BF_3-Catalyzed Intramolecular Fluorocarbamoylation of Alkynes via Halide Recycling

E. Ali McKnight,[1] Ramon Arora,[2] Ekadashi Pradhan,[1] Yuriko H. Fujisato,[1] Ayonitemi J. Ajayi,[1] Mark Lautens,[2] Tao Zeng,[1*] Christine M. Le[1*]

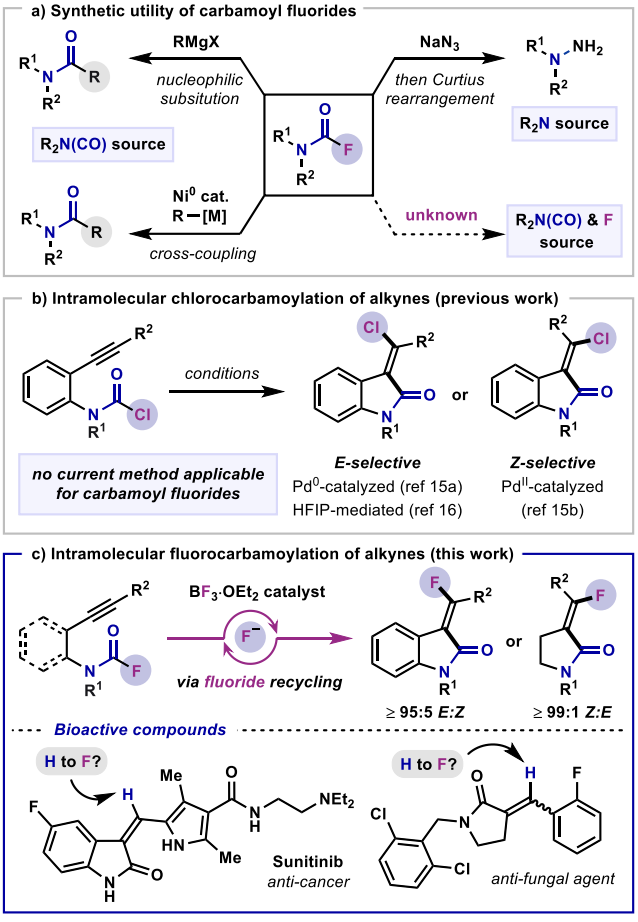
[1]Department of Chemistry, York University, Toronto, Ontario M3J 1P3, Canada

[2]Department of Chemistry, University of Toronto, Toronto, Ontario M5S 3H6, Canada

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 through a halide recycling mechanism. The developed method provides access to 3-(fluoromethylene)oxindoles and γ-lactams with excellent stereoselectivity, including fluorinated derivatives of known protein kinase inhibitors. Experimental and computational studies support a stepwise mechanism for the fluorocarbamoylation reaction involving a turnover-limiting cyclization step, followed by internal fluoride transfer from a BF_3-coordinated carbamoyl adduct. For methylene oxindoles, a thermodynamically driven *Z*-*E* isomerization is facilitated by a transition state with aromatic character. In contrast, this aromatic stabilization is not relevant for γ-lactams, resulting in a higher barrier for isomerization and the exclusive formation of the kinetic *Z*-isomer.

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 C–F bond forming and C–F bond activation reactions, transformations involving both elementary steps 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 fluoride 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 to enable the application of highly electrophilic acyl fluorides in atom-economical addition reactions.[5-7] The Tobisu group has reported both the inter- and intramolecular fluoroacylation of alkynes via $P^{III/IV}$ and Rh^{I}/BF_4 catalysis, respectively.[5,6] Studer and co-workers disclosed an intermolecular alkene fluoroacylation reaction of benzofurans and indoles promoted by cooperative NHC and photoredox catalysis.[7] In these examples, the high reactivity of acyl fluorides towards nucleophilic substitution was harnessed in the C–F bond cleavage step.



