Ring-Opening Fluorination of Bicyclic Azaarenes

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ABSTRACT: We have discovered a ring-opening fluorination of bicyclic azaarenes. Upon treatment of bicyclic azaarenes such as pyrazolopyridines with electrophilic fluorinating agents, fluorination of the aromatic ring is followed by a ring-opening reaction. Although this overall transformation can be classified as an electrophilic fluorination of an aromatic ring, it is a novel type of fluorination that results in construction of tertiary carbon–fluorine bonds. The present protocol can be applied to a range of bicyclic azaarenes, tolerating azines and a variety of functional groups. Additionally, mechanistic studies and enantioselective fluorination have been examined.

Fluorine is one of the most important elements that could be installed onto hydrocarbon frameworks in pharmaceuticals, agrochemicals, and materials science. Particularly, in medicinal chemistry, fluorine has been incorporated into drug molecules to improve their liposolubility and metabolic stability.[1] The effect of fluorine atoms in molecules has been well-studied, and in turn, fluorination methodology has flourished as well.[2] One of the most conventional ways to achieve fluorination is electrophilic fluorination. Nucleophiles used in electrophilic fluorinations can be broadly classified into carbanions (e.g., 1,3-dicarbonyls), electron-rich unsaturated bonds (e.g., alkenes and alkynes), and aromatics.[3] However, in these existing methods, fluorination proceeds while retaining the carbon skeleton of the starting material, and fluorinations involving skeletal transformations are rare.

Ring-opening fluorination, in which a fluorine atom is introduced onto a cyclic compound with concomitant ring cleavage, has recently attracted attention as a useful method for efficiently constructing complex fluorine-containing skeletons (Figure 1A). Although ring-opening fluorinations have recently been reported, most are limited to three- or four-membered ring starting materials such as epoxides, cyclopropanes/butanes, and aziridines, which have strained chemical bonds.[4,5] As one of a few examples of ring-opening fluorination involving C–C bond cleavage in a ring size ≥ 5, the Sarpong group reported an elegant ring-opening fluorination of cyclic amines (Figure 1B).[6] The Leonori group also discovered a ring-opening fluorination of cyclic oxime ethers under visible light irradiation.[7] In the heteroatom–heteroatom (X–Y) bond paradigm, the Yao group reported a ring-opening fluorination using isoxazoline *N*-oxides via O–N bond cleavage (Figure 1C).[8] However, all these methods require the use of highly specific substrates, and fluorinations involving the ring opening of aromatic rings or asymmetric fluorination have not yet been reported.

In contrast to existing methods, we planned to develop a ring-opening fluorination of bicyclic azaarenes such as pyrazolopyridines. We hypothesized that treating bicyclic azaarenes with an electrophilic fluorinating agent would result in fluorination at the C3 position, followed by deprotonation at the C2 position and pyrazole ring opening via N–N bond cleavage. Although this can be considered as a simple electrophilic fluorination using an electron-rich heteroaromatic system as a nucleophile, the resulting compound is an sp^3-fluorinated compound (C(sp^3)–F bond) instead of a fluorine-substituted heteroarene (C(sp^2)–F bond). In other words, we thought that this would be a novel type of fluorination reaction with accompanying skeletal transformation.

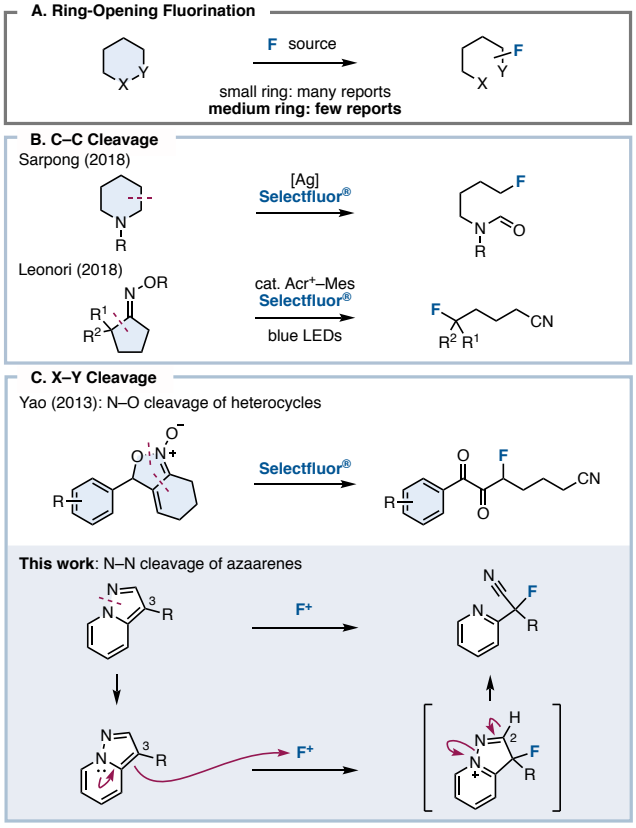
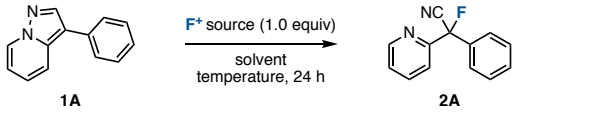


