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Article

Parallel Minisci Reaction of *gem*-Difluorocycloalkyl Building Blocks

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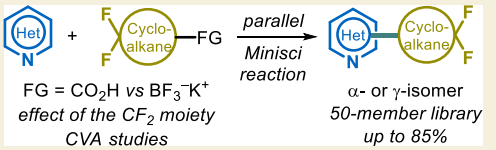
ABSTRACT: Parallel Minisci reactions of nonfluorinated and *gem*-difluorinated C_4−C_7 cycloalkyl building blocks (trifluoroborates and carboxylic acids) with a series of electron-deficient heterocycles were studied. A comparison of the reaction's outcome revealed better product yields in the case of carboxylic acids as the radical precursors in most cases, albeit these reagents were used with three-fold excess under optimized conditions. The nature of the heterocyclic core was found to be important for successful incorporation of the cycloalkyl fragment. The impact of the CF_2 moiety on the oxidation potential of fluorinated cycloalkyl trifluoroborates and the reaction outcome, in general, was also evaluated.



KEYWORDS: *radical reactions, trifluoroborates, carboxylic acids, fluorine, cycloalkanes*

INTRODUCTION

Over the last few decades, fluorinated scaffolds have become an integral part of the drug discovery process as a convenient and valuable tool for fine-tuning the compound's physicochemical properties (acidity/basicity, lipophilicity, or solubility).[1−16] Introduction of the fluorine-containing fragment often shows a significant impact on the compound's affinity to the desired biological target and its general metabolic stability.[17−21] On the other hand, an evident trend for an increased use of sp^3-enriched structures in drug discovery gave rise to an intense investigation of fluorinated saturated (hetero)cycles.[22−26] Since aromatic ring systems nevertheless remain essential and most popular structural elements of drug molecules,[27] the synthetic methods allowing their decoration with fluorinated sp^3-enriched fragments are of high demand (Figure 1).[28]

To date, various strategies to introduce the fluorinated cycloalkyl fragment into the aromatic core are known in the literature, including either fluorination of a preformed scaffold[29] or the construction of a complex structure using fluorinated building blocks via common[30−34] or recently (re)introduced[35] chemical transformations. The latter strategy can be especially promising since in many cases $C(sp^2)$−$C(sp^3)$ bond formation is possible. In particular, the radical C−H functionalization of aromatic heterocycles has become recognized as an effective instrument for late-stage modification of electron-deficient heteroaromatic species.[36−38] While the seminal report on such transformations was made by Minisci and co-workers as early as the 1970s (Scheme 1A),[39] only with recent developments by the groups of Baran, Molander, and others, the Minisci reaction and its boron variant received broad attention from the chemical community.

While the classical Minisci reaction involves the use of carboxylic acids as the radical precursors (which was later demonstrated for a wide range of both aromatic[40] and aliphatic[41,42] substrates), boronic acid derivatives (in particular, trifluoroborates)[43−49] have received much attention as a promising alternative (Scheme 1B). Silver species have been widely used as an oxidant (especially in catalytic amounts in the presence of a stoichiometric co-oxidant, e.g. $AgNO_3$/$K_2S_2O_8$[49−52] or $AgNO_3$/Selectfluor[53]) to generate the corresponding radical intermediate; other reagents included molecular oxygen,[43] $CuCl_2$,[54] $Mn(OAc)_3$,[47] etc. Photoredox methods are also worth outlining, both metalo-[55,56] and organocatalytic.[46,50]

While the reactivity and selectivity of various (cyclo)alkyl radical sources and heteroaromatic partners in the Minisci reaction was studied, fluorinated substituents were largely underexplored at these conditions. Thus, several examples of the photocatalytic C−H activation involving 4,4-difluorocyclohexanecarboxylic acid as the radical source were reported.[57−60] In this regard, achievements of Baran and co-workers on the C−H functionalization of heterocyclic rings with fluorinated sulfinates can also be mentioned.[61] In this work, we evaluate the reactivity of *gem*-difluorinated cycloalkane building blocks (carboxylic acids and trifluoroborates, C_4 to C_7) as the radical sources in the Minisci reaction under parallel synthesis conditions (Scheme 1C). In particular, a small compound library following the design principles shown in Figure 1A has been prepared. In addition, an attempted rationalization of the obtained results based on cyclic voltammetry experiments and molecular geometry data is provided.

