BF_3-Catalyzed Intramolecular Fluorocarbamoylation of Alkynes: Synthesis of 3-Fluoromethylene Oxindoles and γ-Lactams

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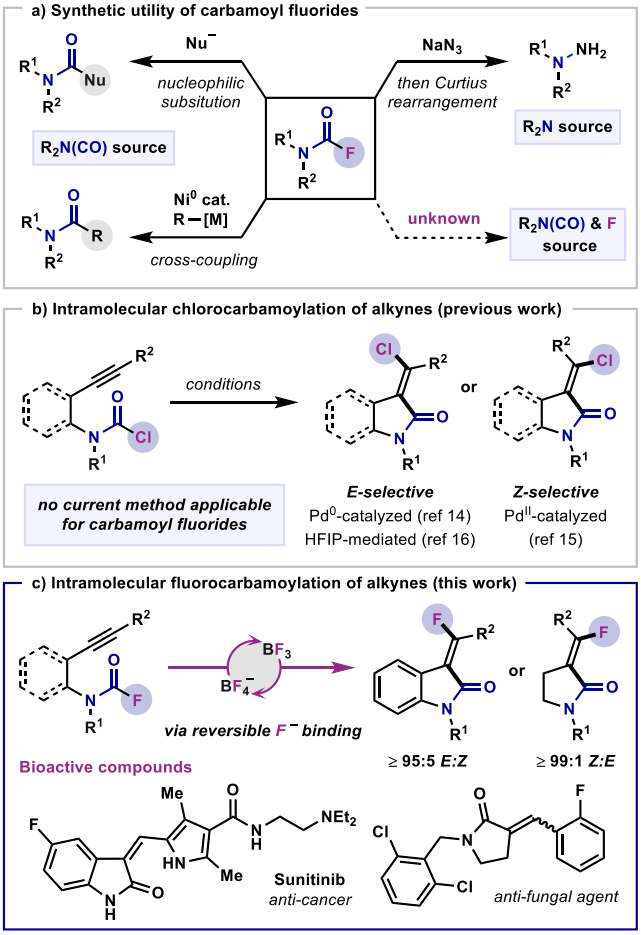
ABSTRACT: A BF_3-catalyzed atom-economical fluorocarbamoylation reaction of alkyne-tethered carbamoyl fluorides is reported. The catalyst acts as both a fluoride source and Lewis acid activator, enabling the formal insertion of alkynes into strong C–F bonds. Our proposed mechanism involves fluoride addition to the alkyne via a nucleophilic fluoroborate species, followed by cyclization onto the carbamoyl moiety with concomitant release of fluoride. The developed method provides access to 3-fluoromethylene oxindoles and γ-lactams with excellent stereoselectivity, including fluorinated derivatives of known protein kinase inhibitors.

Catalytic reactions involving C–F bond formation are of interest to pharmaceutical and agrochemical industries due to the favorable medicinal properties of fluorinated small molecules.[1] More recently, strategies for the direct functionalization of C–F bonds have emerged, typically requiring the use of specialized transition metal catalysts or strong main-group Lewis acids.[2] Despite significant progress in both areas, transformations involving both C–F bond formation and C–F bond activation remain exceedingly rare.[3] Considering the abundance of fluorinated molecules at our disposal, we aim to repurpose such compounds in atom-economical carbofluorination reactions, thus enabling fluorine atom-recycling. Transition metal-catalyzed carbohalogenation reactions have been developed extensively over the last decade, primarily with Pd and Ni catalysts that can facilitate both the oxidative addition and reductive elimination of C–X bonds (X = I, Br, or Cl).[4] Currently, these systems are not capable of promoting reversible C–F bond activation due to the high BDE of both C–F and M–F bonds. Thus, to merge C–F bond cleavage and formation in a single transformation, catalysts operating under new mechanistic regimes are required.

Contemporary catalytic platforms have recently emerged, enabling the application of highly electrophilic acyl fluorides in atom-economical addition reactions.[5-7] The Tobisu group has reported a phosphine-catalyzed intermolecular fluoroacylation of activated alkynoates that proceeds through a C–F bond coupling on a P^V intermediate.[5,6] Recently, Studer and co-workers disclosed an intermolecular alkene fluoroacylation reaction of benzofurans and indoles promoted by cooperative NHC and photoredox catalysis.[7] In both cases, the high reactivity of acyl fluorides towards nucleophilic substitution was harnessed in the C–F bond cleavage step.



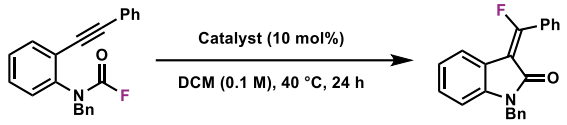
Scheme 1. a) Synthetic utility of carbamoyl fluorides. b) Previously reported intramolecular chlorocarbamoylation reactions. c) This work: BF_3-catalyzed intramolecular fluorocarbamoylation reaction.

