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Communication

BF_3-Catalyzed Intramolecular Fluorocarbamoylation of Alkynes via Halide Recycling

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

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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, thereby 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, which results in a higher barrier for isomerization and the exclusive formation of the *Z*-isomer.

Catalytic reactions involving C−F bond formation are of interest to pharmaceutical and agrochemical industries because of the favorable medicinal properties of fluorinated small molecules.[1] More recently, strategies for the direct functionalization of C−F bonds have emerged, which typically require 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 past 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 because of the high bond dissociation energy 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 $P^{III/V}$ 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 *N*-heterocyclic carbene and photoredox catalysis.[7] In these examples, the high reactivity of acyl fluorides toward nucleophilic substitution was harnessed in the C−F bond cleavage step.

While new synthetic applications of acyl fluorides have been widely developed,[8] the established chemistry of related carbamoyl fluorides has been largely limited because of 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 byproduct. To date, reactions that retain both the carbamoyl fragment and the fluorine atom in the final product remain elusive.

Given recent advances toward the synthesis of carbamoyl fluorides,[13] we were motivated to explore their application in atom-economical carbofluorination reactions. The use of an alkyne as the π-acceptor would provide a direct route to tetrasubstituted alkenyl fluorides, which are present in a number of bioactive compounds and serve as amide bond bioisosteres or enol mimics.[14] The intramolecular chlorocarbamoylation of alkynes has been previously reported by Lautens and co-workers using Pd catalysts[15] or stoichiometric hexafluoroisopropanol (HFIP)[16] (Scheme 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

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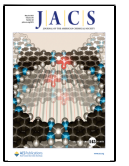

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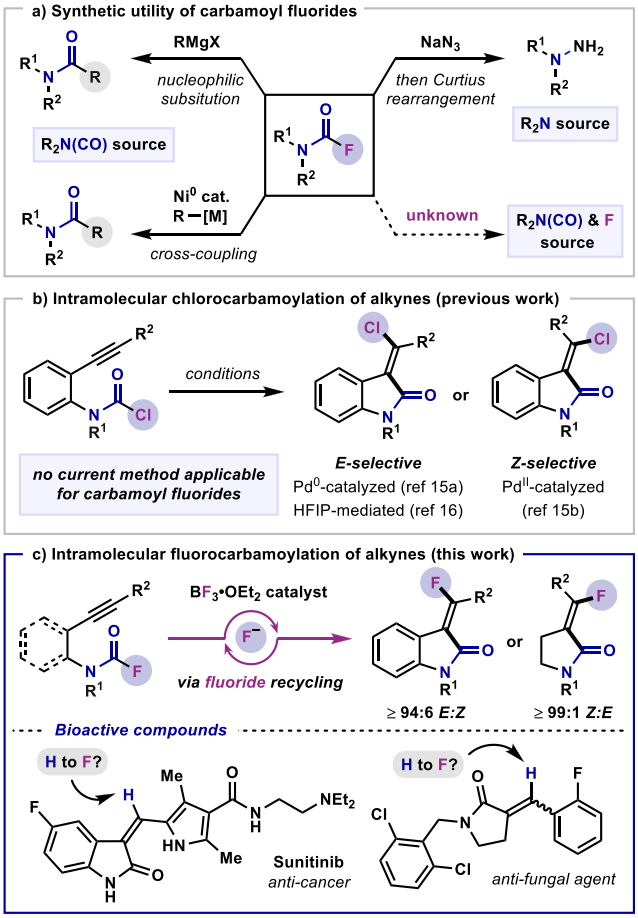
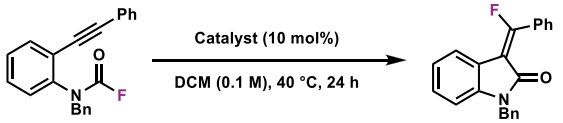
Scheme 1. (a) Synthetic Utility of Carbamoyl Fluorides, (b) Previously Reported Intramolecular Chlorocarbamoylation Reactions, and (c) This Work: BF_3-Catalyzed Intramolecular Fluorocarbamoylation Reaction



