Title

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Journal

Journal of the American Chemical Society, 142(19)

ISSN

0002-7863

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Publication Date

2020-05-13

DOI

10.1021/jacs.0c02331

Peer reviewed

HHS Public Access

Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2021 May 13.

Published in final edited form as:

J Am Chem Soc. 2020 May 13; 142(19): 8946–8952. doi:10.1021/jacs.0c02331.

Regio- and Enantioselective Bromocyclization of Difluoroalkenes as a Strategy to Access Tetrasubstituted Difluoromethylene-Containing Stereocenters

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Abstract

Difluoromethylene-containing compounds have attracted substantial research interest over the past decades for their ability to mimic biological functions of traditional functional groups while providing a wide variety of pharmacological benefits bestowed by the C–F bond. We report a novel strategy to access RCF_2Br-containing heterocycles by regio- and enantioselective bromocyclization of difluoroalkenes enabled by chiral anion phase-transfer catalysis. The utility of this methodology was highlighted through a synthesis of an analogue of efavirenz, a drug used for treating HIV. Additionally, the synthetic versatility of the CF_2Br intermediates was showcased through functionalization to a variety of enantioenriched α,α-difluoromethylene-containing products.

Graphical Abstract

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Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c02331.

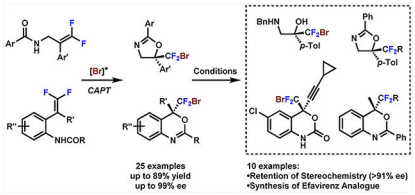
Experimental procedures and miscellaneous data (PDF)

X-ray crystal structure of BDF-efavirenz (CIF)

X-ray crystal structure of 8·HCl (CIF)

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c02331

The authors declare no competing financial interest.



INTRODUCTION

The difluoromethylene unit (RCF_2R'/RCF_2H) can confer a variety of unique pharmacological properties to drug molecules, in addition to the benefits typically associated with fluorinated functional groups, such as increased lipophilicity, oxidative stability, and modulated bioavailability.[1] In a medicinal chemistry setting, the CF_2 moiety acts as a lipophilic mimic for polar functional groups, such as carbonyls and sulfonyls,[2] and as a replacement for a single oxygen atom in phosphates,[3] sulfates,[4] and aryl ethers.[5] Uniquely, the difluoromethyl group (RCF_2H) has been shown to be a lipophilic hydrogen bond donor because of the high polarization of the C–H bond,[6] allowing it to act as a bioisostere of alcohols and thiols.[7] Despite the immense potential for difluoromethylene groups to mimic structural motifs conventionally used for molecular recognition, a survey of fluorine-containing pharmaceuticals reveals relatively few difluoromethylene moieties.[8] Traditional synthetic methods, such as difluorination of carbonyls or carbonyl surrogates (Figure 1A), feature harsh, acidic conditions where heterocycles and acid-sensitive functional groups are not well tolerated. More importantly, substitution at the α-position hinders reactivity and leads to carbocation rearrangement pathways,[9] which precludes the applicability of these protocols to compounds with α-stereocenters.

As a result of these limitations, there has been increased efforts aimed at developing alternate retrosynthetic disconnections to access these difluoromethylene-containing stereocenters. The most developed approach is the enantioselective nucleophilic addition of difluorinated nucleophiles to carbonyl groups (Figure 1B).[10,11] Although this method provides a viable entry to difluoromethylene-substituted secondary alcohols, it is limited to stabilized nucleophiles featuring a strongly electron-withdrawing group (e.g., carbonyl and sulfone), which restricts the products accessible using this strategy. A less commonly demonstrated variant of this disconnection is the asymmetric addition of a nucleophile into a difluorinated aldehyde, typically difluoroacetaldehyde.[12] Although these strategies do provide access to difluoromethyland difluoromethylene-containing stereocenters, they are typically limited to the functionalization of aldehydes, limiting the applicability of this approach to trisubstituted stereocenters. As an alternative, the Jacobsen group recently reported the use of alkenes as precursors to difluoromethylated stereocenters through an aryl iodide-catalyzed enantioselective difluorination (Figure 1C).[13]

A complementary approach to these methods would be the enantioselective synthesis of a tetrasubstituted $C(sp^3)–CF_2Br$ moiety, as the bromodifluoromethyl group would constitute a valuable handle for the synthesis of a wide variety of tetrasubstituted difluoromethylene-containing stereocenters.[14] Although the functionalization of RCF_2Br compounds has been accomplished by a number of synthetic transformations (e.g., cross-coupling,[15] reductive

1,2-addition,[16] and photoredox activation),[17] the dearth of methods for preparing C(sp^3)−CF_2Br motifs, especially in a general enantioselective manner, has limited the application of this strategy.

We posited that the enantioselective bromocyclization of readily accessible difluoroalkene-containing compounds to the corresponding CF_2Br group would enable a general approach for accessing tetrasubstituted difluoromethylene-containing stereocenters (Figure 1D). Herein, we demonstrate that a chiral anion phase-transfer (CAPT)[18] strategy can be employed in a regio- and enantioselective bromocyclization of 1,1-difluoroalkenes, to access oxazoline- and oxazine-containing tetrasubstituted bromodifluoromethylated stereocenters.