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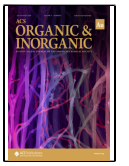


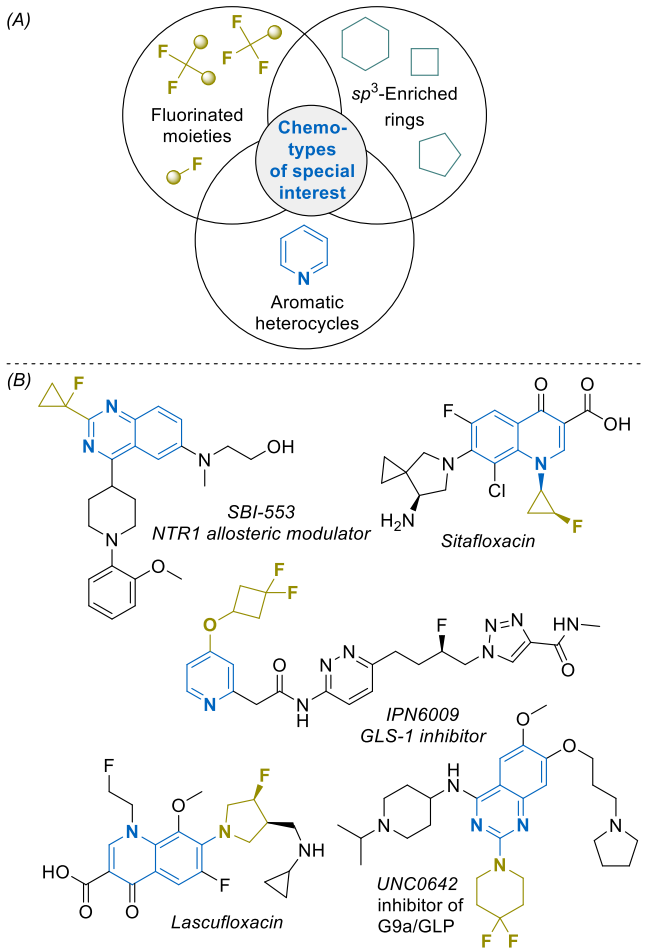
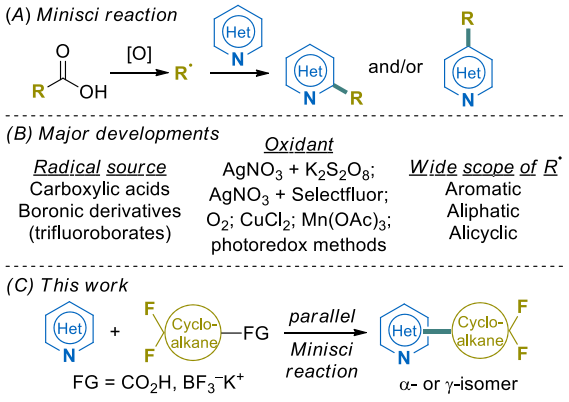


Figure 1. (A) Structural motifs that are increasingly popular in drug discovery. (B) Experimental and marketed drugs designed by a combination of fluorine atoms, saturated rings, and heteroaromatic fragments.

Scheme 1. (A) General Scheme for the Minisci Reaction; (B) Major Developments on the Minisci Reaction; and (C) the Key Transformation of This Work



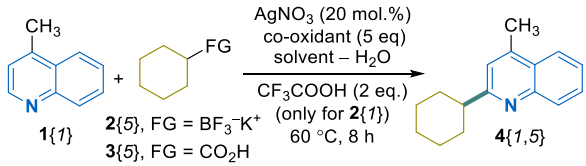
Throughout this paper, a compound numbering system common to combinatorial chemistry has been used. Thus, heterocyclic substrates, carboxylic acids, and trifluoroborates for the library synthesis were labeled as **1**{*i*}, **2**{*j*}, and **3**{*j*}, respectively, where *i* and *j* are positive integer numbers starting with 1. The library members synthesized from reagents **1**{*i*} and **2**{*j*}/**3**{*j*} were designated as **4**{*i*,*j*}.