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, which resulted 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 transformation (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 reaction (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 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,

Table 1. Catalyst Screen for the Fluorocarbamoylation of 1a[a]



entry[b]	catalyst	conversion (%)	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[c]	HFIP	3	0	NA
9	$BF_3{\cdot}OEt_2$	100	>99 (99)[d]	>95:5
10	BCl_3	100	90[e]	>95:5
11	BBr_3	100	81[f]	>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[g]	1 equiv $BF_3{\cdot}OEt_2$ with **1a-Cl**	20	0	NA

[a]NA = not applicable; Tr = trityl; Tro = tropylium. [b]All reactions were run at a 0.1 mmol scale in a sealed 1 dram (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. [c]With HFIP (8 equiv) in PhMe, 100 °C, 12 h (ref 16). [d]Isolated yield. [e]**2a-Cl** formed in 9% yield (>95:5 *E*/*Z*). [f]**2a-Br** formed in 8% yield (>95:5 *E*/*Z*). [g]**2a-Cl** formed in 10% yield (77:23 *E*/*Z*).

they also gave approximately catalytic amounts of halogen exchange products **2a-Cl** and **2a-Br**, respectively, thereby 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 with BBr_3 and BF_3, respectively, on the basis of reported fluoride ion affinity values (FIA).[26] Notably, 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), thereby demonstrating that carbamoyl fluorides are uniquely suited for this transformation.

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*-substituent 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

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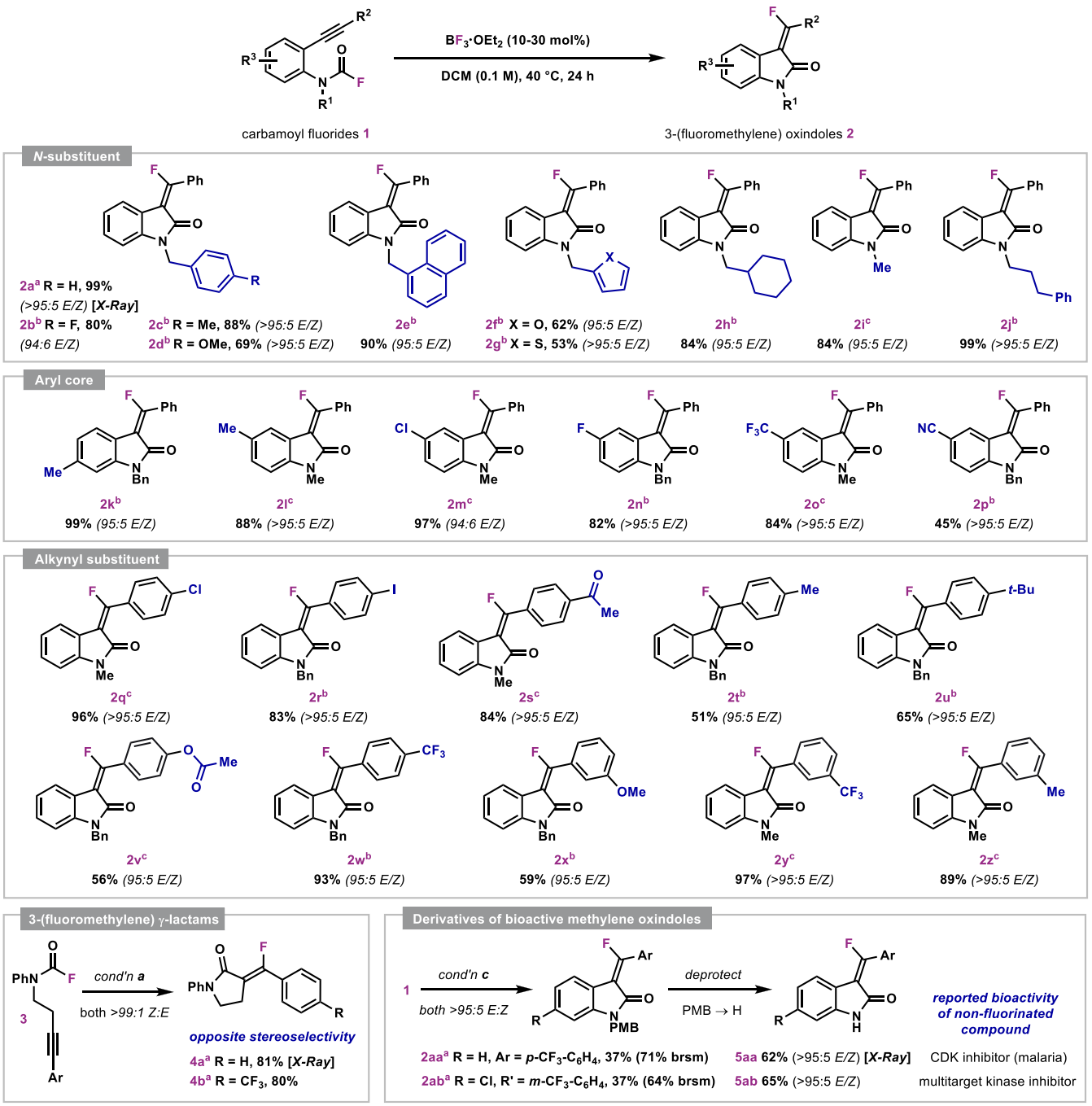