While new synthetic applications of acyl fluorides have been widely developed,[8] the established chemistry of related carbamoyl fluorides has been limited due to their increased stability. Thus, stronger nucleophiles are often required for simple carbamoyl substitution reactions (Scheme 1a).[9-11] In the context of transition metal-catalyzed reactions, only three reports on the cross-coupling of carbamoyl fluoride electrophiles have been disclosed – all of which require a Ni^0 catalyst to facilitate the challenging C–F bond oxidative addition step.[12] Notably, in all reported reactions, the fluorine atom of the carbamoyl fluoride is lost as a wasteful by-product. To date, reactions that retain both the carbamoyl fragment and the fluorine atom in the final product remain elusive.

Given recent advances towards the synthesis of carbamoyl fluorides,[13] we were motivated to explore their application in atom-economical carbofluorination reactions. Although methods for the intramolecular chlorocarbamoylation of alkynes have been reported by Lautens and co-workers using Pd catalysts[14-15] or stoichiometric HFIP[16] (Scheme 1b), the analogous fluorocarbamoylation cannot be achieved under the same conditions (*vide infra*). To achieve this transformation, we turned to a complementary reaction manifold under Lewis acid (LA) catalysis, wherein reversible fluoride binding to a LA can facilitate both the C–F bond cleavage and C–F bond formation steps. The proposed fluorocarbamoylation reaction would provide access to fluorinated isosteres of medicinally relevant methylene oxindoles[17] and lactams (Scheme 1c),[18] which are not generally accessible.[19-20]

Inspired by the use of stoichiometric tetrafluoroborate (BF_4^-) salts in C–F bond forming reactions,[21] we hypothesized that fluoride addition to a π-bond by BF_4^- could release a Lewis acidic BF_3 species capable of promoting the C–F bond cleavage step, thus enabling a catalytic alkyne carbofluorination reaction. We were pleased to find that the use of catalytic $TrBF_4$ with carbamoyl fluoride **1a** provided the desired 3-fluoromethylene oxindole **2a** in 55% yield with >95:5 *E:Z*-selectivity (Table 1, entry 1).[22] The major isomer was unambiguously confirmed by single crystal X-Ray crystallography (see SI). Changing the counteranion to PF_6^- (entry 2) or cation to tropylium (entry 3) led to inferior results. Pd^0 catalysts known to promote the chlorocarbamoylation of alkynes[14,15] could not effect the desired reaction (Table S2); however, $Pd(MeCN)_4(BF_4)_2$ provided **2a** in moderate yield (entry 4). An improved yield of 67% was obtained with $HBF_4{\cdot}OEt_2$ (entry 5);[23] however, other Brønsted acids were unable to promote the chemistry (entries 6-8). We then tested $BF_3{\cdot}OEt_2$ as it is often used interchangeably with $HBF_4{\cdot}OEt_2$ as a nucleophilic fluoride source,[24] and we were pleased to find that **2a** was formed in 99% yield (entry 9). While other boron trihalide species, BCl_3 and BBr_3, demonstrated good reactivity, they also gave approximately catalytic amounts of halogen exchange products **2a-Cl** and **2a-Br**, respectively, suggesting their role as a halide donor (entries 10-11). Triarylboranes $B(C_6F_5)_3$ and $B(4\text{-}F\text{-}C_6H_4)_3$, were ineffective catalysts (entries 13-14), even though their Lewis acidities are comparable to BBr_3 and BF_3, respectively, based on reported fluoride ion affinity values (FIA) (Table SI).[25] Together, these results provide a rationale as to why boron trihalides are the most effective catalysts, despite their wide Lewis acidity range. Notability, 3-fluoromethylene oxindole **2a** cannot be synthesized from the analogous carbamoyl chloride **1a-Cl** in the presence of stoichiometric $BF_3{\cdot}OEt_2$ (entry 14). The application of other fluoride sources led to an intractable mixture of **2a-Cl** and **2a** (Table S4), demonstrating that carbamoyl fluorides are uniquely suited for this transformation.

Table 1. Catalyst screen for the fluorocarbamoylation of **1a**



1a **2a**

Entry[a]	Catalyst	Conv (%)	Yield 2a (%)	E:Z
1	$TrBF_4$	55	55	>95:5
2	$TrPF_6$	5	0	NA
3	$TroBF_4$	1	0	NA
4	$Pd(MeCN)_4(BF_4)_2$	60	45	>95:5
5	$HBF_4{\cdot}OEt_2$	99	67	>95:5
6	$NEt_3{\cdot}HF$	0	0	NA
7	Pyr·HF	9	0	NA
8[b]	HFIP	3	0	NA
9	$BF_3{\cdot}OEt_2$	100	>99 (99)[c]	>95:5
10	BCl_3	100	90[d]	>95:5
11	BBr_3	100	81[e]	>95:5
12	$B(C_6F_5)_3$	30	5	95:5
13	$B(4\text{-}F\text{-}C_6H_4)_3$	3	0	NA
14[f]	1 equiv $BF_3{\cdot}OEt_2$ with **1a-Cl**	20	0	NA

NA = Not applicable; Tr = tritylium; Tro = tropylium. [a]All reactions were run at a 0.1 mmol scale in a sealed 1-dram vial at 40 °C for 24 h. The yield and *E:Z* ratios were determined by ^{19}F NMR spectroscopy using *α,α,α*-trifluorotoluene as internal standard; [b]With HFIP (8 equiv) in PhMe [0.2 M] at 100 °C for 12 h (conditions: ref 16). [c]Isolated Yield; [d]**2a-Cl** formed in 9% yield (>95:5 *E:Z*); [e]**2a-Br** formed in 8% yield (>95:5 *E:Z*); [f]**2a-Cl** was formed in 10% yield (77:23 *E:Z*).