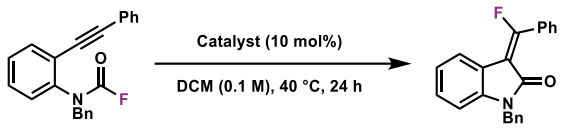
Scheme 1. a) Synthetic utility of carbamoyl fluorides. b) Previously reported intramolecular chlorocarbamoylation reactions. c) This work: BF_3-catalyzed intramolecular fluorocarbamoylation reaction.

While new synthetic applications of acyl fluorides have been widely developed,[8] the established chemistry of related carbamoyl fluorides has been largely limited due to their increased stability. Accordingly, strong nucleophiles are often required for simple substitution reactions (Scheme 1a).[9-11] In the context of transition metal-catalyzed reactions, few 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. The use of an alkynes as the π-acceptor would provide a direct route to tetrasubstituted alkenyl fluorides, which are present in a number of bioactive compounds, serving as amide bond bioisosteres and enol mimics.[14] The intramolecular chlorocarbamoylation of alkynes has been previously reported by Lautens and co-workers using Pd catalysts[15] or stoichiometric HFIP[16] (cheme 1b). These methods provide entry to 3-(chloromethylene)oxindoles, which are precursors to pharmaceutically relevant compounds through C–Cl bond functionalization. Despite the importance of fluorine substitution in medicinal chemistry, there are no general methods to access 3-(fluoromethylene)oxindoles,[17-18] which have reported anticancer activity.[17b] Considering that the known suite of carbohalogenation catalysts are ineffective with less reactive carbamoyl fluorides, we turned to an alternative reaction platform involving Lewis acid (LA) catalysis. In the present study, we demonstrate that a simple BF_3 catalyst can promote the desired fluorocarbamoylation reaction to furnish medicinally relevant fluoromethylene oxindoles[19] and lactams[20] under exceptionally mild conditions (Scheme 1c).

Inspired by the use of stoichiometric BF_4^- salts as fluoride donors,[21] we subjected carbamoyl fluoride **1a** to catalytic trityl BF_4,[22] which provided the desired 3-fluoromethylene oxindole **2a** in 55% yield with >95:5 *E:Z*-selectivity (Table 1, entry 1). The major isomer, resulting from a formal *trans* addition, was unambiguously confirmed by single crystal X-Ray crystallography.[23] 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[15-16] 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),[24] although 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,[25] 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 potential 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).[26] 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 exogenous 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**



