (EI, 70 eV) Calculated ($C_{11}H_{10}F_2O_2$) 212.0649 (M^+) Found 212.0648

methyl 2-(2,2-difluorovinyl)-6-methylbenzoate (1e)

Prepared according to **Method B** using the corresponding 2-bromobenzoic acid (1.1 g, 5.0 mmol). The crude mixture was purified by chromatography on silica gel (hexane only) to afford the product as a yellow oil (0.15 g, 14%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, J = 7.7 Hz, 1H), 7.29 (t, J = 7.7 Hz, 1H), 7.11 (d, J = 7.7 Hz, 1H),

5.36 (dd, J_{H-F} = 24.7, 3.9 Hz, 1H), 3.93 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 156.4 (dd, J_{CF} = 298.5, 288.0 Hz), 135.6, 132.9 (d, J_{CF} = 4.8 Hz), 129.7, 129.1, 127.5 (dd, J_{CF} = 7.6, 5.7 Hz), 125.6 (dd, J_{CF} = 9.1, 1.4 Hz), 79.3 (dd, J_{CF} = 30.5, 13.4 Hz), 52.2 , 19.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ -87.4 (d, J = 24.4 Hz), -87.8 (t, J = 24.4 Hz).

HRMS: (EI, 70 eV) Calculated ($C_{11}H_{10}F_2O_2$) 212.0649 (M^+) Found 212.0648

methyl 2-(2,2-difluorovinyl)-4-fluorobenzoate (1f)

Prepared according to **Method B** using the corresponding 2-bromobenzoic acid (1.1 g, 5.0 mmol). The crude mixture was purified by chromatography on silica gel (hexane only) to afford the product as a yellow oil (87 mg, 8%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 8.8 Hz, d, J_{H-F} = 6.1 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.02-6.97 (m, 1H), 6.39 (dd, J_{H-F} = 25.8, 4.1 Hz, 1H), 3.89 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 164.6 (d, J_{CF} = 253.7 Hz), 156.7 (dd, J_{CF} = 299.5, 289.0 Hz), 134.5 (td, J_{CF} = 9.1, 5.1 Hz), 133.5 (d, J_{CF} = 9.5 Hz), 124.4, 116.2 (dd, J_{CF} = 23.8, 8.6 Hz), 114.1 (d, J_{CF} = 21.9 Hz), 79.8 (dt, J_{CF} = 37.2, 5.5 Hz), 52.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ -85.8 (d, J = 21.4 Hz), -87.3 (t, J = 22.9 Hz), -111.5 (s).

HRMS: (EI, 70 eV) Calculated ($C_{10}H_7F_3O_2$) 216.0398 (M^+) Found 216.0395

methyl 2-(2,2-difluorovinyl)-5-fluorobenzoate (1g)

Prepared according to **Method B** using the corresponding 2-bromobenzoic acid (1.1 g, 5.0 mmol). The crude mixture was purified by chromatography on silica gel (hexane only) to afford the product as a yellow oil (0.13 g, 12%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (m, 1H), 7.53 (m, 1H), 7.21 (m, 1H), 6.24 (dd, J_{H-F} = 25.6, 4.1 Hz, 1H), 3.91 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1 (d, J_{CF} = 1.9 Hz), 160.9 (dd, J_{CF} = 248.2, 1.9 Hz), 156.3 (ddd, J_{CF} = 298.1, 287.5, 1.9 Hz), 131.4-131.1 (m), 130.1-129.9 (m), 127.6-127.4 (m), 119.5 (d, J_{CF} = 22.0 Hz), 117.7 (d, J_{CF} = 24.0 Hz), 79.5 (dd, J_{CF} = 33.5, 11.5 Hz), 52.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ -88.1 (d, J = 27.5 Hz), -90.1 (t, J = 25.9 Hz), -119.1 (s).

HRMS: (EI, 70 eV) Calculated ($C_{10}H_7F_3O_2$) 216.0398 (M^+) Found 216.0399

methyl 2-(2,2-difluorovinyl)-4,5-difluorobenzoate (1h)

Prepared according to **Method B** using the corresponding 2-bromobenzoic acid (1.2 g, 5.0 mmol). The crude mixture was purified by chromatography on silica gel (hexane only) to afford the product as a yellow solid (0.14 g, 12%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81-7.78 (m,1H), 7.17 (dd, J_{H-F} = 16.4, 8.9 Hz, 1H), 5.77 (dd, J_{H-F} = 26.3,

2.2 Hz, 1H), 3.90 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5 (d, J_{CF} = 2.9 Hz), 155.7 (dd, J_{CF} = 297.1, 289.4 Hz), 153.2 (dd, J_{CF} = 255.6, 14.3 Hz), 148.2 (dd, J_{CF} = 250.8, 13.4 Hz), 127.1 (dd, J_{CF} = 7.6, 3.8 Hz), 126.0 , 122.0-121.8 (m), 116.0 (t, J_{CF} = 13.4 Hz), 73.5 (ddd, J_{CF} = 36.7, 16.7, 1.9 Hz), 52.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ -84.2 (d, J = 24.4 Hz), -87.1 (d, J = 18.3 Hz), -134.7 (s), -140.1 (s).

HRMS: (EI, 70 eV) Calculated ($C_{10}H_6F_4O_2$) 234.0304 (M^+) Found 234.0305

methyl 2-chloro-6-(2,2-difluorovinyl)benzoate (1i)

Prepared according to **Method B** using the corresponding 2-bromobenzoic acid (1.2 g, 5.0 mmol). The crude mixture was purified by chromatography on silica gel (hexane only) to afford the product as a colorless oil (0.20 g, 17%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 7.2 Hz, 1H), 7.33-7.28 (m, 2H), 5.30 (dd, J_{H-F} = 24.5, 3.6 Hz, 1H), 3.96 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 156.7 (dd, J_{CF} = 299.5, 290.9 Hz), 132.7 (dd, J_{CF} = 4.8, 1.9 Hz), 131.3, 130.5, 129.4 (dd, J_{CF} = 7.6, 5.7 Hz), 128.1, 126.2 (d, J_{CF} = 9.5 Hz), 78.7 (dd, J_{CF} = 31.9, 13.8 Hz), 52.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ -85.4 (d, J = 21.4 Hz), -85.7 (t, J = 21.4 Hz).

HRMS: (EI, 70 eV) Calculated ($C_{10}H_7ClF_2O_2$) 232.0103 (M^+) Found 232.0101

methyl 4-chloro-2-(2,2-difluorovinyl)benzoate (1j)

Prepared according to **Method B** using the corresponding 2-bromobenzoic acid (1.2 g, 5.0 mmol). The crude mixture was purified by chromatography on silica gel (hexane only) to afford the product as a colorless oil (0.24 g, 21%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 8.6 Hz, 1H), 7.55 (s, 1H), 7.28 (d, J = 8.6 Hz, 1H), 6.31 (dd, J_{H-F} = 25.8, 4.1 Hz, 1H), 3.90 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 156.6 (dd, J_{CF} = 299.5, 289.0 Hz), 138.5, 133.3 (dd, J_{CF} = 8.6, 4.8 Hz), 132.3, 129.3 (d, J_{CF} = 9.5 Hz), 127.1, 126.6 (d, J_{CF} = 4.8 Hz), 79.6 (dd, J_{CF} = 34.3, 10.5 Hz), 52.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ -86.0 (d, J = 21.4 Hz), -87.6 (t, J = 22.9 Hz).

HRMS: (EI, 70 eV) Calculated ($C_{10}H_7ClF_2O_2$) 232.0103 (M^+) Found 232.0101

methyl 4-bromo-2-(2,2-difluorovinyl)benzoate (1k)

Prepared according to **Method C** using the corresponding phthalide (0.43 g, 2.0 mmol). The crude mixture was purified by chromatography on silica gel (hexane only) to afford the product as a yellow solid (0.22 g, 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 8.6 Hz, 1H), 7.72 (s, 1H), 7.44 (dd, J = 8.6, 1.8 Hz, 1H), 6.29 (dd, J_{H-F} = 25.8, 4.1 Hz, 1H), 3.90 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 156.6 (dd, J_{CF} = 299.5, 289.0 Hz), 133.4 (dd, J_{CF} = 8.6, 5.7 Hz), 132.3, 132.2 (d, J_{CF} = 9.5 Hz), 130.1, 127.08 (d, J_{CF} = 4.8 Hz), 127.06, 79.5 (dd, J_{CF} = 33.4, 10.5 Hz), 52.3

^{19}F NMR (376 MHz, $CDCl_3$): δ -85.9 (d, J = 21.4 Hz), -87.6 (t, J = 22.9 Hz).

HRMS: (EI, 70 eV) Calculated ($C_{10}H_7BrF_2O_2$) 275.9597 (M^+) Found 275.9593

methyl 4-cyano-2-(2,2-difluorovinyl)benzoate (1l)

Prepared according to **Method C** using the corresponding phthalide (0.32 g, 2.0 mmol). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a yellow oil (94 mg, 21%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 8.2 Hz, 1H), 7.86 (s, 1H), 7.59 (d, J = 8.2 Hz, 1H), 6.28 (dd, J_{H-F} = 25.4, 3.6 Hz, 1H), 3.95 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.94, 156.8 (dd, J_{CF} = 299.9, 290.8 Hz), 132.8 (d, J_{CF} = 9.8 Hz), 132.6 (dd, J_{CF} = 8.6, 5.3 Hz), 132.1 (d, J_{CF} = 4.1 Hz), 131.5, 130.0, 117.6, 116.0, 79.1 (dd, J_{CF} = 34.0, 10.2 Hz), 52.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ -84.5 (d, J = 18.3 Hz), -86.4 (t, J = 21.4 Hz).

HRMS: (EI, 70 eV) Calculated ($C_{11}H_7F_2NO_2$) 223.0445 (M^+) Found 223.0444

methyl 2-(2,2-difluorovinyl)-5-methoxybenzoate (1m)

Prepared according to **Method B** using the corresponding 2-bromobenzoic acid (1.2 g, 5.0 mmol). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (0.40 g, 35%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.46 (m, 2H), 7.05 (dd, J = 8.6, 2.7 Hz, 1H), 6.17 (dd, J_{H-F} = 26.3, 4.1 Hz, 1H), 3.90 (s, 3H), 3.84 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 158.1, 156.0 (dd, J_{CF} = 296.6, 286.1 Hz), 130.7 (dd, J_{CF} = 8.6, 1.9 Hz), 129.5 (d, J_{CF} = 4.8 Hz), 123.6 (dd, J_{CF} = 8.1, 5.2 Hz), 118.6, 115.4, 79.7 (dd, J_{CF} = 32.4, 11.4 Hz), 55.4, 52.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ -89.8 (d, J = 33.6 Hz), -91.4 (t, J = 25.9 Hz).

HRMS: (EI, 70 eV) Calculated ($C_{11}H_{10}F_2O_3$) 228.0598 (M^+) Found 228.0594

methyl 2-(2,2-difluorovinyl)-4,5-dimethoxybenzoate (1n)

Prepared according to **Method B** using the corresponding 2-bromobenzoic acid (1.3 g, 5.0 mmol). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (0.52 g, 40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 1H), 7.01 (s, 1H), 6.35 (dd, J_{H-F} = 26.3, 4.4 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.89 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 156.1 (dd, J_{CF} = 296.6, 287.1 Hz), 151.9, 147.4, 125.8 (dd, J_{CF} = 8.1, 5.3 Hz), 120.5 (d, J_{CF} = 4.8 Hz), 113.2, 111.5 (d, J_{CF} = 9.6 Hz), 80.3 (dd, J_{CF} = 33.5, 10.5 Hz), 55.94, 55.90, 52.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ -89.1 (d, J = 30.5 Hz), -90.4 (t, J = 29.0 Hz).

HRMS: (EI, 70 eV) Calculated ($C_{12}H_{12}F_2O_4$) 258.0704 (M^+) Found 258.0699

methyl 2-(2,2-difluorovinyl)-4-phenoxybenzoate (1o)

Prepared according to **Method D** using 5-Bromophthalide (2.1 g, 10 mmol). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a pale yellow solid (0.26 g, 9%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 8.8 Hz, 1H), 7.40 (t, J = 7.7 Hz, 2H), 7.20 (t, J = 7.7 Hz, 1H), 7.15 (s, 1H), 7.07 (d, J = 7.7 Hz, 2H), 6.85 (dd, J = 8.8, 2.5 Hz, 1H), 6.36 (dd, J_{H-F} = 25.8, 4.5 Hz, 1H), 3.88 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 160.8, 156.5 (dd, J_{CF} = 299.5, 288.0 Hz), 155.3, 134.0 (dd, J_{CF} = 8.6, 4.8 Hz), 133.1, 130.0, 124.6, 122.5-122.4 (m), 120.0, 118.3 (dd, J_{CF} = 9.5, 1.9 Hz), 115.8, 80.2 (dd, J_{CF} = 33.4, 10.5 Hz), 52.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ -87.1 (s), -88.8 (s).

HRMS: (EI, 70 eV) Calculated ($C_{16}H_{12}F_2O_3$) 290.0755 (M^+) Found 290.0752

methyl 3-(2,2-difluorovinyl)-[1,1'-biphenyl]-4-carboxylate (1p)

Prepared according to **Method E** using compound **1k** (0.55 g, 2.0 mmol). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 99:1) to afford the product as yellow solid (0.20 g, 36%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 8.2 Hz, 1H), 7.77 (s, 1H), 7.61 (d, J = 7.7 Hz, 2H), 7.52 (d, J = 8.6 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 7.40 (t, J = 7.0 Hz, 1H), 6.36 (dd, J_{H-F} = 25.8, 4.1 Hz, 1H), 3.92 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 156.5 (dd, J_{CF} = 297.6, 288.0 Hz), 144.98, 139.6, 132.0 (dd, J_{CF} = 8.6, 5.7 Hz), 131.5, 129.0, 128.3, 128.2 (d, J_{CF} =8.6 Hz), 127.2, 127.0 (d, J_{CF} = 3.8 Hz), 125.6, 80.4 (dd, J_{CF} = 32.4, 10.5 Hz), 52.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ -87.4 (d, J = 27.5 Hz), -89.2 (t, J = 24.4 Hz).

HRMS: (EI, 70 eV) Calculated ($C_{16}H_{12}F_2O_2$) 274.0805 (M^+) Found 274.0804

methyl 2-(2,2-difluorovinyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (1q)

Prepared according to **Method F** using compound **1k** (0.55 g, 2.0 mmol). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 98:2) to afford the product as a white solid (0.47 g, 73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.72 (d, J = 7.7 Hz, 1H), 6.20 (dd, J_{H-F} = 25.8, 4.1 Hz, 1H), 3.90 (s, 3H), 1.35 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 156.3 (dd, J_{CF} = 297.1, 285.6 Hz), 135.8 (d, J_{CF} = 6.7 Hz), 133.1, 130.7-130.6 (m), 130.4 (dd, J_{CF} = 8.6, 4.8 Hz), 129.8, 84.3, 80.1 (dd, J_{CF} = 32.4, 11.4 Hz), 52.2, 24.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ -88.3 (d, J = 27.5 Hz), -89.6 (t, J = 24.4 Hz).

HRMS: (EI, 70 eV) Calculated ($C_{16}H_{19}F_2O_4B$) 324.1344 (M^+) Found 324.1350

methyl 2-(2,2-difluorovinyl)-4-vinylbenzoate (1r)

Prepared according to **Method G** using compound **1k** (0.55 g, 2.0 mmol). The crude mixture was purified

by chromatography on silica gel (Hexane/EtOAc = 85:15) to afford the product as a colorless oil (0.40 g, 89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 8.2 Hz, 1H), 7.55 (m, 1H), 7.35 (dd, J = 8.2, 1.8 Hz, 1H), 6.72 (dd, J = 16.8, 10.9 Hz, 1H), 6.31 (dd, J_{H-F} = 26.1, 4.3 Hz, 1H), 5.86 (d, J = 16.8 Hz, 1H), 5.41 (d, J = 10.9 Hz, 1H), 3.89 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 156.4 (dd, J_{CF} = 298.0, 287.5 Hz), 141.2, 135.6, 131.9 (dd, J_{CF} = 8.6, 4.8 Hz), 131.3, 127.5 (d, J_{CF} = 8.6 Hz), 127.31-127.29 (m), 124.4, 116.9, 80.2 (dd, J_{CF} = 32.9, 11.0 Hz), 52.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ -87.6 (d, J = 27.5 Hz), -89.4 (t, J = 25.9 Hz).

HRMS: (EI, 70 eV) Calculated ($C_{12}H_{10}F_2O_2$) 224.0649 (M^+) Found 224.0648

methyl 4'-acetyl-3-(2,2-difluorovinyl)-[1,1'-biphenyl]-4-carboxylate (1s)

Prepared according to **Method H** using compound **1k** (0.55 g, 2.0 mmol). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 80:20) to afford the product as a pale yellow solid (0.39 g, 62%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07-8.05 (m, 3H), 7.79 (m, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.55 (dd, J = 8.2, 1.8 Hz, 1H), 6.37 (dd, J_{H-F} = 25.8, 4.1 Hz, 1H), 3.93 (s, 3H), 2.65 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 167.0, 156.5 (dd, J_{CF} = 298.0, 288.5 Hz), 144.0, 143.5, 136.5, 132.2 (dd, J_{CF} = 8.6, 5.7 Hz), 131.6, 129.0, 128.3 (d, J_{CF} = 7.6 Hz), 127.8-127.7 (m), 127.4, 125.7, 80.2 (dd, J_{CF} = 32.9, 11.0 Hz), 52.3, 26.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -87.0 (d, J = 24.4 Hz), -88.9 (t, J = 24.4 Hz).

HRMS: (EI, 70 eV) Calculated ($C_{18}H_{14}F_2O_3$) 316.0911 (M^+) Found 316.0911

methyl 2-(2,2-difluorovinyl)-4-(thiophen-3-yl)benzoate (1t)

Prepared according to **Method I** using compound **1k** (0.55 g, 2.0 mmol). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 80:20) to afford the product as a pale yellow solid (0.40 g, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 8.2 Hz, 1H), 7.77 (m, 1H), 7.56 (t, J = 2.0 Hz, 1H), 7.52 (dd, J = 8.2, 1.8 Hz, 1H), 7.42-7.40 (m, 2H), 6.36 (dd, J_{H-F} = 25.8, 4.5 Hz, 1H), 3.91 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 156.4 (dd, J_{CF} = 297.5, 288.0 Hz), 140.7, 139.4, 132.2 (dd, J_{CF} = 8.1, 5.2 Hz), 131.7, 127.3 (d, J_{CF} = 8.6 Hz), 126.9-126.6 (m), 126.1, 124.8, 122.1, 80.4 (dd, J_{CF} = 32.9, 11.0 Hz), 52.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ -87.4 (d, J = 27.5 Hz), -89.2 (t, J = 24.4 Hz).

HRMS: (EI, 70 eV) Calculated ($C_{14}H_{10}F_2O_2S$) 280.0370 (M^+) Found 280.0373

methyl 2-(2,2-difluorovinyl)-4-(furan-3-yl)benzoate (1u)

Prepared according to **Method I** using compound **1k** (0.55 g, 2.0 mmol). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 80:20) to afford the product as a yellow solid (0.23 g, 44%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 8.2 Hz, 1H), 7.81 (s, 1H), 7.65 (s, 1H), 7.51 (s, 1H), 7.41 (d, J

= 8.2 Hz, 1H), 6.73 (s, 1H), 6.34 (dd, J_{H-F} = 25.8, 4.1 Hz, 1H), 3.90 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 156.4 (dd, J_{CF} = 297.5, 288.0 Hz), 144.1, 139.7, 136.4, 132.2 (dd, J_{CF} = 8.6, 5.7 Hz), 131.6, 126.7-126.5 (m), 125.3, 124.1, 108.6, 80.3 (dd, J_{CF} = 32.9, 11.0 Hz), 52.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ -87.4 (d, J = 24.4 Hz), -89.2 (s).

HRMS: (EI, 70 eV) Calculated ($C_{14}H_{10}F_2O_3$) 264.0598 (M^+) Found 264.0601

methyl 2-(1,1-difluorohex-1-en-2-yl)benzoate (1v)

Prepared according to **Method J** using methyl 2-iodobenzoate (1.2 g, 4.5 mmol). The crude mixture was purified by chromatography on silica gel (hexane only) to afford the product as a yellow solid (0.74 g, 65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 7.7 Hz, 1H), 7.50 (t, J = 7.7 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 7.25 (d, J = 7.7 Hz, 1H), 3.88 (s, 3H), 2.32 (m, 2H), 1.34-1.26 (m, 4H), 0.89-0.83 (m, 3H).

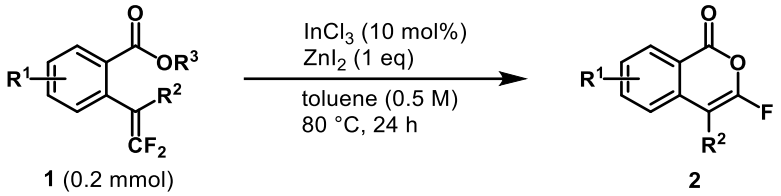
^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 152.4 (dd, J_{CF}= 286.1, 284.2 Hz), 135.2 (d, J_{CF} = 4.8 Hz), 131.8, 131.3, 130.7, 130.3, 127.7, 92.1 (dd, J_{CF} = 23.8, 16.2 Hz), 52.1, 29.6, 28.9, 22.3, 13.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ -96.9 (d, J = 48.8 Hz), -100.4 (d, J = 48.8 Hz).

HRMS: (EI, 70 eV) Calculated ($C_{14}H_{16}F_2O_2$) 254.1118 (M^+) Found 254.1119

Products

Synthesis of isocoumarins



1 (0.2 mmol) **2**

General procedure A

To an oven-dried 5.0 mL sealed vial equipped with a magnetic stirring bar was charged with $InCl_3$ (0.020 mmol), ZnI_2 (0.20 mmol), toluene (0.40 mL) and *gem*-difluoroalkene (0.20 mmol) inside glove box. After being stirred at 80 °C for 24 h, the mixture was diluted with EtOAc (5.0 mL) and water (2.0 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (5.0 mL x 3). The collected organic layer was dried over $MgSO_4$, filtered the mixture and the solution was concentrated in vacuo and purified the residue by chromatography on silica gel (Hexane/EtOAc) to afford the pure product.

General procedure B

To an oven-dried 5 mL sealed vial equipped with a magnetic stirring bar was charged with InI_3 (0.10 mmol), toluene (0.40 mL) and *gem*-difluoroalkene (0.20 mmol) inside glove box. After being stirred at 80 °C for 1 h, a small amount of Na_2CO_3 was added, and then the mixture was diluted with EtOAc (5.0 mL) and Na_2CO_3 aq (2.0 mL), the layers was separated, and the aqueous layer was extracted with EtOAc (5.0 mL x 3). The collected organic layer was dried over $MgSO_4$, filtered the mixture and the solution was concentrated in vacuo and purified the residue by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the pure product.

3-fluoro-1*H*-isochromen-1-one (2a)

*Prepared from **1a**, 2 mmol scale*

Prepared according to **General procedure A** using *gem*-difluoroalkene **1a** (0.40 g, 2.0 mmol), $InCl_3$ (44 mg, 0.20 mmol), ZnI_2 (0.64 g, 2.0 mmol), and toluene (4.0 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (0.32 g, 97%).

*Prepared from **1ab-1ae***

Prepared according to **General procedure B** using *gem*-difluoroalkene **1ab-1ae** (0.2 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 8.7 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.48-7.42 (m, 2H), 5.97 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 156.5 (d, J_{CF} = 272.8 Hz), 138.0 (d, J_{CF} = 9.0 Hz), 135.6, 130.4, 127.3 (d, J_{CF} = 1.6 Hz), 125.7 (d, J_{CF} = 7.4 Hz), 118.5 (d, J_{CF} = 3.3 Hz), 82.0 (d, J_{CF} = 22.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -87.7 (s).

HRMS: (EI, 70 eV) Calculated ($C_9H_5FO_2$) 164.0274 (M^+) Found 164.0276

3-fluoro-5-methyl-1*H*-isochromen-1-one (**2b**)

Prepared according to **General procedure A** using *gem*-difluoroalkene **1b** (42 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.4 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (25 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 7.7 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.34 (t, J = 7.7 Hz, 1H), 6.06 (s, 1H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9 (d, J_{CF} = 2.9 Hz), 156.3 (d, J_{CF} = 272.8 Hz), 136.8 (d, J_{CF} = 8.6 Hz), 136.4, 133.4 (d, J_{CF} = 7.6 Hz), 128.1, 126.8 (d, J_{CF} = 1.9 Hz), 118.5 (d, J_{CF} = 3.8 Hz), 79.1 (d, J_{CF} = 21.9 Hz), 18.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -87.1 (s).