RESULTS AND DISCUSSION

We began our investigation with an intramolecular amide as the nucleophilic component (**1a**, Scheme 1) to synthesize bromodifluoromethyl-containing oxazoline **2a**. Compounds of this type are of particular interest, as they can be reduced to the corresponding acyclic amino alcohol in high yield and with retention of stereochemistry.[19] Subjecting amide **1a** to electrophilic bromination reagent [(**DAB^1**)$_2$**Br**](**BF$_4$**)$_3$, in the presence of 10 mol % (*R*)-TRIP as the phase-transfer catalyst, provided the desired oxazoline in an unsatisfactory 19% yield and 30% ee (Scheme 1A). Additionally, we observed the formation of a significant amount of *endo*-cyclization product, **2a′**, with a yield of 25% and 49% ee. The formation of *endo*cyclization product, while initially surprising, is rationalized on the basis of fluorine's ability to stabilize α-carbocations, which can be sufficient enough to invert Markovnikov selectivity.[20]

On the basis of recent results demonstrating the identity of the Lewis base and ion pairing with cations can influence reaction regioselectivity,[21] we hypothesized that modification of the 1,4-diazabicyclo[2.2.2]octane (DABCO)nium reagent could provide a means to improve the regio- and enantioselectivity of the bromocyclization through cooperativity of the phase-transfer catalyst/reagent ion pair (Scheme 1B). A variety of DABCOnium-based brominating reagents[18e] were tested to assess the impact of the halogen source on the regio- and enantioselectivity of cyclization products. Increasing the steric bulk of the DABCOnium reagent, by examination of [(**DAB^2**)$_2$**Br**](**BF$_4$**)$_3$ and [(**DAB^3**)$_2$**Br**](**BF$_4$**)$_3$, had a deleterious effect on the selectivity of the reaction, with both reagents providing the *exo*-cyclization adduct in lower regioand enantioselectivities. In the case of [(**DAB^3**)$_2$**Br**](**BF$_4$**)$_3$ as the achiral halogen source, the previously observed enantioselectivity was overridden and **2a** was isolated in −25% ee.

Examination of electron-deficient arenes at the distal position of the DABCOnium-based brominating reagent proved to be more promising. Specifically, reagent [(**DAB^4**)$_2$**Br**](**BF$_4$**)$_3$, containing a perfluoro phenyl group, was able to provide the *exo*-cyclization product as the major regioisomer, with a yield of 26% and a promising 77% ee. Following this result, brominating reagent [(**DAB^5**)$_2$**Br**]-(**BF$_4$**)$_3$, which contains an additional electron-deficient arene, yielded the product in 49% yield with 91% ee. An increase in the reaction time to 48 h resulted in full conversion of the starting material and provided **2a** in an isolated yield of 75% in good enantioselectivity (90% ee, Table 1).

Initial investigation of the substrate scope of the reaction revealed that the yield and enantioselectivity were mostly unaffected by the steric and electronic nature of the nucleophile. Perturbing the electronics of the aryl ring of the amide via installation of electron-donating groups or *para*-fluorine (Table 1, entries **2a–2d**) had little effect on the yield and enantioselectivity (58–75% yield, 89–90% ee). The introduction of a sterically large arene featuring an *ortho*-methyl group did not interfere with the reaction efficacy, providing the product in a similar 53% yield and 92% ee (entry **2e**). Modification of the aromatic ring to introduce heterocycles such as thiophene and pyrimidine were also well tolerated (Table 1, entries **2f** and **2i**).

Alteration of the styrenal component proved to have more dramatic effects on the yield and enantioselectivity of the reaction. Replacement of Ar′ with naphthalene provided the product in 37% yield, with a high enantioselectivity of 90% ee (**2g**). Importantly, heterocycles were also well tolerated at the styrenal position, albeit with a slight reduction in enantioselectivity. Bromocyclization of *N*-Boc-indole-containing substrate **1j** provided the product in 62% yield, with 76% ee. In the case of pyrazole substrate **1k**, the product was isolated in 68% yield and a modest 60% ee. Similar results were seen with benzofuran substrate **1l**, producing product **2l** in 36% yield and 82% ee.

With the ability to overcome issues of competing 5-*exo* and 6-*endo* cyclization modes, this strategy was applied to the enantioselective synthesis of CF_2Br-containing oxazines, a system presenting potential 6-*exo* and 7-*endo* cyclization modes. The heterocyclic core also bears a close structural relationship to efavirenz (Scheme 2), an antiretroviral used for treating HIV.[22] This substrate class was amenable to a chiral anion phase-transfer strategy by using $[(\mathbf{DAB^3})_2\mathbf{Br}](\mathbf{BF_4})_3$ as the electrophilic bromine source in combination with (*R*)-TRIP as the catalyst.