A preliminary version of this manuscript was published as a preprint.[62]

RESULTS AND DISCUSSION

Keeping in mind the application of the Minisci reaction under parallel synthesis conditions, we have turned our attention to the classical Ag-catalyzed version of the method. We started our experimentation from the model reaction of 4-methylquinoline **1**{1}[43,44,47,63] and cyclohexyl trifluoroborate (**2**{5}) under the conditions proposed by Molander's group ($AgNO_3$ (20 mol %), $K_2S_2O_8$ (5 equiv), TFA (2 equiv), $(CH_2Cl)_2$–H_2O, 60 °C, 8 h).[48] At these conditions, the desired product **4**{1,5} was obtained in 46% isolated yield (Table 1, entry 1).

Table 1. Optimization of the Minisci Reaction Conditions



#	radical source	amount of 2{1}/3{1}, eq	co-oxidant	organic solvent	yield, %[ab]
1	**2**{5}	1.1	$K_2S_2O_8$	$(CH_2Cl)_2$	85 (46)
2	**2**{5}	3	$K_2S_2O_8$	$(CH_2Cl)_2$	84
3	**2**{5}	1.1	$K_2S_2O_8$	CH_3CN	traces
4	**2**{5}	3	$K_2S_2O_8$	CH_3CN	traces
5	**2**{5}	3	$(NH_4)_2S_2O_8$	CH_3CN	71
6	**3**{5}	1.1	$(NH_4)_2S_2O_8$	$(CH_2Cl)_2$	8
7	**3**{5}	3	$(NH_4)_2S_2O_8$	$(CH_2Cl)_2$	20
8	**3**{5}	1.1	$(NH_4)_2S_2O_8$	CH_3CN	47
9	**3**{5}	3	$(NH_4)_2S_2O_8$	CH_3CN	81 (42)
10	**3**{5}	3	$K_2S_2O_8$	CH_3CN	68

[a]Yield of **4**{1,5} by LC–MS. [b]Isolated yield is given in parentheses.

Meanwhile, carboxylic acid **3**{5} did not work well under the aforementioned conditions: minor amounts of product **4**{1,5} were detected, and starting quinoline **1**{1} was mostly recovered (entry 6).

Therefore, an alternative protocol described by Shore and co-authors was considered [$AgNO_3$ (20 mol %), $(NH_4)_2S_2O_8$ (5 equiv), MeCN–H_2O, 60 °C, 8 h].[64] After some additional experiments (entries 6–10), an optimized version of the synthetic protocol with increased quantities of radical precursor **3**{1} (3 equiv), $(NH_4)_2S_2O_8$ as the stoichiometric oxidant, and CH_3CN–H_2O as the solvent was elaborated (42% isolated yield, entry 9) and therefore implemented in further studies with carboxylic acids as the radical sources. Notably, this protocol did not give significant advantages in the case of trifluoroborates.

Next, we applied the above-optimized conditions to five model heterocyclic compounds **1**{1–5} covering a variety of chemotypes (quinoline, pyrimidine, quinoxaline, pyridine, and benzothiazole) and functional groups (Cl, Br, and CN), as well as 10 cycloalkane-derived trifluoroborates **2**{1–10}/carboxylic acids **3**{1–10} (C_4 to C_7) for the parallel synthesis of compound library **4**{1–5,1–10} (Scheme 2).

Since analysis of the isolated yields for library **4** can be complicated by product losses after HPLC due to their volatility, we mainly rely on the LC–MS-based yields in the following discussion. It was found that the average yields of the library members (as detected by LC–MS) were somewhat