HRMS: (EI, 70 eV) Calculated ($C_{10}H_7FO_2$) 178.0430 (M^+) Found 178.0432

3-fluoro-6-methyl-1*H*-isochromen-1-one (2c)

Prepared according to **General procedure A** using *gem*-difluoroalkene **1c** (42 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (23 mg, 65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8.2 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.21 (s, 1H), 5.90 (s, 1H), 2.47 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6 (d, J_{CF} = 1.9 Hz), 156.6 (d, J_{CF} = 272.8 Hz), 147.0, 138.2 (d, J_{CF} = 9.5 Hz), 130.3, 128.7 (d, J_{CF} = 1.9 Hz), 125.8 (d, J_{CF} = 6.7 Hz), 116.0 (d, J_{CF} = 3.8 Hz), 81.8 (d, J_{CF} = 21.9 Hz), 22.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ -87.8 (s).

HRMS: (EI, 70 eV) Calculated ($C_{10}H_7FO_2$) 178.0430 (M^+) Found 178.0433

3-fluoro-7-methyl-1*H*-isochromen-1-one (2d)

Prepared according to **General procedure A** using *gem*-difluoroalkene **1d** (42 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (25 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 5.93 (s, 1H), 2.45 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 156.0 (d, J_{CF} = 271.8 Hz), 137.5 (d, J_{CF} = 1.9 Hz), 136.9, 135.4 (d, J_{CF} = 8.6 Hz), 130.0, 125.6 (d, J_{CF} = 7.6 Hz), 118.4 (d, J_{CF} = 3.8 Hz), 81.7 (d, J_{CF} = 22.9 Hz), 21.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ -89.2 (s).

HRMS: (EI, 70 eV) Calculated ($C_{10}H_7FO_2$) 178.0430 (M^+) Found 178.0432

3-fluoro-8-methyl-1*H*-isochromen-1-one (2e)

Prepared according to **General procedure A** using *gem*-difluoroalkene **1e** (42 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (27 mg, 74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (t, J = 7.7 Hz, 1H), 7.26-7.21 (m, 2H), 5.88 (s, 1H), 2.78 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8 (d, J_{CF} = 1.9 Hz), 156.0 (d, J_{CF} = 272.8 Hz), 144.3, 139.6 (d, J_{CF} = 8.6 Hz), 134.6, 130.1 (d, J_{CF} = 1.9 Hz), 123.8 (d, J_{CF} = 7.6 Hz), 116.9 (d, J_{CF} = 3.8 Hz), 82.1 (d, J_{CF} = 21.9 Hz), 23.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ -88.4 (s).

HRMS: (EI, 70 eV) Calculated ($C_{10}H_7FO_2$) 178.0430 (M^+) Found 178.0430

3,6-difluoro-1*H*-isochromen-1-one (2f)

Prepared according to **General procedure A** using *gem*-difluoroalkene **1f** (43 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (24 mg, 66%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 8.8 Hz, d, J_{H-F} = 5.7 Hz, 1H), 7.19-7.07 (m, 2H), 5.96 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2 (d, J_{CF} = 257.5 Hz), 158.5 (d, J_{CF} = 1.9 Hz), 157.2 (d, J_{CF} = 274.7 Hz), 140.9 (t, J_{CF} = 11.0 Hz), 133.6 (d, J_{CF} = 10.5 Hz), 115.7 (dd, J_{CF} = 23.4, 2.4 Hz), 114.9 (t, J_{CF} = 2.9 Hz), 111.7 (dd, J_{CF} = 22.9, 7.6 Hz), 81.8 (dd, J_{CF} = 23.8, 2.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -85.8 (s), -105.5 (s).

HRMS: (EI, 70 eV) Calculated ($C_9H_4F_2O_2$) 182.0179 (M^+) Found 182.0177

3,7-difluoro-1*H*-isochromen-1-one (2g)

Prepared according to **General procedure A** using *gem*-difluoroalkene **1g** (43 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by

chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (20 mg, 55%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 2.0 Hz, d, J_{H-F} =8.4 Hz, 1H), 7.48-7.44 (m, 2H), 5.99 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2 (dd, J_{CF} = 248.9, 2.9 Hz), 158.7-158.6 (m), 156.2 (dd, J_{CF} = 272.8, 2.9 Hz), 134.3 (dd, J_{CF} = 9.1, 2.4 Hz), 127.8 (t, J_{CF} = 7.6 Hz), 124.1 (d, J_{CF} = 23.8 Hz), 120.0 (dd, J_{CF} = 8.6, 3.8 Hz), 115.8 (d, J_{CF} = 23.8 Hz), 81.5 (d, J_{CF} = 22.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -89.2 (s), -117.3 (s).

HRMS: (EI, 70 eV) Calculated ($C_9H_4F_2O_2$) 182.0179 (M^+) Found 182.0179

3,6,7-trifluoro-1*H*-isochromen-1-one (2h)

Prepared according to **General procedure A** using *gem*-difluoroalkene **1h** (47 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (24 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09-8.05 (m, 1H), 7.30-7.23 (m, 1H), 6.21 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 156.63 (d, J_{CF} = 184.1 Hz), 154.4 (dd, J_{CF} = 259.4, 10.5 Hz), 144.9 (ddd, J_{CF} = 253.2, 7.3, 3.7 Hz), 129.6-129.4 (m), 127.5 (dd, J_{CF} = 8.6, 4.8 Hz), 116.4 (dd, J_{CF} = 19.6, 2.4 Hz), 115.4-115.2 (m), 75.6 (dt, J_{CF} = 25.7, 4.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -83.6 (s), -130.8 (s), -150.5 (s).

HRMS: (EI, 70 eV) Calculated ($C_9H_3F_3O_2$) 200.0085 (M^+) Found 200.0081

8-chloro-3-fluoro-1*H*-isochromen-1-one (2i)

Prepared according to **General procedure A** using *gem*-difluoroalkene **1i** (47 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (27 mg, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (t, J = 7.7 Hz, 1H), 7.47 (d, J = 7.7 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 5.94 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4 (d, J_{CF} = 274.7 Hz), 156.0 (d, J_{CF} = 2.9 Hz), 141.2 (d, J_{CF} = 9.5 Hz), 137.9, 135.2, 130.1 (d, J_{CF} = 1.9 Hz), 124.6 (d, J_{CF} = 6.7 Hz), 115.7 (d, J_{CF} = 4.8 Hz), 82.0 (d, J_{CF} = 21.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -86.1 (s).

HRMS: (EI, 70 eV) Calculated ($C_9H_4ClFO_2$) 197.9884 (M^+) Found 197.9881

6-chloro-3-fluoro-1*H*-isochromen-1-one (2j)

Prepared according to **General procedure A** using *gem*-difluoroalkene **1j** (47 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (32 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 8.2 Hz, 1H), 7.44-7.38 (m, 2H), 5.92 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 157.1 (d, J_{CF} = 274.7 Hz), 142.5, 139.4 (d, J_{CF} = 9.5 Hz), 131.8, 127.9 (d, J_{CF} = 1.9 Hz), 125.3 (d, J_{CF} = 7.6 Hz), 116.8 (d, J_{CF} = 4.8 Hz), 81.4 (d, J_{CF} = 23.8 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -85.6 (s).

HRMS: (EI, 70 eV) Calculated ($C_9H_4ClFO_2$) 197.9884 (M^+) Found 197.9886

6-bromo-3-fluoro-1*H*-isochromen-1-one (2k)

Prepared according to **General procedure A** using *gem*-difluoroalkene **1k** (55 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (36 mg, 74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 8.5 Hz, 1H), 7.60 (s, 1H), 7.57 (d, J = 8.5 Hz, 1H), 5.91 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 157.1 (d, J_{CF} = 275.3 Hz), 139.5 (d, J_{CF} = 9.8 Hz), 131.8, 131.3, 130.7 (d, J_{CF} = 1.6 Hz), 128.4 (d, J_{CF} = 7.4 Hz), 117.2 (d, J_{CF} = 4.1 Hz), 81.3 (d, J_{CF} = 23.8 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -85.3 (s).

HRMS: (EI, 70 eV) Calculated ($C_9H_4BrFO_2$) 241.9379 (M^+) Found 241.9378

3-fluoro-1-oxo-1*H*-isochromene-6-carbonitrile (2l)

Prepared according to **General procedure A** using *gem*-difluoroalkene **1l** (45 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (22 mg, 58%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, J = 8.2 Hz, 1H), 7.77 (s, 1H), 7.70 (d, J = 8.2 Hz, 1H), 6.05 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 157.0 (d, J_{CF} = 204.1 Hz), 138.4 (d, J_{CF} = 10.5 Hz), 131.3, 129.7-129.5 (m), 121.3 (d, J_{CF} = 3.8 Hz), 119.1, 117.1, 81.4 (d, J_{CF} = 22.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -84.0 (s).

HRMS: (EI, 70 eV) Calculated ($C_{10}H_4FNO_2$) 189.0226 (M^+) Found 189.0221

3-fluoro-7-methoxy-1*H*-isochromen-1-one (2m)

Prepared according to **General procedure A** using *gem*-difluoroalkene **1m** (46 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (36 mg, 93%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 2.7 Hz, 1H), 7.38-7.29 (m, 2H), 5.94 (s, 1H), 3.90 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7 (d, J_{CF} = 1.9 Hz), 158.8 (d, J_{CF} = 1.9 Hz), 155.4 (d, J_{CF} = 271.8 Hz), 131.4 (d, J_{CF} = 8.6 Hz), 127.0 (d, J_{CF} = 7.6 Hz), 125.4, 119.5 (d, J_{CF} = 4.8 Hz), 110.6, 81.6 (d, J_{CF} = 22.9 Hz), 55.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -91.3 (s).

HRMS: (EI, 70 eV) Calculated ($C_{10}H_7FO_3$) 194.0379 (M^+) Found 194.0377

3-fluoro-6,7-dimethoxy-1*H*-isochromen-1-one (2n)

Prepared according to **General procedure A** using *gem*-difluoroalkene **1n** (52 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (32 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (s, 1H), 6.79 (s, 1H), 5.90 (s, 1H), 4.01 (s, 3H), 3.97 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3 (d, J_{CF} = 1.9 Hz), 156.0 (d, J_{CF} = 271.8 Hz), 154.6, 148.9 (d, J_{CF} = 1.9 Hz), 133.9 (d, J_{CF} = 8.6 Hz), 111.0 (d, J_{CF} = 3.8 Hz), 109.8, 106.3 (d, J_{CF} = 6.7 Hz), 81.7 (d, J_{CF} = 22.9 Hz), 56.3, 56.2.
^{19}F NMR (376 MHz, $CDCl_3$): δ -89.2 (s).
HRMS: (EI, 70 eV) Calculated ($C_{11}H_9FO_4$) 224.0485 (M^+) Found 224.0483

3-fluoro-6-phenoxy-1*H*-isochromen-1-one (2o)
Prepared according to **General procedure A** using *gem*-difluoroalkene **1o** (58 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (38 mg, 74%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 9.1 Hz, 1H), 7.47-7.40 (m, 2H), 7.30-7.23 (m, 1H), 7.11 (m, 2H), 7.02 (m, 1H), 6.80 (s, 1H), 5.82 (s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 159.0, 156.9 (d, J_{CF} = 272.8 Hz), 154.4, 140.5 (d, J_{CF} = 10.5 Hz), 132.8, 130.3, 125.4, 120.7, 117.2 (d, J_{CF} = 1.9 Hz), 112.6 (d, J_{CF} = 3.8 Hz), 111.8 (d, J_{CF} = 7.6 Hz), 81.9 (d, J_{CF} = 22.9 Hz).
^{19}F NMR (376 MHz, $CDCl_3$): δ -86.7 (s).
HRMS: (EI, 70 eV) Calculated ($C_{15}H_9FO_3$) 256.0536 (M^+) Found 256.0535

3-fluoro-6-phenyl-1*H*-isochromen-1-one (2p)
Prepared according to **General procedure A** using *gem*-difluoroalkene **1p** (55 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (47 mg, 97%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 8.2 Hz, 1H), 7.67-7.61 (m, 3H), 7.59 (s, 1H), 7.53-7.42 (m, 3H), 6.00 (s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5 (d, J_{CF} = 1.9 Hz), 156.7 (d, J_{CF} = 272.8 Hz), 148.5, 139.0, 138.5 (d, J_{CF} = 9.5 Hz), 130.9, 129.1, 128.9, 127.4, 126.4 (d, J_{CF} = 1.9 Hz), 123.8 (d, J_{CF} = 7.6 Hz), 117.1 (d, J_{CF} = 3.8 Hz), 82.1 (d, J_{CF} = 22.9 Hz).
^{19}F NMR (376 MHz, $CDCl_3$): δ -87.3 (s).
HRMS: (EI, 70 eV) Calculated ($C_{15}H_9FO_2$) 240.0587 (M^+) Found 240.0589

3-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-isochromen-1-one (2q)
Prepared according to **General procedure A** using *gem*-difluoroalkene **1q** (65 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (43 mg, 74%).
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, J = 7.7 Hz, 1H), 7.87-7.82 (m, 2H), 5.96 (s, 1H), 1.38 (s, 12H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7 (d, J_{CF} = 1.9 Hz), 156.3 (d, J_{CF} = 272.8 Hz), 136.9 (d, J_{CF} = 9.5 Hz), 132.8 (d, J_{CF} = 1.9 Hz), 132.3 (d, J_{CF} = 7.6 Hz), 129.1, 120.2 (d, J_{CF} = 3.8 Hz), 84.6, 81.9 (d, J_{CF} = 21.0

Hz), 24.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ -88.0 (s).

HRMS: (EI, 70 eV) Calculated ($C_{15}H_{16}FO_4B$) 290.1126 (M^+) Found 290.1124

3-fluoro-6-vinyl-1*H*-isochromen-1-one (2r)

Prepared according to **General procedure A** using *gem*-difluoroalkene **1r** (45 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (21 mg, 56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 8.2 Hz, 1H), 7.51 (d, J = 8.2 Hz, 1H), 7.37 (s, 1H), 6.78 (dd, J = 17.6, 10.9 Hz, 1H), 5.97 (d, J = 17.6 Hz, 1H), 5.95 (s, 1H), 5.52 (d, J = 10.9 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 156.7 (d, J_{CF} = 273.7 Hz), 144.6, 138.5 (d, J_{CF} = 9.5 Hz), 135.3, 130.7, 124.9 (d, J_{CF} = 1.9 Hz), 123.3 (d, J_{CF} = 7.6 Hz), 118.8, 117.5 (d, J_{CF} = 3.8 Hz), 81.9 (d, J_{CF} = 22.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -87.5 (s).

HRMS: (EI, 70 eV) Calculated ($C_{11}H_7FO_2$) 190.0430 (M^+) Found 190.0428

6-(4-acetylphenyl)-3-fluoro-1*H*-isochromen-1-one (2s)

Prepared according to **General procedure A** using *gem*-difluoroalkene **1s** (63 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (32 mg, 57%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, J = 8.2 Hz, 1H), 8.09 (d, J = 8.2 Hz, 2H), 7.75 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.2 Hz, 1H), 7.64 (s, 1H), 6.04 (s, 1H), 2.67 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 159.2 (d, J_{CF} = 1.9 Hz), 156.8 (d, J_{CF} = 273.7 Hz), 147.0, 143.3, 138.5 (d, J_{CF} = 9.5 Hz), 137.0, 131.0, 129.0, 127.6, 126.3 (d, J_{CF} = 2.9 Hz), 124.1 (d, J_{CF} = 7.6 Hz), 117.8 (d, J_{CF} = 3.8 Hz), 82.0 (d, J_{CF} = 21.9 Hz), 26.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -88.1 (s).

HRMS: (EI, 70 eV) Calculated ($C_{17}H_{11}FO_3$) 282.0692 (M^+) Found 282.0692

3-fluoro-6-(thiophen-3-yl)-1*H*-isochromen-1-one (2t)

Prepared according to **General procedure A** using *gem*-difluoroalkene **1t** (56 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (36 mg, 74%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15 (dd, J = 2.7, 1.4 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 1.8 Hz, 1H), 7.87 (dd, J = 8.2, 1.8 Hz, 1H), 7.72 (dd, J = 5.0, 2.7 Hz, 1H), 7.65 (dd, J = 5.0, 1.4 Hz, 1H), 6.42 (s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 158.9 (d, J_{CF} = 1.9 Hz), 156.0 (d, J_{CF} = 269.3 Hz), 141.8, 139.6, 138.7 (d, J_{CF} = 9.6 Hz), 130.3, 128.0, 126.2, 125.4 (d, J_{CF} = 1.9 Hz), 124.6, 123.0 (d, J_{CF} = 7.7 Hz), 116.4 (d, J_{CF} = 3.8 Hz), 82.2 (d, J_{CF} = 22.0 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -86.9 (s).

HRMS: (EI, 70 eV) Calculated ($C_{13}H_7FO_2S$) 246.0151 (M^+) Found 246.0155

3-fluoro-6-(furan-3-yl)-1*H*-isochromen-1-one (2u)

Prepared according to **General procedure A** using *gem*-difluoroalkene **1u** (53 mg, 0.20 mmol), $InCl_3$ (4.4 mg, 0.020 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (45 mg, 97%).

^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.21 (d, *J* = 8.2 Hz, 1H), 7.89 (s, 1H), 7.57-7.52 (m, 2H), 7.48 (s, 1H), 6.77 (s, 1H), 5.96 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.3 (d, J_{CF} = 1.9 Hz), 156.8 (d, J_{CF} = 272.8 Hz), 144.5, 140.4, 139.9, 138.7 (d, J_{CF} = 9.5 Hz), 130.9, 125.0, 124.8 (d, J_{CF} = 1.9 Hz), 122.0 (d, J_{CF} = 7.6 Hz), 116.7 (d, J_{CF} = 2.9 Hz), 108.4, 81.9 (d, J_{CF} = 22.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -87.3 (s).

HRMS: (EI, 70 eV) Calculated ($C_{13}H_7FO_3$) 230.0379 (M^+) Found 230.0379

4-butyl-3-fluoro-1*H*-isochromen-1-one (2v)

Prepared according to **General procedure A** using *gem*-difluoroalkene **1v** (51 mg, 0.20 mmol), $InCl_3$ (8.8 mg, 0.040 mmol), ZnI_2 (64 mg, 0.20 mmol), and toluene (0.40 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (35 mg, 80%).

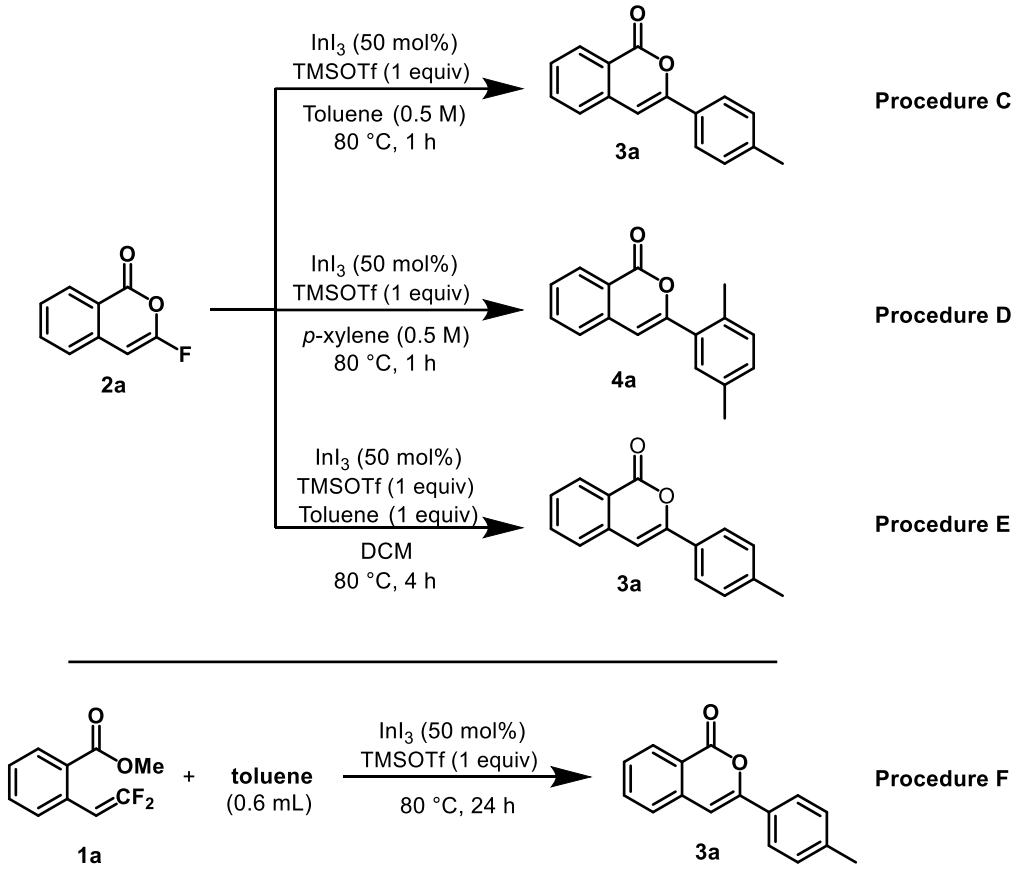
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.29 (d, *J* = 7.5 Hz, 1H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 2.64-2.60 (m, 2H), 1.61-1.54 (m, 2H), 1.48-1.37 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.6 (d, J_{CF} = 1.9 Hz), 153.2 (d, J_{CF} = 268.9 Hz), 138.7 (d, J_{CF} = 6.7 Hz), 135.4, 130.7, 126.7 (d, J_{CF} = 1.9 Hz), 122.9 (d, J_{CF} = 8.6 Hz), 119.3 (d, J_{CF} = 2.9 Hz), 92.3 (d, J_{CF} = 19.1 Hz), 30.7, 22.3, 22.2, 13.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ -94.3 (s).

HRMS: (EI, 70 eV) Calculated ($C_{13}H_{13}FO_2$) 220.0900 (M^+) Found 220.0898

Friedel-Crafts type alkenylation and domino reaction



Procedure C

To an oven-dried 5 mL sealed vial equipped with a magnetic stirring bar was charged with InI_3 (0.10 mmol), toluene (0.40 mL), 3-fluoro-1*H*-isochromen-1-one **2a** (33 mg, 0.20 mmol), and TMSOTf (36 μL, 0.20 mmol) inside glovebox. After being stirred at 80 °C, 1 h, the mixture was diluted with $CHCl_3$ (5.0 mL) and water (2.0 mL), the layers was separated, and the aqueous layer was extracted with $CHCl_3$ (5.0 mL x 3). The collected organic layer was dried over $MgSO_4$, filtered the mixture and the solution was concentrated in vacuo and purified the residue by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the target product **3a** as a white solid (34 mg, 71%). The NMR date was agreement with the literature[27]. The ^1H and ^{13}C NMR spectra are shown below.

Procedure D

To an oven-dried 5 mL sealed vial equipped with a magnetic stirring bar was charged with InI_3 (0.10 mmol), *m*-xylene (0.40 mL), 3-fluoro-1*H*-isochromen-1-one **2a** (33 mg, 0.20 mmol) and TMSOTf (36 μL, 0.20 mmol) inside glovebox. After being stirred at 80 °C, 1 h, the mixture was diluted with $CHCl_3$ (5.0 mL) and water (2.0 mL), the layers was separated, and the aqueous layer was extracted with $CHCl_3$ (5.0 mL x 3). The collected organic layer was dried over $MgSO_4$, filtered the mixture and the solution was concentrated in vacuo and purified the residue by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the target product **4a** as a white solid (31 mg, 61%)

^1H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, J = 7.8 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.52-7.41 (m, 3H), 7.11-

7.05 (m, 2H), 6.58 (s, 1H), 2.47 (s, 3H), 2.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7, 155.7, 139.8, 137.6, 136.5, 134.7, 131.8, 129.9, 129.5, 129.1, 128.0, 126.7, 125.7, 120.2, 105.6, 21.2, 20.7.

HRMS: (EI, 70 eV) Calculated ($C_{17}H_{14}O_2$) 250.0994 (M^+) Found 250.0990

Procedure E

To an oven-dried 5 mL sealed vial equipped with a magnetic stirring bar was charged with InI_3 (0.10 mmol), toluene (21 μL, 0.20 mmol), TMSOTf (36 μL, 0.20 mmol), 3-fluoro-1*H*-isochromen-1-one **2a** and DCM (0.4 mL) inside glovebox. After being stirring at 80 °C, 4 h, the mixture was diluted with $CHCl_3$ (5.0 mL) and water (2.0 mL), the layers was separated, and the aqueous layer was extracted with $CHCl_3$ (5.0 mL x 3). The collected organic layer was dried over $MgSO_4$, filtered the mixture and the solution was concentrated in vacuo and purified the residue by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the target product **3a** as a white solid (23 mg, 49%) The NMR date was agreement with the literature[27]. The ^{1}H and ^{13}C NMR spectra are shown below.