During studies to assess the scope, we found that increasing the catalyst loading to 20-30 mol% enabled most reactions to reach full conversion within 24 h. In all cases, the desired 3-fluoromethylene oxindole products **2** were formed with ≥95:5 *E:Z*-selectivity (Figure 1). Remote modifications to the nitrogen protecting group were well tolerated (**2b-j**), although reduced yields were observed for substrates bearing additional Lewis basic sites (**2d**, **2f**, **2g**).

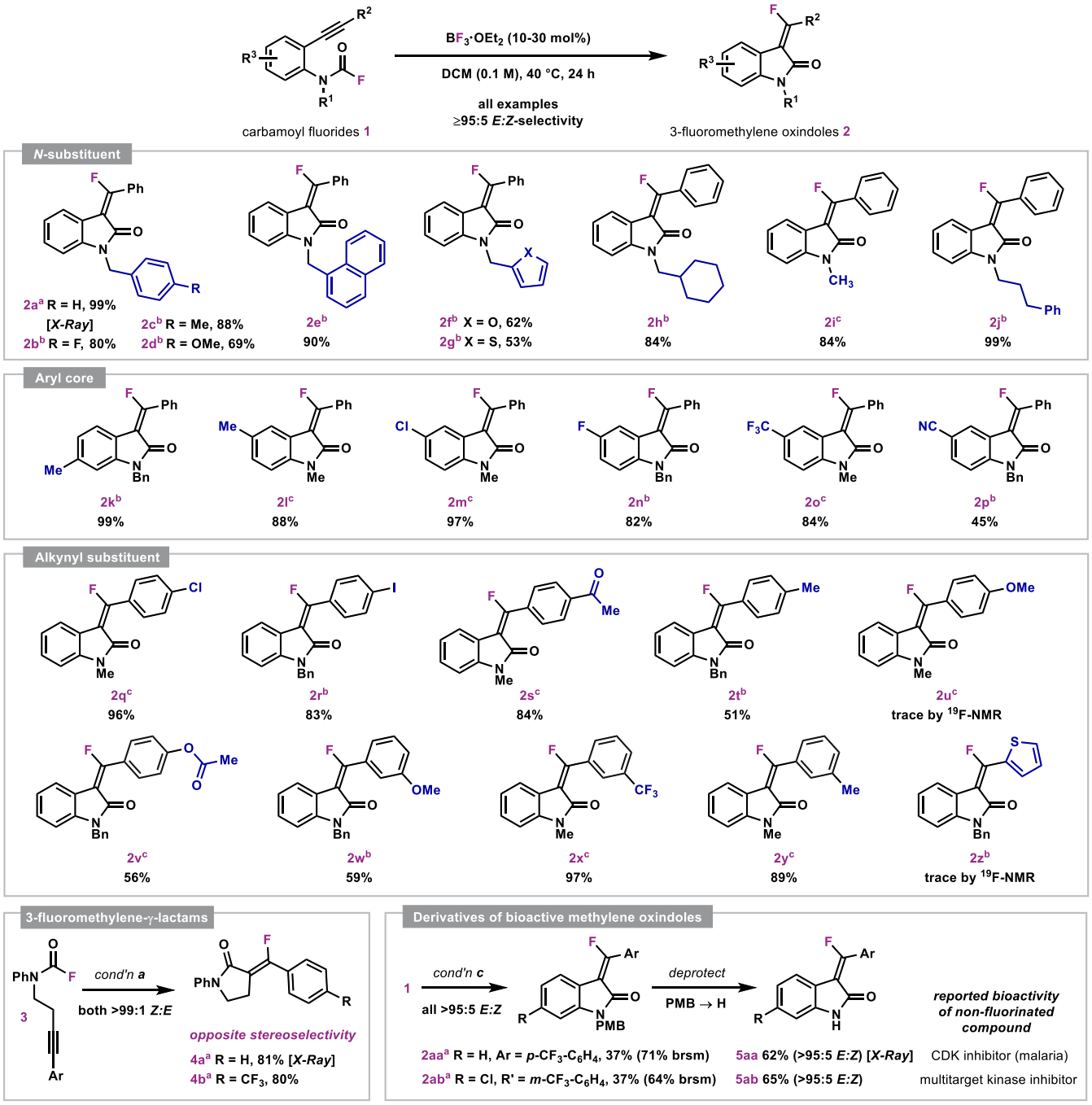
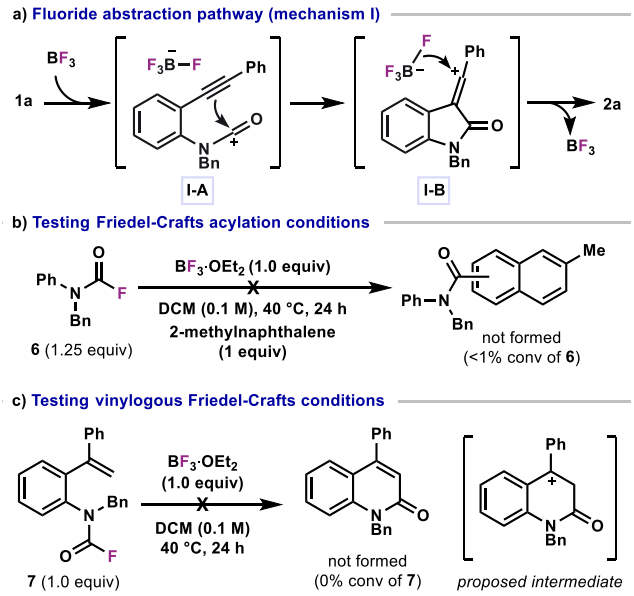