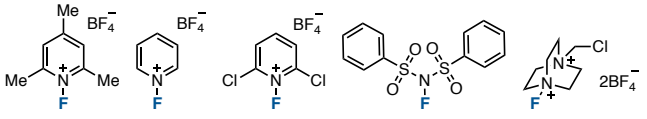
Figure 1. (A) Ring-opening fluorination. (B) Fluorination of cyclic compounds via C–C bond cleavage. (C) Fluorination of cyclic compounds via X–Y bond cleavage.

First, we selected 3-phenylpyrazolopyridine (**1A**) as the model substrate (which was readily prepared in three steps from a commercially available compound) to examine electrophilic fluorinating agents and reaction conditions (Table 1). When *N*-fluoropyridinium salts (**F1**–**F3**) were used in MeCN at 80 °C, ring-opening fluorinated product **2A** was successfully obtained, albeit in low yields (Entries 1–3). The use of stronger fluorinating agents such as NFSI and Selectfluor® gave fluorinated products in high yields (Entries 4 and 5).[9] As for the reaction temperature, the yield of **2A** was 68% even at 50 °C. The yield increased as the temperature was increased, and the fluorinated product was obtained quantitatively at 80 °C (Entries 6–8 vs. Entry 5). The reaction proceeded in polar solvents such as acetone and DMF (which is able to dissolve Selectfluor®), and gave the fluorinated product **2A** (Entries 9–11). Finally, we conformed the optimal conditions: Selectfluor® (1.0 equiv) at 80 °C in MeCN for 24 h.

Table 1. Screening of reaction conditions.[a]



entry	F^+ source	temp/ °C	solvent	**2A** (%)
1[b]	F1	80	MeCN	39
2	F2	80	MeCN	27
3	F3	80	MeCN	5
4	NFSI	80	MeCN	94
5	Selectfluor®	80	MeCN	>99
6	Selectfluor®	50	MeCN	68
7	Selectfluor®	60	MeCN	74
8	Selectfluor®	70	MeCN	87
9	Selectfluor®	80	Acetone	65
10	Selectfluor®	80	DMF	64
11	Selectfluor®	80	MeOH	58



[a] Conditions; **1A** (0.20 mmol), F^+ source (1.0 equiv), solvent (1.0 mL), 50–80 °C, 24 h. NFSI = *N*-Fluorobenzenesulfonimide

