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Nickel-Catalyzed Coupling Reaction of α-Bromo-α-fluoroketones with Arylboronic Acids toward the Synthesis of α-Fluoroketones

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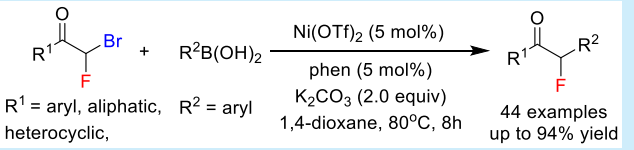
Supporting Information

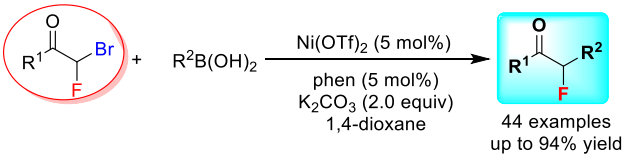
ABSTRACT: A nickel-catalyzed coupling reaction of α-bromo-α-fluoroketones with arylboronic acids was reported, which provides an efficient pathway to access 2-fluoro-1,2-diarylethanones in high yields. We also disclosed the synthesis of the monofluorination agents α-bromo-α-fluoroketones by using a trifluoroacetate release protocol. Mechanistic investigation indicated that a monofluoroalkyl radical is involved in the catalytic circle. Moreover, an important medical intermediate of flindokalner was synthesized via a nickel-catalyzed coupling reaction of α-bromo-α-fluoro-2-indolone and boronic ester.



The introduction of fluorine or fluorine-containing functional groups into organic molecules can significantly change their lipophilicity, bioavailability, and metabolic stability. Hence, different classes of fluorine-containing organic compounds have been developed and used as pharmaceuticals and agrochemicals.[1] Over the past decades, significant progress has been made on the construction of trifluoromethyl compounds[2] and difluoroalkyl compounds.[3] In contrast, the monofluoroalkylation reactions for the synthesis of diverse fluorine-containing molecules have been less intensively investigated. There are only a few monofluorinating agents, such as BrCFHCOOEt, $(EtO)_2P(O)CFHBr$, 1-halo-1-fluoroalkanes, $PhSO_2CHFI$, CH_2FI, CH_2FBr, and monofluoromalonate, that have served as building blocks to incorporate monofluoroalkylated groups or monofluoromethyl groups.[4] Therefore, the development of novel monofluorinating agents as well as their utility in the diversity-oriented synthesis of monofluorinated compounds, which might have potential use in drug synthesis and drug discovery, is in high demand.

Ketones are ubiquitous structural motifs in synthetic chemistry and life science related fields. The literature showed that α-fluorination to a carbonyl group could increase the electrophilicity of the carbonyl carbon, making it very susceptible toward attack by nucleophiles.[5] Hence, they could serve as fluorinated synthons (or intermediate)[6] in the construction of fluorinated heterocycles as well as chiral catalysts for epoxidation reactions.[7] Moreover, fluorinated ketones have been widely used in new drug designs as enzyme inhibitors,[8] potential antibacterial agents,[9] potassium channel inhibitors,[10] and potential antimalarial agents.[11] During the past decades, methods for the synthesis of fluorinated ketones have been rapidly developed, especially those for α,α-difluoroketones.[12] However, the synthesis of α-fluoroketones was rarely reported.[13] α-Fluorocarbonyl compounds were successfully used as building blocks in palladium-catalyzed coupling reactions with phenylboronic acids or bromobenzenes to access α-fluoro-α-arylketones by Qing, Shreeve, and Wu, respectively.[13a−c] Fu and co-workers reported the enantioselective synthesis of tertiary alkyl fluorides through nickel-catalyzed Negishi reactions of racemic α-halo-α-fluoroketone.[13d] Ando also disclosed the stereoselective Suzuki reaction of α-bromo-α-fluoro-β-lactam with aryl-(9-BBN) reagents to generate α-aryl-α-fluoro-β-lactams.[13e] Therefore, we could find that α-halo-α-fluoroketones have great importance as bifunctional intermediates, which could undergo a vast array of useful transformations to construct valuable fluorinated molecules but remain underutilized. Herein, we describe a novel and efficient nickel-catalyzed coupling reaction of α-bromo-α-fluoroketones with arylboronic acids, giving a series of 2-fluoro-1,2-diarylethanones in high yields (Scheme 1).