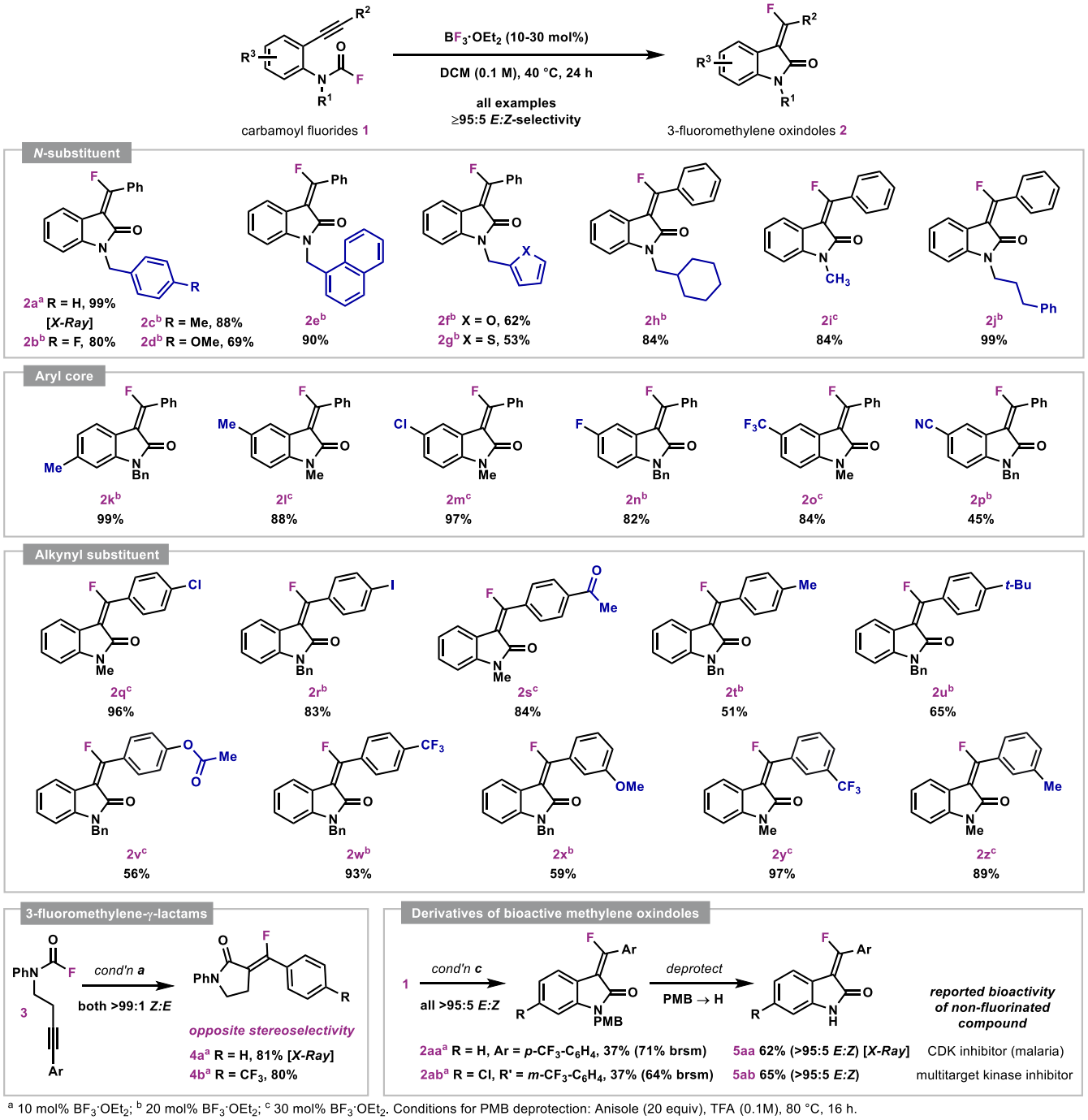
1a 2a

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 = trityl; Tro = tropylium. [a]All reactions were run at a 0.1 mmol scale in a sealed 1-dr vial at 40 °C for 24 h. Yield and *E:Z* ratios determined by ^{19}F NMR spectroscopy using α,α,α-trifluorotoluene as internal standard; [b]With HFIP (8 equiv) in PhMe, 100 °C, 12 h (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** 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 ≥94:6 *E:Z*-selectivity (Figure 1). Remote modifications to the *N*-protecting group were well tolerated (**2b-j**), although reduced yields were observed for substrates bearing additional Lewis basic sites (**2d**, **2f**, **2g**). The reaction was relatively insensitive to substitution on the core aromatic ring (**2k-2o**) except for **2p**, which bears a coordinating nitrile functionality. The yield of **2p** could be improved to 68% by increasing the loading of $BF_3{\cdot}OEt_2$ to 1 equiv. Various functionality on the distal aryl ring were tolerated, including halogen atoms (**2q, 2r**), moderately donating alkyl groups (**2t**, **2u**), an acetate derivative (**1v**), as well as

electron-withdrawing acetyl (**2s**) and CF_3 groups (**2w**). Carbamoyl fluorides bearing *m*-substituents also underwent the reaction smoothly to give **2x**, **2y** and **2z**. 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**. This reversal in stereoselectivity, previously observed for related HFIP-promoted reactions run in the absence of a metal catalyst,[16] can now be explained by density functional theory (DFT) studies (*vide infra*). To demonstrate the utility of our method towards the synthesis of medicinally relevant compounds, we prepared oxindoles **2aa-2ab**, which upon PMB deprotection provided access to the 3-fluoro-derivatives (**5aa-5ab**) of known protein kinase inhibitors.[27] The stereochemistry of **5aa** remained unchanged upon deprotection.[23]



[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.