Under these conditions, **3a** was effectively cyclized to bromodifluoromethyl oxazine **4a** in 80% yield and 96% ee (Table 2). Similar to the oxazoline class of substrates, this reaction was efficient regardless of the aromatic nucleophile explored (Table 2, entries **4a–4d**), where electronic and steric changes provided the products in >75% yield with excellent enantioselectivities (>94% ee). Replacement of the aryl ring with an adamantyl group on the amide moiety resulted in 68% yield with a diminished 69% ee (entry **4e**). Alteration of the alkyl component (R′) on the difluoroalkene also appeared to have little effect on the yield and enantioselectivity of the reaction (entries **4f**, **4g**, and **4i**). Interestingly, incorporation of a terminal alkene within the alkyl fragment provided the product in 43% yield and similarly high ee of 93%, with no detected bromination of the terminal nonfluorinated alkene. Modification of the central core of the substrate had the most dramatic effect on the efficacy of the reaction, where dioxane-containing substrate **3j** afforded oxazine **4j** in 62% yield and 73% ee, and the incorporation of pyridine as the aromatic core produced **4k** in 41% yield and 61% ee.

The applicability of this methodology to the synthesis of pharmaceutically relevant targets was examined with the synthesis of a bromodefluoro efavirenz analogue (BDF-efavirenz). After slight adjustment of the reaction conditions, the bromocyclization of substrate **3m** to **4m** was achieved with a 60% isolated yield and 99% ee on a 1.0 mmol scale (Scheme 2).

Treatment of this compound with $NaBH_3CN$ in acetic acid afforded PMB-protected amino alcohol 5, which closely resembles a key intermediate in Merck's commercial synthesis of efavirenz.[23] Subjecting this intermediate to the final two steps in the efavirenz synthesis provided access to BDF-efavirenz, in an overall yield of 59% over three steps from **4m**.

To demonstrate the synthetic utility of the tetrasubstituted $C(sp^3)–CF_2Br$ stereocenters, a diverse set of enantioenriched difluoromethylene-containing heterocycles were synthesized from the products of the enantioselective bromocyclization of difluoroalkenes (Scheme 3). Notably, enantioenriched difluor omethyl products **6a** and **7a** were easily accessed in high yields and fidelity of the stereocenter via Bu_3SnH reduction of the *in situ* generated RCF_2 radicals. Alternatively, the difluoromethyl radical intermediate engaged in Keck radical allylation to produce difluoroallyl product **7b** in 91% yield and 93% ee. The RCF_2 radical of **2a** was also generated under photoredox conditions and intercepted by *N*-isopropylacrylamide to generate amide-containing oxazoline **6b** in 70% yield and 93% ee.

In addition to modification of the bromodifluoromethyl group under radical conditions with no loss of stereochemistry, orthogonal and complementary derivatization was achieved via anionic RCF_2Li intermediates. Lithium-halogen exchange of 4a in the presence of ethyl chloroformate at −130 °C afforded difluoroester **7c** in 56% yield and 95% ee.[24] Difluoroesters have been shown to be key intermediates in the synthesis of ^{18}F-containing CF_3 groups via decarboxylative fluorination.[25] Similar anionic reactivity was found with the oxazoline class, showing competent interception with diethyl chlorophosphate, yielding difluorophosphonate **6c** in 42% yield and no loss of stereochemistry. Difluorophosphonates have been shown to act as bioisosteres of phosphates, as the difluoromethylene group confers similar pK_a properties to that of an oxygen linker, but cannot be hydrolyzed under biological conditions.[3] The *in situ* generated RCF_2Li species also reacted with 3-oxetanone to provide tertiary alcohol product **6d** in 54% yield and 91% ee. Finally, oxazine **4m** and oxazoline **2a** were reduced to their corresponding benzyl-protected amino alcohols, which serve as valuable building blocks for organic synthesis.

In summary, we have developed an approach for synthesizing bromodifluoromethyled stereocenters from difluoroalkenes via an enantioselective bromocyclization strategy. This transformation was facilitated by chiral anion phase-transfer catalysis and featured a strong dependence of the achiral brominating reagent on a variety of observed selectivities. Enantioenriched bromodifluoro-containing heterocycles, including an efavirenz analogue, were synthesized using this approach. Importantly, further derivatization of the bromodifluoromethyl group provides access to cyclic and acyclic compounds bearing difluoromethylene- and difluoromethyl-containing tetrasubstituted stereocenters from a common precursor.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We gratefully acknowledge the National Institutes of Health (R35 GM118190) for financial support and the College of Chemistry CheXray (NIH Shared Instrumentation Grant S10-RR027172) for X-ray crystallographic data. We thank Dr. Hasan Celik and UC Berkeley's NMR facility in the College of Chemistry (CoC-NMR) for spectroscopic assistance. Instruments in the CoC-NMR are supported in part by NIH S10OD024998. We also thank Dr. Richard Thornbury, Dr. Alec Christian, Banruo Huang, Dr. René Rahimoff, and Danny Thach for helpful discussions.