Procedure F

To an oven-dried 5 mL sealed vial equipped with a magnetic stirring bar was charged with InI_3 (0.10 mmol), toluene (0.40 mL), TMSOTf (36 μL, 0.20 mmol), methyl 2-(2,2-difluorovinyl)benzoate **1a** and DCM (0.40 mL) inside glovebox. After being stirring at 80 °C, 4 h, the mixture was diluted with $CHCl_3$ (5.0 mL) and water (2.0 mL), the layers was separated, and the aqueous layer was extracted with $CHCl_3$ (5.0 mL x 3). The collected organic layer was dried over $MgSO_4$, filtered the mixture and the solution was concentrated in vacuo and purified the residue by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the target product **3a** as a white solid (21 mg, 45%) The NMR date was agreement with the literature[27]. The ^{1}H and ^{13}C NMR spectra are shown below.

X-ray Structure Data

See CIF files

3-fluoro-1*H*-isochromen-1-one (2a) (CCDC 2051246)

Reaction Optimization

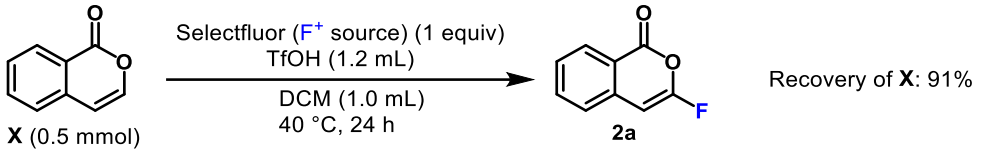
To an oven-dried 5 mL sealed vial equipped with a magnetic stirring bar was charged with catalyst, Additive, solvent (0.40 mL) and *gem*-difluoroalkene **1a** (0.20 mmol) inside glovebox. After being stirred at 80 °C for 24 h, the mixture was diluted with EtOAc (5.0 mL) and water (2.0 mL), the layers was separated, and the aqueous layer was extracted with EtOAc (5.0 mL x 3). The collected organic layer was dried over $MgSO_4$, filtered the mixture and the solution was concentrated in vacuo. The crude mixture was measured by ^{1}H NMR using CH_2Br_2 as an internal standard.

Entry	Catalyst (x mol%)	Additive	Solvent	Temp	Time	NMR Yield of 1a /%[a]	Conv. /%
1	$InCl_3$ (50)	-	Toluene	RT	20 h	6	7
2	$InBr_3$ (50)	-	Toluene	RT	18 h	73	81
3	InI_3 (50)	-	Toluene	RT	20 h	70	70
4	$In(OTf)_3$ (50)	-	Toluene	RT	20 h	0	0
5	InF_3 (50)	-	Toluene	RT	24 h	0	12
6	ClBcat (50)	-	Toluene	RT	20 h	0	4
7	GaI_3 (50)	-	Toluene	RT	20 h	52	73
8	$AlCl_3$ (50)	-	Toluene	RT	15 h	0	0
9	$AlBr_3$ (50)	-	Toluene	RT	15 h	0	0
10	AlI_3 (50)	-	Toluene	RT	24 h	0	47
11	InI_3 (50)	-	DCE	RT	24 h	43	47
12	InI_3 (50)	-	Dioxane	RT	24 h	0	0
13	InI_3 (50)	-	THF	RT	24 h	36	40
14	InI_3 (50)	-	Hexane	RT	24 h	48	50
15	InI_3 (50)	-	DCM	RT	24 h	49	49
16	InI_3 (50)	-	PhCl	RT	24 h	57	57
17	$InCl_3$ (50)	-	Toluene	80 °C	18 h	58	100
18	$InBr_3$ (50)	-	Toluene	80 °C	24 h	71	100
19	InI_3 (50)	-	Toluene	80 °C	18 h	>97	100
20	$GaBr_3$ (50)	-	Toluene	80 °C	18 h	15	74
21	GaI_3 (50)	-	Toluene	80 °C	18 h	33	80
22	$BiCl_3$ (50)	-	Toluene	80 °C	18 h	18	18
23	$BiBr_3$ (50)	-	Toluene	80 °C	18 h	33	37
24	$ZnBr_2$ (50)	-	Toluene	80 °C	18 h	4	4
25	ZnI_2 (50)	-	Toluene	80 °C	18 h	6	6
26	$AlCl_3$ (50)	-	Toluene	80 °C	18 h	0	44
27	$AlBr_3$ (50)	-	Toluene	80 °C	18 h	0	57
28	AlI_3 (50)	-	Toluene	80 °C	18 h	0	90
29	$PdCl_2$ (50)	-	Toluene	80 °C	24 h	0	0
30	$Pd(OAc)_2$ (50)	-	Toluene	80 °C	24 h	0	100
31	$CuBr_2$ (50)	-	Toluene	80 °C	24 h	0	2
32	AgOTf (50)	-	Toluene	80 °C	24 h	0	2
33	$AgSbF_6$ (50)	-	Toluene	80 °C	24 h	29	41

34	AuCl (50) + AgOTf (50)	-	Toluene	80 °C	24 h	2	70
35	AuCl (50)	-	Toluene	80 °C	24 h	15	53
36	$AuCl_3$ (50)	-	Toluene	80 °C	24 h	33	84
37	$FeBr_3$ (50)	-	Toluene	80 °C	24 h	0	74
38	InI_3 (10)	-	Toluene	80 °C	24 h	23	39
39	InI_3 (10)	TMSBr	Toluene	80 °C	24 h	5	86
40	InI_3 (10)	LiI	Toluene	80 °C	24 h	0	0
41	InI_3 (20)	TMSOTf	Toluene	80 °C	24 h	0	100
42	InI_3 (20)	TMSOTf	Toluene	RT	24 h	3	92
43	InI_3 (20)	TMSI	Toluene	RT	24 h	40	86
44	InI_3 (20)	$BF_3{\cdot}OEt_2$	Toluene	80 °C	24 h	58	62
45	InI_3 (10)	Bu_4NI	Toluene	80 °C	24 h	0	0
46	InI_3 (10)	CaI_2	Toluene	80 °C	24 h	0	16
47	InI_3 (10)	$ZnCl_2$	Toluene	80 °C	24 h	39	39
48	InI_3 (10)	$ZnBr_2$	Toluene	80 °C	24 h	82	82
49	InI_3 (10)	ZnI_2	Toluene	80 °C	24 h	72	100
50	InI_3 (10)	ZnI_2	Toluene	80 °C	6h	66	66
51	$InCl_3$ (10)	ZnI_2	Toluene	80 °C	24 h	>97	100
52	$InCl_3$ (10)	ZnI_2 (0.5 eq)	Toluene	80 °C	24 h	>97	100
53	InF_3 (10)	ZnI_2	Toluene	80 °C	24 h	39	43
54	InF_3 (10)	$ZnBr_2$	Toluene	80 °C	24 h	72	72
55	InF_3 (10)	$ZnCl_2$	Toluene	80 °C	24 h	33	33
56	InF_3 (10)	$BiCl_3$	Toluene	80 °C	24 h	23	100
57	InF_3 (10)	$BiBr_3$	Toluene	80 °C	24 h	45	55
58	InF_3 (10)	ClBcat	Toluene	80 °C	24 h	0	0
59	$AlCl_3$	ZnI_2	Toluene	80 °C	24 h	5	19
60	$AlBr_3$	ZnI_2	Toluene	80 °C	24 h	15	20
61	$GaCl_3$	ZnI_2	Toluene	80 °C	24 h	9	33
62	$GaBr_3$	ZnI_2	Toluene	80 °C	24 h	7	34
63	$BiCl_3$	ZnI_2	Toluene	80 °C	24 h	15	25
64	$BiBr_3$	ZnI_2	Toluene	80 °C	24 h	21	22
65	$InCl_3$ (5)	ZnI_2	Toluene	80 °C	24 h	95	97
66	$InCl_3$ (1)	ZnI_2	Toluene	80 °C	72 h	75	90

[a]NMR yields were calibrated using CH_2Br_2 as an internal standard.

Investigation of fluorination of isocoumarin



When starting material **X** (73 mg, 0.50 mmol) was reacted with Selectfluor (0.18 g, 1.0 equiv) as a fluorine cation source and TfOH (1.2 mL) in DCM (0.50 mL) at 40 °C for 24 hours in sealed tube, the fluorinated isocoumarin (**2a**) was not observed. This reaction condition is referenced by the reaction system of electrophilic fluorination of aromatics[28].

Mechanistic studies

Oxymetalation v.s. Addition-Elimination path

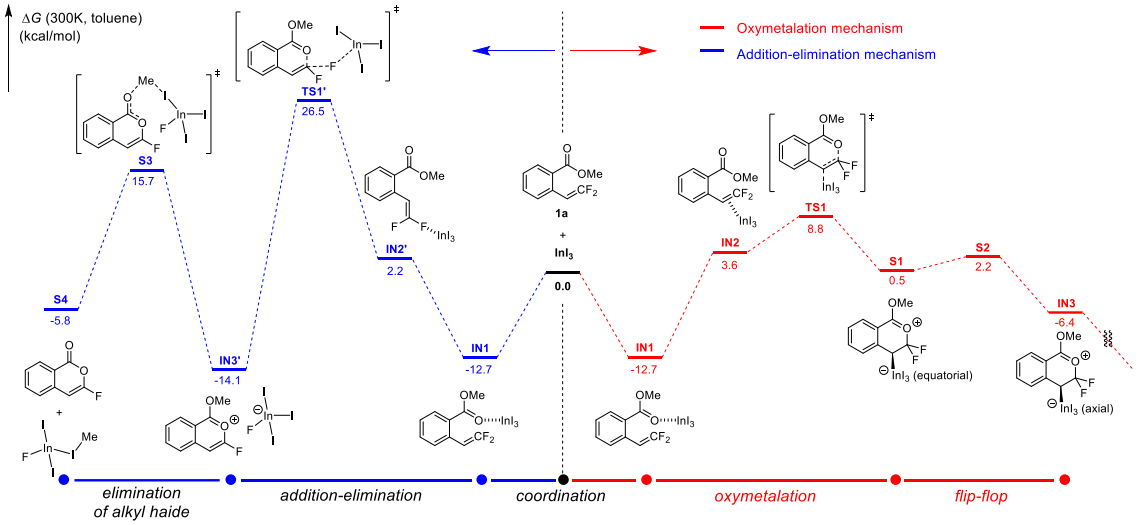


Figure S1. Mechanism for the annulation through oxymetalation pathway or addition-elimination pathway

In the addition-elimination mechanism (left side, blue), cyclization and elimination of fluoride proceed in a concerted mechanism (**IN1-IN2'-TS1'-IN3'**), and then elimination of alkyl halide from **IN3'** gives complex **S4** via transition state **S3**. In the oxymetalation mechanism (right side, red), oxymetalation proceeds via **TS1** to give a zwitterionic intermediate **S1.** The intermediate **S1** undergoes a ring flip to give a more stable intermediate **IN3**. The addition-elimination scenario can be ruled out by comparing the activation energies of oxymetalation path and addition-elimination path.

Feasibility of intramolecular elimination of MeI

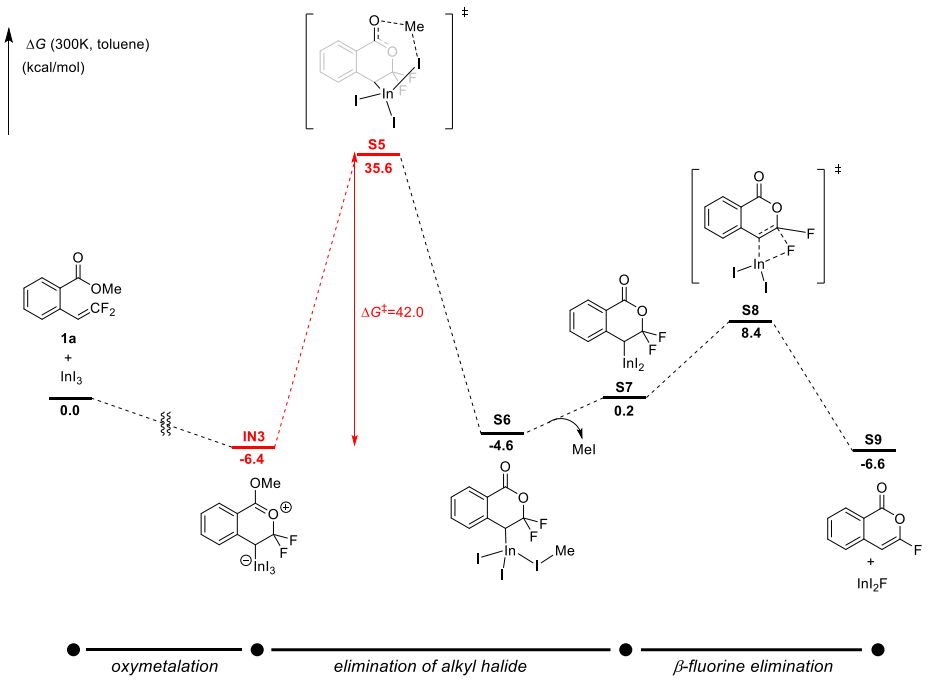


Figure S8-2. The energy profile of the reaction via intramolecular elimination of MeI (oxymetalation → elimination of alkyl halide →*β*-fluorine elimination)

In this pathway, oxyindation proceeds in a concerted mechanism, and then elimination of MeI from **IN3** gives complex **S6** via transition state **S5** in S_N2-like fashion. The elimination of MeI in the intramolecular fashion proceeds via **TS S5** ($\Delta G^{\ddagger}$=42.0 kcal/mol), which has a higher activation barrier than that of the reaction pathway via intermolecular elimination of alkyl halide ($\Delta G^{\ddagger}$=22.0 kcal/mol). So, the intermolecular version is facile pathway.

^{1}H NMR spectra to observe alkyl halide

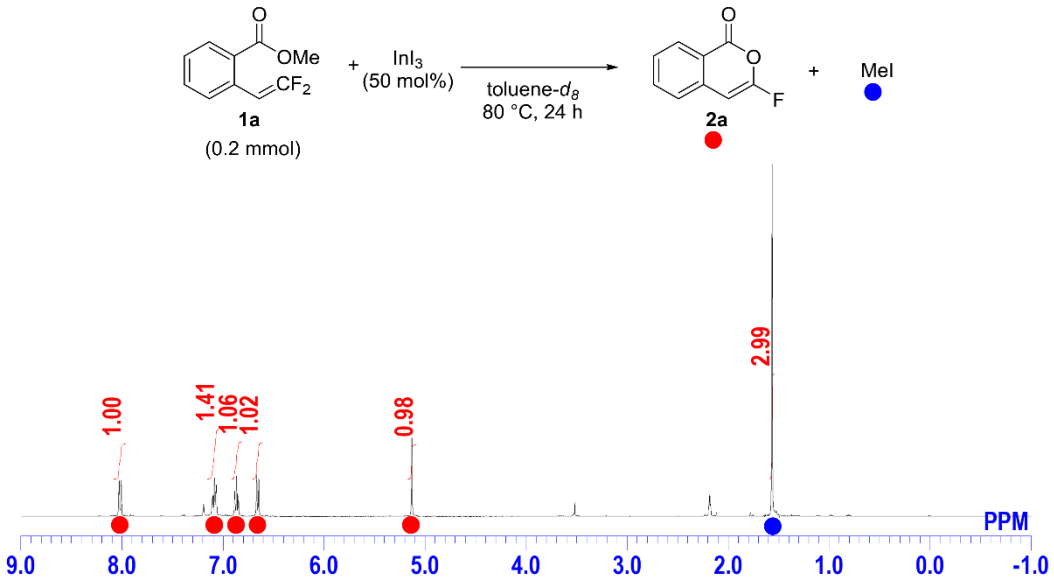
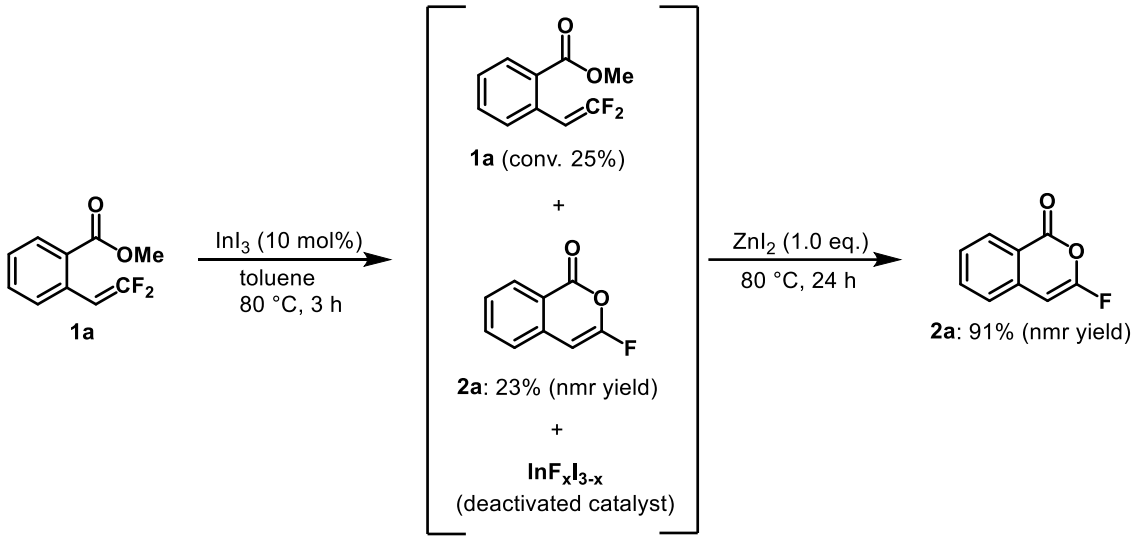


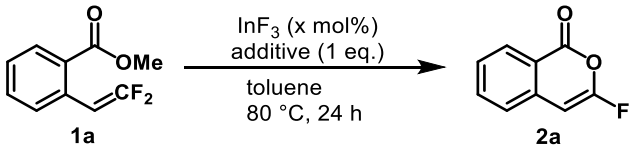
Figure S8-3. Observation of methyl iodide by ^{1}H NMR in toluene-d_8

We monitored the reaction mixture after completing reaction using toluene-d_8 and then only MeI was detected. The amount of target product **2a** and MeI are same, while MeF was not detected.

Investigation for evidence of halide exchange



The difluoro alkene **1a** was reacted with InI_3 (10 mol%) at 80 °C for 3 h. After stirring, a small of fluorinated isocoumarin **2a** and 75% of **1a** were observed by ^{1}H NMR. At this point, a fluorinated indium salt (InF_xI_{3-x}) would be generated. After that, ZnI_2 was added to the reaction mixture, and then the reaction mixture was stirred at 80 °C for 24 h to give the target compound **2a** was observed in a high yield. The result suggested that the halogen exchange between fluorinated indium salt (InF_xI_{3-x}) and ZnI_2 would occur.



entry	InF_3 (x mol%)	Additive	Yield of **2a** /%	Conv.
1	InF_3 (10 mol%)	ZnI_2	39	45
2	InF_3 (10 mol%)	-	0	10
3	-	ZnI_2 (50 mol%)	6	6
4	InF_3 (50 mol%)	-	0	12

To prove whether the halogen exchange between fluorinated indium salt and ZnI_2 occur, the investigation using InF_3 were conducted. Althrough the reactions using only InF_3 or ZnI_2 did not proceed (entries 2-4), the fluorinated isocoumarin was obtained in the presence of both InF_3 and ZnI_2. These results indicate that the halogen exchange between InF_3 and ZnI_2 occur to give iodinated indium salts (InF_xI_{3-n}) and this salt would act as active catalytic species.

2-5. Reference

[1] P. Kirsch, *Modern Fluorroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, **2004**.

[2] a) I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chichester, **2009**. b) W. K. Hagmann, *J. Med. Chem*. **2008**, *51*, 4359-4369. c) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev*. **2008**, *37*, 320-330. d) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881-1886. e) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed*. **2013**, *52*, 8214-8264; *Angew. Chem*. **2013**, *125*, 8372-8423. f) D. O'Hagan, H. Deng, *Chem. Rev*. **2015**, *115*, 634-649.

[3] For examples of synthesis of fluorinated heterocycles, see: a) A. W. McCarter, M. Sommer, J. M. Percy, C. Jamieson, A. R. Kennedy, D. J. Hirst, *J. Org. Chem*. **2018**, *83*, 8888-8905. b) X. Yuan, J. -F. Yao, Z. -Y. Tang, *Org. Lett*. **2017**, *19*, 1410-1413. c) J. -Q. Qu, S. -S. Zhang, H. Gao, Z. Qi, C. -J. Zhou, W. -W. Ji, Y. Liu, Y. Chen, Q. Li, X. Li, H. Wang, *J. Am. Chem. Soc*. **2017**, *139*, 3537-3545. d) T. Fujimoto, T. Ritter, *Org. Lett*. **2015**, *17*, 544-547.

[4] For selected reviews, see: a) S. Pal, V. Chatare, M. Pal, *Curr. Org. Chem*. **2011**, *15*, 782-800. b) P. Saikia, S. Gogoi, *Adv. Synth. Catal*. **2018**, *360*, 2063-2075. c) G. Kuang, G. Liu, X. Zhang, N. Lu, Y. Peng, Q. Xiao, Y. Zhou, *Synthesis*, **2020**, *52*, 993-1006.

[5] a) Y. V. Zonov, V. M. Karpov, V. E. Platonov, *J. Fluor. Chem*. **2014**, *162*, 71-77. b) Y. V. Zonov, T. V. Mezhenkova, V. M. Karpov, V. E. Platonov, *Russ. J. Org. Chem*. **2008**, *44*, 1652-1656. c) Ya. V. Zonov, V. M. Karpov, T. V. Mezhenkova, *Russ. J. Org. Chem*. **2019**, *55*, 1103-1111. d) H. Gao, S. Lin, S. Zhang, W. Chem, X. Liu, G. Yang, R. A. Lerner, H. Xu, Z. Zhou, W. Yi, *Angew. Chem. Int. Ed.* **2021**, *60*, 1959-1966; *Angew. Chem*. **2021**, *133*, 1987-1994.

[6] a) G. Cerichelli, M E. Crestoni, S. Fornarini, *Gazz. Chim. Ital.* **1990**, *120*, 749-755. b) E. Dvornikova, M. Bechcicka, K. Kamien´ska-Trela, A. Kro o´wczyn´ski, *J. Fluor. Chem*, **2003**, *124*, 159-168.

[7] a) T. Rueckle, X. Jiang, P. Gaillard, D. Church, T. Vallotton, US Pat. Appl. US20060122176 A1, 2006. b) A.D. Borthwick, R.J. Hately, D.M.B. Hickey, J. Liddle, D.G.H. Livermore, A.M. Mason, N.D. Miller, F. Nerozzi, S.L. Sollis, A.K. Szardengings, P.G. Wyatt, US Pat. Appl. US20050148572 A1, 2005

[8] S. Martínez-Monteroa, S. Fernándeza, Y. S. Sanghvic, E. A. Theodorakisb, M. A. Detoriod, T. R. Mcbrayere, T. Whitakere, R. F. Schinazid, V. Gotor and M. Ferrero, *Bioorg. Med. Chem.* **2012**, *20*, 6885–6893.

[9] a) M. Badland, D. Compere, K. Courte, A. -C. Dublanchet, S. Blais, A. Manage, G. Peron, R. Wrigglesworth, *Bioorg. Med. Chem. Lett.* **2011**, 21, 528–530. b) D. Heeran, G. Sandford, *Tetrahedron* **2016**, *72*, 2456-2463., c) M. Wang, X. Liu, L. Zhou, J. Zhu, X. Sun, *Org. Biomol. Chem*. **2015**, *13*, 3190-3193.

[10] T. Shamma, H. Buchholz, G. K. S. Prakash, G. A. Olah, *Isr. J. Chem*. **1999**, *39*, 207-210.

[11] a) X. Zhang, S. Cao, *Tetrahedron Lett.* **2017**, *58*, 375-392. b) S. Koley, R. A. Altman, *Isr. J. Chem*. **2020**, *60*, 313-339.

[12] For selected review and paper, see a) T. Fujita, K. Fuchibe, J. Ichikawa. *Angew. Chem. Int. Ed*. **2019**, *58*, 390-402; *Angew. Chem*. **2019**, *131*, 396-408. b) P. Tian, C. Feng, T. -P. Loh, *Nat. Commun.* **2015**, *6*,

7472.

[13] a) Y. Kita, T. Yata, Y. Nishimoto, K. Chiba, M. Yasuda, *Chem. Sci*. **2018**, *9*, 6041-6052. b) T. Yata, Y. Kita, Y. Nishimoto, M. Yasuda, *J. Org. Chem*. **2019**, *84*, 14330-14341.