Figure 1. Substrate scope and synthesis of fluorinated kinase inhibitors: [a]10 mol % BF_3·OEt_2, [b]20 mol % BF_3·OEt_2, and [c]30 mol % BF_3·OEt_2. Conditions for PMB deprotection: anisole (20 equiv), TFA (0.1 M), 80 °C, 16 h.

2x, **2y** and **2z**. We were pleased to see that our method was also applicable toward the synthesis of γ-lactams **4a** and **4b** with complete *Z*-selectivity, as confirmed by X-ray crystallography for **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) calculations (*vide infra*). To demonstrate the utility of our method toward the synthesis of medicinally relevant compounds, we prepared oxindoles **2aa** and **2ab**, which upon PMB deprotection provided access to the 3-fluoro-derivatives (**5aa** and **5ab**) of known protein kinase inhibitors.[27] The stereochemistry of **5aa** remained unchanged upon deprotection.[23]

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 coworkers revealed that carbamoyl fluorides are reluctant to form isocyanate cations, even in the presence of strong Lewis and

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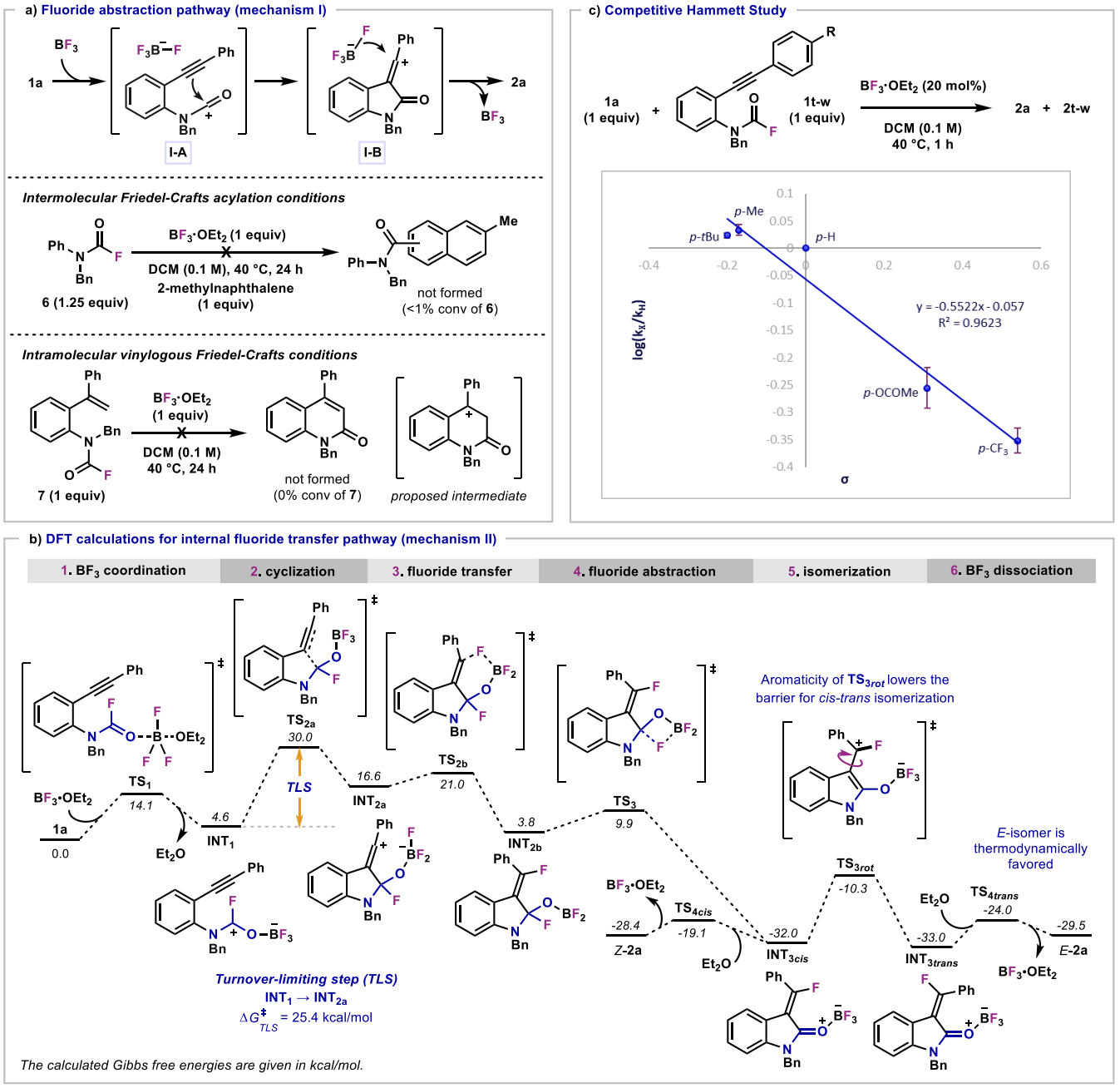

Figure 2. (a) Probing the feasibility of a fluoride abstraction mechanism via Friedel–Crafts test reactions; (b) calculated energy profile for the proposed internal fluoride transfer mechanism; and (c) competitive Hammett study for *para*-substituted carbamoyl fluorides.

Brønsted acids, and instead form coordination complexes.[29] To probe the possibility of isocyanate cation formation under our reaction conditions, we ran a series of Friedel–Crafts test reactions. When we subjected carbamoyl fluoride **6** to stoichiometric $BF_3{\cdot}OEt_2$ in the presence of 2-methylnaphthalene[30] or *p*-xylene (see SI),[23] no arylation products were observed. Furthermore, a vinylogous intramolecular Friedel–Crafts reaction[16] of *ortho*- alkenyl carbamoyl fluoride **7** failed to produce the expected quinolinone product. Together, these experiments indicate that carbamoyl fluorides are reluctant to undergo BF_3-mediated fluoride abstraction, suggesting that mechanism I is unlikely.