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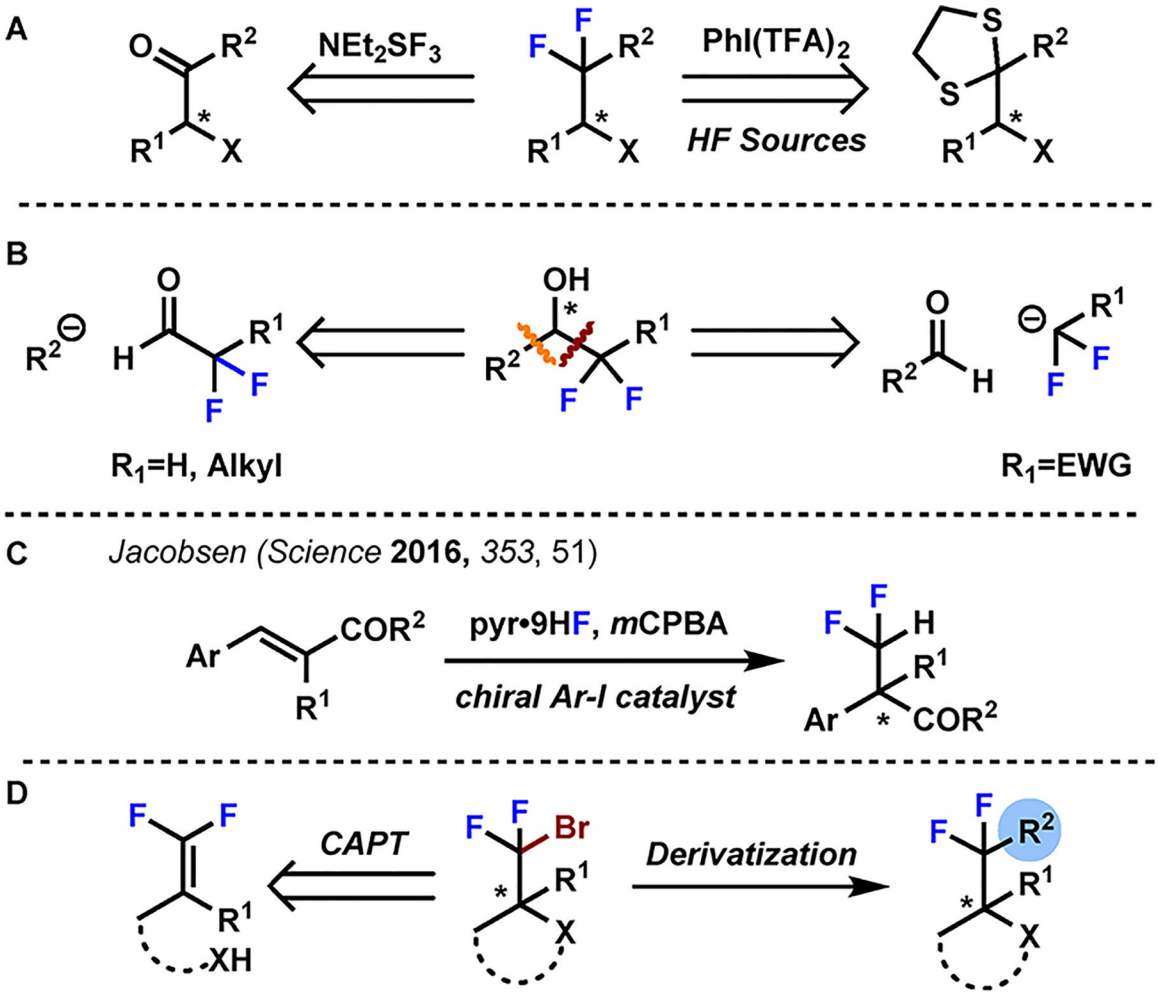
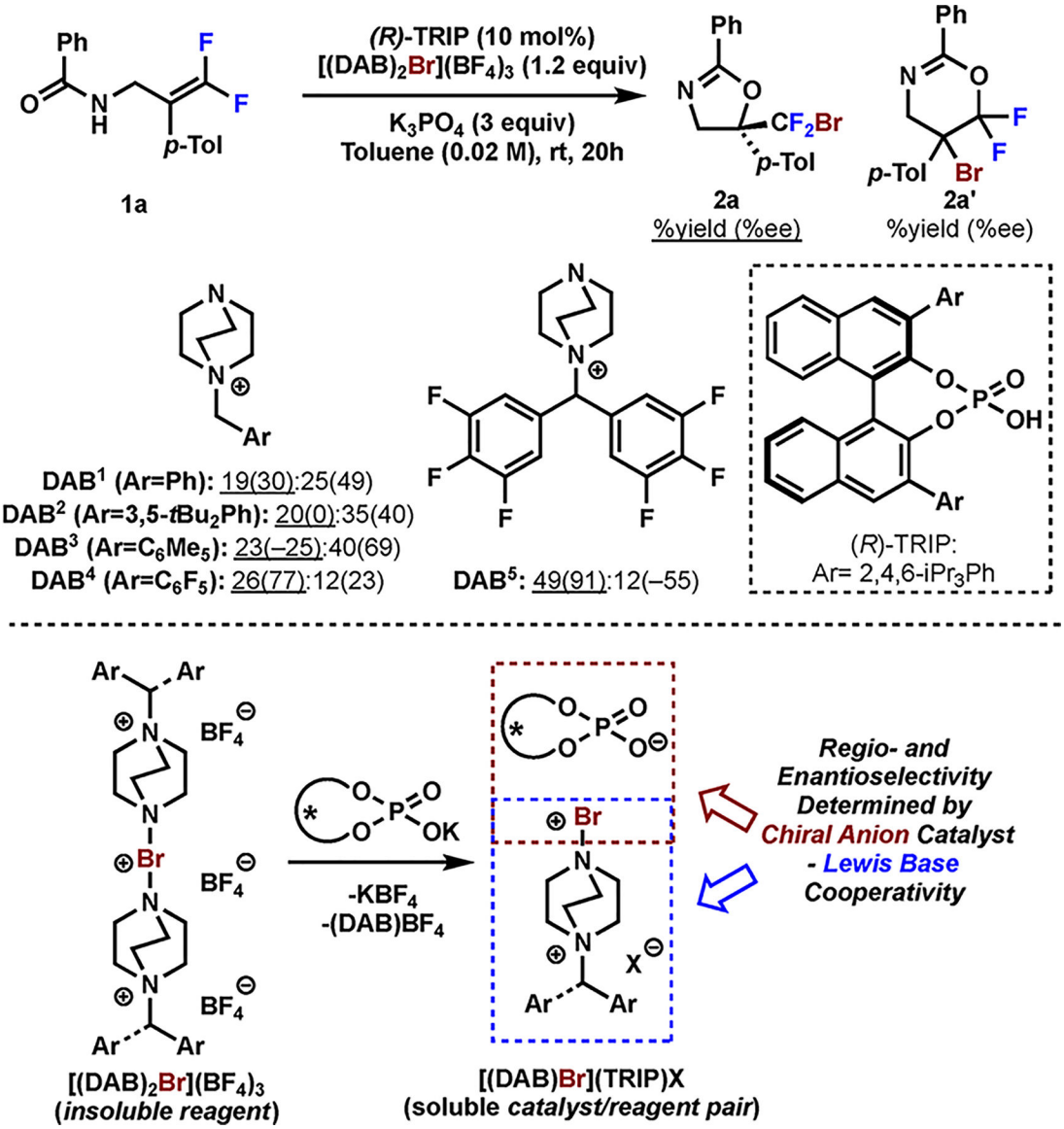