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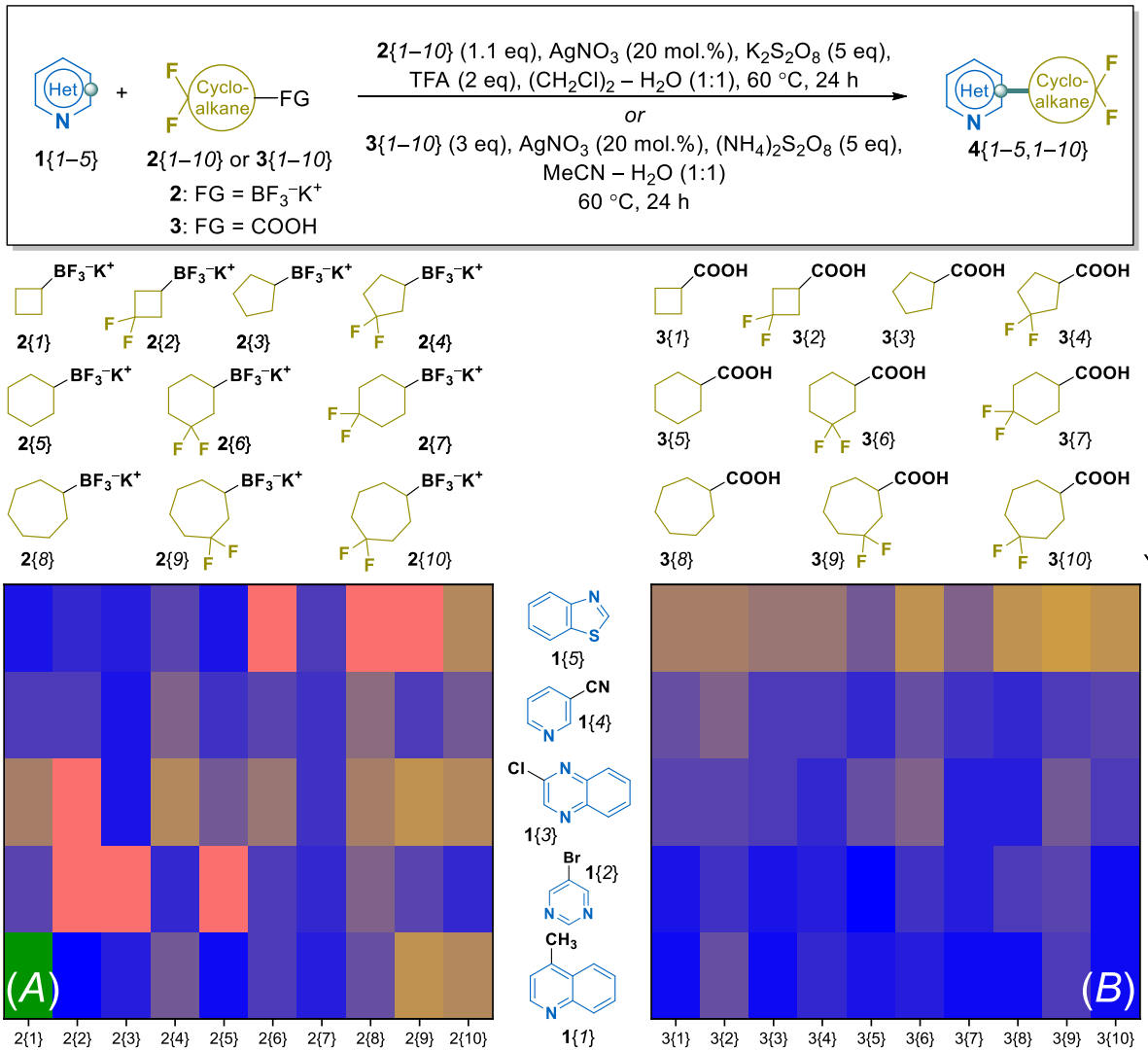
Scheme 2. Synthesis of Compound Library 4{1−5,1−10} and Heatmap of the Reaction Yields According to LC−MS [(A)—for Trifluoroborates 2, (B)—for Carboxylic Acids 3]