Figure 1. Substrate scope and synthesis of fluorinated kinase inhibitors

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 undergo cyclization and fluoride rebound from BF_4^- to give **2a** (Figure 2a). A concerted pathway involving concomitant C–C and C–F bond formation can also be envisioned. Notably, BF_3 has been recently implicated in the catalytic C–F bond cleavage of fluoroalkanes for diazo insertion and HF

shuttling reactions.[28] However, there is no literature precedent 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, and instead, form coordination complexes.[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. Using conditions developed for the acylation of naphthalenes using acyl fluorides,[30] no carbamoyl substitution products were observed. Additionally, no reaction was observed with *p*-xylene in solvent quantities.[23] Both experiments indicate that carbamoyl fluorides are significantly more stable towards LAs. Additionally, a vinylogous intramolecular Friedel-Crafts reaction[16] of *ortho*-alkenyl carbamoyl fluoride **7** also failed, further suggesting that a LA-mediated fluoride abstraction pathway is unlikely.

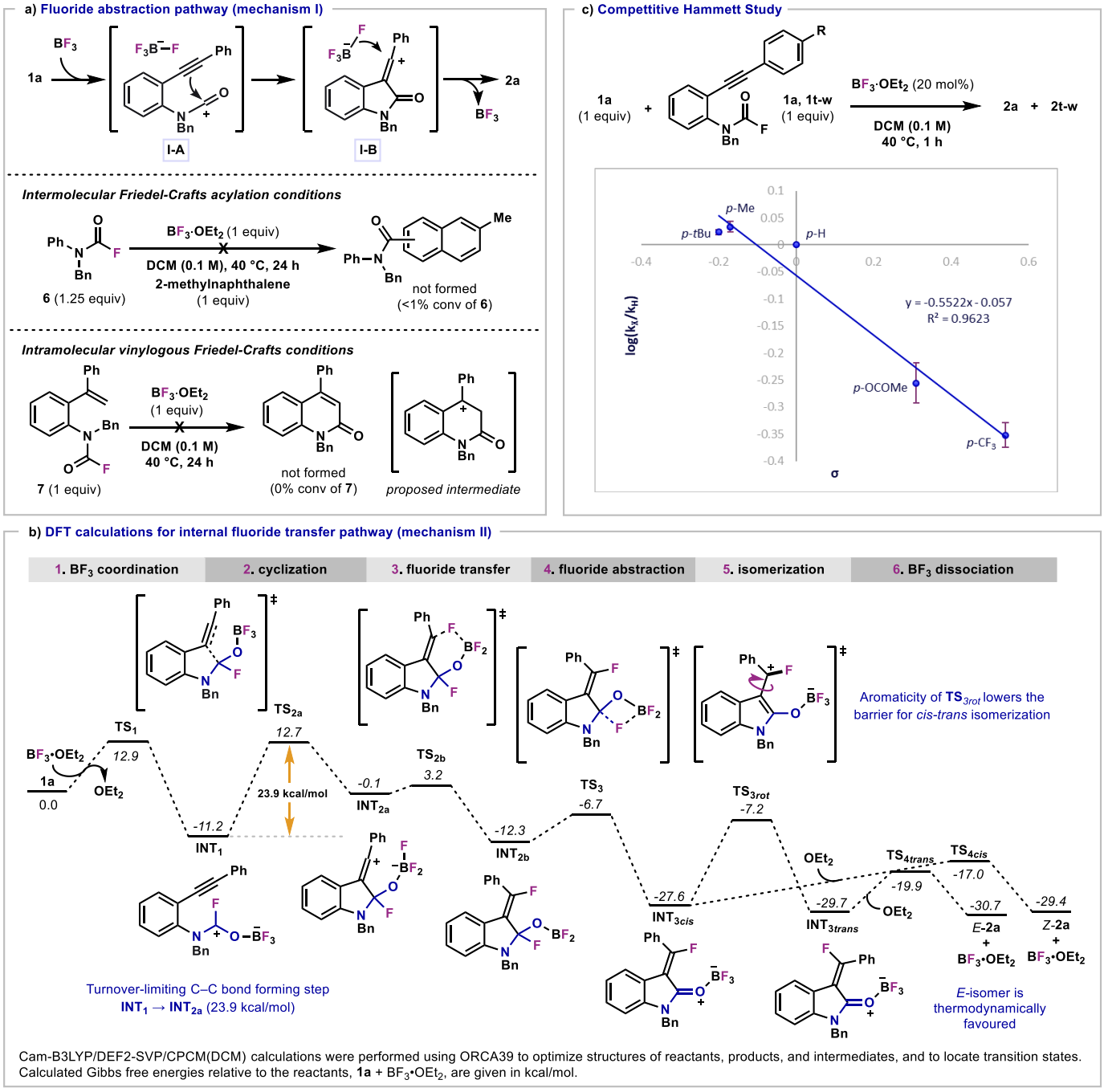


Figure 2. (a) Probing the feasibility of a fluoride abstraction mechanism via Friedel-Crafts test reactions; (b) Calculated energy profile for the proposed internal fluoride transfer mechanism; (c) Competitive Hammett study for *para*-substituted carbamoyl fluorides.

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,[31] we surmised that BF_3 acts as both a fluoride source and a Lewis acid activator in the fluorocarbamoylation reaction. It has been previously reported that Lewis adducts of aldehydes,[32] imines,[33] and

hypervalent iodine reagents[34] with BF_3 are sufficiently activated to liberate nucleophilic fluoride. Based on this literature precedent, we hypothesized that BF_3 coordination to **1a** could deliver a fluoride ion internally, while simultaneously triggering nucleophilic addition of the alkyne into the LA-activated carbamoyl group.