Given that the reaction is exclusively promoted by halide-containing boron-based catalysts and that 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. On the basis of 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/MA-DEF2-SVP/CPCM(DCM) calculations[35−37] were performed using ORCA4.2[38] to optimize the structures of reactants, products, and intermediates and to locate transition states.[39] The full energetic profile of the proposed mechanism is shown

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in Figure 2b. Migration of the oxophilic BF_3 from OEt_2 to the carbamoyl oxygen of **1a** comes at a mild energetic cost. From $\mathbf{INT}_1$, cyclization to form the 5-membered ring was determined to be turnover-limiting with a surmountable barrier of 25.4 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 $\mathbf{INT}_{3cis}$, which can undergo C=C bond rotation to give $\mathbf{INT}_{3trans}$. Dissociation of BF_3 can occur from $\mathbf{INT}_{3cis}$ or $\mathbf{INT}_{3trans}$ 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 29.5 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 ($\Delta G^{\ddagger}_{isom}$ = 21.7 kcal/mol). In contrast, the transition state 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 ($\Delta G^{\ddagger}_{isom}$ = 37.7 kcal/mol) (Figure 3).[23] Overall, these calculations

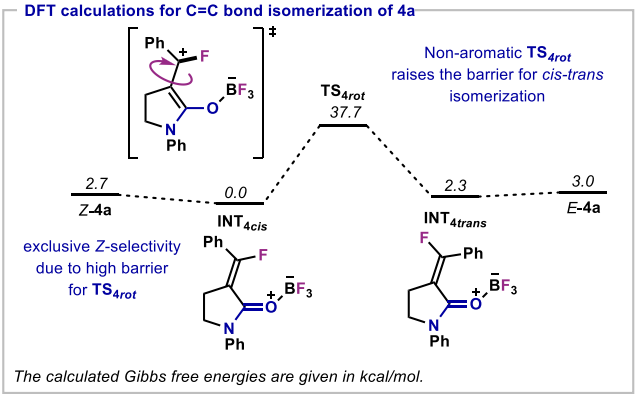

Figure 3. Calculated energy profile for γ-lactam isomerization barrier.

provide insight into the origin of stereoselectivity, with the initially formed *Z*-isomer being exclusively observed for γ-lactams and the thermodynamically favored *E*-isomer being observed for oxindoles.

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, thereby 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**−**1w** 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 toward a unique halide recycling mechanism involving fluoride transfer from 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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c03982.

Reaction optimization tables; experimental procedures for the 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)

Calculated energies, optimized structures, transition state structures, and animations of imaginary frequency modes are provided in a folder called "Additional Computational Data" (ZIP)

Accession Codes

CCDC 2215309, 2215312, and 2215313 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Tao Zeng − *Department of Chemistry, York University, Toronto, Ontario M3J 1P3, Canada;* orcid.org/0000-0002-1553-7850; Email: tzeng@yorku.ca

Christine M. Le − *Department of Chemistry, York University, Toronto, Ontario M3J 1P3, Canada;* orcid.org/0000-0003-2543-4414; Email: cmle@yorku.ca

Authors

E. Ali McKnight − *Department of Chemistry, York University, Toronto, Ontario M3J 1P3, Canada*

Ramon Arora − *Department of Chemistry, University of Toronto, Toronto, Ontario M5S 3H6, Canada;* orcid.org/0000-0003-4585-4328

Ekadashi Pradhan − *Department of Chemistry, York University, Toronto, Ontario M3J 1P3, Canada;* orcid.org/0000-0002-5087-3761

Yuriko H. Fujisato − *Department of Chemistry, York University, Toronto, Ontario M3J 1P3, Canada*

Ayonitemi J. Ajayi − *Department of Chemistry, York University, Toronto, Ontario M3J 1P3, Canada*

Mark Lautens − *Department of Chemistry, University of Toronto, Toronto, Ontario M5S 3H6, Canada;* orcid.org/0000-0002-0179-2914

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.3c03982

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Notes

The authors declare no competing financial interest.

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