[14] We developed the carboindation of alkenes using indium salts and organosilicon nucleophiles via the activation of alkene moiety by indium salts; a) Y. Nishimoto, H. Ueda, Y. Inamoto, M. Yasuda, A. Baba, *Org. Lett*. **2010**, *12*, 3390-3393. b) Y. Nishimoto, T. Nishimura, M. Yasuda, *Chem. Eur. J*. **2015**, *21*, 18301-18308.

[15] For selectid review, see a) T. Stahl, H. F. T. Klare, M. Oestreich, *ACS Catal.* **2013**, *3*, 1578-1587. b) G. Coates, F. Rekhroukh, M. R. Crimmin. *Synlett* **2019**, *30*, 2233-2246.

[16] Lu et al. reported the hydrodefluorination of aryl C–F bonds using a bimetallic Rhodium-Indium catalyst: J. T. Moore, C. C. Lu, *J. Am. Chem. Soc*. **2020**, *142*, 11641-11646.

[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.

[18] a) K. Komeyama, K. Takahashi, K. Takaki, *Org. Lett*. **2008**, *10*, 5119-5122. b) Y. Soltani, L. C. Wilkins, R. L. Melen, *Angew. Chem. Int. Ed*. **2017**, *56*, 11995-11999; *Angew. Chem*. **2017**, *129*, 12157-12161.

[19] a) A. Kondoh, K. Koda, M. Terada, *Org. Lett*. **2019**, *21*, 2277-2280. b) A. E. Feiring, *J. Org. Chem*. **1980**, *45*, 1962-1964. c) J. Ichikawa, Y. Wada, M. Fujiwara, K. Sakoda, *Synthesis* **2002**, 1917-1936. d) T. Fujita, K. Sakoda, M. Ikeda, M. Hattori, J. Ichikawa, *Synlett* **2013**, *24*, 57-60. e) K. Burger, B. Helmreich, *J. Chem. Soc., Chem. Commun*. **1992**, 348-349. f) J. Ichikawa, K. Sakoda, H. Moriyama, Y. Wada, *Synthesis* **2006**, 1590-1598. g) J. Ichikawa, Y. Wada, T. Okauchi, T. Minami, *Chem. Commun*. **1997**, *6*, 1537-1538. h) J. Ichikawa, K. Sakoda, Y. Wada, *Chem. Lett*. **2002**, *3*, 282-283. i) A. Saito, M. Okada, Y. Nakamura, O. Kitagawa, H. Horikawa, T. Taguchi, *J. Fluor. Chem*. **2003**, *123*, 75-80. j) J. Yang, A. Mao, Z. Yue, W. Zhu, X. Luo, C. Zhu, Y. Xiao, J. Zhang. *Chem. Commun*. **2015**, *51*, 8326-8329. k) K. Burger, B. Helmreich, *J. Chem. Soc., Chem. Commun*. **1992**, 348-349.

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

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

[22] a) J. Ichikawa, M. Kaneko, M. Yokota, M. Itonaga, T. Yokoyama, *Org. Lett*. **2006**, *8*, 3167-3170. b) W. Nakanishi, T. Matsuno, J. Ichikawa. H. Isobe, *Angew. Chem. Int. Ed*. **2011**, *50*, 6048-6051; *Angew. Chem*. **2011**, *123*, 6172-6175. c) N. Suzuki, T. Fujita, J. Ichikawa, *Org. Lett*. **2015**, *17*, 4984-4987.

[23] Tang, H.-J.; Lin, L.-Z.; Feng, C.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2017**, *56*, 9872−9876.

[24] Kim, R.; Kuduk, S. D.; Liverton, N.; Zhuo, G. PCT Int. Appl. (2016), WO 2016100161 A1.

[25] Cai, J.; Xie, Y.; You, Z.; Song, C.; Zhang, J.; Li, L.; Zhang, Q.; Wang, Y.; Chen, X.; Jiao, S.; Li, Y.;

Wang, T.; Zeng, H.; Song, H.; Ye, Q.; Su, D.; Zhou, X.; Zhang, S.; Wang, L.; Wang, J. Faming Zhuanli Shenqing (2018), CN 108341777 A.

[26] Wada, Y.; Ichikawa, J.; Katsume, T.; Nohiro, T.; Okauchi, T.; Minami, T. *Bull. Chem. Soc. Jpn.*, **2001**, *74*, 971-977.

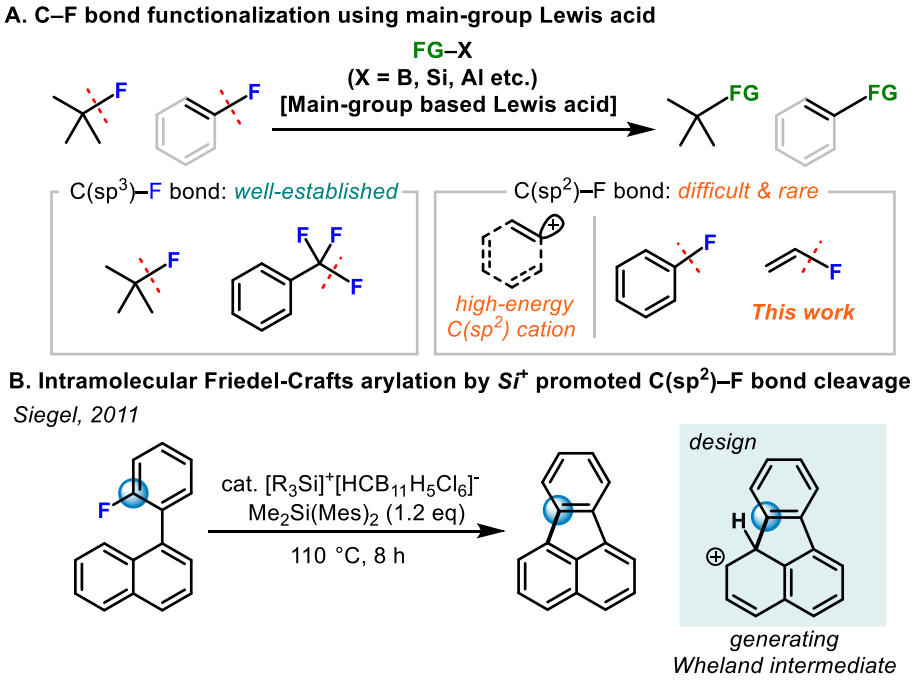
[27] Y. Huang, X. Lyu, H. Song, Q. Wang, *Adv. Synth. Catal*. **2019**, *361*, 5272-5276.

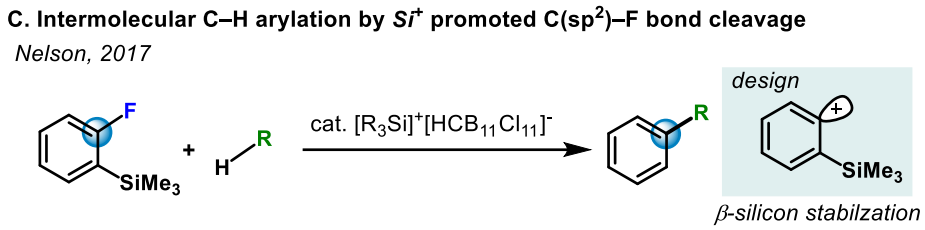
[28] T. Shamma, H. Buchholz, G. K. S. Prakash, G. A. Olah, *Isr. J. Chem*, **1999**, *39*, 207-210.

Chapter 3: Carboboration-Driven Generation of a Silylium Ion for Vinylic C–F Bond Functionalization by $B(C_6F_5)_3$ Catalysis

3-1. Introduction

Fluorine atoms possess the highest level of electronegativity and form quite strong bonds with carbon atoms, which has made C–F bond functionalization the most challenging task in organic syntheses. [1] Recently, C–F bond activation using main-group Lewis acids has emerged as a promising strategy to transform the fluorine group to other functional groups in fluorocarbons.[2] Specifically, silylium ions (R_3Si^+) are attractive for C–F bond activation because of their high Lewis acidity and fluoride ion affinity.[3] While silylium ions work well to heterolytically activate C(sp^3)–F bonds, cleavage of the C(sp^2)–F bonds of aromatic or vinylic fluorocarbons remains a significant challenge due to the intrinsic instability of aryl or vinyl cations (Scheme 1A).[3b] Seminal work by Reed, Baldridge, Siegel and co-workers showed that silylium ions are capable of C(sp^2)–F bond cleavage when paired with an extremely weakly coordinating carborane anion.[4] After their breakthrough, Siegel and co-workers developed an intramolecular Friedel-Crafts-type reaction with fluoroarenes that affords various polycyclic aromatic hydrocarbons and graphene frameworks (Scheme 1B), in which a concerted C–F bond cleavage/cyclization mechanism through a Wheland intermediate avoids the generation of aryl cations.[5] Nelson and co-workers successfully addressed the cross-coupling of aryl fluorides with hydrocarbons in selective intermolecular processes by taking advantage of the *β*-silicon effect (Scheme 1C).[6] However, these reactions require highly reactive free silylium ions to cleave the C(sp^2)–F bond, which might become a cause of low tolerance of the functional groups. Moreover, few studies have reported C(sp^2)–F bond cleavage using a main-group Lewis acid, and no studies have focused on vinylic C(sp^2)–F bond transformations using silylium ions.

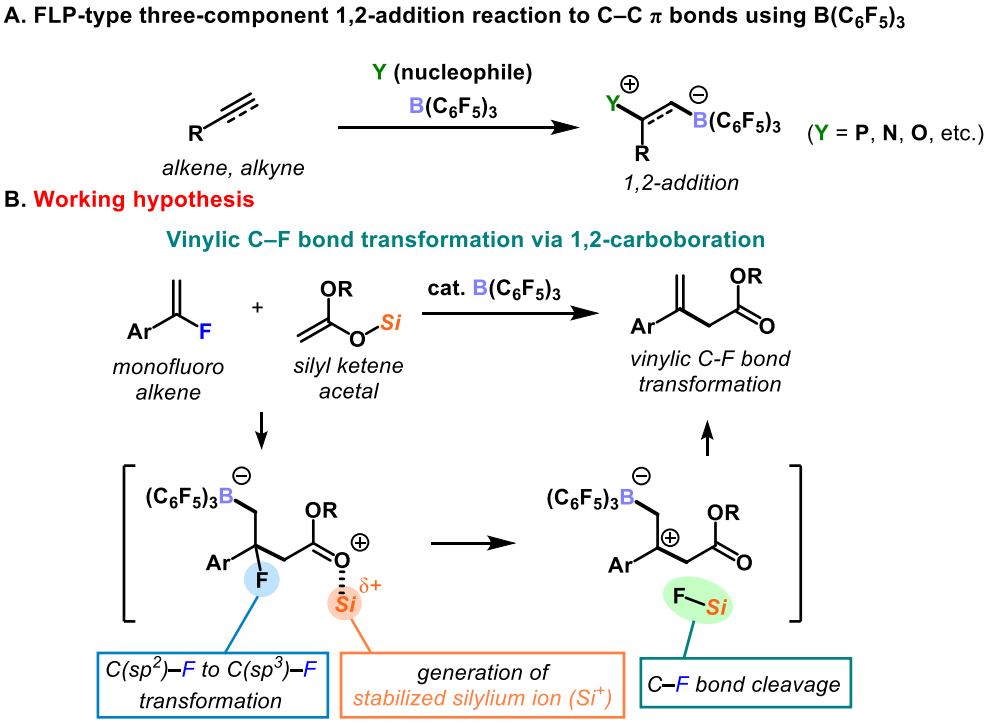




Scheme 1. C(sp^2)–F bond functionalization using main-group Lewis acid.

To address this issue, we focused on frustrated Lewis pairs (FLP)-type three-component reaction with C–C π bonds using $B(C_6F_5)_3$ (Scheme 2A). These reactions have a wide variety of nucleophiles that provide zwitterionic molecules.[7] In our hypothesis (Scheme 2B), the 1,2-carboboration to fluorostyrenes with silyl ketene acetals and $B(C_6F_5)_3$ generates a zwitterionic intermediate with an oxygen-stabilized silylium ion[8] and transforms C(sp^2)–F to C(sp^3)–F. We envisioned how this oxygen-stabilized silylium ion could lead to an intramolecular C(sp^3)–F bond cleavage to give the C–C coupling product because some oxygen-stabilized silylium allow the C(sp^3)–F bond cleavage.[9] Moreover, the nucleophilic substitution of perfluorinated alkenes is a well-known process,[10] and the substitution of monofluoroalkenes has been studied much less due to an intrinsically lower level of reactivity.[11] Thus, conversion of the vinylic C–F bond of monofluoroalkenes into a C–C bond under mild conditions would be highly significant.

Herein we report a strategy for the vinylic C(sp^2)–F bond functionalization that is enabled by oxygen-stabilized silylium ions, which are generated by carboboration from silyl ketene acetals with $B(C_6F_5)_3$ catalysis. Theoretical calculation showed that a cooperation of the silylium ion generated from silyl ketene acetals and $B(C_6F_5)_3$ is essential for C–F bond cleavage. In addition, a comparative study of halides indicated that our strategy could be used for C–F bond selective transformation in the presence of other halides.

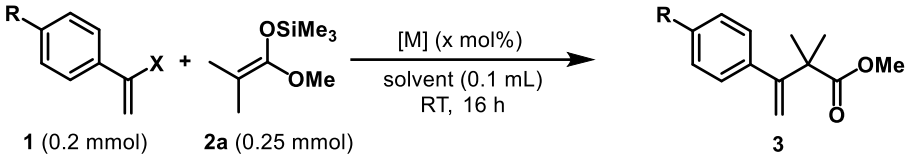


Scheme 2. Working hypothesis for vinylic C–F bond functionalization.

3-2. Results and Discussion

Extensive screening of the conditions was performed using 1-(*tert*-butyl)-4-(1-fluorovinyl)benzene **1a** and silyl ketene acetal **2a** as a model reaction (Table 1). We discovered that the treatment of a catalytic amount of $B(C_6F_5)_3$ and $CHCl_3$ as a solvent at room temperature afforded the desired product **3aa** in 96% yield (entry 1). Coordinating solvents such as THF, MeCN, and DMF retarded the reaction (entries 2-4) due to a deactivation of the Lewis acidity of $B(C_6F_5)_3$, and the use of low-polarity solvents such as ether and toluene exhibited much lower reactivity (entries 5 and 6). Other metal salts were examined. Even the use of a stoichiometric amount of transition-metal salts, which generally activates alkenes such as Fe, Ag, Cu, and Au salts, was not effective in this system (entries 7-10). Notably, InI_3 gave the target product in a moderate yield (entry 11), whereas reducing the amount of InI_3 to 50 mol% diminished the yield of **3aa** (entry 12) (See Supporting Information). Use of other boron catalysts resulted in no products (entries 13-15). Even 2 mol% of $B(C_6F_5)_3$ smoothly led to the formation of the target product, although the yield was moderate (entries 16-18). Surprisingly, α-chlorostyrene or α-bromostyrene were not applicable to our reaction system (entries 19-21), which indicates that our reaction has high specificity for C–F bond.

Table 1. Reaction optimization of vinylic C–F bond functionalization.

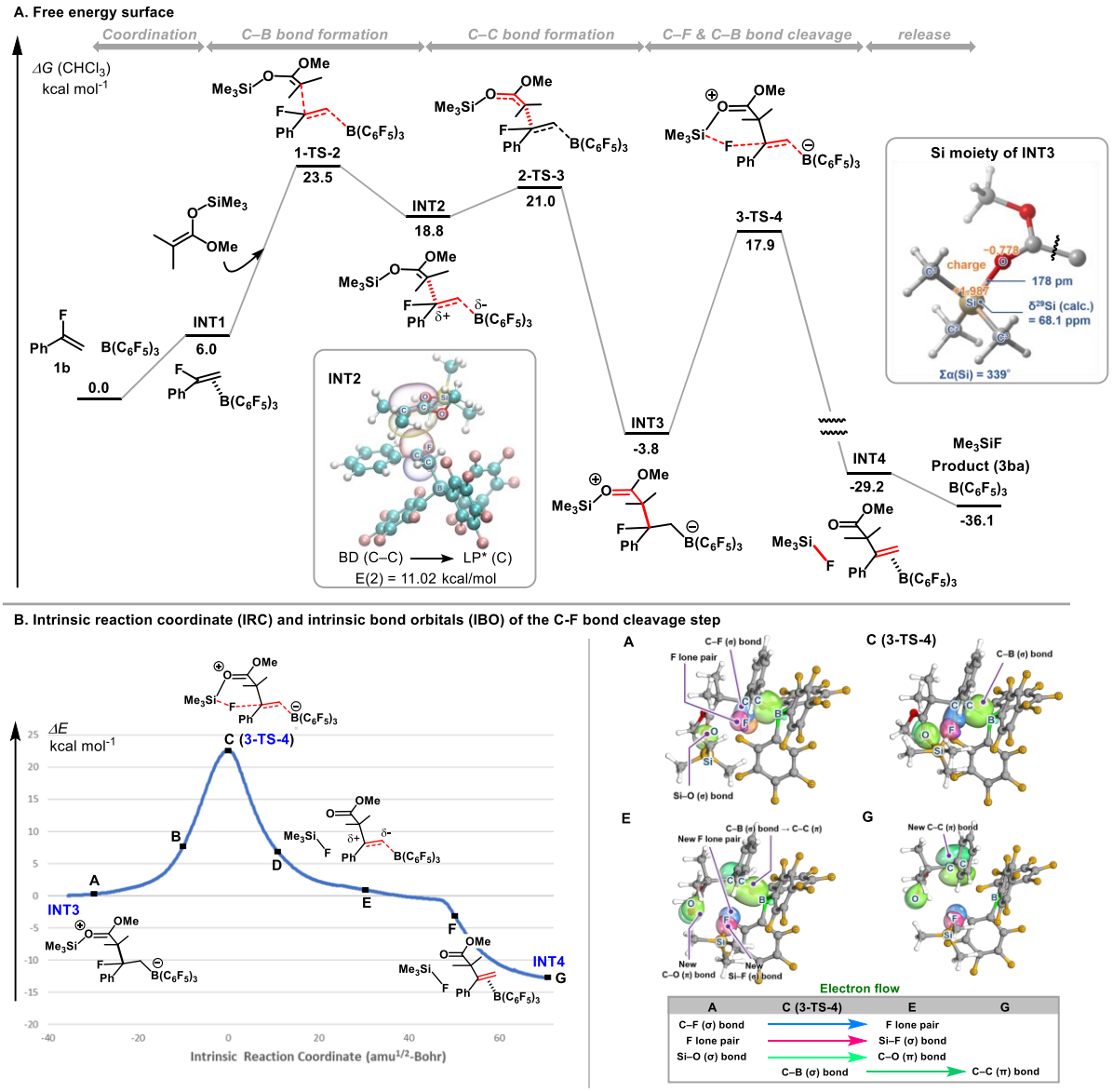


1 (0.2 mmol) **2a** (0.25 mmol) **3**

Entry	R	X	[M] (x mol%)	Solvent	Yield (%) [a]
1	*t*Bu	F	$B(C_6F_5)_3$ (15)	$CHCl_3$	96
2	*t*Bu	F	$B(C_6F_5)_3$ (15)	THF	0
3	*t*Bu	F	$B(C_6F_5)_3$ (15)	MeCN	0
4	*t*Bu	F	$B(C_6F_5)_3$ (15)	DMF	0
5	*t*Bu	F	$B(C_6F_5)_3$ (15)	Ether	10
6	*t*Bu	F	$B(C_6F_5)_3$ (15)	Toluene	23
7	*t*Bu	F	Fe salt (100)	$CHCl_3$	0
8	*t*Bu	F	Ag salt (100)	$CHCl_3$	0
9	*t*Bu	F	Cu salt (100)	$CHCl_3$	0
10	*t*Bu	F	$AuCl_3$ (100)	$CHCl_3$	0
11	*t*Bu	F	InI_3 (100)	$CHCl_3$	59
12	*t*Bu	F	InI_3 (50)	$CHCl_3$	40
13	*t*Bu	F	ClBcat (15)	$CHCl_3$	0
14	*t*Bu	F	BCl_3 (15)	$CHCl_3$	0
15	*t*Bu	F	$BF_3 \cdot OEt_2$	$CHCl_3$	0
16	*t*Bu	F	$B(C_6F_5)_3$ (10)	$CHCl_3$	91
17	*t*Bu	F	$B(C_6F_5)_3$ (5)	$CHCl_3$	74
18	*t*Bu	F	$B(C_6F_5)_3$ (2)	$CHCl_3$	40
19	H	F	$B(C_6F_5)_3$ (20)	$CHCl_3$	82
20	H	Cl	$B(C_6F_5)_3$ (20)	$CHCl_3$	0
21	H	Br	$B(C_6F_5)_3$ (20)	$CHCl_3$	0

[a] The yields were determined by ^1H NMR using CH_2Br_2 as an internal standard. [b] $FeBr_2$ and $FeBr_3$. [c] AgOTf, $AgBF_4$, and $AgSbF_6$. [d] CuI, $Cu(OAc)_2$, and $Cu(OTf)_2$.

DFT calculations were performed to determine the reaction mechanism of the present C–F bond transformation. The overall potential energy surface of the reaction appears in Scheme 3A. In this reaction, *α*-fluorostyrene **1b** coordinates to $B(C_6F_5)_3$ (**INT1**) and undergoes 1,2-carboboration wherein C–B bond formation occurs to give **INT2** via **1-TS-2.** Sequential C–C bond formation proceeds via **2-TS-3** to give zwitterionic species **INT3** that possesses an oxygen-stabilized silylium ion. This 1,2-carboboration proceeds stepwise rather than in a concerted manner. NBO analysis for **INT2** revealed a significant level of electron donation from the π orbital of the C–C bond of silyl ketene acetal **2a** [BD (C–C)] to the cationic carbon atom at the benzylic position of *α*-fluorostyrene **1b** (LP). This interaction stabilizes **INT2** to facilitate the C–B bond formation. The sum of the bond angles of the three Si–C bonds of the Me_3Si group in **INT3**, Σ*α*(Si), is 339°, which indicates a relatively trigonal flattening of the tetrahedral coordination of the silicon atom. The Si–O distance (178.0 pm) in **INT3** is consistent with values reported for silylated oxonium ions (Si–O: 177.7-185.4 pm).[12] The positive charge at the silicon atom is large and the Si–O bond is polarized (Si: +1.987, O: –0.778). Calculation using the GIAO method shows that the ^{29}Si NMR of **INT3** is 68.1 ppm. This is in agreement with the reported experimental and calculated data for oxygen-stabilized silylium ions that are available for C–F bond cleavage.[9] After 1,2-carboboration (**INT1-INT3**), the cleavage of C–F and C–B bonds proceeds via **3-TS-4** to give product **3ba**, $B(C_6F_5)_3$, and Me_3SiF (**INT4**). In this step, the cleavage of Si–O, C–F, and C–B bonds proceeds simultaneously with the formation of C–C π and Si–F bonds. To obtain further insight into the mechanism of C–F bond cleavage, we performed an intrinsic reaction coordinate (IRC) calculation of transition state **3-TS-4** (Scheme 3B). The course from coordinate **A** to **E** includes the C–F cleavage, the Si–O bond cleavage, and the Si–F bond formation. Notably, both C–F cleavage and Si–F bond formation occur in a concerted manner in transition state **C**. On the other hand, C–C π bond formation and C–B bond cleavage start from **C** and then complete at **G**. These results revealed that the course from **A** to **G** is energetically concerted but has a stepwise bonding pattern. We studied this process using the intrinsic bond orbital (IBO) methodology to analyze the electron flow along the IRC.[13] The IBOs of coordinate **A** and transition state **C** show that a lone pair of the F atom gradually migrates to the Si atom, which suggests that interactions of the silylium ion with the F atom trigger the C–F bond cleavage. After transition state **C**, the electrons of the C–B bond gradually delocalize on two carbon atoms (coordinate **C** to **E**) and finally form a C–C π bond (coordinate **E** to **G**). This electron flow indicates that the electron transfer from the C–B σ bond confers thermodynamic stabilization to the C–F bond cleavage step. Thus, $B(C_6F_5)_3$ facilitates both the C–F bond cleavage and the 1,2-carboboration step. A summary of the electron flow is shown in Scheme 3B (bottom right).

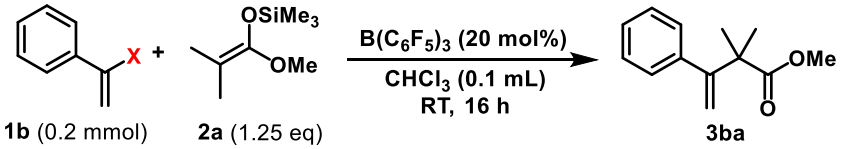


Scheme 3. Mechanistic studies.