To investigate the feasibility of this internal fluoride transfer pathway, we turned to DFT calculations. Cam-B3LYP/DEF2-SVP/CPCM(DCM) calculations[35-37] were performed using ORCA[38] to optimize structures of reactants, products, and intermediates, and to locate transition states.[39] In line with Olah's study,[29] coordination of oxophilic BF_3 to the carbamoyl oxygen of **1a** was calculated to be a favorable interaction (Figure 2d). From $\mathbf{INT_1}$, cyclization to form the 5-membered ring was determined to be turnover-limiting with a surmountable barrier of 23.9 kcal/mol, wherein the developing δ^+ charge is stabilized by the conjugated aromatic ring. The resulting alkenyl cation ($\mathbf{INT_{2a}}$) undergoes a facile internal fluoride transfer to forge the C–F bond. Fluoride migration from the carbamoyl C to B in $\mathbf{INT_{2b}}$ forms $\mathbf{INT_{3}}_{cis}$ which can undergo C=C bond rotation to give $\mathbf{INT_{3}}_{trans}$. Dissociation of BF_3 can occur from $\mathbf{INT_{3}}_{cis}$ or $\mathbf{INT_{3}}_{trans}$ to provide *Z*-**2a** or *E*-**2a**, respectively, but these pathways are reversible and therefore the thermodynamically favored *E*-isomer is formed as the major product. Overall, the reaction to form *E*-**2a** is 30.7 kcal/mol exoergic. For methylene oxindoles, $\mathbf{TS_{3rot}}$ possesses significant aromatic character (10 π electrons in the bicyclic framework), thus easing the barrier for C=C bond isomerization ($\Delta G^{\ddagger}_{isom}$ = 20.4 kcal/mol). In contrast, the TS for the isomerization of γ-lactam **4a** does not benefit from this aromatic stabilization and the barrier for C=C bond rotation was determined to be significantly higher ($\Delta G^{\ddagger}_{isom}$ = 38.1 kcal/mol) (Figure 3).[23] Overall, these calculations provide insight into the origin of stereoselectivity, with the kinetic *Z*-isomer being observed for γ-lactams and the thermodynamic *E*-isomer being observed for oxindoles.