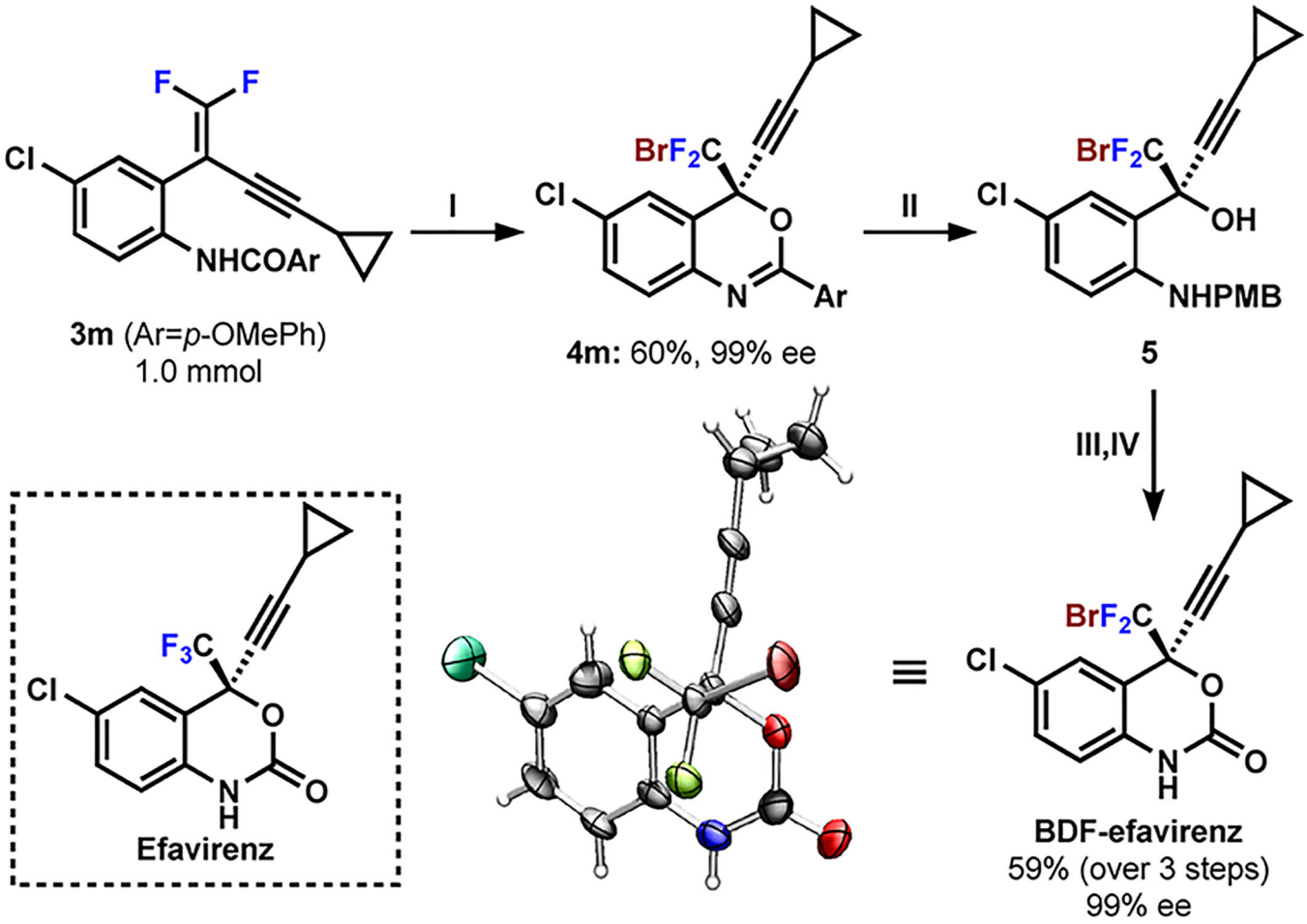
Figure 1.