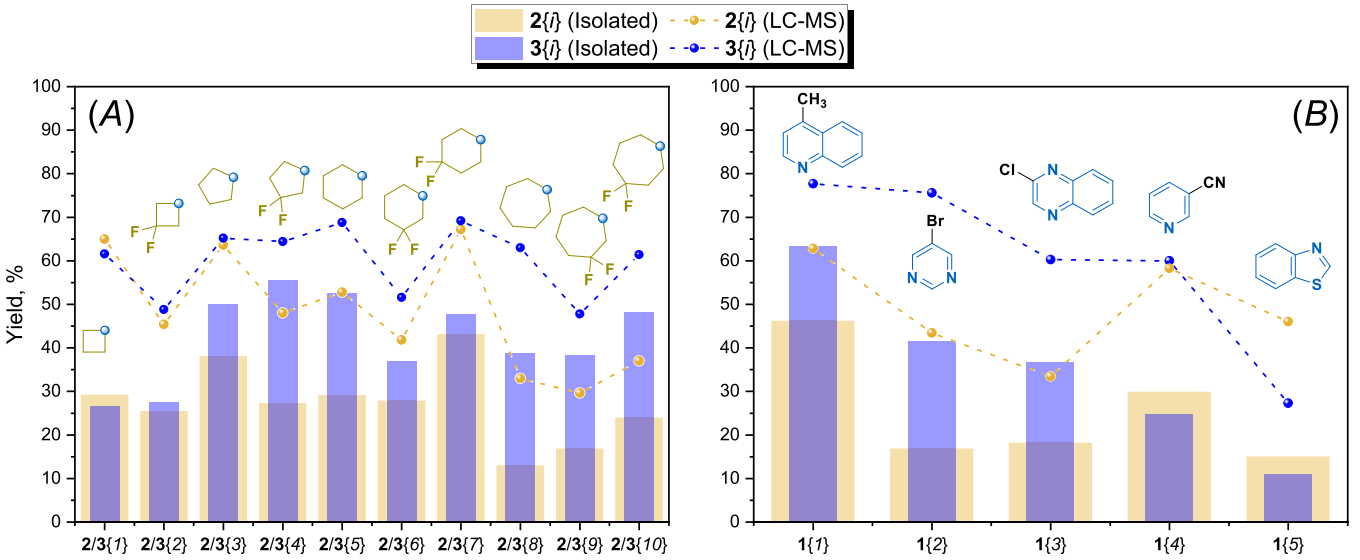


Figure 2. (A) LC−MS-based and isolated yields of products **4** as functions of building blocks **2**/**3** (A) and heterocycles **1** (B).

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lower for trifluoroborates **2**{1−10} (48%) than that for carboxylic acids **3**{1−10} (60%). The yield distribution range was narrower for reagents **3**{1−10}, which can be considered as an indicator of better method reproducibility under the parallel synthesis conditions. On the other hand, the optimized protocol involved the use of three-fold excess of carboxylic acids **3**{1−10}, which in some cases resulted in the formation of double alkylation products—up to 36% for **4**{3,9}, as detected by LC−MS.

A more detailed analysis of the studied building block performance revealed several tendencies. In particular, the average product yield was affected by the compound's fluorination pattern in a following manner: nonfluorinated (60%) ≈ 4,4-difluorinated (59%) > 3,3-difluorinated (47%) (Figure 2A). We have also evaluated 2,2-difluorocycloalkane-carboxylic acids (C_4 to C_7) in the reaction with heterocycles under the standard conditions; although minor amounts of the target products were detected by LC−MS, none of them could be isolated in a pure form. Cycloheptane-containing trifluoroborates **2**{7−10} showed relatively poor results compared to other substrates.

On the other hand, the reaction outcome strongly depended on the nature of the heterocyclic partner: the highest average yields were observed for 4-methylquinoline **1**{1} (69%) and the lowest—for benzothiazole **1**{5} (37%) (Figure 2B). The latter fact can be rationalized by limited stability of benzothiazole toward radical oxidants (including $Ag^+/S_2O_8^{2-}$ system).[65] Interestingly, trifluoroborates **2** worked better with this particular heterocycle compared to carboxylic acids **3** (almost 20% higher average product yield).