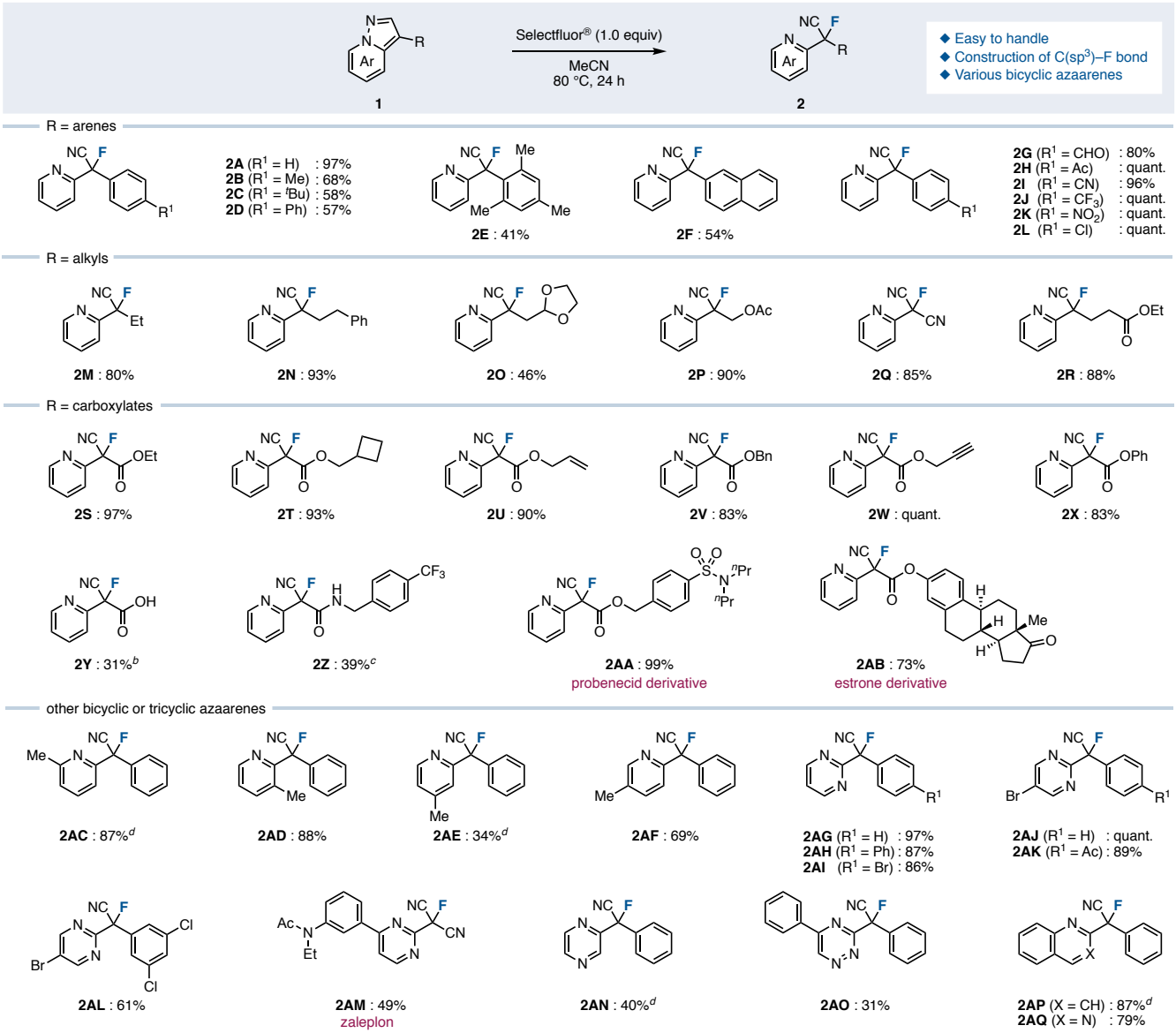
With the optimal conditions in hand, the substrate scope was investigated (Scheme 1). Various 3-arylpyrazolopyridines were examined: Methyl (**1B**), *tert*-butyl (**1C**), and phenyl (**1D**) at the *para*-position on the aryl group gave the ring-opening fluorinated products **2B**–**2D** in moderate yields. It should be noted that fluorination of these aryl groups was detected. When using trimethylphenyl (**1E**) and naphthyl (**1F**) starting materials, the corresponding products **2E** and **2F** were obtained in moderate yields, and occurred decomposition of **1E** or fluorinated the aryl group of **1F** (less than 10% yields). The reaction showed good functional group tolerance in the presence of formyl (**1G**), acetyl (**1H**), cyano (**1I**), trifluoromethyl (**1J**), nitro (**1K**), and chloro (**1L**) groups, as the reaction worked to give the corresponding products **2G**–**2L** in excellent yields. Next, 3-alkylpyrazolopyridines were investigated. The fluorination using bicyclic azaarenes bearing alkyl groups (**1M** and **1N**) or acetal (**1O**) proceeded smoothly to give the corresponding fluorinated products **2M**–**2O** in moderate to excellent yields. Pyrazolopyridines with alkyl acetate (**1P**), cyano (**1Q**), and ethylcarboxylate (**1R**) afforded the corresponding products (**2P**–**2R**) in good yields. Pyrazolopyridine carboxylates were also examined. Substrates with alkyl groups including alkene (**1U**) and alkyne (**1W**) remained intact to give products **2S**–**2X** in high yields. Carboxylic acid **1Y** also reacted well, but the product was difficult to purify, resulting in a low yield of **2Y**. In the case of compounds with amides such as **1Z**, deamidation occurred to give 3-fluoropyrazolopyridine as a byproduct. Therefore, the fluorinated product **2Z** was obtained in moderate yield (39%) by reacting at a lower temperature (–30 °C). Furthermore, azaarenes **1AA** and **1AB** derived from probenecid and estrone also gave fluorinated compounds **2AA** and **2AB** in high yields. Of note, in the case of an unsaturated ester or iodine at the C3 position, the desired fluorinated product could not be obtained, giving a complex mixture.