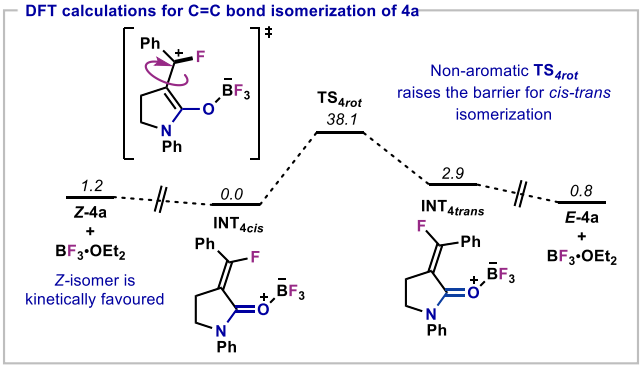


Figure 3. Calculated energy profile for γ-lactam isomerization barrier.

The reaction mechanism derived from DFT calculations was further supported by experimental studies. Kinetic runs using variable time normalization analysis[40] revealed that the reaction was first-order in both **1a** and catalyst, suggesting that the turnover-limiting step occurs from a 1:1 coordination complex of BF_3 to **1a**. Additionally, competitive Hammett studies with *p*-substituted carbamoyl fluorides **1t-w** imply the development of δ^+ in the turnover-limiting C–C bond formation step prior to fluoride addition (Figure 2c). Overall, the combined computational and experimental evidence points towards a unique halide recycling mechanism, involving initial fluoride transfer from the BF_3, thus supporting the critical role of boron trihalide catalysts in this chemistry.

In conclusion, we have developed an atom-economical fluorocarbamoylation reaction of alkyne-tethered carbamoyl fluorides that is enabled by a simple, inexpensive, and widely available 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. Overall, the ability to activate strong C–F bonds via a halide recycling mechanism provides a new platform for exploring atom-economical carbofluorination reactions more generally.

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, computational details, copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra for new compounds, and single crystal X-ray crystallography data for **2a**¸ **4a**, and **5aa** (PDF).

AUTHOR INFORMATION

Corresponding Authors

* **Tao Zeng –** York University, Department of Chemistry, 4700 Keele St., Toronto, Ontario M3J 1P3, Canada; E-mail: tzeng@yorku.ca
* **Christine M. Le –** York University, Department of Chemistry, 4700 Keele St., Toronto, Ontario M3J 1P3, Canada; E-mail: cmle@yorku.ca

Funding Sources

This work was financially supported by the NSERC Discovery Grant Program (C.M.L, M.L.), CFI John R. Evans Leaders Fund (C.M.L), and the American Chemical Society Petroleum Research Fund (C.M.L). TZ thanks NSERC (RGPIN-2016-06276) and York University (481333) for research funding, and Digital 493 Research Alliance of Canada for computational resources, and Digital Research Alliance of Canada for computational resources.

ACKNOWLEDGMENT

We thank YSciCore Facility at York University for the use of their analytical instruments. This study made use of NMRbox: National Center for Biomolecular NMR Data Processing and Analysis, a Biomedical Technology Research Resource (BTRR), which is supported by NIH grant P41GM111135 (NIGMS). We thank Dr. Alan Lough (U of T) and Jesse LeBlanc (YorkU) for obtaining the single crystal X-ray structures of **2a** (CCDC 2215313), **4a** (CCDC 2215309), and **5aa** (CCDC 2215312). We thank the Neese group (MPI Kohlenforschung) for their continuous development of the ORCA program package.