We discovered marked differences in reactivity when comparing *α*-fluorostyrene with *α*-chlorostyrene and *α*-bromostyrene (Table 1, entries 19 and 20). The reactions of either *α*-chlorostyrene or *α*-bromostyrene with **2a** in the presence of $B(C_6F_5)_3$ catalyst resulted in almost total recovery of the starting materials despite the bond dissociation energies of C–Cl and C–Br bonds that were both smaller than that of the C–F bond (Scheme 4A). To understand the differences among them, we calculated the reaction energy profile for each halide (See Figure S2 in Supporting Information). First, we focused on the activation barriers at the C–B bond formation step (from starting materials to **INT2**). The values of the activation energy are on the order of *α*-chloro- (24.9 kcal/mol) > *α*-fluoro- (23.5 kcal/mol) > *α*-bromostyrene (12.7 kcal/mol). NBO analysis of the orbital interactions between $B(C_6F_5)_3$ and *α*-halostyrenes in **INT1**s indicates that *α*-bromostyrene more effectively interacts with the boron center via electron donation compared with either *α*-fluorostyrene or *α*-chlorostyrene, which is due to the lower electron negativity of the Br atom (Scheme 4B). The donor-acceptor interaction of *α*-fluorostyrene approximates that of *α*-bromostyrene (2.52 kcal/mol) despite the high electron

negativity of the F atom.That result is caused by the coulombic or Pauli repulsion in unsaturated fluorocarbon systems that occurs between electron pairs on fluorine and π-electrons to enhance the electron donating ability.[14] Thus, the electron donation of *α*-halostyrene determines the order of activation energy at the C–B bond formation step (**1-TS-2, Cl>F>Br**). Second, in the C–C bond formation step (from **INT2** to **INT3**), the barrier in the case of *α*-fluorostyrene ($\Delta G^{\ddagger}$ = 2.2 kcal/mol) is the lowest among the other halostyrenes (*α*-chlorostyrene: $\Delta G^{\ddagger}$ = 4.1 kcal/mol, *α*-bromostyrene: $\Delta G^{\ddagger}$ = 4.6 kcal/mol) because the strong electronegativity of the F atom enhances the electrophilicity to facilitate a nucleophilic attack of the silyl ketene acetal. Overall, the highest transition state during the 1,2-carboboration of *α*-chlorostyrene is higher than that of *α*-fluorostyrene and *α*-bromostyrene. Thus, the reaction using *α*-chlorostyrene resulted in no product.

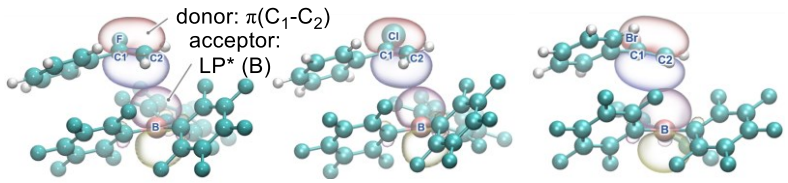
A. Comparative study of halides



1b (0.2 mmol) **2a** (1.25 eq) **3ba**

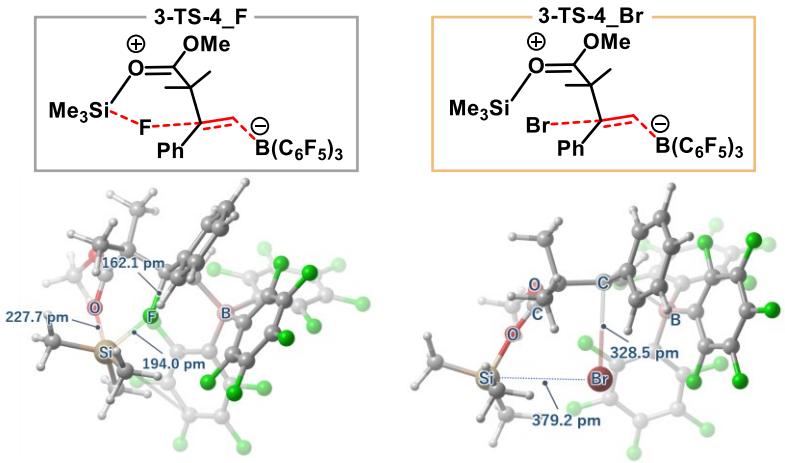
X	Yield of **3ba** /%	Recovery of **1**	BDE of C(sp^2)–X bond (kcal/mol)
F	82	0	117.7
Cl	0	90	84.9
Br	0	81	69.6

B. Charge distributions and donor-acceptor interaction energies



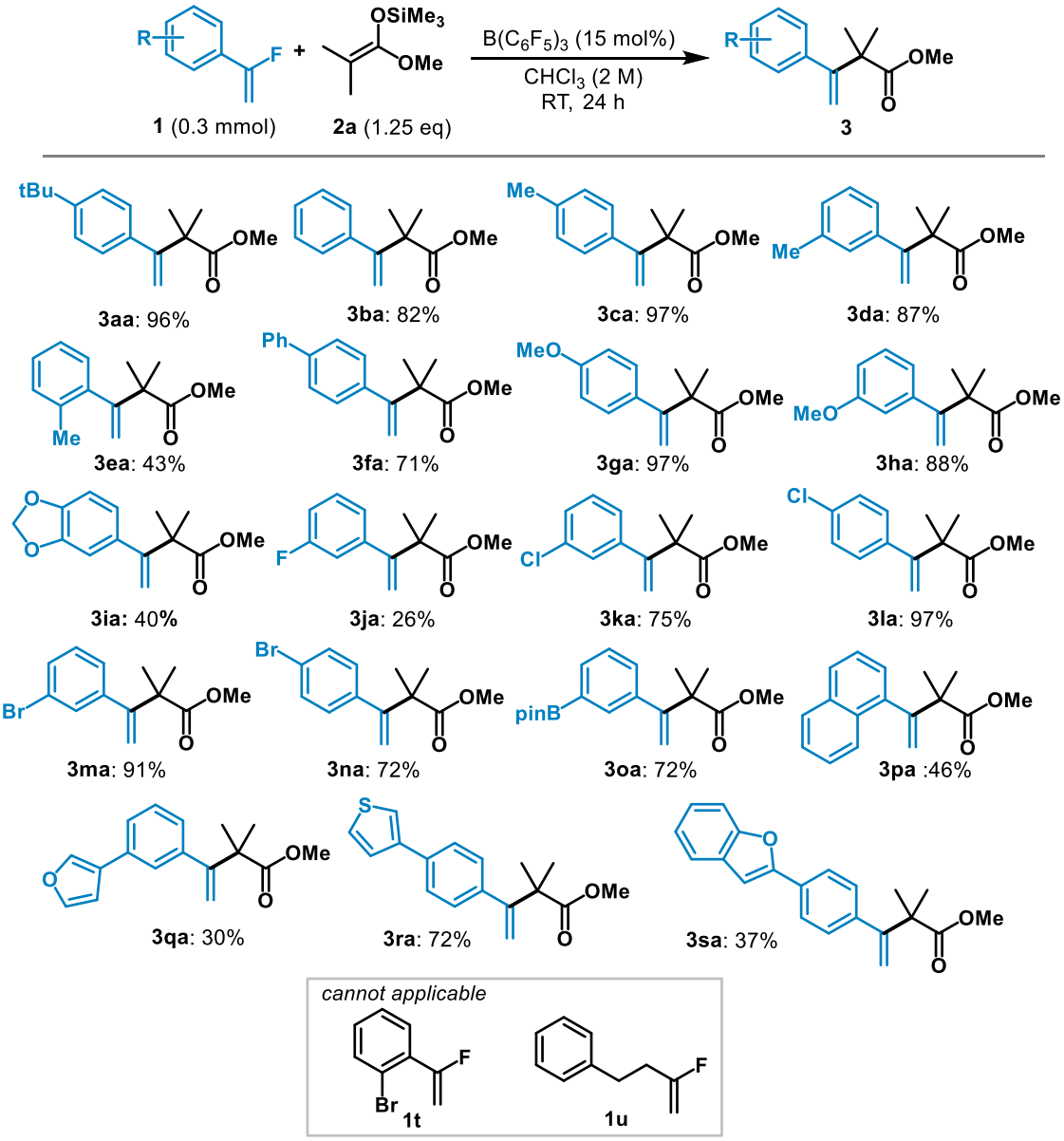
INT1_F 2.52 kcal/mol **INT1_Cl** 1.71 kcal/mol **INT1_Br** 2.63 kcal/mol

C. Optimized structure of transition states of 3-TS-4_F and 3-TS-4_Br



Scheme 4. Comparative studies of halides.

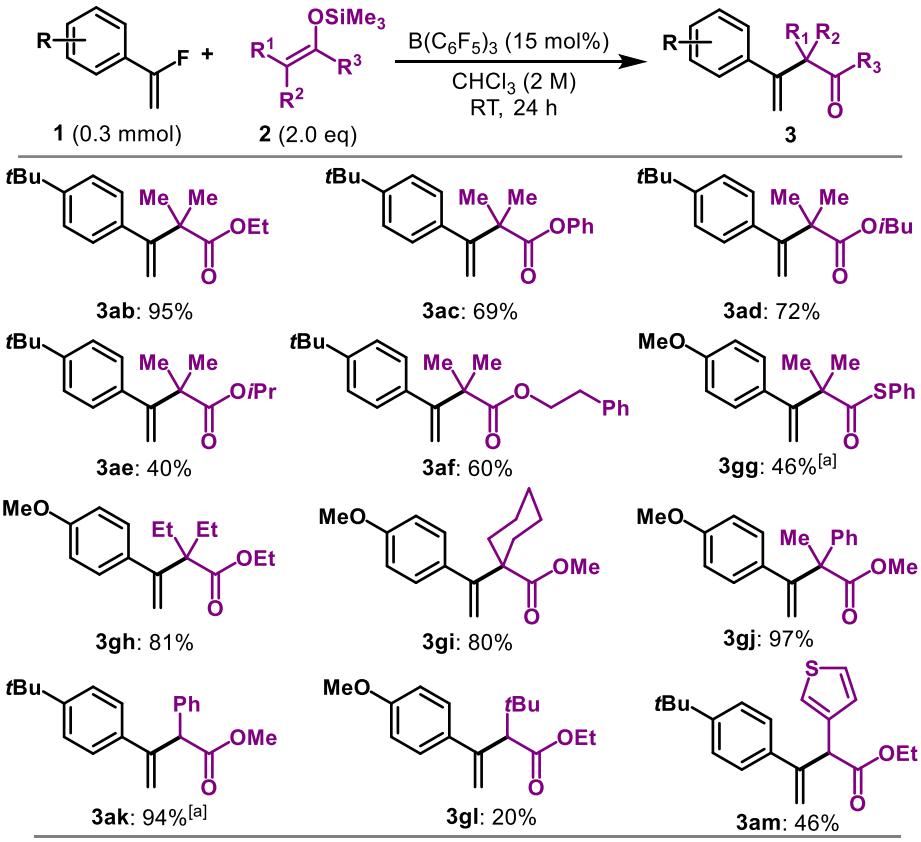
Lastly, we considered the C–X bond cleavage step. There is no high activation barrier in the 1,2-carboboration process of α-bromostyrene, but the examination resulted in no reaction. The reason is a high activation barrier ($\Delta G^{\ddagger}$ = 27.2 kcal/mol) in the C–Br bond cleavage step (**3-TS-4_Br**). On the other hand, the activation energy of the C–F bond cleavage is much lower ($\Delta G^{\ddagger}$ = 21.7 kcal/mol) despite its robust bond strength. Each transition state (**3-TS-4**) has a different structure, as shown in Scheme 4C. The Si–F bond formation is almost completed (194.0 pm) during the transition state (**3-TS-4_F**), while the C–F bond remains almost unchanged (162.1 pm). In the case of **3-TS-4_Br**, the bromide is gradually eliminated without assistance from other atoms, which requires a higher activation energy. These results support the efficiency of our strategy to activate the robust formation of a C–F bond via a transient silylium moiety.



Scheme 5. Substrate scope of α-fluorostyrenes **1** for vinylic C–F bond transformation.

The substrate scope of the boron-catalyzed C(sp^2)–F bond functionalization was explored (Scheme 5). Non-substituted α-fluorostyrene proceeded to afford the desired product **3ba**. Substrates with alkyl or aryl groups at different positions in the benzene ring were applicable to afford the target products **3ca-3fa** in high yields. Substrates bearing electron-donating groups such as methoxy (**3ga** and **3ha**) were well tolerated. The compound bearing acetal moiety also applicable to give the target product in a moderate yield (**3ia**). The fluorine substituted substrate gave the target product in a lower yield (**3ja**) and remained in 60% nmr yield with no side reaction, because the strong electron-withdrawing effect of the F atom raises the transition state of the C–B bond formation step (**1-TS-2** in Scheme 3A). The use of substrates with other electron-withdrawing groups such as chloro (**3ka** and **3la**) and bromo (**3ma** and **3na**) afforded the desired product. The substrate bearing a pinacolatoboronyl (Bpin) group furnished the desired product **3oa** in 72% yield. The reaction of α-fluorostyrene containing a naphthalene structure or heterocycles proceeded uneventfully to afford the target compound **3pa-3sa** in a moderate yield. Unfortunately, no desired compounds were obtained bearing either a large substituent at the ortho position (**1t**) or a di-alkyl substituted fluoroalkene (**1u**).

Subsequently, we investigated the use of various silyl ketene acetals in this boron-catalyzed C–F bond functionalization reaction (Scheme 6). Substrates with various esters or a thioester were applicable to afford the desired products **3ab-3gg**. Diverse di- or mono-substituted silyl ketene acetals could be applied (**3ah-3am**).



Scheme 6. Substrate scope of silyl ketene acetals **2** for vinylic C–F bond transformation. [a] silyl ketene acetal **2** (1.25 equiv)

3-3. Conclusion

In summary, we developed a $B(C_6F_5)_3$-catalyzed C–F bond functionalization of *α*-fluorostyrene derivatives using silyl ketene acetals via 1,2-carboboration. This reaction proceeded under mild and transition-metal free conditions. DFT study suggested that *α*-fluorostyrene underwent 1,2-carboboration in the presence of silyl ketene acetals and $B(C_6F_5)_3$ catalyst, subsequently undergoing C–F bond cleavage to give the desired product. The IRC calculation and IBO analysis revealed that the vinyl $C(sp^2)$–F bond cleavage is caused by an oxygen-stabilized silylium ion generated from silyl ketene acetals. Moreover, comparison of the energy diagrams for the α-halostyrenes indicated a conformation in the transition state for *α*-fluorostyrene that differed from those of chloro and bromo analogues because of the affinity of halogen and silicon.

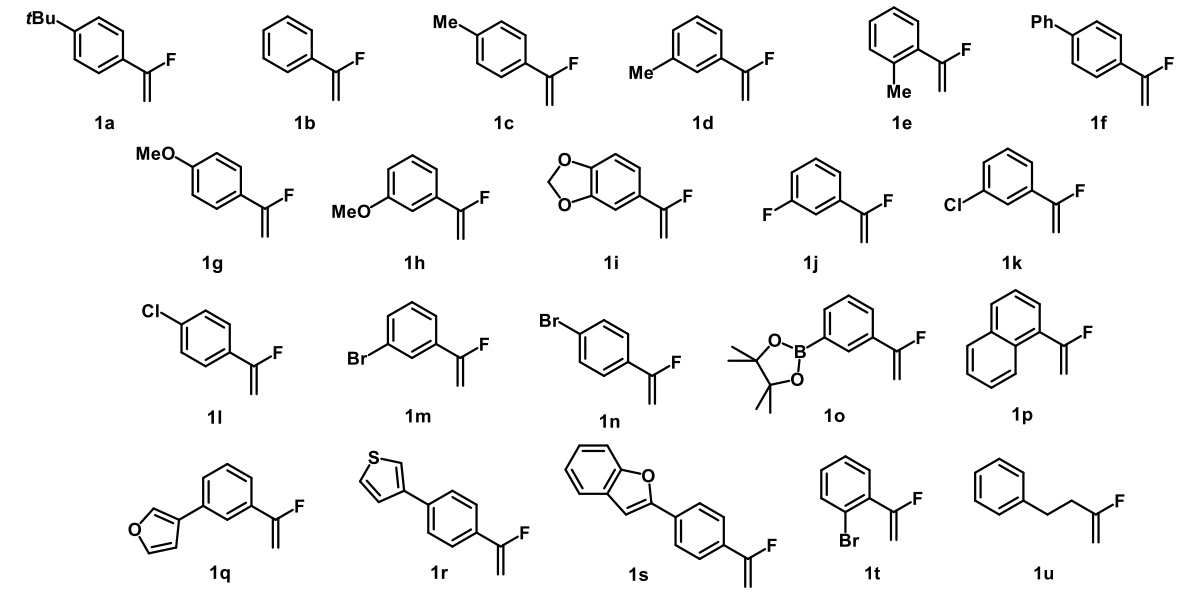
3-4. Experimental Section

General Information

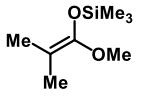
NMR spectra were recorded on JEOL-AL400, JEOL-ECS400 (400 MHz for ^1H, 100 MHz for ^{13}C, 376 MHz for ^{19}F) with TMS as an internal standard and $BF_3{\cdot}OEt_2$ as an external standard. High-resolution mass spectra were recorded on a JEOL JMS-700 or JMS-T100LP. Column chromatography was performed on silica gel (MERK C60 or Fuji Silysia FL100DX). Purification by recycled HPLC was performed using a SHIMADZU recycling HPLC system (SPD-20A, RID-10A, DGU-20A, LC-6AD, and FCV-20H2) and Japan Analytical Industry Co. (NEXT recycling preparative HPLC). All reactions were carried out under nitrogen. Yields were determined by ^1H NMR using internal standards (CH_2Br_2).

Materials

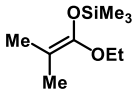
Fluoroalkenes



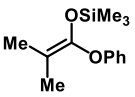
Organosilicon compounds



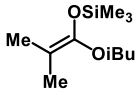
2a



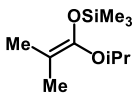
2b



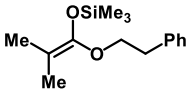
2c



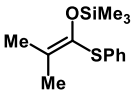
2d



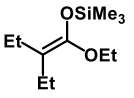
2e



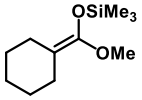
2f



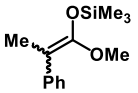
2g



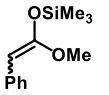
2h



2i

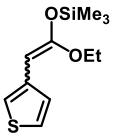


2j



2k

2l



2m

The known fluoroalkenes **1b**[15], **1c**[16], **1d**[17], **1e**[18], **1f**[15], **1g**[15], **1h**[19], **1j**[17], **1k**[17], **1l**[16], **1m**[15], **1n**[15], **1p**[20], **1t**[16], and **1u**[21] were prepared according to the literatures, and the spectral data are in agreement with the reports. The new fluoroalkenes **1a**, **1i**, **1o**, **1q**, **1r**, and **1s** were prepared by the methods described in the supporting information, and their spectral data are shown in this document. Silyl ketene acetal **2a** is commercially available. The known silyl ketene acetals **2b**[22], **2c**[22], **2d**[23], **2e**[24], **2f**[25], **2g**[26], **2h**[27], **2i**[22], **2j**[22], **2k**[22], **2l**[22], and **2m**[22] were prepared according to the literatures, and the spectral data except for **2d** are in agreement with the reports. Spectral data of **2d** is shown in this supporting information. All dry solvent and metal salts were purchased from Aldrich or Tokyo Chemical Industry Co., Ltd. (TCI), FUJIFILM Wako Pure Chemical Corporation and used after purification by distillation or used without purification for solid substrates.

Synthesis of **1a**

In a 100 mL oven-dried round-bottom flask with a stir bar, the 1-(*tert*-butyl)-4-vinylbenzene (3.21 g, 20.0 mmol, 1.0 equiv) and *N*-Bromosuccinimide (5.34 g, 30.0 mmol, 1.5 equiv) were dissolved in $CHCl_3$ (40 mL). To the resulting mixture was added triethylamine trihydrofluoride (4.89 mL, 30 mmol, 1.5 equiv) at 0 °C, then the mixture was stirred for 16 h at room temperature. The resulting mixture was cooled to 0 °C, quenched with $NaHCO_3$ and extracted with $CHCl_3$. The combined organic layers were washed with 1N HCl aq. and dried over $MgSO_4$. After solvent was removed under reduced pressure, the crude residue was filtrated by a pad of silica gel (hexane only) to afford 1-(2-bromo-1-fluoroethyl)-4-(*tert*-butyl)benzene. This compound was used for next step without purification.

In a 50 mL oven-dried round-bottom flask with a stir bar, KO*t*Bu (2.24 g, 20 mmol, 1.0 equiv) and THF (20 mL) were charged. To the resulting mixture was added the 1-(2-bromo-1-fluoroethyl)-4-(*tert*-butyl)benzene (1.0 equiv) at 0 °C, then the mixture was stirred for 16 h at room temperature. The resulting mixture was quenched with water, and extracted by hexane, followed by drying over $MgSO_4$. After filtration, solvent was removed in vacuo carefully (***1a*** *is a volatile compound*). The residual crude was purified by flash column chromatography on silica gel (hexane only) followed by a recycled HPLC system to give the product **1a** (2.6

g, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 4.98 (dd, J = 49.6, 2.9 Hz, 1H), 4.79 (dd, J = 18.1, 2.9 Hz, 1H), 1.32 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0 (d, J_{C-F} = 249.9 Hz), 152.6 (s), 129.2 (d, J_{C-F} = 29.5 Hz), 125.4 (s), 124.4 (d, J_{C-F} = 7.4 Hz), 88.7 (d, J_{C-F} = 22.9 Hz), 34.7 (s), 31.2 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -107.8 (dd, J = 50.4, 16.8 Hz).

HRMS (DART+) Calculated ($C_{12}H_{16}F$): 179.12306 ($[M+H]^+$), Found: 179.12371

Synthesis of **1i**

In a 20 mL oven-dried round-bottom flask with a stir bar, 5-vinyl-1,3-benzodioxole (1.38 g, 9.3 mmol, 1.0 equiv) and *N*-Bromosuccinimide (2.49 g, 14.0 mmol, 1.5 equiv) were dissolved in DCM (12.5 mL). To the resulting mixture was added triethylamine trihydrofluoride (2.28 mL, 14.0 mmol, 1.5 equiv) at 0 °C slowly, then the mixture was stirred for 4 h at room temperature. The resulting mixture was cooled to 0 °C and added KO*t*Bu (8.35 g, 74 mmol, 8.0 equiv) separately (3 or 4 portions), then the mixture was stirred for 16 h at room temperature. The resulting mixture was quenched with water and extracted by DCM, followed by drying over $MgSO_4$. After filtration, solvent was removed in vacuo. The residual crude was purified by flash column chromatography on silica gel (hexane/EtOAc = 99:1) to give the product **1i** (0.78 g, 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, J = 8.0 Hz, 1H), 6.90 (s, 1H), 6.70 (d, J = 8.0 Hz, 1H), 5.88 (s, 2H), 4.77 (dd, J = 49.7, 3.4 Hz, 1H), 4.65 (dd, J = 18.1, 3.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (d, J_{C-F} = 249.1 Hz), 148.6 (s), 147.8 (d, J_{C-F} = 1.6 Hz), 126.2 (d, J_{C-F} = 30.3 Hz), 118.9 (d, J_{C-F} = 8.2 Hz), 108.2 (s), 105.1 (d, J_{C-F} = 7.4 Hz), 101.4 (s), 88.1 (d, J_{C-F} = 22.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -106.8 (dd, J = 52.0, 17.3 Hz).

HRMS: (DART+) Calculated ($C_9H_8O_2F$): 167.05028 ($[M+H]^+$), Found: 167.05071

Synthesis of **1o**

In a 50 mL oven-dried round-bottom flask with a stir bar, **1m** (402 mg, 2.0 mmol, 1.0 equiv) and $PdCl_2(PPh_3)_2$ (140 mg, 0.2 mmol) were charged in 1,4-dioxane (24 mL), then the mixture was heated to 50 °C. To the reaction mixture at 50 °C were added B_2pin_2 (102 mg, 4.0 mmol, 2.0 equiv) and AcOK (39.3 mg, 4.0 mmol, 2.0 equiv) then the mixture was stirred for 16 h at 80 °C. After cooling to room temperature, water (15 mL) was added and the mixture was extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered the mixture and the solution was concentrated in vacuo and purified the residue by chromatography on silica gel (Hexane/EtOAc = 98:2) to afford the compound **1o** (198 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.80 (d, J = 7.2 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 5.08 (dd, J = 49.9, 3.3 Hz, 1H), 4.84 (dd, J = 17.9, 3.3 Hz, 1H), 1.35 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0 (d, J_{C-F} = 250.7 Hz), 135.7 (s), 131.4 (d, J_{C-F} = 29.5 Hz), 130.9 (d, J_{C-F} = 5.7 Hz), 127.8 (s), 127.3 (d, J_{C-F} = 6.6 Hz), 89.6 (d, J_{C-F} = 22.1 Hz), 84.0 (s), 24.9 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -107.7 (dd, J = 48.8, 18.3 Hz).