Enantioselective incorporation of the difluoromethylene group. (A) Traditional retrosynthetic disconnection for difluoromethylenes. (B) Enantioselective carbonyl functionalization. (C) Chiral aryl iodide catalyzed enantioselective oxidative difluorination of alkenes. (D) Proposed retrosynthetic disconnection to access CF_2Br-containing stereocenters via an intramolecular enantioselective bromocyclization.



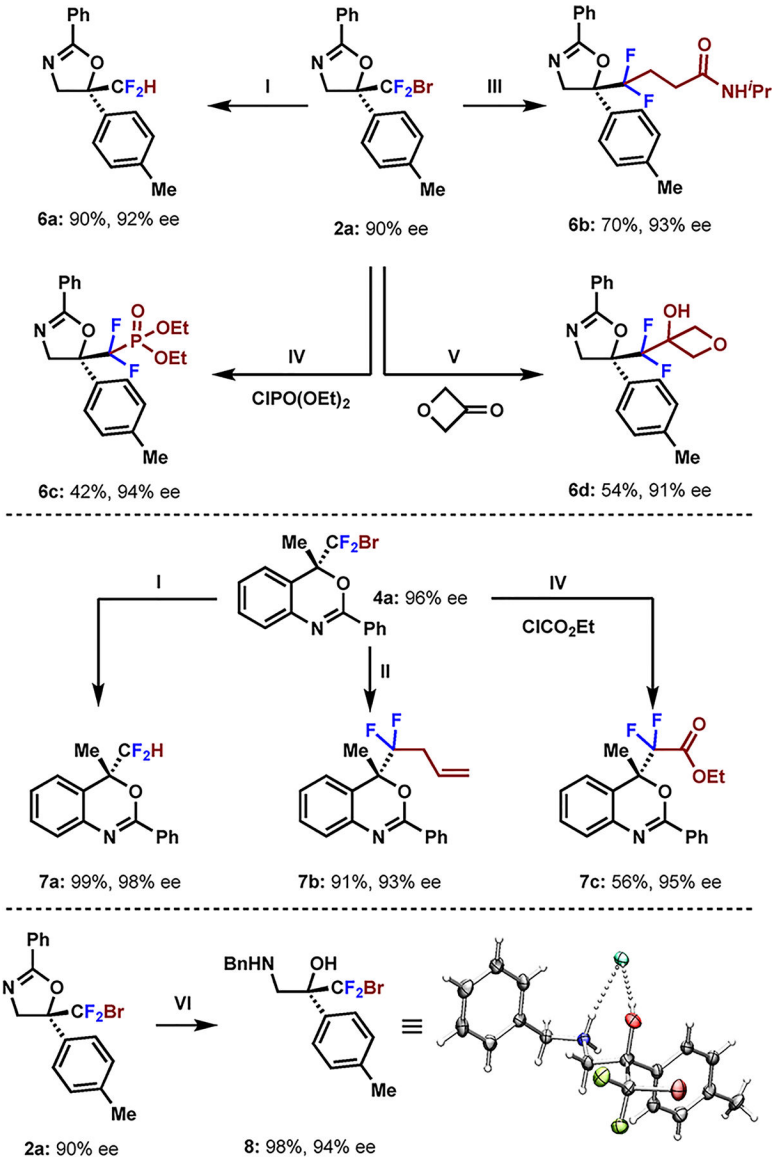
Scheme 1.

(A) Effect of Achiral Brominating Reagent on Regio- and Enantioselectivity of Bromocyclization; (B) Phase Transfer of Achiral Reagent as Catalyst/Reagent Ion Pair



Scheme 2. Synthesis of an Efavirenz Analogue[a]

[a]Conditions: (I) [(**DAB**^{3})$_{2}$**Br**](**BF**$_{4}$)$_{3}$ (2.0 equiv), (*S*)-TRIP (10 mol %), $NaHCO_3$ (4.0 equiv), PhH (50 mL), rt, 48 h. (II) $NaBH_3CN$, AcOH, rt, 12 h. (III) $(Cl_3CO)_2CO$, Et_3N, PhMe, 0 °C, 1 h. (IV) CAN, 2:5 H_2O/MeCN, rt, 1 h. Solid-state structure of BDF-efavirenz from single-crystal X-ray diffraction analysis. Thermal ellipsoids are plotted at 30% probability level; solvent omitted for clarity.