For aromatic substrates having a singly defined electrophilic center (namely, **1**{1}, **1**{3}, and **1**{5}), only monoalkylation product **4** was formed (Figure 3). For pyrimidine derivatives

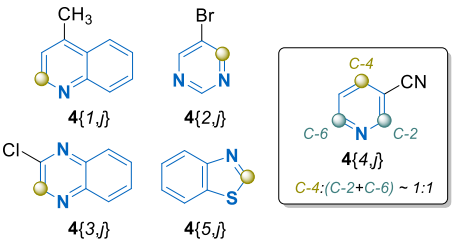
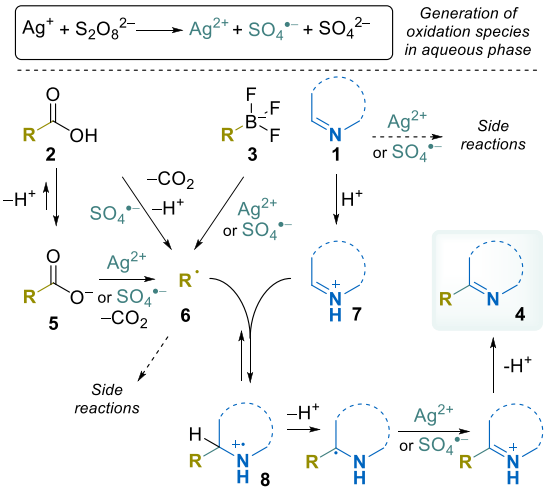


Figure 3. Regioselectivity of the Minisci reaction with heterocycles **1**{1−5}.

4{2,*j*}, regiospecific formation of the C-4 alkylation products was observed, which is in full accordance with the previously reported data.[66] For pyridine-derived compounds **4**{4,*j*}, all possible isomers (i.e., C-2, C-4, and C-6) were formed. In most cases, C-4 substitution occurred predominantly (ca. 50%), and the corresponding products **4a**{4,*j*} were isolated in pure form after reverse phase HPLC. At the same time, separation of C-2 and C-6 isomers appeared to be more challenging, so that their mixtures with varied ratios containing up to 40% of the C-2 isomer (according to ^{1}H NMR spectroscopy) could be obtained.

Somewhat higher efficiency of carboxylic acids **3** as the radical source as compared to trifluoroborates **2** might be rationalized through the radical generation mechanism. According to literature data,[36,67] water-soluble trifluoroborate salts **2** readily undergo direct oxidation to corresponding reactive species **6** (Scheme 3).[68,69] In contrast, the main route

Scheme 3. Plausible Reaction Pathways Based on the Literature Data[36,73]



for carboxylic acids **3** involves in single electron oxidation of corresponding carboxylate anion **5** by reactive species generated in the $Ag^+/S_2O_8^{2-}$ system.[70−72] An alternative pathway, albeit less probable, includes hydrogen atom transfer from carboxylic acid to $SO_4^{\bullet-}$ radical with subsequent decarboxylation generates radical **6**.[58] At the acidic reaction conditions, concentration of carboxylate anions **5** is relatively low, which results in low steady-state concentration of corresponding radicals **6** and their slow release for the reaction with protonated heterocycle **7**. This might lead to suppression of undesired second-order radical side reactions (e.g., dimerization or disproportionation) and therefore to higher product yields. On the other hand, low concentration of the radical species can be disadvantageous in the Minisci reaction with substrates sensitive to oxidation (e.g., benzothiazole **1**{5}). In this case, efficient formation of alkyl radicals **6** from trifluoroborates **2** overcomes slower competitive side reactions of heterocycle **1** and enhances the yield of desired product **4**.

To have a deeper inside in the observed reactivity profiles, we have measured cyclic voltammograms for the trifluoroborates **2**{1−10} (Figure 4).[74] The $E_{a,p}$ values for non-

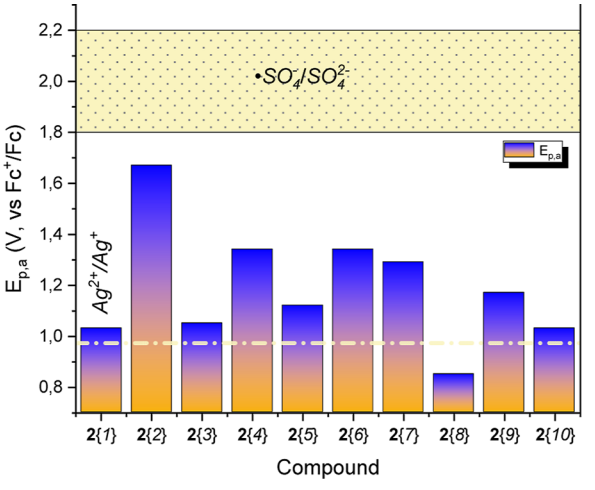


Figure 4. $E_{a,p}$ values of trifluoroborates **2**{1−10} obtained from CVA as compared to $E(Ag^{2+}/Ag^+)$ and $E(SO_4^{\bullet-}/SO_4^{2-})$ (recalculated from the literature values[87,88] vs ferrocene).