Figure 1. Substrate scope for methylene oxindoles; Conditions **a**. 10 mol% $BF_3{\cdot}OEt_2$; **b**. 20 mol% $BF_3{\cdot}OEt_2$; **c**. 30 mol% $BF_3{\cdot}OEt_2$. Conditions for PMB deprotection: Anisole (20 equiv), TFA (0.1M), 80 °C, 16 h.

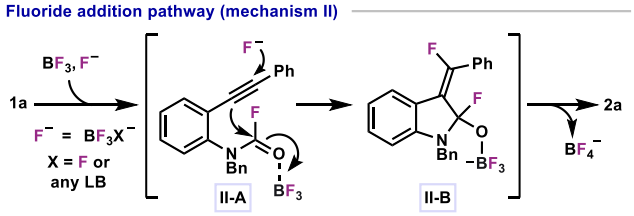
The reaction was relatively insensitive to substitution on the core aromatic ring (**2k-2o**) except for **2p**, which bears a coordinating nitrile functionality.[26] Various substituents on the distal aryl ring were tolerated, including halogen atoms (**2q, 2r**), an acetyl group (**2s**), and a methyl group (**2t**) at the *para* positions. Unfortunately, substrates bearing electron-rich (hetero)aryl groups (**1u**, **1z**) were completely unreactive. We believe that this poor reactivity is due to an electronic effect rather than a catalyst deactivation pathway, since Lewis basic groups are tolerated in substrates **1d, 1g**, and **1w**. The successful application of **1v** containing a less electron-releasing *p*-OAc group supports this hypothesis. Carbamoyl fluorides bearing a *m*-CF_3 or *m*-Me group underwent the reaction smoothly, providing excellent yields of **2x** and **2y**. We were pleased to see that our method was also applicable towards the synthesis of γ-lactams **4a** and **4b** with complete Z-selectivity, as confirmed by X-ray crystallography of **4a** (see SI). The switch in stereoselectivity from oxindoles to lactams has been previously observed in the HFIP-mediated cycloisomerization of carbamoyl chlorides.[16] Methylene oxindoles are a privileged motif, well-represented in a number of medicinally important scaffolds.[17] Our method could be applied to the synthesis of 3-fluoromethylene oxindoles **2aa-2ab**, which upon PMB deprotection provides access to the 3-fluoro-derivatives (**5aa-5ab**) of known protein kinase inhibitors.[27] The stereochemistry of **5aa** remained unchanged upon deprotection (see SI).

Two possible mechanisms were considered for the BF_3-catalyzed fluorocarbamoylation of **1a**. The first pathway involves fluoride abstraction from **1a** to form isocyanate cation **I-A**, which can be intercepted by the pendant alkyne to produce a vinyl cation **I-B** (Scheme 2a). Fluoride transfer from BF_4^- to **I-B** produces **2a** and regenerates the BF_3 catalyst. A concerted pathway involving concomitant C–C and C–F bond formation can also be envisioned. This mechanism draws similarities to a recent report by Nishimoto and co-workers on the BF_3-catalyzed insertion of diazoesters into benzylic C–F bonds.[28] However, there is no literature precedence for LA-promoted fluoride abstraction from carbamoyl fluorides. In fact, pioneering work by Olah and co-workers revealed that carbamoyl fluorides are reluctant to form isocyanate cations, even in the presence of strong Lewis and Brønsted acids.[29] Nevertheless, we wanted to probe the possibility of forming an isocyanate cation from model substrate **6**, which lacks a pendant alkyne, in a standard Friedel-Crafts reaction. In the presence of stoichiometric BF_3, **6** was unreactive and no carbamoyl substitution products were observed using 2-methylnaphthalene as the arene (Scheme 2b).[30] Additionally, a vinylogous Friedel-Crafts reaction of *ortho*-alkenyl carbamoyl fluoride **7** also failed, further suggesting that a fluoride abstraction pathway is unlikely (Scheme 2c).[16] This conclusion is indirectly supported by the fact that the reactivity of the boron-based Lewis acids do not parallel reported FIA values (Table S1).[25] Moreover, given that electron-releasing groups in **1u** and **1z** shut down the reactivity, formation of **I-B** seems unlikely, as the development of δ+ at the vinylic site should be promoted by electron-rich substituents.