Substituted bicyclic arenes gave fluorination products **2AC**–**2AF**, however, for some substrates such as **1AC** and **1AE**, the fluorination reactions were more difficult. After extensive screening of additives, we found that $NaClO_4$ (1.0 equiv) was effective for increasing yields (see the Supporting Information for details). For example, without this additive, **1AC** gave **2AC** in only 51% yield, but with the additive, the yield improved to 87%. The role of the additive remains unclear, but we hypothesize that the counter anion exchange in the intermediate might affect the acidity of the proton at the C3 position.[10]

This fluorination was also applicable to other pyrazoloazines: pyrazolopyrimidine with a phenyl group at the C3 position gave fluorinated compounds **2AG**–**2AI** in high yields. 6-Bromopyrazolopyrimidine with various aryl groups at the C3 position gave fluorinated compounds **2AJ**–**2AL** as well. The ring-opening fluorination proceeded well even when using zaleplon, a hypnotic agent, for which the desired product **2AM** was obtained. The reaction was also applicable to pyrazolopyrazine, triazine, quinoline, and quinazoline, giving fluorinated products **2AN**–**2AQ** in moderate yields.

In order to elucidate the reaction mechanism, we performed reaction tracking by ^{1}H NMR analysis using **1M** (Figure 2A). When Selectfluor® was added to **1M** in an NMR tube without stirring, **1M** was immediately consumed to produce tetrafluoroborate **3** as the intermediate, which is thought to be the result of electrophilic fluorination at the C3 position. After 2 to 4 hours of reaction time, **1M** almost entirely disappeared, and NMR peaks showed a mixture of **2M** and **3**; finally, practically only **2M** resulted in the ^{1}H NMR spectrum. This experiment indicated that the fluorination and the cleavage of the N–N bond proceeds in a stepwise fashion. When the reaction was stirred in a flask, **1M** disappeared after 10 min at room temperature, giving intermediate **3** and the residue **4** of Selectfluor® (Figure 2B). Upon removal of **4** from the resulting mixture, further reaction did not procced by heating at 80 °C for 24 h (see Supporting Information for experimental details). Therefore, triethylamine (1.0 equiv) was added, and the reaction proceeded quickly to give the desired **2M** quantitatively. This supports the role of Selectfluor® as the fluorinating agent in the reaction and the residue **4** as the base that promotes the N–N bond cleavage.

Scheme 1. Substrate scope[a]



[a] Conditions; **1A** (0.20 mmol), Selectfluor® (1.0 equiv), MeCN (1.0 mL), 80 °C, 24 h. [b] Selectfluor® (5.0 equiv) was added. [c] The reaction was performed at –30 °C. [d] $NaClO_4$ (1.0 equiv) was added.

Next, the fluorination reaction was carried out with **5**, where the C2 position was substituted (Figure 2C). As a result, only trifluoroborate salt **6** was obtained in a good yield, with no ring-opened product was obtained upon heating. When the fluorination reaction was attempted using **7**, which is unsubstituted at the C3 position, one equivalent of Selectfluor® gave the fluorinated compound **8** as the main product (50%) and the ring-opened compound **9** as a byproduct, demonstrating further fluorination. When the amount of Selectfluor® was increased to two equivalents, **9** became the main product (58%). These results demonstrated that the ring-opening fluorination can proceed as long as an appropriate substituent is present at the C3 position.