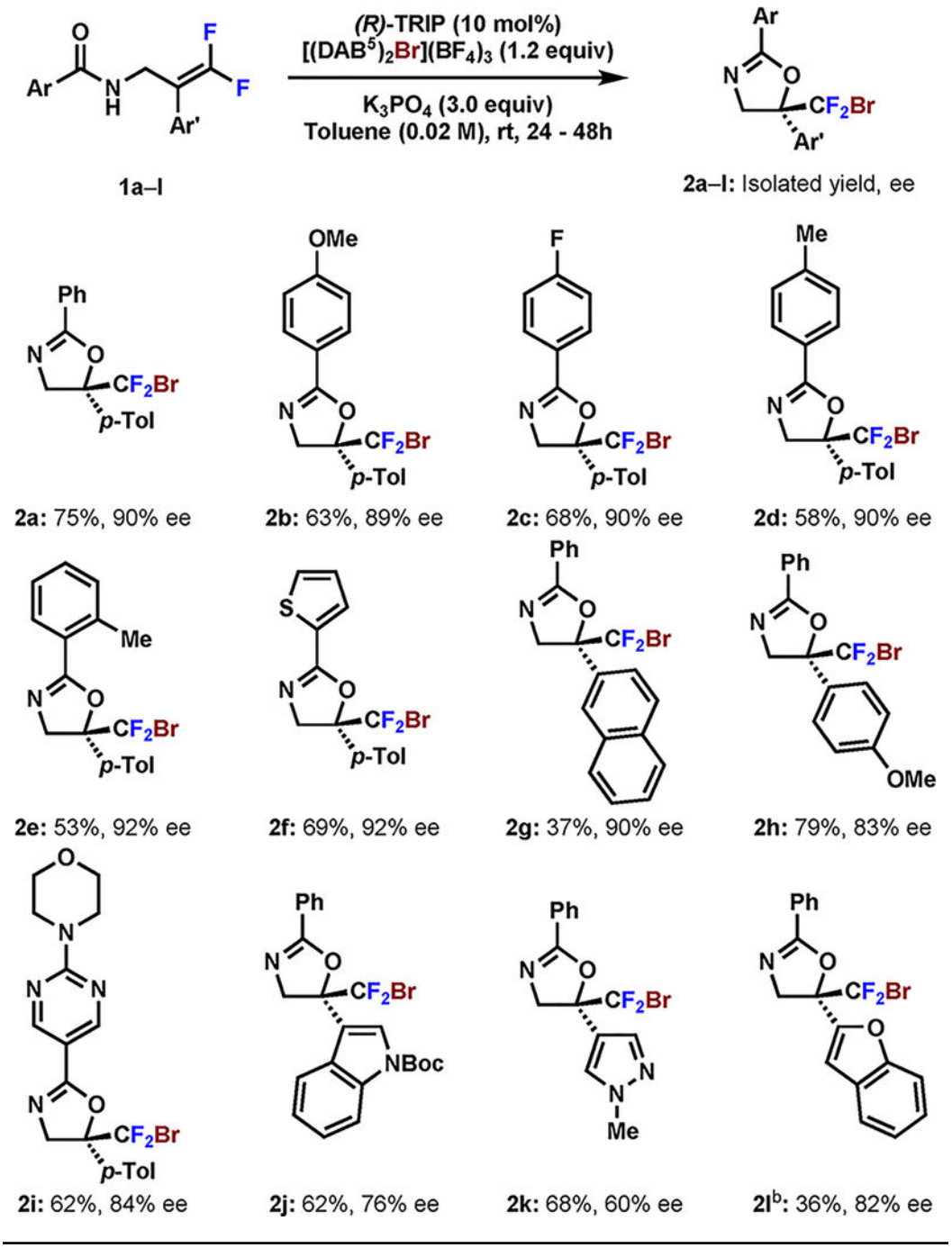


Scheme 3. Derivatization of RCF_2Br Products[a]

[a]All reactions run on a 0.050 mmol scale. Conditions: (I) AIBN (10 mol %), Bu_3SnH, PhH, 80 °C, 12 h. (II) AIBN (20 mol %), $Bu_3Snallyl$ PhH, 80 °C, 12 h. (III) $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$ (2 mol %), *N*-isopropylacrylamide, TMS_3SiOH, Na_2CO_3, MeOH, Blue LEDs, rt, 1 h. (IV) Electrophile, *n*BuLi, 2,5-Me_2THF, −130 °C, 1 h. (V) Electrophile, *n*BuLi, $CeCl_3$, 2,5-Me_2THF, −130 °C, 1 h. (VI) $NaBH_3CN$, AcOH, rt, 12 h. Solid-state structure of **8·HCl** from single-crystal X-ray diffraction analysis. Thermal ellipsoids are plotted at 50% probability level.

Table 1.