Scheme 2. Mechanistic test studies on the feasibility of a fluoride abstraction pathway involving isocyanate cation intermediate **I-A**.

With the gathered evidence, our postulated mechanism begins with fluoride addition to the alkyne by a fluoride-releasing BF_3X^- species. This step triggers a nucleophilic substitution reaction at the carbamoyl fluoride, which may be facilitated by coordination of BF_3 to the carbamoyl group (Scheme 3). While the identity of the initial BF_3X^- species remains unclear, any Lewis adduct of BF_3 (e.g., **1a**·BF_3) can serve as a fluoride source. For example, Lewis adducts of aldehydes,[31] imines,[32] and hypervalent iodine reagents[33] with BF_3 have been previously reported to liberate fluoride. It is also possible that trace amounts of HBF_4 present in commercial $BF_3{\cdot}OEt_2$ can initiate this process.[21,34] Regardless of the initiation mechanism, collapse of tetrahedral intermediate **II-B** would generate an equivalent of BF_4^- that could re-enter the catalytic cycle. Given that the reaction is exclusively promoted by halide-containing boron-based catalysts and exogenous halide incorporation is observed with BCl_3 and BBr_3, it is likely that BF_3 plays a dual role as both a halide source and a Lewis acid activator.



Scheme 3. Plausible mechanism for the fluorocarbamoylation reaction.

In conclusion, we have developed an atom-economical fluorocarbamoylation reaction of alkyne-tethered carbamoyl fluorides that is enabled by an inexpensive BF_3 catalyst. The protocol provides access to fluorinated heterocycles that map directly onto privileged methylene oxindole and γ-lactam scaffolds, which may be further explored in medicinal chemistry programs. The ability to activate strong C–F bonds under mild conditions offers an advancement for future catalyst design in carbofluorination chemistry.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Reaction optimization tables, experimental procedures for synthesis of starting materials and products, mechanistic studies, copies of ^1H, ^{13}C, and ^{19}F NMR spectra for new compounds, and single crystal X-ray crystallography data for **2a**, **4a**, and **5aa** (PDF).