We then studied the enantioselective version of this fluorination reaction (Figure 3D). Fluorinations using a chiral phosphoric acid and decarboxylative asymmetric allylation reaction were unsuccessful (see the Supporting Information for details).[11] Therefore, we attempted asymmetric fluorinations using chiral fluorinating agents. Shibata reported that a chiral fluorinating agent, *N*F–$(DHQD)_2PHAL$, can be prepared by mixing $(DHQD)_2PHAL$ and Selectfluor® at room temperature.[12] A reaction using stoichiometric amounts of these agents with 3-phenyl-6-bromopyrazolopyrimidine **1AJ** in MeCN at 50 °C gave the corresponding product in 68:32 *e.r.*, albeit in a low yield. However, when $(DHQD)_2PHAL$ was reduced to catalytic amount, enantioselectivity was dropped whereas the yield was increased. The substrate without a bromo atom at the C6 position (**1AG**) gave the fluorinated product in moderate yield (44%) and 65:35 *e.r.* By lowering the temperature, changing the fluorinating agent, and changing the solvent, we finally succeeded in obtaining the fluorinated compound **2AJ** with an enantioselectivity of 84:16 *e.r.*

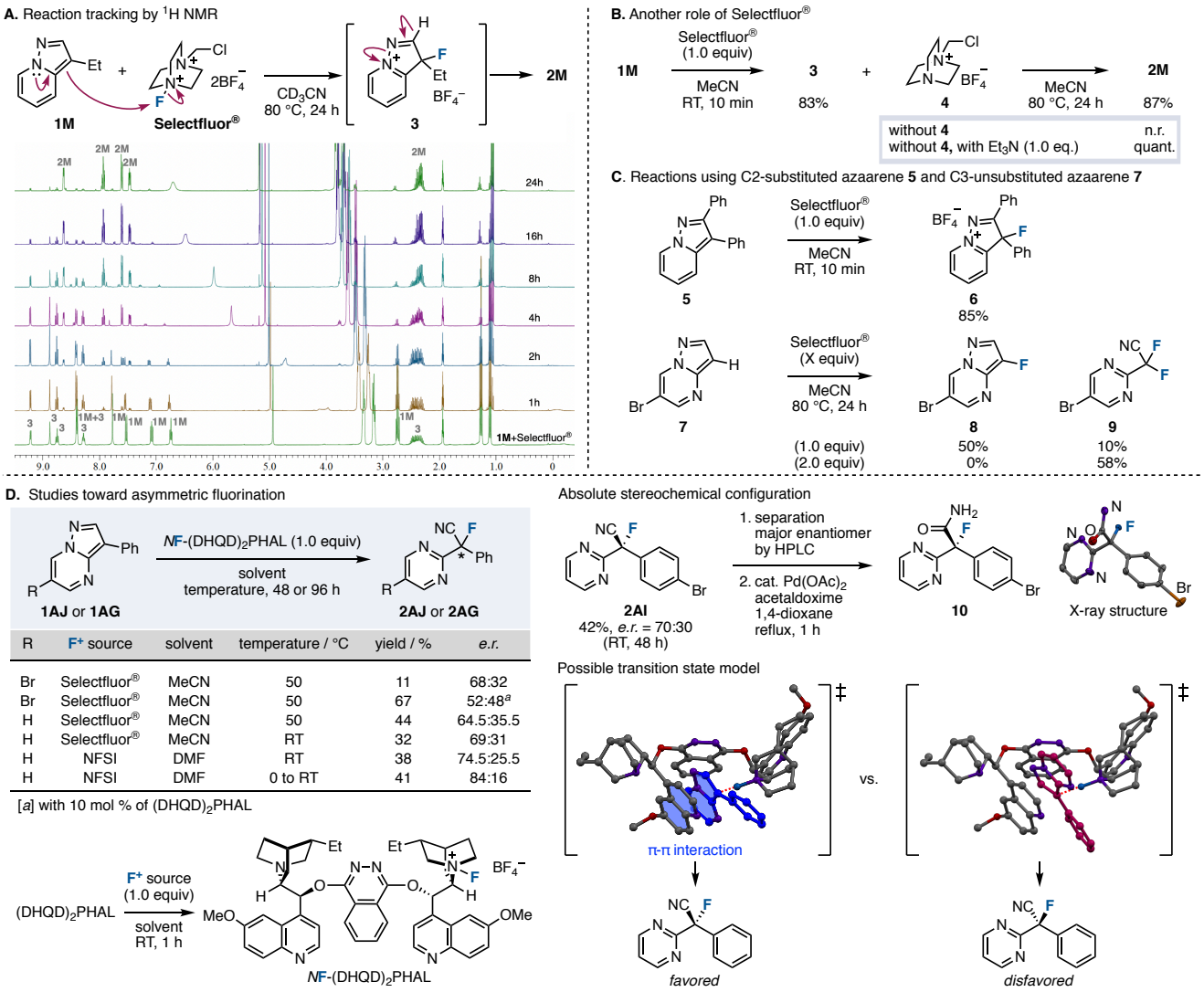
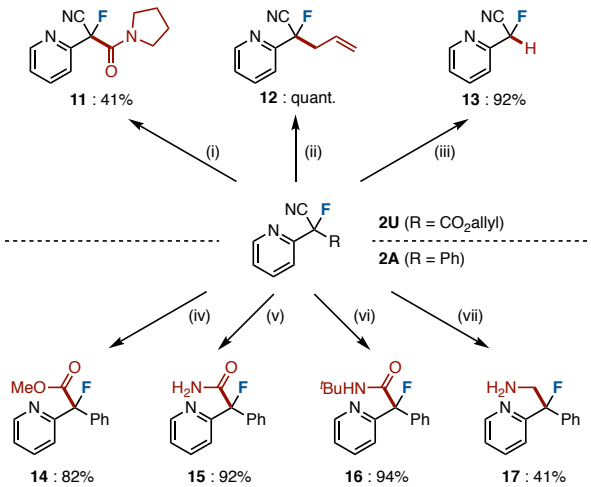