HRMS: (DART+) Calculated ($C_{14}H_{19}BO_2F$): 249.14566 ($[M+H]^+$) Found: 249.14656

Synthesis of **1q**

In a 30 mL oven-dried round-bottom flask equipped with a stir bar, compound **1m** (402 mg, 2.0 mmol, 1.0 equiv), $PdCl_2(PPh_3)_2$ (140 mg, 0.2 mmol, 0.1 equiv), furan-3-ylboronic acid (448 mg, 4.0 mmol, 2.0 equiv), and K_2CO_3 (553 mg, 4.0 mmol, 2.0 equiv) were dissolved in THF (8.0 mL), then the mixture was refluxed at 70 °C. After being stirred at 70 °C for 16 h, the mixture was diluted with EtOAc (15 mL) and water (10 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered the mixture and the solution was concentrated in vacuo and purified the residue by chromatography on silica gel (Hexane/EtOAc = 85:15) to afford the compound **1q** (252 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.65 (s, 1H), 7.49-7.41 (m, 3H), 7.36 (d, J = 7.7 Hz, 1H), 6.70 (s, 1H), 5.06 (dd, J = 49.9, 3.5 Hz, 1H), 4.88 (dd, J = 17.9, 3.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (d, J_{C-F} = 249.9 Hz), 143.8 (s), 138.7 (s), 132.8 (s), 132.5 (d, J_{C-F} = 29.5 Hz), 128.9 (s), 126.8 (s), 125.9 (s), 123.2 (d, J_{C-F} = 6.6 Hz), 121.9 (d, J_{C-F} = 6.6 Hz), 108.7 (s), 89.9 (d, J = 22.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -107.63 (dd, J = 48.8, 18.3 Hz).

HRMS: (DART+) Calculated: ($C_{12}H_{10}OF$) 189.07102 ($[M+H]^+$) Found: 189.07101

Synthesis of **1r**

In a 30 mL oven-dried round-bottom flask equipped with a stir bar, compound **1n** (402 mg, 2.0 mmol, 1.0 equiv), $PdCl_2(PPh_3)_2$ (140 mg, 0.2 mmol, 0.1 equiv), thiophen-3-ylboronic acid (512 mg, 4.0 mmol, 2.0 equiv), and K_2CO_3 (553 mg, 2.0 equiv, 4.0 mmol) were dissolved in THF (8.0 mL), then the mixture was refluxed at 70 °C. After being stirred at 70 °C for 16 h, the mixture was diluted with EtOAc (15 mL) and water (10 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered the mixture and the solution was concentrated in vacuo and purified the residue by chromatography on silica gel (Hexane/EtOAc = 85:15) to afford the compound **1r** (192 mg, 47%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.58 (m, 4H), 7.50 (s, 1H), 7.41-7.40 (m, 2H), 5.05 (dd, J = 49.7, 3.4 Hz, 1H), 4.86 (dd, J = 17.9, 3.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (d, J_{C-F} = 249.9 Hz), 141.4 (s), 136.6 (s), 130.6 (d, J_{C-F} = 29.5 Hz), 126.41 (d, J_{C-F} = 13.1 Hz), 126.37 (s), 126.1 (s), 125.0 (d, J_{C-F} = 7.4 Hz), 120.9 (s) 89.4 (d, J_{C-F} = 22.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -108.0 (dd, J = 51.9, 18.3 Hz).

HRMS: (DART+) Calculated ($C_{12}H_{10}FS$) 205.04818 ($[M+H]^+$) Found: 205.04727

Synthesis of **1s**

In a 30 mL oven-dried round-bottom flask equipped with a stir bar, compound **1n** (402 mg, 2.0 mmol, 1.0 equiv), $PdCl_2(PPh_3)_2$ (140 mg, 0.2 mmol, 0.1 equiv), Benzofuran-2-boronic acid (648 mg, 4.0 mmol, 2.0

equiv), and K_2CO_3 (553 mg, 4.0 mmol, 2.0 equiv) were dissolved in THF (8 mL), then the mixture was refluxed at 70 °C. After being stirred at 70 °C for 16 h, the mixture was diluted with EtOAc (15 mL) and water (10 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered the mixture and the solution was concentrated in vacuo and purified the residue by chromatography on silica gel (Hexane/EtOAc = 85:15) to afford the compound **1s** (200 mg, 42%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.02 (s, 1H), 5.07 (dd, *J* = 49.5, 3.1 Hz, 1H), 4.88 (dd, *J* = 17.7, 3.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 (d, J_{C-F} = 249.9 Hz), 155.0 (d, J_{C-F} = 7.4 Hz), 131.8 (d, J_{C-F} = 29.5 Hz), 131.2 (s), 129.1 (s), 125.0 (s), 124.92 (s), 124.86 (s), 124.6 (s), 123.1 (s), 121.0 (s), 111.2 (s), 102.2 (s), 90.0 (d, J_{C-F} = 22.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -108.2 (dd, *J* = 48.8, 18.3 Hz).

HRMS: (DART+) Calculated ($C_{16}H_{12}OF$) 239.08667 ($[M+H]^+$) Found: 239.08574

Synthesis of **2d**

2d was prepared according to a known literature procedure[23]. A small amount of some by-product was included.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 (d, *J* = 6.5 Hz, 2H), 1.92-1.85 (m, 1H), 1.58 (s, 3H), 1.51 (s, 3H), 0.94 (d, *J* = 6.5 Hz, 6H), 0.19 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 91.0, 75.6, 28.5, 19.4, 17.0, 16.3, 0.1.

HRMS: (DART+) Calculated ($C_{11}H_{25}O_2Si$) 217.16183 ($[M+H]^+$) Found: 217.16114

Products

General procedure

To an oven-dried 2 mL PTFE/silicone-lined septa screw cap vial equipped with a magnetic stirring bar was charged with $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), $CHCl_3$ (0.15 mL) and silyl ketene acetal **2** inside glove box. The resulting solution was stirred for several seconds, and fluoroalkene **1** (0.3 mmol, 1.0 equiv) was added to the solution in glove box. After being stirred at room temperature for 24 h, the reaction mixture was filtered through silica pad and the solution was concentrated in vacuo and purified the residue by chromatography on silica gel (Hexane/EtOAc) to afford the pure product.

methyl 3-(4-(*tert*-butyl)phenyl)-2,2-dimethylbut-3-enoate (3aa)

Prepared according to general procedure using fluoroalkene **1a** (53.5 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2a** (65.4 mg, 0.375 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (75 mg, 96%). The NMR spectrum is in agreement with the literature data[28].

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 8.2 Hz, 2H), 5.25 (s, 1H), 5.13 (s, 1H),

3.63 (s, 3H), 1.35 (s, 6H), 1.27 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 152.7, 149.8, 138.4, 127.4, 124.7, 114.0, 52.0, 47.5, 34.4, 31.3, 25.7.

methyl 2,2-dimethyl-3-phenylbut-3-enoate (3ba)

Prepared according to general procedure using fluoroalkene **1b** (36.6 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2a** (65.4 mg, 0.375 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (50 mg, 82%). The NMR spectrum is in agreement with the literature data[28].

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.24 (m, 3H), 7.13 (d, *J* = 7.2 Hz, 2H), 5.32 (s, 1H), 5.16 (s, 1H), 3.67 (s, 3H), 1.38 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 153.0, 141.6, 127.88, 127.85, 127.1, 114.5, 52.0, 47.6, 25.7.

methyl 2,2-dimethyl-3-(*p*-tolyl)but-3-enoate (3ca)

Prepared according to general procedure using fluoroalkene **1c** (40.9 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2a** (65.4 mg, 0.375 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (64 mg, 97%). The NMR spectrum is in agreement with the literature data[28].

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 7.7 Hz, 2H), 7.01 (d, *J* = 7.7 Hz, 2H), 5.28 (s, 1H), 5.13 (s, 1H), 3.65 (s, 3H), 2.32 (s, 3H), 1.37 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 153.0, 138.6, 136.6, 128.5, 127.8, 114.0, 51.9, 47.6, 25.7, 21.0.

methyl 2,2-dimethyl-3-(*m*-tolyl)but-3-enoate (3da)

Prepared according to general procedure using fluoroalkene **1d** (40.9 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2a** (65.4 mg, 0.375 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (57 mg, 87%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 7.7, 7.5 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.96 (s, 1H), 6.93 (d, *J* = 7.7 Hz, 1H), 5.31 (s, 1H), 5.14 (s, 1H), 3.68 (s, 3H), 2.34 (s, 3H), 1.39 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 153.2, 141.6, 137.3, 128.7, 127.8, 127.7, 124.9, 114.2, 51.9, 47.6, 25.7, 21.4.

HRMS: (DART+) Calculated ($C_{14}H_{19}O_2$) 219.13796 ($[M+H]^+$) Found: 219.13777

methyl 2,2-dimethyl-3-(*o*-tolyl)but-3-enoate (3ea)

Prepared according to general procedure using fluoroalkene **1e** (40.9 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2a** (65.4 mg, 0.375 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (28 mg, 43%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.15 (m, 2H), 7.10 (dd, *J* = 7.5, 7.1 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H),

5.43 (s, 1H), 5.01 (s, 1H), 3.67 (s, 3H), 2.26 (s, 3H), 1.35 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 151.5, 140.9, 135.8, 130.1, 128.5, 126.9, 124.8, 115.7, 51.9, 48.4, 25.6, 20.2.

HRMS: (DART+) Calculated ($C_{14}H_{19}O_2$) 219.13796 ($[M+H]^+$) Found: 219.13839

methyl 3-([1,1'-biphenyl]-4-yl)-2,2-dimethylbut-3-enoate (3fa)

Prepared according to general procedure using fluoroalkene **1f** (59.5 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2a** (65.4 mg, 0.375 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (60 mg, 71%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.5 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 5.26 (s, 1H), 5.13 (s, 1H), 3.59 (s, 3H), 1.34 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 152.7, 140.7, 140.6, 139.9, 128.7, 128.3, 127.2, 126.9, 126.5, 114.5, 52.0, 47.6, 25.8.

HRMS: (DART+) Calculated ($C_{19}H_{21}O_2$) 281.15361 ($[M+H]^+$) Found: 281.15490

methyl 3-(4-methoxyphenyl)-2,2-dimethylbut-3-enoate (3ga)

Prepared according to general procedure using fluoroalkene **1g** (45.7 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2a** (65.4 mg, 0.375 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (68 mg, 97%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 5.25 (s, 1H), 5.10 (s, 1H), 3.76 (s, 3H), 3.64 (s, 3H), 1.36 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 158.6, 152.5, 133.9, 128.9, 113.8, 113.2, 55.1, 51.9, 47.6, 25.7.

HRMS: (DART+) Calculated ($C_{14}H_{19}O_3$) 235.13287 ($[M+H]^+$) Found: 235.13384

methyl 3-(3-methoxyphenyl)-2,2-dimethylbut-3-enoate (3ha)

Prepared according to general procedure using fluoroalkene **1h** (45.7 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2a** (65.4 mg, 0.375 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (62 mg, 88%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 7.8, 7.5 Hz, 1H), 6.80 (d, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 2H), 6.69 (s, 2H), 5.31 (s, 1H), 5.16 (s, 1H), 3.78 (s, 3H), 3.67 (s, 3H), 1.38 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 159.0, 152.9, 143.0, 128.8, 120.4, 114.4, 113.9, 112.4, 55.1, 52.0, 47.6, 25.7.

HRMS: (DART+) Calculated ($C_{14}H_{19}O_3$) 235.13287 ($[M+H]^+$) Found: 235.13395

methyl 3-(benzo[*d*][1,3]dioxol-5-yl)-2,2-dimethylbut-3-enoate (3ia)

Prepared according to general procedure using fluoroalkene **1i** (49.8 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2a** (65.4 mg, 0.375 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (30 mg, 40%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, *J* = 7.7 Hz, 1H), 6.63 (s, 1H), 6.58 (d, *J* = 7.7 Hz, 1H), 5.94 (s, 2H), 5.27 (s, 1H), 5.12 (s, 1H), 3.68 (s, 3H), 1.37 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 152.5, 147.0, 146.5, 135.5, 121.3, 114.4, 108.7, 107.7, 100.9, 52.1, 47.7, 25.7.

HRMS: (DART+) Calculated ($C_{14}H_{17}O_4$) 249.11214 ($[M+H]^+$) Found: 249.11140

methyl 3-(3-fluorophenyl)-2,2-dimethylbut-3-enoate (3ja)

Prepared according to general procedure using fluoroalkene **1j** (42 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2a** (65.4 mg, 0.375 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (17 mg, 26%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (td, *J* = 8.1, 6.3 Hz, 1H), 6.95 (tdd, *J* = 8.5, 2.4, 0.9 Hz, 1H), 6.90 (dq, *J* = 7.8, 0.9 Hz, 1H), 6.85 (dq, *J* = 10.1, 1.4 Hz, 1H), 5.35 (s, 1H), 5.17 (s, 1H), 3.68 (s, 3H), 1.38 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7 (s), 162.3 (d, J_{C-F} = 245.4 Hz), 151.9 (s), 143.8 (d, J_{C-F} = 7.7 Hz), 129.3 (d, J_{C-F} = 8.6 Hz), 123.6 (d, J_{C-F} = 2.9 Hz), 115.2 (s), 115.1 (d, J_{C-F} = 22.0 Hz), 114.0 (d, J_{C-F} = 21.1 Hz), 52.1 (s), 47.5 (s), 25.6 (s).

^{19}F NMR (376 MHz, $CDCl_3$) δ -113.83 (dd, *J* = 15.3, 9.2 Hz).

HRMS: (DART+) Calculated ($C_{13}H_{16}O_2F$) 223.11288 ($[M+H]^+$) Found: 223.11262

methyl 3-(3-chlorophenyl)-2,2-dimethylbut-3-enoate (3ka)

Prepared according to general procedure using fluoroalkene **1k** (47 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2a** (65.4 mg, 0.375 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (54 mg, 75%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.09 (m, 2H), 7.06 (s, 1H), 6.92 (d, *J* = 7.0 Hz, 1H), 5.26 (s, 1H), 5.06 (s, 1H), 3.59 (s, 3H), 1.30 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 151.9, 143.4, 133.7, 129.1, 128.3, 127.2, 126.1, 115.4, 52.0, 47.6, 25.6.

HRMS: (DART+) Calculated ($C_{13}H_{16}O_2Cl$) 239.08333 ($[M+H]^+$) Found: 239.08389

methyl 3-(4-chlorophenyl)-2,2-dimethylbut-3-enoate (3la)

Prepared according to general procedure using fluoroalkene **1l** (47 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2a** (65.4 mg, 0.375 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the

product as a colorless oil (69 mg, 97%). The NMR spectrum is in agreement with the literature data[28].

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 5.34 (s, 1H), 5.14 (s, 1H), 3.66 (s, 3H), 1.38 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 152.0, 140.0, 133.0, 129.3, 128.0, 115.0, 52.0, 47.5, 25.6.

methyl 3-(3-bromophenyl)-2,2-dimethylbut-3-enoate (3ma)

Prepared according to general procedure using fluoroalkene **1m** (60.3 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2a** (65.4 mg, 0.375 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (77 mg, 91%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 7.5 Hz, 1H), 7.17 (s, 1H), 7.02 (dd, *J* = 7.5, 7.2 Hz, 1H), 6.92 (d, *J* = 7.2 Hz, 1H), 5.22 (s, 1H), 5.01 (s, 1H), 3.55 (s, 3H), 1.25 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 151.8, 143.7, 131.2, 130.1, 129.3, 126.5, 121.9, 115.4, 52.0, 47.6, 25.6.

HRMS: (DART+) Calculated ($C_{13}H_{16}O_2Br$) 283.03282 ($[M+H]^+$) Found: 283.03291

methyl 3-(4-bromophenyl)-2,2-dimethylbut-3-enoate (3na)

Prepared according to general procedure using fluoroalkene **1n** (60.3 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2a** (65.4 mg, 0.375 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (61 mg, 72%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 5.21 (s, 1H), 5.01 (s, 1H), 3.53 (s, 3H), 1.25 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 152.0, 140.5, 131.0, 129.6, 121.2, 115.1, 52.1, 47.5, 25.6.

HRMS: (DART+) Calculated ($C_{13}H_{16}O_2Br$) 283.03282 ($[M+H]^+$) Found: 283.03297

methyl 2,2-dimethyl-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)but-3-enoate (3oa)

Prepared according to general procedure using fluoroalkene **1o** (74.4 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2a** (65.4 mg, 0.375 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (71 mg, 72%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.6 Hz, 1H), 7.58 (s, 1H), 7.28 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 5.31 (s, 1H), 5.14 (s, 1H), 3.68 (s, 3H), 1.37 (s, 6H), 1.34 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 153.0, 140.9, 134.5, 133.4, 130.6, 127.1, 114.5, 83.7, 52.0, 47.7, 25.6, 24.8.

HRMS: (DART+) Calculated ($C_{19}H_{28}BO_4$) 331.20752 ($[M+H]^+$) Found: 331.20789

methyl 2,2-dimethyl-3-(naphthalen-1-yl)but-3-enoate (3pa)

Prepared according to general procedure using fluoroalkene **1p** (51.7 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2a** (65.4 mg, 0.375 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (35 mg, 46%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (td, *J* = 6.3, 3.0 Hz, 1H), 7.82 (td, *J* = 6.3, 3.0 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.45 (td, *J* = 6.3, 3.0 Hz, 2H), 7.40 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.18 (dd, *J* = 7.0, 1.1 Hz, 1H), 5.64 (s, 1H), 5.17 (s, 1H), 3.63 (s, 3H), 1.37 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 150.2, 138.9, 133.6, 132.5, 128.1, 127.4, 126.4, 125.65, 125.55, 124.7, 117.1, 52.0, 48.8, 25.6.

HRMS: (DART+) Calculated ($C_{17}H_{19}O_2$) 255.13796 ($[M+H]^+$) Found: 255.13686

methyl 3-(3-(furan-3-yl)phenyl)-2,2-dimethylbut-3-enoate (3qa)

Prepared according to general procedure using fluoroalkene **1q** (56.5 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2a** (65.4 mg, 0.375 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (24 mg, 30%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.47 (s, 1H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.32-7.24 (m, 2H), 7.02 (d, *J* = 7.7 Hz, 1H), 6.68 (s, 1H), 5.35 (s, 1H), 5.20 (s, 1H), 3.68 (s, 3H), 1.40 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 152.9, 143.6, 142.1, 138.5, 131.9, 128.3, 126.5, 126.3, 125.5, 124.6, 114.6, 108.8, 52.1, 47.6, 25.7.

HRMS: (DART+) Calculated ($C_{17}H_{19}O3$) 271.13287 ($[M+H]^+$) Found: 271.13422

methyl 2,2-dimethyl-3-(4-(thiophen-3-yl)phenyl)but-3-enoate (3ra)

Prepared according to general procedure using fluoroalkene **1r** (61.3 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2a** (65.4 mg, 0.375 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (62 mg, 72%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 2H), 7.43-7.36 (m, 3H), 7.16 (d, *J* = 8.0 Hz, 2H), 5.33 (s, 1H), 5.21 (s, 1H), 3.67 (s, 3H), 1.41 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 152.5, 141.8, 140.3, 134.5, 128.2, 126.2, 126.1, 125.8, 120.1, 114.4, 52.0, 47.5, 25.7.

HRMS: (DART+) Calculated ($C_{17}H_{19}O_2S$) 287.11003 ($[M+H]^+$) Found: 287.10995

methyl 3-(4-(benzofuran-2-yl)phenyl)-2,2-dimethylbut-3-enoate (3sa)

Prepared according to general procedure using fluoroalkene **1s** (71.5 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2a** (65.4 mg, 0.375 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a white solid (36 mg, 37%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.31-7.18 (m, 4H), 7.00 (s, 1H), 5.36 (s, 1H), 5.23 (s, 1H), 3.68 (s, 3H), 1.42 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 155.6, 154.8, 152.5, 141.8, 129.2, 129.1, 128.3, 124.4, 124.2, 122.9, 120.8, 114.8, 111.1, 101.3, 52.1, 47.5, 25.8.
HRMS: (DART+) Calculated ($C_{21}H_{21}O_3$) 321.14852 ($[M+H]^+$) Found: 321.14828

ethyl 3-(4-(*tert*-butyl)phenyl)-2,2-dimethylbut-3-enoate (3ab)

Prepared according to general procedure using fluoroalkene **1a** (53.5 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2b** (113 mg, 0.6 mmol, 2.0 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (78 mg, 95%)

^{1}H NMR (400 MHz, $CDCl_3$) δ7.15 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 5.16 (s, 1H), 5.03 (s, 1H), 3.97 (q, *J* = 7.2 Hz, 2H), 1.26 (s, 6H), 1.17 (s, 9H), 1.02 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 152.9, 149.8, 138.6, 127.4, 124.6, 113.9, 60.6, 47.5, 34.3, 31.3, 25.9, 13.9.
HRMS: (DART+) Calculated ($C_{18}H_{27}O_2$) 275.20056 ($[M+H]^+$) Found: 275.19931

phenyl 3-(4-(*tert*-butyl)phenyl)-2,2-dimethylbut-3-enoate (3ac)

Prepared according to general procedure using fluoroalkene **1a** (53.5 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2c** (142 mg, 0.60 mmol, 2.0 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (67 mg, 69%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.21 (m, 6H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 2H), 5.41 (s, 1H), 5.28 (s, 1H), 1.58 (s, 6H), 1.33 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 152.7, 151.0, 150.2, 138.8, 129.2, 127.5, 125.6, 124.9, 121.3, 114.3, 47.9, 34.5, 31.3, 26.4.
HRMS: (DART+) Calculated ($C_{22}H_{27}O_2$) 323.20056 ($[M+H]^+$) Found: 323.20205

isobutyl 3-(4-(*tert*-butyl)phenyl)-2,2-dimethylbut-3-enoate (3ad)

Prepared according to general procedure using fluoroalkene **1a** (53.5 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2d** (130 mg, 0.60 mmol, 2.0 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (65 mg, 72%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 5.24 (s, 1H), 5.12 (s, 1H), 3.77 (d, *J* = 6.5 Hz, 2H), 1.86-1.76 (m, 1H), 1.35 (s, 6H), 1.25 (s, 9H), 0.81 (d, *J* = 6.5 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 152.9, 149.7, 138.7, 127.4, 124.7, 113.9, 70.8, 47.7, 34.4, 31.3, 27.6,

25.9, 19.0.

HRMS: (DART+) Calculated ($C_{20}H_{31}O_2$) 303.23186 ($[M+H]^+$) Found: 303.23315

isopropyl 3-(4-(*tert*-butyl)phenyl)-2,2-dimethylbut-3-enoate (3ae)

Prepared according to general procedure using fluoroalkene **1a** (53.5 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2e** (121 mg, 0.60 mmol, 2.0 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (35 mg, 40%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 5.28 (s, 1H), 5.17 (s, 1H), 4.98-4.92 (m, 1H), 1.39 (s, 6H), 1.30 (s, 9H), 1.11 (d, *J* = 6.3 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 153.0, 149.8, 138.9, 127.4, 124.6, 113.8, 67.8, 47.5, 34.4, 31.3, 26.1, 21.4.

HRMS: (DART+) Calculated ($C_{19}H_{29}O_2$) 289.21621 ($[M+H]^+$) Found: 289.21509

phenethyl 3-(4-(*tert*-butyl)phenyl)-2,2-dimethylbut-3-enoate (3af)

Prepared according to general procedure using fluoroalkene **1a** (53.5 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2f** (159 mg, 0.60 mmol, 2.0 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (63 mg, 60%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.15 (m, 7H), 7.03 (d, *J* = 8.5 Hz, 2H), 5.27 (s, 1H), 5.16 (s, 1H), 4.24 (t, *J* = 7.1 Hz, 2H), 2.83 (t, *J* = 7.0 Hz, 2H), 1.35 (s, 6H), 1.29 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 152.7, 149.8, 138.6, 137.8, 128.9, 128.4, 127.4, 126.4, 124.7, 114.0, 65.3, 47.5, 34.8, 34.4, 31.3, 25.9.

HRMS: (DART+) Calculated ($C_{24}H_{31}O_2$) 351.23186 ($[M+H]^+$) Found: 351.23077

S-phenyl 3-(4-methoxyphenyl)-2,2-dimethylbut-3-enethioate (3gg)

Prepared according to general procedure using fluoroalkene **1g** (45.7 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2g** (152 mg, 0.60 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (43 mg, 46%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.35 (m, 5H), 7.22 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.51 (s, 1H), 5.37 (s, 1H), 3.80 (s, 3H), 1.46 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 158.8, 151.5, 134.8, 133.4, 129.2, 129.11, 129.08, 128.3, 116.7, 113.3, 55.2, 26.2.