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REFERENCES

1. (a) Inoue, M.; Sumii, Y.; Shibata, N. Contribution of Organofluorine Compounds to Pharmaceuticals. *ACS Omega* **2020**, *5*, 10633. (b) Ogawa, Y.; Tokunaga, E.; Kobayashi, O.; Hirai, K.; Shibata, N. Current Contributions of Organofluorine Compounds to the Agrochemical Industry. *iScience* **2020**, *23*, 101467. (c) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315.
2. (a) Amii, H.; Uneyama, K. C–F Bond Activation in Organic Synthesis. *Chem. Rev.* **2009**, *109*, 2119. (b) Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T. Functionalization of Fluorinated Molecules by Transition-Metal-Mediated C–F Bond Activation To Access Fluorinated Building Blocks. *Chem. Rev.* **2015**, *115*, 931. (c) Stahl, T.; Klare, H. F. T.; Oestreich, M. Main-Group Lewis Acids for C–F Bond Activation. *ACS Catal.* **2013**, *3*, 1578.
3. For select examples of transition metal-catalyzed formal carbofluorination reactions using nucleophilic or electrophilic fluorine sources, see: (a) Cochrane, N. A.; Nguyen, H.; Gagne, M. R. Catalytic Enantioselective Cyclization and C3-Fluorination of Polyenes. *J. Am. Chem. Soc.* **2013**, *135*, 628. (b) Wolstenhulme, J. R.; Rosenqvist, J.; Lozano, O.; Ilupeju, J.; Wurz, N.; Engle, K. M.; Pidgeon, G. W.; Moore, P. R.; Sandford, G.; Gouverneur, V. Asymmetric Electrophilic Fluorocyclization with Carbon Nucleophiles. *Angew. Chem. Int. Ed.* **2013**, *52*, 9796. (c) Braun, M.-G.; Katcher, M. H.; Doyle, A. G. Carbofluorination via a Palladium-Catalyzed Cascade Reaction. *Chem. Sci.* **2013**, *4*, 1216. (d) Talbot, E. P. A.; Fernandes, T. de A.; McKenna, J. M.; Toste, F. D. Asymmetric Palladium-Catalyzed Directed Intermolecular Fluoroarylation of Styrenes. *J. Am. Chem. Soc.* **2014**, *136*, 4101. (e) Sim, J.; Campbell, M. W.; Molander, G. A. Synthesis of α-Fluoro-α-Amino Acid Derivatives via Photoredox-Catalyzed Carbofluorination. *ACS Catal.* **2019**, *9*, 1558.
4. (a) Petrone, D. A.; Le, C. M.; Newman, S. G.; Lautens, M. Pd(0)-Catalyzed Carboiodination: Early Developments and Recent Advances. In *New Trends in Cross-Coupling: Theory and Applications*; Colacot, T., Ed.; Royal Society of Chemistry: Cambridge, 2014; pp 276–321. (b) Jones, D. J.; Lautens, M.; McGlacken, G. P. The Emergence of Pd-Mediated Reversible Oxidative Addition in Cross Coupling, Carbohalogenation and Carbonylation Reactions. *Nat Catal* **2019**, *2*, 843. (c) Bag, D.; Mahajan, S.; Sawant, S. D. Transition-Metal-Catalyzed Carbohalogenative 1,2-Difunctionalization of C–C Multiple Bonds. *Adv. Synth. Catal.* **2020**, *362*, 3948. (d) Marchese, A. D.; Adrianov, T.; Lautens, M. Recent Strategies for Carbon–Halogen Bond Formation Using Nickel. *Angew. Chem. Int. Ed.* **2021**, *60*, 16750.
5. Fujimoto, H.; Kodama, T.; Yamanaka, M.; Tobisu, M. Phosphine-Catalyzed Intermolecular Acylfluorination of Alkynes via a P(V) Intermediate. *J. Am. Chem. Soc.* **2020**, *142*, 17323.
6. Fujimoto, H.; Yamamura, S.; Takenaka, N.; Tobisu, M. Phosphine-Catalyzed Z-Selective Carbofluorination of Alkynoates Bearing an *N*-Heteroarene Unit. *Synthesis* **2022**, in press (DOI: 10.1055/a-1948-3234).
7. Yu, X.; Meng, Q.-Y.; Daniliuc, C. G.; Studer, A. Aroyl Fluorides as Bifunctional Reagents for Dearomatizing Fluoroaroylation of Benzofurans. *J. Am. Chem. Soc.* **2022**, *144*, 7072.
8. (a) Ogiwara, Y.; Sakai, N. Acyl Fluorides in Late-Transition-Metal Catalysis. *Angew. Chem. Int. Ed.* **2020**, *59*, 574. (b) Karbakhshzadeh, A.; Heravi, M. R. P.; Rahmani, Z.; Ebadi, A. G.; Vessally, E. Aroyl Fluorides: Novel and Promising Arylating Agents. *J. Fluor. Chem.* **2021**, *248*, 109806. (c) Tian, T.; Chen, Q.; Li, Z.; Nishihara, Y. Recent Advances in C–F Bond Activation of Acyl Fluorides Directed toward Catalytic Transformation by Transition Metals, *N*-Heterocyclic Carbenes, or Phosphines. *Synthesis* **2022**, *54*, 3667.
9. Olofson, R. A.; Cuomo, J. A Regiospecific and Stereospecific Route to Enol Carbonates and Carbamates: Closer Look at a "Naked Anion." *Tetrahedron Lett.* **1980**, *21*, 819.