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fluorinated trifluoroborates **2**{1}, **2**{3}, **2**{5}, and **2**{8} (0.85−1.12 V) are close to those previously reported for analogous cycloalkyl trifluoroborates.[55,68,75−77] At the same time, *gem*-difluorinated compounds **2**{2}, **2**{4}, **2**{6}, **2**{7}, **2**{9}, and **2**{10} demonstrated significantly higher oxidation potentials (1.03−1.67 V) as compared to their nonfluorinated counterparts.[78,79] This effect might be partially responsible for the lower efficiency of some *gem*-difluorinated cycloalkyl building blocks as the radical sources in the Minisci reaction. Nevertheless, other factors (e.g., radical nucleophilicity[80−82]) are likely important since there is no direct correlation between $E_{a,p}$ and the reaction outcome. It should also be mentioned that the redox-potentials, measured by CVA, are the potentials of heterogeneous electron transfer involving the solid electrode, while radical generation under Ag-catalyzed oxidation is homogeneous reaction. Thus, 4,4-difluorocyclobutyl derivative **2**{2} has the highest oxidation potential (1.67 V), but the corresponding average product yield is not particularly low. Also, 4,4-difluorinated building blocks **2**{7} and **2**{10} demonstrate even slightly better performance as compared to nonfluorinated counterparts **2**{5} and **2**{8}, respectively, while the corresponding $E_{a,p}$ values are considerably higher.

Comparison of the obtained oxidation potentials with those for the oxidative species [i.e., $E(Ag^{2+}/Ag^{+})$ and $E(SO_4^{\bullet-}/SO_4^{2-})$][70,83,84] shows that in the case of nonfluorinated trifluoroborates **2**{1}, **2**{3}, **2**{5}, and **2**{7}, both Ag^{2+} and $SO_4^{\bullet-}$ can participate in the radical generation. On the contrary, for most *gem*-difluorinated trifluoroborates studied, $E(Ag^{2+}/Ag^{+})$ is not sufficient for the reaction, so that $SO_4^{\bullet-}$ is the likely oxidant.

Anomalously low yields for cycloheptane-derived trifluoroborates **2**{8−10} might be referred to increased lipophilicity of the corresponding fragments,[85] increasing the role of boundary effects in the biphasic system.[86]

In summary, the Minisci reaction of *gem*-difluorinated cycloalkyl trifluoroborates and carboxylic acids is a very promising approach for the C−H modification of heterocyclic systems with *gem*-diflorocycloalkyl substituents. The corresponding carboxylic acids demonstrate somewhat higher efficiency as the radical sources in the reaction studied under optimized conditions as compared to trifluoroborates. This advantage can be overcome by necessity to use the three-fold excess of the former reagents. Also, trifluoroborates can be advantageous with heterocyclic substrates that are sensitive to oxidation.

The *gem*-difluorination pattern has a significant impact on the reaction outcome. Thus, 4,4-difluorinated cycloalkyl building blocks have nearly the same efficiency as their nonfluorinated counterparts, while 3,3- and especially 2,2-difluorinated analogues demonstrate diminished activity. Oxidation potentials obtained from cyclic voltammograms of the trifluoroborates studied are considerably higher for the fluorinated compounds; therefore, they may only be partially responsible for the observed effects. Other factors like radical nucleophilicity or the cycloalkyl fragment lipophilicity (e.g., for cycloheptane derivatives) should also be taken into account.

The proposed method for the parallel synthesis allows for the preparation of compound libraries comprising structural features attractive from the medicinal chemist's viewpoint: fluorinated substituent, sp^3-rich moiety, and aromatic heterocycle. Therefore, it should be useful for early drug discovery programs as well as for late-stage modification of organic molecules with fluorinated substituents.