HRMS: (DART+) Calculated ($C_{19}H_{21}O_2S$) 313.12568 ($[M+H]^+$) Found: 313.12633

ethyl 2,2-diethyl-3-(4-methoxyphenyl)but-3-enoate (3gh)

Prepared according to general procedure using fluoroalkene **1g** (45.7 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2h** (130 mg, 0.60 mmol, 2.0 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (67 mg, 81%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 5.25 (s, 1H), 5.22 (s, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 3H), 1.89 (dq, *J* = 14.4, 7.5 Hz, 2H), 1.71 (dq, *J* = 14.4, 7.5 Hz, 2H), 1.20 (t, *J* = 7.2 Hz, 3H), 0.77 (t, *J* = 7.5 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 158.5, 150.1, 134.6, 128.9, 116.3, 113.1, 60.4, 55.2, 55.1, 24.2, 14.1, 8.1.

HRMS: (DART+) Calculated ($C_{17}H_{25}O_3$) 277.17982 ($[M+H]^+$) Found: 277.18049

methyl 1-(1-(4-methoxyphenyl)vinyl)cyclohexane-1-carboxylate (3gi)

Prepared according to general procedure using fluoroalkene **1g** (45.7 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2i** (129 mg, 0.60 mmol, 2.0 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (66 mg, 80%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.2 Hz, 2H), 6.81 (d, *J* = 8.2 Hz, 2H), 5.31 (s, 1H), 5.10 (s, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 2.24-2.06 (m, 2H), 1.66-1.43 (m, 5H), 1.43-1.29 (m, 2H), 1.29-1.16 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6 158.5, 152.1, 134.0, 129.4, 115.7, 112.9, 55.1, 52.1, 51.8, 33.7, 25.5, 23.1.

HRMS: (DART+) Calculated ($C_{17}H_{23}O_3$) 275.16417 ($[M+H]^+$) Found: 275.16422

methyl 3-(4-methoxyphenyl)-2-methyl-2-phenylbut-3-enoate (3gj)

Prepared according to general procedure using fluoroalkene **1g** (45.7 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2j** (142 mg, 0.60 mmol, 2.0 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (86 mg, 97%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.28 (q, *J* = 7.4 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.72 (d, *J* = 8.5 Hz, 2H), 5.36 (s, 1H), 5.08 (s, 1H), 3.73 (s, 3H), 3.63 (s, 3H), 1.71 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 158.6, 151.4, 142.1, 133.5, 129.2, 128.0, 127.9, 126.8, 116.8, 113.0, 57.1, 55.0, 52.2, 25.5.

HRMS: (DART+) Calculated ($C_{19}H_{21}O_3$) 297.14852 ($[M+H]^+$) Found: 297.14935

methyl 3-(4-(tert-butyl)phenyl)-2-phenylbut-3-enoate (3ak)

Prepared according to general procedure using fluoroalkene **1a** (53.5 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2k** (83.4 mg, 0.60 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (87 mg, 94%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.20 (m, 9H), 5.55 (s, 1H), 5.06 (s, 1H), 4.92 (s, 1H), 3.61 (s, 3H), 1.24 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 150.6, 145.2, 137.6, 136.8, 128.9, 128.5, 127.4, 125.7, 125.2, 115.7, 56.1, 52.2, 34.4, 31.2.

HRMS: (DART+) Calculated ($C_{21}H_{25}O_2$) 309.18491 ($[M+H]^+$) Found: 309.18556

ethyl 2-(*tert*-butyl)-3-(4-methoxyphenyl)but-3-enoate (3gl)

Prepared according to general procedure using fluoroalkene **1g** (45.7 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2l** (121mg, 0.60 mmol, 2.0 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a colorless oil (17 mg, 20%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.43 (s, 1H), 5.36 (s, 1H), 4.22-4.10 (m, 2H), 3.81 (s, 3H), 3.50 (s, 1H), 1.27 (t, J = 7.1 Hz, 3H), 0.94 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 158.8, 143.9, 137.1, 127.6, 116.0, 113.6, 60.1, 58.8, 55.2, 34.7, 28.0, 14.2.

HRMS: (DART+) Calculated ($C_{17}H_{25}O_3$) 277.17982 ($[M+H]^+$) Found: 277.18066

ethyl 3-(4-(*tert*-butyl)phenyl)-2-(thiophen-3-yl)but-3-enoate (3am)

Prepared according to general procedure using fluoroalkene **1a** (53.5 mg, 0.30 mmol, 1.0 equiv), $B(C_6F_5)_3$ (23 mg, 0.045 mmol, 15 mol%), silyl ketene acetal **2m** (145 mg, 0.60 mmol, 1.25 equiv), and $CHCl_3$ (0.15 mL). The crude mixture was purified by chromatography on silica gel (Hexane/EtOAc = 95:5) to afford the product as a pale yellow oil (45 mg, 46%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.27 (m, 4H), 7.19 (d, J = 5.1 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 6.92-6.91 (m, 1H), 5.53 (s, 1H), 5.24 (s, 1H), 5.10 (s, 1H), 4.15-4.06 (m, 2H), 1.25 (s, 9H), 1.12 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 151.0, 145.8, 139.9, 137.4, 126.9, 126.8, 126.1, 125.5, 125.4, 115.7, 61.5, 51.6, 34.7, 31.4, 14.1.

HRMS: (DART+) Calculated ($C_{20}H_{25}O_2S$) 329.15698 ($[M+H]^+$) Found: 329.15751

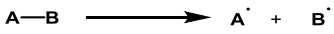
Theoretical calculation

General

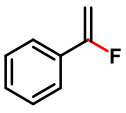
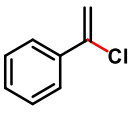
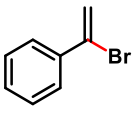
All geometry optimizations using density functional theory (DFT) were performed with Gaussian16 (rev. C.01)[31]. The geometries of all relevant structures were optimized using ωB97X-D density functional in the 6-31+G(d,p) (C, H, O, F, Si, B, Cl, and Br) and LanL2DZ (In and I) basis set with the IEF-PCM solvation model (presets for $CHCl_3$). were used. Optimized geometries were verified to be local minima on the respective potential energy landscape by the absence of negative eigenvalues of the Hessian, as obtained from a harmonic frequency calculation at the same level. Transition states were characterized by one negative eigenvalue of the Hesse matrix and the respective eigenvector vibration. Intrinsic reaction coordinate (IRC) calculations were carried out to confirm the transition states connecting the correct reactants and products on the potential energy surface. The thermal energy corrections were calculated for the optimized geometry at ωB97X-D level of theory in the 6-31+G(d,p) (C, H, O, F, Si, and B) and LanL2DZ (In and I) basis set with the IEFPCM solvation model (presets for $CHCl_3$). The zero-point energy (ZPE) and thermal energy corrections were calculated using vibrational frequencies with GoodVibes v3.0.1[32] employing a quasi-harmonic approximation for entropy calculation at pressure of 1.0 atm and temperature of 298.15 K with frequency cut-off value of 100 cm^{-1}, as proposed by Grimme. Intrinsic bond orbital (IBO) analysis was conducted by IBOview programs[33]. The reference molecular orbitals were calculated for the optimized geometry at PBE level of theory with Def2-SVPD as a basis set. Natural bond orbital (NBO) analyses were performed by NBO version 3.0 or 7.0 programs as including in Gaussian. The calculated structures were visualized with CYL view or VMD.

Calculated bond dissociation energies

Calculations were carried out at the uM06 or uωB97X-D level of theory in gas phase with the 6-311+G(d,p) basis set. The results performed at the uM06 were used in main text. Bond dissociation energies were calculated using the following equiation;



$BDE = (E_{Aradical} + E_{Bradical}) - E_{A\text{-}B}$

				
		F	Cl	Br
BDE (kcal/mol)	uM06	117.7	84.9	69.6
	uωB97X-D	117.4	85.7	72.5

Mechanistic investigation of vinylic C–F bond transformation using InI_3

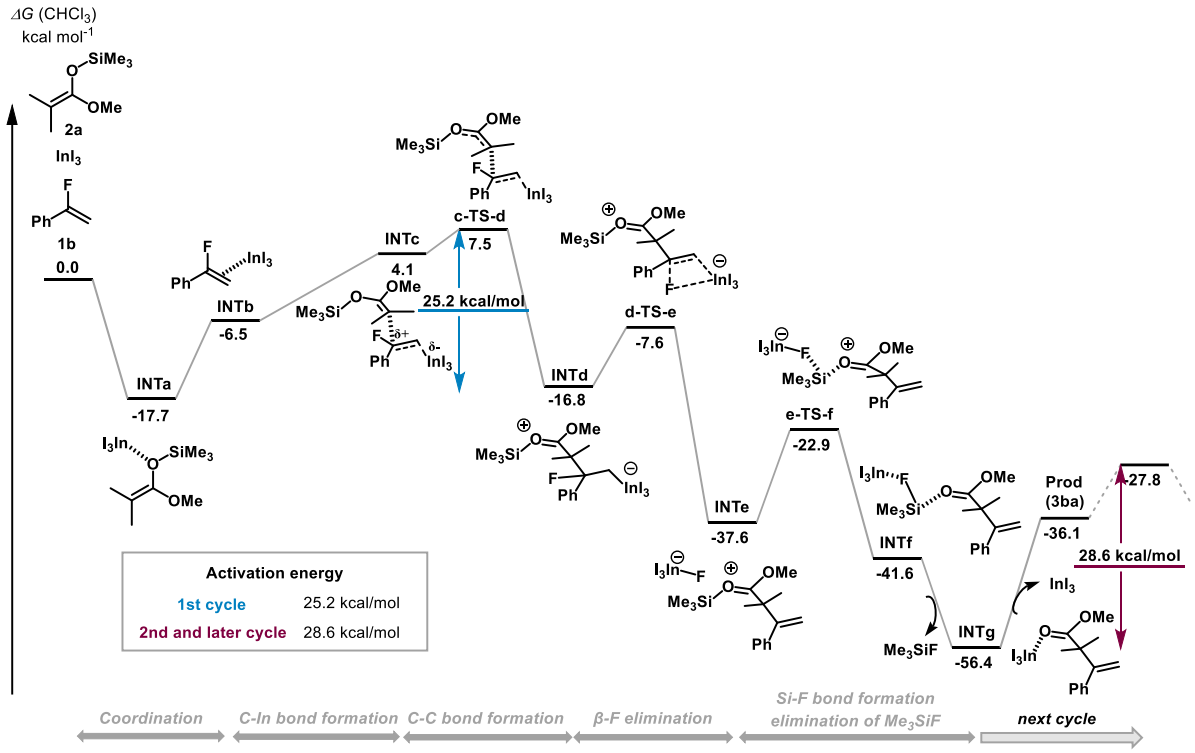


Figure S1. Potential energy surface of C–F bond functionalization using InI_3

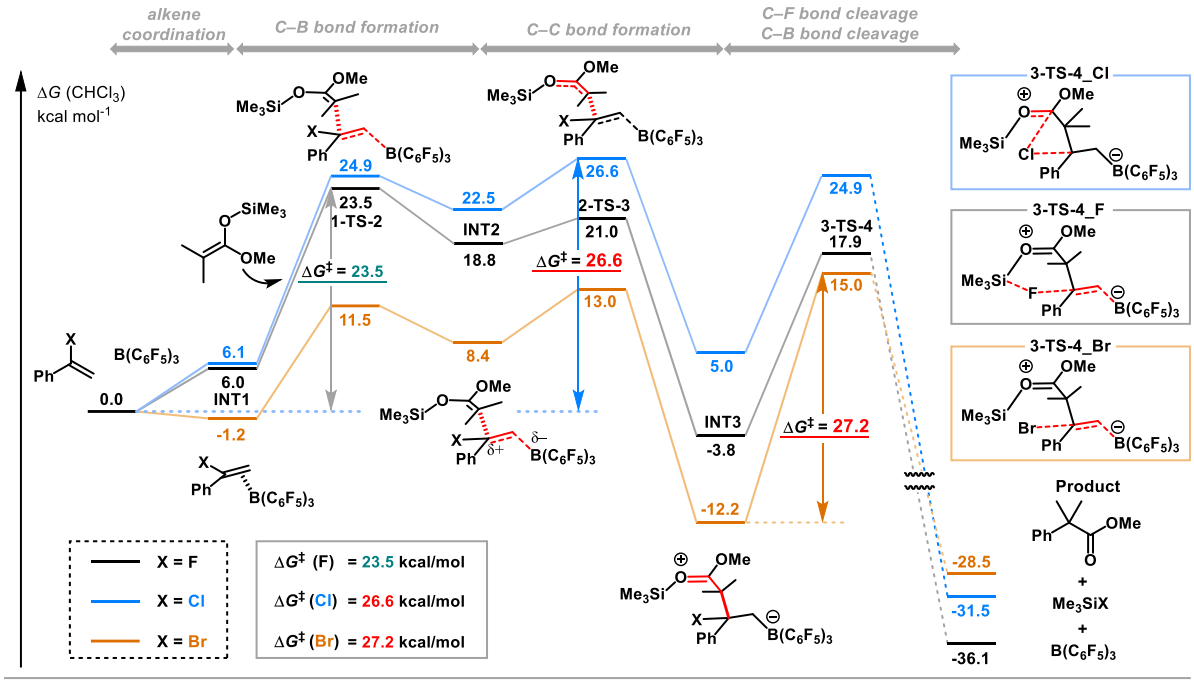
To understand the mechanism, the DFT calculation of the vinylic C–F bond functionalization using InI_3 was conducted. The obtained potential energy surface was shown in Figure S1. At first, The silyl ketene acetal **2a** is coordinated with InI_3 to give **INTa**, which act as a resting state of this reaction. The 1,2-carbometalation proceed through C–In bond formation and C–C bond formation (from **INTb** to **INTd**) with an activation energy of 25.2 kcal/mol. The β-fluorine elimination from **INTe** occurs via transition state **e-TS-f** to give **INTf**, and then the elimination of Me_3SiF produce the **INTg**.

The highest activation energy in 1st cycle is 25.2 kcal/mol (from **INTa** to **c-TS-d**), while that in next cycles is 27.8 kcal/mol, which is relatively higher value. This is because there is a strong interaction between InI_3 and the ester moiety of target product (interaction energy: 20.3 kcal/mol). In addition, the competitive decomposition reaction of **1b** with InI_3 was observed because α-fluorostyrene is unstable in acidic conditions. These are the reason why the stoichiometric amount of InI_3 was required to get the target product in moderate yield.

In the case of vinylic C–F bond functionalization using InI_3, C–F bond cleavage occurs via not direct Si–F bond formation but β-fluorine elimination. Indium(III) complexes can have five coordination, facilitating the β-fluorine elimination.

Reaction mechanism after 1,2-carboboration with α-chlorostyrene & α-bromostyrene

Overall potential energy surfaces



α-chlorostyrene

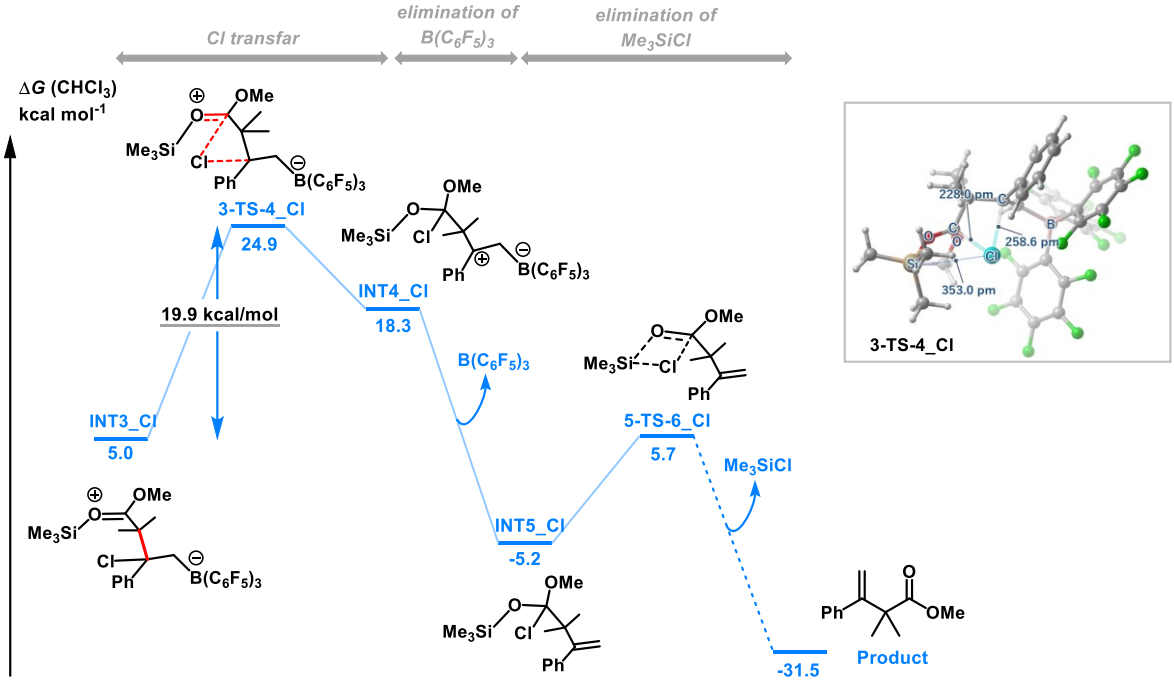
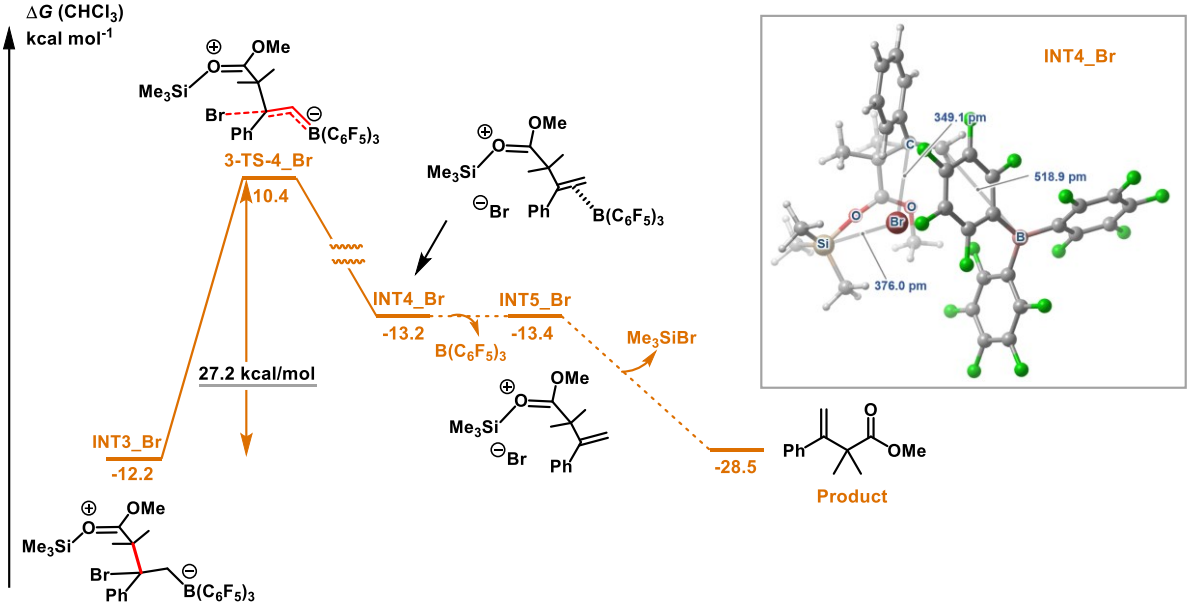


Figure S2. Potential energy surface at the C–Cl bond cleavage step

The nucleophilic attack of chloride to carbonyl moiety occurs to give **INT4_Cl** via **3-TS-4_Cl** and subsequently the elimination of $B(C_6F_5)_3$ and Me_3SiCl occur to give the target product. In this step, the value of the highest activation energy is 19.9 kcal/mol which means the 1,2-carboboration step (before **INT3_cl**) is the rate determining step.

β-chlorostyrene



As discussed in main text, the C–Br bond cleavage required the high energy (27.2 kcal/mol). In **INT4_Br**, no interaction between olefin moiety and $B(C_6F_5)_3$ was observed (C–B bond length: 518.9 pm).

Vinylic C–F bond cleavage without $B(C_6F_5)_3$

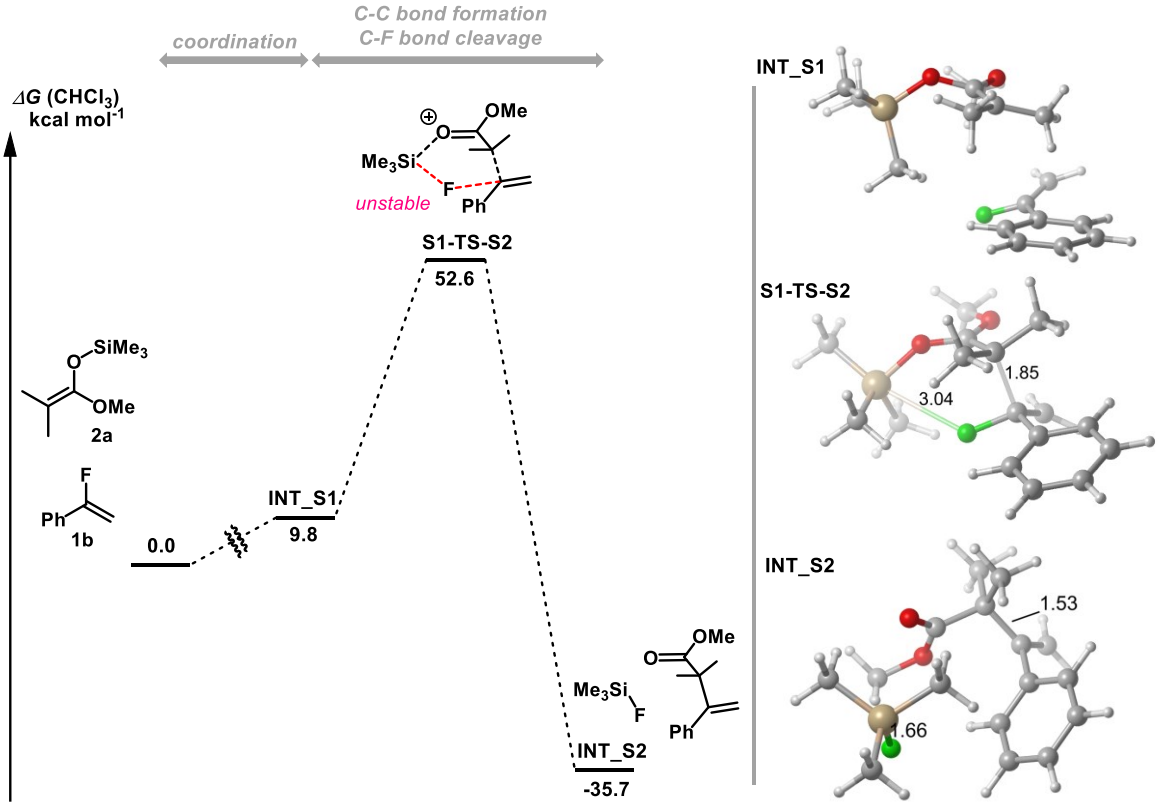


Figure S3. Potential energy surface of direct coupling reaction between **1b** and **2a**

Our DFT calculation revealed that the C–F bond functionalization without $B(C_6F_5)_3$ proceed through quite unstable transition state **S1-TS-S2**. The carboboration of α-fluorostyrene **1a** with silyl ketene acetal **2a** and $B(C_6F_5)_3$ (from INT1 to INT3 in main text) is essential to facilitate the desired C–F bond cleavage.