10. Scattolin, T.; Bouayad-Gervais, S.; Schoenebeck, F. Straightforward Access to *N*-Trifluoromethyl Amides, Carbamates, Thiocarbamates and Ureas. *Nature* **2019**, *573*, 102.
11. Bouayad-Gervais, S.; Scattolin, T.; Schoenebeck, F. *N*-Trifluoromethyl Hydrazines, Indoles and Their Derivatives. *Angew. Chem. Int. Ed.* **2020**, *59*, 11908.
12. (a) Li, Y.; Zhang, F.-P.; Wang, R.-H.; Qi, S.-L.; Luan, Y.-X.; Ye, M. Carbamoyl Fluoride-Enabled Enantioselective Ni-Catalyzed Carbocarbamoylation of Unactivated Alkenes. *J. Am. Chem. Soc.* **2020**, *142*, 19844. (b) Nielsen, C. D.-T.; Zivkovic, F. G.; Schoenebeck, F. Synthesis of *N*-CF_3 Alkynamides and Derivatives Enabled by Ni-Catalyzed Alkynylation of *N*-CF_3 Carbamoyl Fluorides. *J. Am. Chem. Soc.* **2021**, *143*, 13029. (c) He, F.; Hou, L.; Wu, X.; Ding, H.; Qu, J.; Chen, Y. Enantioselective Synthesis of α-Alkenylated γ-Lactam Enabled by Ni-Catalyzed 1,4-Arylcarbamoylation of 1,3-Dienes. *CCS Chem* **2022**, in press (DOI: 10.31635/ccschem.022.202202010).
13. (a) Pichette Drapeau, M.; Tlili, A. Modern Synthesis of Carbamoyl Fluorides. *Tetrahedron Lett.* **2020**, *61*, 152539. (b) Song, J. W.; Lim, H. N. Synthesis of Carbamoyl Fluorides via a Selective Fluorinative Beckmann Fragmentation. *Org. Lett.* **2021**, *23*, 5394. (c) Bonnefoy, C.; Chefdeville, E.; Tourvieille, C.; Panossian, A.; Hanquet, G.; Leroux, F.; Toulgoat, F.; Billard, T. Study of Carbamoyl Fluoride: Synthesis, Properties and Applications. *Chem. Eur. J.* **2022**, *28*, e202201589. (d) Taponard, A.; Jarrosson, T.; Krouz, L.; Médebielle, M.; Broggi, J.; Tlili, A. Metal-Free SF_6 Activation: A New SF_5-Based Reagent Enables Deoxyfluorination and Pentafluorosulfanylation Reactions. *Angew. Chem. In. Ed.* **2022**, *61*, e202204623. (e) Cadwallader, D.; Tiburcio, T. R.; Cieszynski, G. A.; Le, C. M. Synthesis of Carbamoyl Fluorides Using a Difluorophosgene Surrogate Derived from Difluorocarbene and Pyridine-*N*-Oxides. *J. Org. Chem.* **2022**, *87*, 11457.
14. Le, C. M.; Hou, X.; Sperger, T.; Schoenebeck, F.; Lautens, M. An Exclusively *Trans*-Selective Chlorocarbamoylation of Alkynes Enabled by a Palladium/Phosphaadamantane Catalyst. *Angew. Chem. Int. Ed.* **2015**, *54*, 15897.
15. Le, C. M.; Sperger, T.; Fu, R.; Hou, X.; Lim, Y. H.; Schoenebeck, F.; Lautens, M. Stereoselective Synthesis of Methylene Oxindoles via Palladium(II)-Catalyzed Intramolecular Cross-Coupling of Carbamoyl Chlorides. *J. Am. Chem. Soc.* **2016**, *138*, 14441.
16. Rodríguez, J. F.; Zhang, A.; Bajohr, J.; Whyte, A.; Mirabi, B.; Lautens, M. Cycloisomerization of Carbamoyl Chlorides in Hexafluoroisopropanol: Stereoselective Synthesis of Chlorinated Methylene Oxindoles and Quinolinones. *Angew. Chem. Int. Ed.* **2021**, *60*, 18478.
17. Millemaggi, A.; Taylor, R. J. K. 3-Alkenyl-oxindoles: Natural Products, Pharmaceuticals, and Recent Synthetic Advances in Tandem/Telescoped Approaches. *Eur. J. Org. Chem.* **2010**, *2010*, 4527.
18. (a) Caruano, J.; Muccioli, G. G.; Robiette, R. Biologically Active γ-Lactams: Synthesis and Natural Sources. *Org. Biomol. Chem.* **2016**, *14*, 10134. (b) Delong, W.; Lanying, W.; Yongling, W.; Shuang, S.; Juntao, F.; Xing, Z. Natural α-Methylenelactam Analogues: Design, Synthesis and Evaluation of α-Alkenyl-γ and δ-Lactams as Potential Antifungal Agents against Colletotrichum Orbiculare. *Eur. J. Med. Chem.* **2017**, *130*, 286.
19. Synthesis of 3-fluoroalkenyloxindole ring-fused 3-trifluoromethyloxindoles: (a) Liu, Y.; Zhang, K.; Huang, Y.; Pan, S.; Liu, X.-Q.; Yang, Y.; Jiang, Y.; Xu, X.-H. Synthesis of 3-Fluoroalkenyl-3-Trifluoromethyl-2-Oxindoles by the Reaction of Indoline-2,3-Diones with Difluoromethylene Phosphabetaine. *Chem. Commun.* **2016**, *52*, 5969. (b) Liu, Y.; Zhou, F.; He, K.; Cheng, T.; Zhong, Z.; Liu, Y.; Yang, Y. Design, Synthesis and Biological Evaluation of 3-Fluoroalkenyloxindole Ring-Fused 3-Trifluoromethyloxindoles Obtained from Indoline-2,3-Diones and Difluoromethylene Phosphabetaine. *Phosphorus, Sulfur, and Silicon and the Related Elements* **2018**, *193*, 201.