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 carbofluorination reactions using exogenous fluorine sources that do not involve C–F bond activation, 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. For a recent review on carbofluorination, see: (f) McKnight, E. A.; Cadwallader, D.; Le, C.M. Carbofluorination of π-Bonds and Related Reactions Involving Tandem C–C/C–F Bond Formation. *Eur. J. Org. Chem.* **2023**, e202300017.
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. (a) 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. (b) 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).
6. T. Yoshida, M. Ohta, T. Emmei, T. Kodama, M. Tobisu, Cationic Rhodium(I) Tetrafluoroborate Catalyzed Intramolecular Carbofluorination of Alkenes via Acyl Fluoride C–F Bond Activation**,** *Angew. Chem. Int. Ed.* **2023**, e202303657.
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. (a) Bouayad-Gervais, S.; Scattolin, T.; Schoenebeck, F. *N*-Trifluoromethyl Hydrazines, Indoles and Their Derivatives. *Angew. Chem. Int. Ed.* **2020**, *59*, 11908. (b) Zivkovic, F. G.; Nielsen, C. D.-T.; Schoenebeck, F. *Angew. Chem. Int. Ed.* **2022**, e202213829.
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. (a) Meanwell, N. A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61*, 5822. (b) Drouin, M.; Hamel, J.-D.; Paquin, J.-F. Synthesis of Monofluoroalkenes: A Leap Forward. *Synthesis* **2018**, *50*, 881.
15. (a) 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. (b) 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. 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.
18. 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.

19. 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.
20. (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.
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. See ESI for more details.
24. 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.
25. 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.
26. 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.
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. (a) 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. (b) Mulryan, D.; Rekhroukh, F.; Farley, S. E. S.; Crimmin, M. R. *ChemRxiv* **2023**, DOI: 10.26434/chemrxiv-2023-lxv28.
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. Corkovic, A., Dorian, A., Williams, F. Improvements in Efficiency and Selectivity for C–F Bond Halogen-Exchange Reactions using Boron Reagents. *Synlett* **2022**. doi: 10.1055/a-1941-2205
32. 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.
33. 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.
34. (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.
35. Yanai, T.; Tew, D. P.; Handy, N. C. A new hybrid exchange-correlation functional using the Coulomb-attenuating method (CAM-B3LYP), *Chem. Phys. Lett.*, **2004**, *393*, 51.
36. Weigend, F.; Ahlrichs, R. Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy, *Phys. Chem. Chem. Phys.*, **2005**, *7*, 3297.
37. Barone, V.; Cossi, M. Quantum Calculation of Molecular Energies and Energy Gradients in Solution by a Conductor Solvent Model, *J. Phys. Chem. A*, **1998**, *102*, 1995.
38. Neese, F. The ORCA program system, Wiley Interdiscip. Rev.: Comput. Mol. Sci., **2012**, 2, 73.
39. Calculated Gibbs free energies relative to the reactants, **1a** + $BF_3 \bullet OEt_2$, are given in kcal/mol. Since the reaction occurs in solution, where the translation and rotation of the molecules are, at least partially, quenched, only the vibrational contribution to the Gibbs free energy is included.
40. (a) Burés, J. A Simple Graphical Method to Determine the Order in Catalyst. *Angew. Chem. Int. Ed.* **2016**, *55*, 2028. (b) Burés, J. Variable Time Normalization Analysis: General Graphical Elucidation of Reaction Orders from Concentration Profiles. *Angew. Chem. Int. Ed.* **2016**, *55*, 16084. (c) Nielsen, C. D.-T.; Burés, J. Visual Kinetic Analysis. *Chem. Sci.* **2019**, *10*, 348.

Table of Contents artwork