Bromocyclization of Difluoroalkenes: Oxazoline Scope[a]

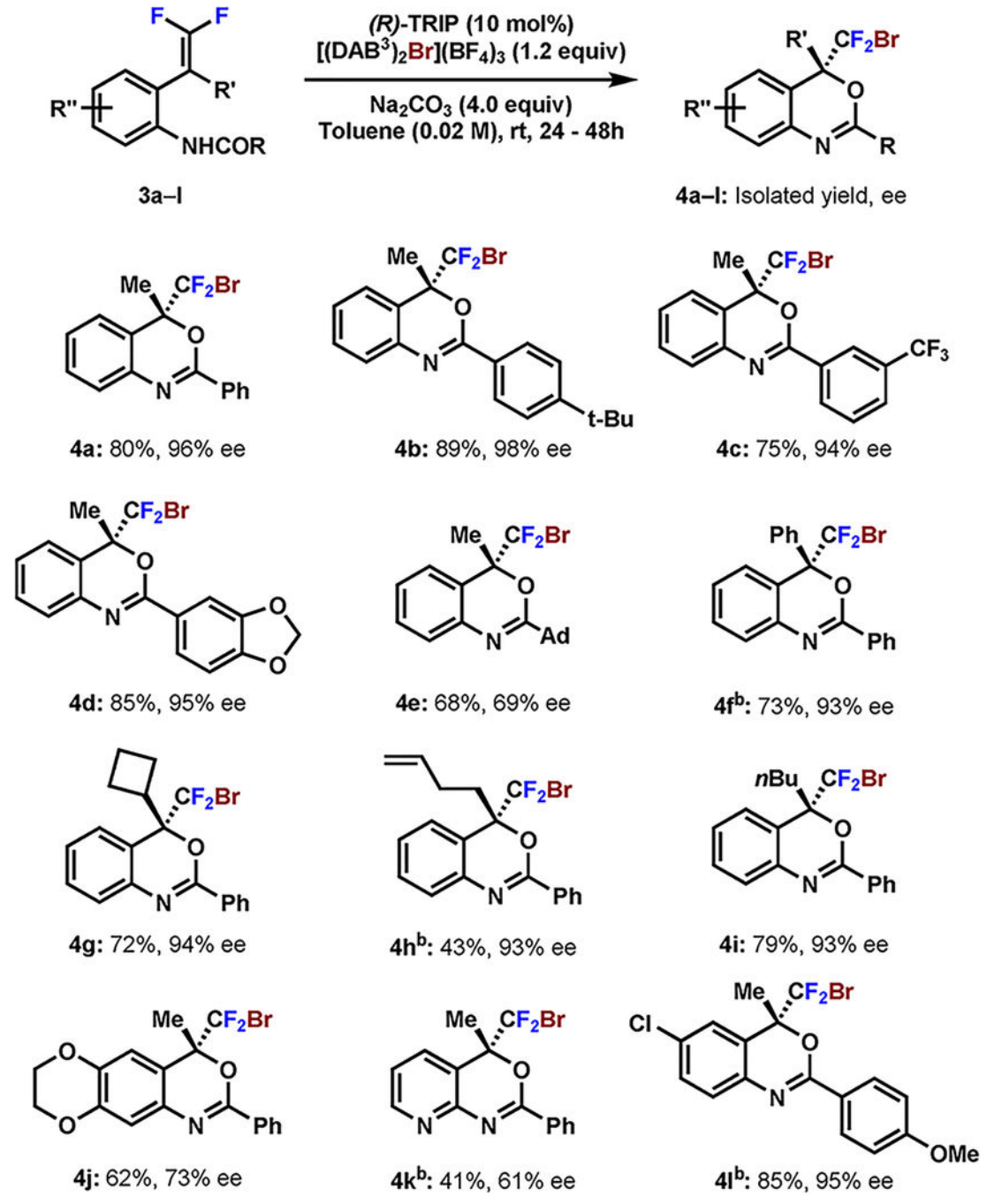


[a]Standard conditions: **1a–1l** (0.10 mmol, 1.0 equiv), [(**DAB**^{5})$_2$**Br**]-(**BF**$_4$)$_3$ (1.2 equiv), (*R*)-TRIP (10 mol %), K_3PO_4 (3.0 equiv), toluene (5.0 mL), rt, 24–48 h. Yields are of isolated **2a–2l**. Enantioselectivity determined by HPLC with a chiral stationary phase.

[b]**2l** was isolated as the hydrolyzed product (see Supporting Information).

Table 2.

Bromocyclization of Difluoroalkenes: Oxazine Scope[a]



[a]Standard conditions: **3a–3l** (0.10 mmol, 1.0 equiv), [**(DAB^3)$_2$Br**]-**(BF$_4$)$_3$** (1.2 equiv), (*R*)-TRIP (10 mol %), Na_2CO_3 (4.0 equiv), toluene (5.0 mL), rt, 24–48 h. Yields represent isolated **4a–4m**. Enantioselectivity determined by HPLC with a chiral stationary phase.

[b]After 48 h, additional 0.80 equiv of [(**DAB^3)$_2$Br**](**BF$_4$)$_3$** added and solution stirred for an additional 24 h.