Figure 2. (A) Reaction tracking by ^{1}H NMR. (B) The role of Selectfluor®. (C) Reactions using C2-substituted azaarene **5** and C3-unsubstituted azaarene **7**. (D) Studies toward asymmetric fluorination.

The absolute stereochemical configuration was determined by derivatization of the optically pure product to amide **10**, recrystallization, and then X-ray structural analysis. This enantioselectivity could be explained using the proposed transition state model. Although the direction in which the substrate reacts with the chiral fluorinating agent determines the enantioselectivity, we believe that the transition state of the desired compound has a π-π interaction between the substrate and the methoxyquinoline moiety of (DHQD)$_2$PHAL, which fixes the conformation.[12c, 13]

Finally, the obtained fluorinated compounds were derivatized into various compounds (Scheme 2). The ring-opened fluorinated products of pyrazolopyridine **2U** (R = CO_2allyl) were condense with amines to give amide **11** in 41% yield. Palladium-catalyzed decarboxylative allylation and removal of allyl esters proceeded to give derivatives **12** and **13** in high yields. Furthermore, we attempted to convert the cyano group of the product of the fluorination reaction. Fluorinated product **2A** (R = Ph) was converted to methyl ester **14** by methanolysis. **2A** was also converted to amides **15** and **16** by hydrolysis and Ritter reaction.[14] Furthermore, borane reduction gave amine **17**. In this way, we have succeeded in synthesizing a variety of fluorine-containing compounds by orthogonal functional group transformations following ring-opening fluorination.

Scheme 2. Derivatization of products.



Conditions: (i) pyrrolidine (5.0 equiv), MeCN, RT, 12 h; (ii) $Pd(PPh_3)_4$ (5.0 mol %), toluene, RT, 1 h; (iii) $Pd_2(dba)_3$ (5.0 mol %), PPh_3 (20 mol %), pyridine (3.0 equiv), MeCN, RT, 1 h; (iv) TMSCl (5.0 equiv), MeOH, 50 °C, 6 h; (v) $Pd(OAc)_2$ (4.0 mol %), acetaldoxime (10 equiv), 1,4-dioxane, reflux, 1 h; (vi) ^{t}BuOAc (6.0 equiv), conc. H_2SO_4 (10 μL), 40 °C, 2 h; (vii) BH_3·SMe_2 (3.0 equiv), THF, 0 °C to RT, 19 h.

In summary, we developed a ring-opening fluorination of bicyclic azaarenes leading to sp^3-fluorinated compounds via N–N bond cleavage. Studies revealed that the electrophilic fluorinating reagent functioned not only as the fluorine source, but also as the base required for ring opening. Expanding the range of substrates and other electrophiles for this type of transformation is currently underway in our laboratory.

ASSOCIATED CONTENT

Accession Codes

CCDC 2113745 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.

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Notes

No competing financial interests have been declared.

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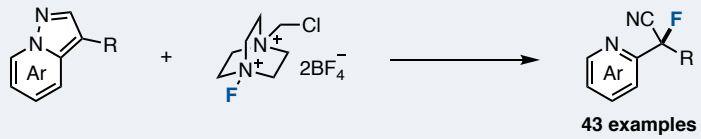
Ring-Opening Fluorination of Bicyclic Azaarenes



43 examples

▪ ***Easy to Handle*** ▪ ***Various Azaarenes*** ▪ ***Construction of C(sp^3)–F Bond***