20. No current method is available for the synthesis of medicinally relevant 3-fluoromethylene oxindoles and γ-lactams bearing an aryl group at the 3-position. For related compounds, see: (a) 3-fluoromethyleneoxindole with a ketone at the 3-position: Liao, F.-M.; Cao, Z.-Y.; Yu, J.-S.; Zhou, J. Highly Stereoselective Gold-Catalyzed Coupling of Diazo Reagents and Fluorinated Enol Silyl Ethers to Tetrasubstituted Alkenes. *Angew. Chem. Int. Ed.* **2017**, *56*, 2459. (b) 3-fluoromethylene-γ-lactam (one example in scope): Duchemin, N.; Buccafusca, R.; Daumas, M.; Ferey, V.; Arseniyadis, S. A Unified Strategy for the Synthesis of Difluoromethyl- and Vinylfluoride-Containing Scaffolds. *Org. Lett.* **2019**, *21*, 8205.
21. Cresswell, A. J.; Davies, S. G.; Roberts, P. M.; Thomson, J. E. Beyond the Balz–Schiemann Reaction: The Utility of Tetrafluoroborates and Boron Trifluoride as Nucleophilic Fluoride Sources. *Chem. Rev.* **2015**, *115*, 566.
22. Yeh, M.-C. P.; Chen, H.-F.; Huang, Y.-Y.; Weng, Y.-T. Diastereoselective Synthesis of Fluorine-Containing Pyrrolizidines via Triphenylcarbenium Tetrafluoroborate-Promoted Carbofluorination of *N* -3-Arylpropargylpyrrolidine-Tethered Tertiary Allylic Alcohols. *J. Org. Chem.* **2015**, *80*, 10892.
23. Xiang, Y.; Li, Z.; Wang, L.-N.; Yu, Z.-X. TfOH- and HBF_4-Mediated Formal Cycloisomerizations and [4+3] Cycloadditions of Allene-Alkynylbenzenes. *J. Org. Chem.* **2018**, *83*, 7633.
24. Yeh, M.-C. P.; Liang, C.-J.; Huang, T.-L.; Hsu, H.-J.; Tsau, Y.-S. Transition-Metal-Free Carbofluorination of TBS-Protected Nitrogen-Containing Cyclic Enynols: Synthesis of Fluorinated Azabicycles. *J. Org. Chem.* **2013**, *78*, 5521.
25. Reported FIA values ($kJ \cdot mol^{-1}$) from refs a-c: $B(C_6F_5)_3$ = 448; BBr_3 = 428; BCl_3 = 404; $B(4\text{-}F\text{-}C_6H_4)_3$ = 377; BF_3 = 346. (a) Kirschner, S.; Peters, M.; Yuan, K.; Uzelac, M.; Ingleson, M. J. Developing Organoboranes as Phase Transfer Catalysts for Nucleophilic Fluorination Using CsF. *Chem. Sci.* **2022**, *13*, 2661. (b) Timoshkin, A. Y.; Frenking, G. Gas-Phase Lewis Acidity of Perfluoroaryl Derivatives of Group 13 Elements. *Organometallics* **2008**, *27*, 371. (c) Erdmann, P.; Leitner, J.; Schwarz, J.; Greb, L. An Extensive Set of Accurate Fluoride Ion Affinities for *p* -Block Element Lewis Acids and Basic Design Principles for Strong Fluoride Ion Acceptors. *ChemPhysChem* **2020**, *21*, 987.
26. The yield of **2p** could be improved to 68% by increasing the loading of $BF_3 \cdot OEt_2$ to 1 equiv.
27. (a) Woodard, C. L.; Li, Z.; Kathcart, A. K.; Terrell, J.; Gerena, L.; Lopez-Sanchez, M.; Kyle, D. E.; Bhattacharjee, A. K.; Nichols, D. A.; Ellis, W.; Prigge, S. T.; Geyer, J. A.; Waters, N. C. Oxindole-Based Compounds Are Selective Inhibitors of *Plasmodium Falciparum* Cyclin Dependent Protein Kinases. *J. Med. Chem.* **2003**, *46*, 3877. (b) Chen, X.; Yang, T.; Deivasigamani, A.; Shanmugam, M. K.; Hui, K.-M.; Sethi, G.; Go, M.-L. *N*′-Alkylaminosulfonyl Analogues of 6-Fluorobenzylideneindolinones with Desirable Physicochemical Profiles and Potent Growth Inhibitory Activities on Hepatocellular Carcinoma. *ChemMedChem* **2015**, *10*, 1548.
28. Wang, F.; Nishimoto, Y.; Yasuda, M. Insertion of Diazo Esters into C–F Bonds toward Diastereoselective One-Carbon Elongation of Benzylic Fluorides: Unprecedented BF_3 Catalysis with C–F Bond Cleavage and Re-Formation. *J. Am. Chem. Soc.* **2021**, *143*, 20616.
29. Olah, G. A.; Nishimura, Jun.; Kreienbuehl, Paul. Stable Carbocations. CLXI. Protonation and Lewis Acid Halide Complex Formation of Carbamyl Halides and Alkyl (Aryl) Isocyanates and Isothiocyanates. Carbamyl, Thiocarbamyl, and Allophanyl Cations. *J. Am. Chem. Soc.* **1973**, *95*, 7672.
30. Hyatt, J. A.; Raynolds, P. W. Acyl Fluoride Friedel-Crafts Reactions. Regioselective Synthesis of 3-Acylacenaphthenes and 2-Acyl-6-Alkylnaphthalenes. *J. Org. Chem.* **1984**, *49*, 384.
31. Sultana, S.; Lee, Y. R. Construction of Halofunctionalized Indenes via a Cascade Prins-Nazarov Cyclization Promoted by Dual Roles of BX_3. *Adv. Synth. Catal.* **2020**, *362*, 927.
32. Wölfling, J.; Frank, É.; Schneider, G.; Tietze, L. F. Synthesis of Novel Steroid Alkaloids by Cyclization of Arylimines from Estrone. *Eur. J. Org. Chem.* **1999**, 3013.
33. (a) Cui, J.; Jia, Q.; Feng, R.-Z.; Liu, S.-S.; He, T.; Zhang, C. Boron Trifluoride Etherate Functioning as a Fluorine Source in an Iodosobenzene-Mediated Intramolecular Aminofluorination of Homoallylic Amines. *Org. Lett.* **2014**, *16*, 1442. (b) Zhu, W.; Zhen, X.; Wu, J.; Cheng, Y.; An, J.; Ma, X.; Liu, J.; Qin, Y.; Zhu, H.; Xue, J.; Jiang, X. Catalytic Asymmetric Nucleophilic Fluorination Using $BF_3 \cdot Et_2O$ as Fluorine Source and Activating Reagent. *Nat Commun* **2021**, *12*, 3957.
34. Wamser, C. A. Equilibria in the System Boron Trifluoride–Water at 25°C. *J. Am. Chem. Soc.* **1951**, *73*, 409.

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