EXPERIMENTAL SECTION

The solvents were purified according to the standard procedures.[89] Compounds **1**{1−5}, **2**{1−10}, and **3**{1−10} were obtained from Enamine Ltd.; all other starting materials were available commercially. Melting points were measured on the MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230−400 mesh) as the stationary phase. HPLC purification was performed on a Chromatorex 18 SMB 100-ST 100 × 19 mm 5 μm column, using a H_2O/ACN gradient. ^1H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^1H NMR, 126 MHz for ^{13}C NMR, and 470 MHz for ^{19}F NMR) and a Varian Unity Plus 400 spectrometer (at 400 MHz for ^1H NMR, 101 MHz for ^{13}C NMR, and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^1H and ^{13}C in $CDCl_3$, and 2.50 and 39.52 ppm for ^1H and ^{13}C in DMSO-d_6. Coupling constants (J) are given in Hz. Spectra are reported as follows: chemical shift (δ, parts per million), multiplicity, integration, and coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument [chemical ionization (CI)] and Agilent 5890 Series II 5972 MS instrument [electron impact ionization (EI)]. High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

General Procedure for the Minisci Reaction with Trifluoroborates 2 (Method A)

Trifluoroborate **2** (0.55 mmol, 1.1 equiv), heteroaromatic compound **1** (0.50 mmol, 1.0 equiv), $AgNO_3$ (17 mg, 0.10 mmol, 0.2 equiv), and $K_2S_2O_8$ (675 mg, 2.50 mmol, 5 equiv) were put into a glass vial equipped with a magnetic stirring bar. To this solid mixture, $ClCH_2CH_2Cl$ (2.5 mL) and H_2O (2.5 mL) were added subsequently (to a total 0.1 M of compound **1**), followed by addition of TFA (76 μL, 1.00 mmol, 2 equiv) with intensive stirring. The reaction mixture was stirred at 60 °C for 24 h, then poured into a mixture of saturated aq $NaHCO_3$ and 10% aq $Na_2S_2O_3$ (1:1 v/v, 25 mL), the organic layer was separated, and the water layer was extracted with CH_2Cl_2 (3× 10 mL). Combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude material was subjected to reverse phase HPLC to give pure product **4** as a thin film.

General Procedure for the Minisci Reaction with Carboxylic Acids 3 (Method B)

Corresponding acid **3** (1.50 mmol, 3 equiv), heteroaromatic compound **1** (0.50 mmol, 1 equiv), $AgNO_3$ (17 mg, 0.10 mmol, 0.2 equiv), and $(NH_4)_2S_2O_8$ (570 mg, 2.50 mmol, 5 equiv) were weighted in a glass vial, equipped with a magnetic stirring bar. To this solid mixture, CH_3CN (2.5 mL) and H_2O (2.5 mL) were subsequently added (to a total 0.1 M of compound **1**), and the obtained slurry was heated to 60 °C with intensive stirring. After 24 h, the reaction mixture was poured into a mixture of saturated aq $NaHCO_3$ and 10% aq $Na_2S_2O_3$ (1:1 v/v, 25 mL), the organic layer was separated, and the water layer was extracted with CH_2Cl_2 (3× 10 mL). Combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude material was subjected to a reverse phase HPLC to give a pure product **4** as a thin film.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

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Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.4c00028.

Synthesized compound characterization data, cyclic voltammograms of the utilized cycloalkyltrifluoroborates, and photographs of the reaction setup (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Serhii Holovach** investigation, validation; **Illia Poroshyn** investigation, validation; **Kostiantyn P. Melnykov** conceptualization, methodology, project administration; **Oleksandr S. Liashuk** data curation, visualization, writing-original draft; **Olena O. Pariiska** data curation, investigation; **Sergey V. Kolotilov** data curation, resources, supervision; **Alexander B. Rozhenko** project administration, supervision; **Dmytro M. Volochnyuk** conceptualization, funding acquisition, methodology, supervision; **Oleksandr O. Grygorenko** conceptualization, funding acquisition, methodology, project administration, supervision, visualization, writing-review & editing.

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ABBREVIATIONS

CVA, cyclic voltammetry; HPLC, high-performance liquid chromatography; LC-MS, liquid chromatography with mass spectral detector; NMR, nuclear magnetic resonance

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