Investigation of possible resting state

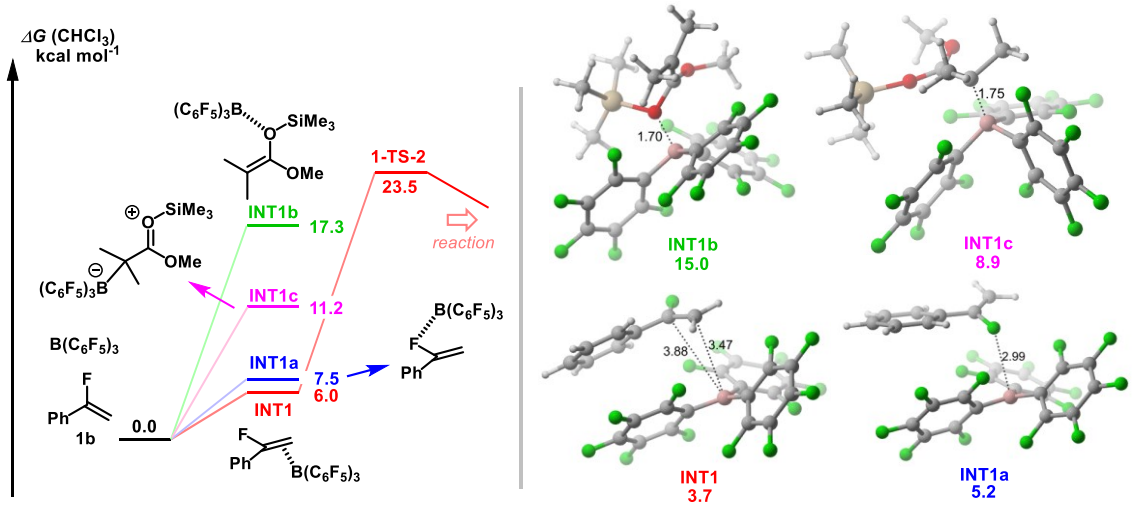


Figure S4. Calculated energies of possible resting state

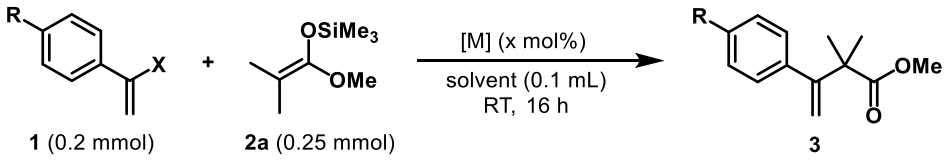
In **INT1**, the fluorostyrene **1b** was coordinated with $B(C_6F_5)_3$ to give **INT1,** which undergo the desired reaction via **1-TS-2**. In **INT1a**, the lone pair of F atom in fluorostyrene **1b** interacts with $B(C_6F_5)_3$. In **INT1b**, the lone pair of O atom of silyl ketene acetal **2a** interact with $B(C_6F_5)_3$. In **INT1c**, the C–B bond formation occur between silyl keten acetal **2a** and $B(C_6F_5)_3$. These all reactions are endothermic reaction and the **INT1** has the lowest energy among them.

Computed ^{29}Si NMR chemical shifts

^{29}Si NMR chemical shifts were calculated by the GIAO methods at the ωB97X-D/6-31+G(d,p)//ωB97X-D/6-31+G(d,p) level and were referenced to tetramethylsilane (TMS). The calculated SCF GIAO Magnetic shielding tensor is 412.5237 (δ^{29}Si = 0.0). At our calculation condition, the ^{29}Si chemical shift for Me_3Si^+ is at 352.3 ppm. Olah and co-workers reported it at 354.2 ppm using IGLO II//B3LYP.6-31G(d) [29] and Reed and co-wokers estimated the ^{29}Si chemical shifts for Me^3Si^+ at 354 ppm in HF/6-31G(d) level[30]. These values are close to those obtained, which demonstrate that our selected level is adequate to discuss about the ^{29}Si NMR chemical shifts.

(ppm)	GIAO/ωB97X-D/6-31+G(d,p)(our method)	**Ref. 15**	**Ref. 16**
δ ^{29}Si of **INT3_F**	68.0973		
δ ^{29}Si of $^+SiMe_3$	352.2999	354	354.2
The tensor of **INT3_F**	344.4264		
The tensor of $+SiMe_3$	60.2238		
The tensor of $SiMe_4$	412.5237		

Reaction optimization



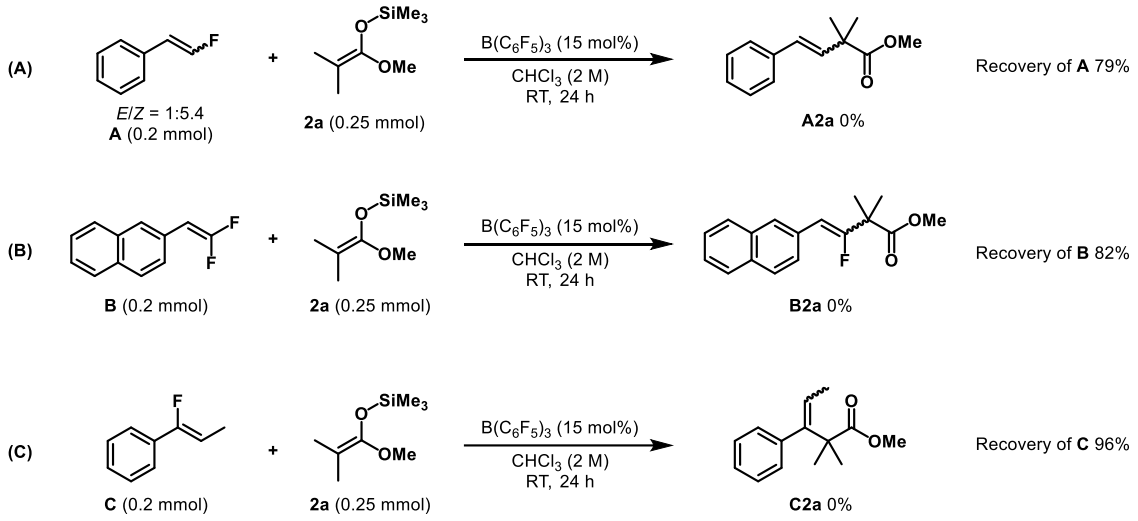
1 (0.2 mmol) **2a** (0.25 mmol) **3**

To an oven-dried 2 mL PTFE/silicone-lined septa screw cap vial equipped with a magnetic stirring bar was charged with Lewis acid, $CHCl_3$ (0.1 mL) and silyl ketene acetal **2** (44 mg, 0.25 mmol, 1.25 equiv) inside glove box. The resulting solution was stirred for several seconds, and fluoroalkene **1** (0.2 mmol, 1.0 equiv) was added to the solution in glove box. After being stirred at room temperature for 16 h, the layers were separated, and the aqueous layer was extracted with $CHCl_3$ (5.0 mL x 3). The collected organic layer was dried over $MgSO_4$, filtered the mixture and the solution was concentrated in vacuo. The crude mixture was measured by ^1H NMR using CH_2Br_2 as an internal standard.

Entry	R	X	[M] (x mol%)	Solvent	Yield of **3** /%[a]	Recovery of **1** /%
1	*t*Bu	F	$B(C_6F_5)_3$ (15)	$CHCl_3$	96	0
2	*t*Bu	F	AgOTf (100)	$CHCl_3$	0	0
3	*t*Bu	F	$AgBF_4$	$CHCl_3$	0	0
4	*t*Bu	F	$AgSbF_6$	$CHCl_3$	0	0
5	*t*Bu	F	$FeBr_2$	$CHCl_3$	0	84
6	*t*Bu	F	$FeBr_3$	$CHCl_3$	0	0
7	*t*Bu	F	CuI	$CHCl_3$	0	79
8	*t*Bu	F	$Cu(OAc)_2$	$CHCl_3$	0	67
9	*t*Bu	F	$Cu(OTf)_2$	$CHCl_3$	0	0
10	*t*Bu	F	$CeCl_3$	$CHCl_3$	0	87
11	*t*Bu	F	$AuCl_3$	$CHCl_3$	0	0
12	*t*Bu	F	$BiCl_3$	$CHCl_3$	0	64
13	*t*Bu	F	$BiBr_3$	$CHCl_3$	Trace	0
14	*t*Bu	F	$GaCl_3$	$CHCl_3$	0	90
15	*t*Bu	F	$GaBr_3$	$CHCl_3$	0	0
16	*t*Bu	F	GaI_3	$CHCl_3$	0	0
17	*t*Bu	F	ClBcat	$CHCl_3$	0	0
18	*t*Bu	F	$AlCl_3$	$CHCl_3$	0	68
19	*t*Bu	F	$TiCl_4$	$CHCl_3$	0	80
20	*t*Bu	F	$In(acac)_3$	$CHCl_3$	0	100
21	*t*Bu	F	$In(OAc)_3$	$CHCl_3$	0	100
22	*t*Bu	F	$InBr_3$ (50)	$CHCl_3$	Trace	0
23	*t*Bu	F	InI_3 (100)	$CHCl_3$	59	0
24	*t*Bu	F	InI_3 (50)	$CHCl_3$	40	18
25	*t*Bu	F	BCl_3 (15)	$CHCl_3$	0	100

26	*t*Bu	F	$BF_3 \cdot OEt_2$	$CHCl_3$	0	100
27	*t*Bu	F	$B(C_6F_5)_3$ (10)	$CHCl_3$	91	0
28	*t*Bu	F	$B(C_6F_5)_3$ (5)	$CHCl_3$	74	26
29	*t*Bu	F	$B(C_6F_5)_3$ (2)	$CHCl_3$	40	60
30	*t*Bu	F	$B(C_6F_5)_3$ (15)	THF	0	NA
31	*t*Bu	F	$B(C_6F_5)_3$ (15)	MeCN	0	NA
32	*t*Bu	F	$B(C_6F_5)_3$ (15)	Ether	10	0
33	*t*Bu	F	$B(C_6F_5)_3$ (15)	Toluene	23	40
34	*t*Bu	F	$B(C_6F_5)_3$ (15)	PhCl	62	0
35	*t*Bu	F	$B(C_6F_5)_3$ (15)	DMF	0	NA
36	*t*Bu	F	$B(C_6F_5)_3$ (15)	DCM	70	0
37	H	F	$B(C_6F_5)_3$ (20)	$CHCl_3$	82	0
38	H	Cl	$B(C_6F_5)_3$ (20)	$CHCl_3$	0	0
39	H	Br	$B(C_6F_5)_3$ (20)	$CHCl_3$	0	0

Investigation using *β*-fluorostyrene, *gem*-difluoroalkene, and *β*-substituted *α*-fluorostyrene



We have examined *β*-fluorostyrene (**A**), *gem*-difluoroalkene (**B**), and *β*-substituted *α*-fluorostyrene(**C**) for C–F bond transformation, but no reaction proceeded due to the repulsion between substituent (Ph, naphtyl or Me moiety) and $B(C_6F_5)_3$.

In our reaction system, a terminal olefin moiety is essential for the carboboration with $B(C_6F_5)_3$.

The known fluoroalkenes **A**[34a], **B**[34b], and **C**[34c] were prepared according to the literatures, and the spectral data are in agreement with the reports.

3-5. References

[1] For recent reviews on C–F bond functionalization, see: (a) H. Amii, K. Uneyama, *Chem. Rev.* **2009**, *109*, 2119-2183; (b) T. A. Unzner, T. Magauer, *Tetrahedron Lett.* **2015**, *56*, 877-883; (c) T. Ahrens, J. Kohlmann, M. Ahrens, T. Braun, *Chem. Rev.* **2015**, *115*, 931-972; (d) J. -D. Hamel, J. -F. Paquin, *Chem.*

Commun. **2018**, *54*, 10224-10239.

[2] (a) T. Stahl, H. F. T. Klare, M. Oestreich, *ACS Catal.* **2013**, *3*, 1578-1587; (b) W. Chen, C. Bakewell, M. R. Crimmin, *Synthesis* **2017**, *49*, 810-821.

[3] (a) H. F. T. Klare, L. Albers, L. Süsse, S. Keess, T. Müller, M. Oestreich, *Chem. Rev.* **2021**, *121*, 5889-5985; (b) H. F. T. Klare, *ACS Catal.* **2017**, *7*, 6999-7002.

[4] A. Duttwyler, C. Douvris, N. L. P. Fackler, F. S. Tham, C. A. Reed, K. K. Baldridge, J. S. Siegel, *Angew. Chem. Int. Ed.* **2010**, *49*, 7519-7522; *Angew. Chem.* **2010**, *122*, 7691-7684.

[5] (a) O. Allemann, S. Duttwyler, P. Romanato, K. K. Baldridge, J. S. Siegel, *Science* **2011**, *332*, 574-577; (b) O. Allemann, K. K. Baldridge, J. S. Siegel, *Org. Chem. Front.* **2015**, *2*, 1018-1021. This strategy has also found application in material science, see: (c) J. Dosso, J. Tasseroul, F. Fasano, D. Marinelli, N. Biot, A. Fermi, D. Bonifazi, *Angew. Chem. Int. Ed*. **2017**, *56*, 4483-4487; *Angew. Chem.* **2017**, *129*, 4554-4558; (d) Y. Wang, O. Allemann, T. S. Balaban, N. Vanthuyne, A. Linden, K. K. Baldridge, J. S. Siegel, *Angew. Chem. Int. Ed.* **2018**, *57*, 6470-6474; *Angew. Chem.* **2018**, *130*, 6580-6584; (e) S. Liu, L. M. Roch, O. Allemann, J. Xu, N. Vanthuyne, K. K. Baldridge, J. S. Siegel, *J. Org. Chem.* **2018**, *83*, 3979-3986.

[6] B. Shao, A. L. Bagdasarian, S. Popov, H. M. Nelson, *Science* **2017**, *355*, 1403-1407.

[7] For selected reviews relating to Frustrated Lewis Pairs (FLP) chemistry, see: (a) D. W. Stephan, *J. Am. Chem. Soc.* **2015**, *137*, 10018-10032; (b) R. L. Melen, *Chem. Commun.* **2014**, *50*, 1161-1174; (c) J. R. Lawson, R. L. Melen, *Inorg. Chem.* **2017**, *56*, 8627-8643; (d) D. W. Stephan, *Acc Chem. Res.* **2015**, *48*, 306-316. For selected papers relating to FLP-type three component reactions using alkynes or olefins, see; (e) J. S. J. McCahill, G. C. Welch, D. W. Stephan, *Angew. Chem. Int. Ed.* **2007**, *46*, 4968-4971; *Angew. Chem.* **2007**, *119*, 5056-5059; (f) T. Voss, C. Chen, G. Kehr, E. Nauha, G. Erker, D. W. Stephan, *Chem. Eur. J.* **2010**, *16*, 3005-3008; (g) M. A. Dureen, D. W. Stephan, *J. Am. Chem. Soc.* **2009**, *131*, 8396-8397; (h) M. A. Dureen, C. C. Brown, D. W. Stephan, *Organometallics* **2010**, *29*, 6422-6432; (i) C. Jiang, O. Blacque, H. Berke, *Organometallics* **2010**, *29*, 125-133; (j) X. Zhao, D. W. Stephan, *Chem. Sci.* **2012**, *3*, 2123-2132.

[8] List and co-workers has established the asymmetric Diels-Alder reaction catalyzed by oxygen-stabilized silylium ion pair generated by Brønsted-acid activation of a silyl ketene acetal, see: (a) T. Gatzenmeier, M. van Gemmeren, Y. Xie, D. Höfler, M. Leutzsch, B. List, *Science* **2016**, *351*, 949-952; (b) T. Gatzenmeier, M. Turberg, D. Yepes, Y. Xie, F. Neese, G. Bistoni, B. List, *J. Am. Chem. Soc*, **2018**, *140*, 12671-12676. Our group observed the oxygen-stabilized silylium ion, which is generated via carbometallation and sequential migration. This species was characterized by X-ray crystallographic analysis: (c) K. Kang, K. Sakamoto, Y. Nishimoto, M. Yasuda, *Chem. Eur. J.* **2020**, *26*, 4930-4934.

[9] N. Kordts, S. Künzler, S. Rathjen, T. Sieling, H. Groβekappenberg, M. Schmidtmann, T. Müller, *Chem. Eur. J.* **2017**, *23*, 10068-10079.

[10] For selected reviews see, (a) G. G. Furin, *Russ. J. Org. Chem.* **2002**, *38*, 921-961. (b) J. D. Moody, D. VanDerveer, D. W. Smith Jr. S. T. Iacono, *Org. Biomol. Chem.* **2011**, *9*, 4842-4849. (c) T. Fujita, K. Fuchibe, J. Ichikawa, *Angew. Chem. Int. Ed.* **2019**, *58*, 390-402; *Angew. Chem.* **2019**, *131*, 396-408. (d)

X. Zhang, S. Cao, *Tetrahedron Lett.* **2017**, *58*, 375-392.

[11] Comparative studies of styrene derivatives such as difluoro- and monofluoro compounds were investigated to demonstrate that two vinylic fluorine atoms were important to underwent the desired reaction, see (a) J. Ichikawa, Y. Wada, M. Fujiwara, K. Sakoda, *Synthesis* **2002** *13*, 1917-1936. Another report showed the difference of reaction conditions between mono- and difluoroalkenes, see (b) Y. Xiong, X. Zhang, T. Huang, S. Cao, *J. Org. Chem.* **2014**, *79*, 6395-6402.

[12] (a) A. Schäfer, M. Reiβmann, A. Schäfer, M. Schmidtmann, T. Müller, *Chem. Eur. J.* **2014**, *20*, 9381-9386; (b) Z. Xie, R. Bau, C. A. Reed, *J. Chem. Soc. Chem. Commun.* **1994**, 2519-2520; (c) M. Driess, R. Barmeyer, C. Monsé, K. Merz, *Angew. Chem. Int. Ed.* **2001**, *40*, 2308-2310; *Angew. Chem.* **2001**, *113*, 2366-2369.

[13] (a) G. Knizia, *J. Chem. Theory Comput.* **2013**, *9*, 4834-4843; (b) G. Knizia, J. E. M. N. Klein, *Angew. Chem. Int. Ed.* **2015**, *54*, 5518-5522; *Angew. Chem.* **2015**, *127*, 5609-5613.

[14] R. D. Chambers, *Fluorine in Organic Chemistry*, 2nd ed., **2004**, Blackwell, Oxford

[15] C. J. Thomson, Q. Zhang, N. AlMaharik, M. Bhl, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan *Chem. Commun.* **2018**, *54*, 8415-8418.

[16] R. Guo, X. Qi, H. Xiang, P. Geaneotes, R. Wang, P. Liu, Y. -M. Wang *Angew. Chem. Int. Ed.* **2020**, *59*, 16651–16660.

[17] G. Zhang, J. D. McCorvy, S. Shen, J. Cheng, B. L. Roth, A. P. Kozikowski, *Eur. J. Med. Chem.* **2019**, *182*, 111626.

[18] J. Kikuchi, H. Ye, M. Terada *Org. Lett.* **2020**, *22*, 8957–8961.

[19] M. -H. Yang, S. S. Matikonda, R. A. Altman, *Org. Lett.* **2013**, *15*, 3894–3897.

[20] M. Ohashi, H. Saijo, M. Shibata, S. Ogoshi, *Eur. J. Org. Chem.* **2013**, 443–447.

[21] T. -H. Nguyen, M. Abarbri, D. Guilloteau, S. Mavel, P. Emond, *Tetrahedron* **2011**, *67*, 3434–3439.

[22] Y. Nishimoto, Y. Kita, H. Ueda, H. Imaoka, K. Chiba, M. Yasuda, *Chem. Eur. J.* **2016**, *22*, 11837–11845.

[23] A. J. Woodhead et al., WO 2013/0604543 A1

[24] M. Hatano, E. Takagi, K. Ishihara, *Org. Lett.* **2007**, *9*, 4527–4530.

[25] D. Katayev, V. Matoušek, R. Koller, A. Togni et al., *Org. Lett.* **2015**, *17*, 5898–5901.

[26] A. Iida, S. Nakazawa, T. Okabayashi, A. Horii, T. Misaki, Y. Tanabe, *Org. Lett*. **2006**, *8*, 5215–5218.

[27] Y. Nishimoto, H. Ueda, Y. Inamoto, M. Yasuda, A. Baba, *Org. Lett.* **2010**, *12*, 3390–3393.

[28] Y. Nishimoto, R. Moritoh, M. Yasuda, A. Baba, *Angew. Chem. Int. Ed*. **2009**, *48*, 4577–4580.

[29] Olah, G. A.; Rasul, G.; Prakash, G. K. S. *J. Organomet. Chem*. **1996**, *521*, 271.

[30] Z. Xie, J. Manning, R. W. Reed, R. Mathur, P. D. W. Boyd, A. Benesi, C. A. Reed, *J. Am*. *Chem*. *Soc*. **1996**, *118*, 2922.

[31] Gaussian 16, Revision C.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M.

Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.

[32] G. Luchini, J. V. Alegre-Requena, I. Funes-Ardoiz, R. S. Paton, GoodVibes: Automated Thermochemistry for Heterogeneous Computational Chemistry Data. *F1000Research*, **2020**, *9*, 291 DOI: 10.12688/f1000research.22758.1

[33] (a) G. Knizia, Intrinsic Atomic Orbitals: An Unbiased Bridge between Quantum Theory and Chemical Concepts. *J. Chem. Theory Comput.* **2013**, *9*, 4834–4843. (b) G. Knizia, J. E. M. N. Klein, Electron Flow in Reaction Mechanism – Revealed from First Principles. *Angew. Chem., Int. Ed.* **2015**, *54*, 5518–5522.

[34] (a) C. -T. Li, X. Yuan, Z. -Y. Tang *Tetrahedron Lett.* **2016**, *57*, 5624–5627. (b) H. Sakaguchi, Y. Uetake, M. Ohashi, T. Niwa, S. Ogoshi, T. Hosoya *J. Am. Chem. Soc*. **2017**, *139*, 12855–12862. (c) R. Guo, X. Qi, H. Xiang, P. Geaneotes, R. Wang, P. Liu, Y. -M. Wang *Angew. Chem. Int. Ed*. **2020**, *59*, 16651–16660.

Conclusion

In this study, the synthetic methodologies via carbometalation or oxymetalation have been developed for the synthesis of various heterocycles or the transformation of C–F bonds.

Firstly, the synthesis of multi-substituted 2-pyrones bearing a carbon-indium bond via oxyindation of carbonyl-ene-yne compounds with indium trihalides was described in Chapter 1. This strategy is a novel selective synthetic method for multi-substituted 2-pyrones. The metalated 2-pyrones and zwitterion intermediate were fully characterized by X-ray crystallographic analysis and NMR spectroscopy. The synthesized tetrasubstituted 2-pyrones showed aggregation-induced emission. The DFT calculation revealed the difference among group 13 metal salts.

Secondly, I mentioned that the indium-catalyzed C–F bond transformation of *gem*-difluoroalkenes bearing ester moiety to give a wide variety of fluorinated isocoumarins in Chapter 2. This is the first comprehensive and efficient method for the synthesis of fluorinated isocoumarins from readily accessible starting materials. The present reaction proceeds smoothly using main-group metal salts: a catalytic amount of $InCl_3$ in the presence of ZnI_2. DFT calculation of potential energy surfaces showed that the reaction consisted of oxyindation with the elimination of an alkyl halide and *β*-fluorine elimination. The obtained fluorinated compound was transformed via Friedel-Crafts type alkenylation. The double C‑F bonds transformation from *gem*-difluoroalkene compounds was also established.

Finally, I described the development of a new and simple methodology for vinylic $C(sp^2)$–F bond transformation of *α*-fluorostyrenes with silyl ketene acetals catalyzed by $B(C_6F_5)_3$ in chapter 3. DFT studies showed that *α*-fluorostyrene underwent 1,2-carboboration in the presence of silyl ketene acetals and $B(C_6F_5)_3$ catalyst, subsequently undergoing C–F bond cleavage was caused by an oxygen-stabilized silylium ion generated from silyl ketene acetal. The IRC calculation and IBO analysis revealed that the vinyl $C(sp^2)$–F bond cleavage was caused by an oxygen-stabilized silylium ion generated from silyl ketene acetals. Moreover, a comparison of *α*-fluorostyrene with *α*-chloro- or *α*-bromostyrenes demonstrated that this reaction was specific to *α*-fluorostyrenes because of the strong-fluorine affinity of a silylium ion. A broad range of *α*-fluorostyrenes and silyl ketene acetals underwent this C–F bond transformation.

Knowledges obtained from Chapter 1 and 2 are that the intramolecular oxymetalation using indium salts is useful for the synthesis of heterocycles bearing a carbon–metal bond or a carbon–fluorine bond using activation of carbon-carbon multiple bonds. This strategy will be more suitable for further .work to be aimed at other heterocycles. Chapter 2 gives us an important knowledge that a carbon–fluorine bond is cleaved via *β*-fluorine elimination in organoindium species. This fact is significant not only in fluorine chemistry but also in organoindium chemistry and can be expanded for further carbon-fluorine or carbon-hetero bonds transformation. In chapter 3, the fact that an oxygen-stabilized silylium ion, which is generated from silyl ketene acetal via carboboration, is able to activate a carbon–fluorine bond is one of the most striking features in boron, silicon, fluorine, and Lewis acid chemistry.

The obtained knowledge provides an unprecedent strategy to form a wide array of heterocycles and to activate carbon–fluorine bonds via oxymetalation or heterometalation using main-group metals. The insights obtained from the present works are expected to contribute to main-group metal chemistry.