Scheme 1. Nickel-Catalyzed Coupling Reaction of α-Bromo-α-fluoroketones with Arylboronic Acids



Despite the importance of α-halo-α-fluoroketones, very few synthetic methods for their preparation have been reported.[14] Except for the halogenation of α-fluoroenoxysilanes,[14b] Burtoloso reported a direct synthesis of α-halo-α-fluoroketones using sulfoxonium ylides as intermediates through dihalogenation in moderate yields.[14c] Therefore, we are interested in developing an alternative method to assemble α-halo-α-fluoroketones with structure diversity in more mild conditions. In recent years, our group has used a trifluoroacetate release/

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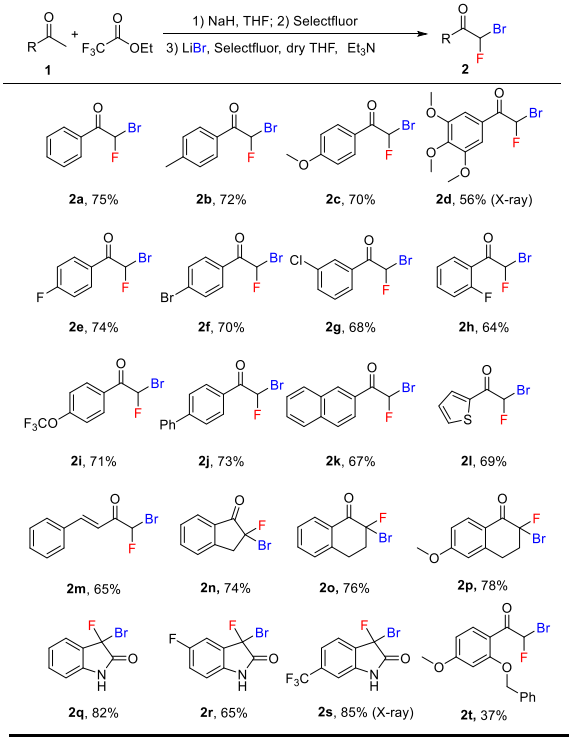
halogenation protocol of Colby to prepare diverse α-iodo-α,α-difluoroketones, which were served as difluorinating building blocks, from available α,α-difluorinated *gem*-diols.[12a] Furthermore, we have previously reported the synthesis of trifluoromethyl α-fluorinated *gem*-diols from Selectfluor and trifluoro-1,3-diones obtained by trifluoroacetylation of methyl ketones.[15] Thus, we envisioned that Colby's protocol could be used to give α-halo-α-fluoroketones directly through a trifluoroacetate release/halogenation process. Initially, acetophenone **1a** was used as the starting material to produce trifluoromethyl α-fluorinated *gem*-diols according to our previously reported procedure.[15] The *gem*-diol intermediates were then used without purification in the next trifluoroacetate release/halogenation reaction according to the procedure reported by Colby.[12a] Gratifyingly, the reaction proceeded smoothly to afford the desired product 2-bromo-2-fluoro-1-phenylethan-1-one **2a** in relatively high total yield. Next, different ketones **1a**−**t** were employed in this protocol, routinely giving the desirable α-bromo-α-fluoroketones **2a**−**t** in good yields (Table 1). The structures of compounds **2d** and **2s** were confirmed by X-ray diffraction analysis (see the SI). The reaction was revealed to be compatible with a broad range of ketones, including aryl ketones with various substituents on the aryl ring, as well as aliphatic and cyclic ketones. The method provides an alternative method for the facile synthesis of α-halo-α-fluoroketones in high yields (Table 1).

Table 1. Synthesis of α-Bromo-α-monofluoroketones[a]



[a]Reaction conditions: (1) **1** (10 mmol), trifluoromethyl ethyl acetate (1.78 g, 12.5 mmol), NaH (1 g, 25 mmol), THF (25 mL), rt; (2) for compounds **2a**−**2m** and **2t**: $Cu(NO_3)_2{\cdot}3H_2O$ (483.2 mg, 2.0 mmol), Selectfluor (4.25 g, 12 mmol), CH_3CN/H_2O = 50/4, −20 °C, 6 h; for compounds **2n**−**2s**: Selectfluor (4.25 g, 12 mmol), CH_3CN (50 mL), rt, N_2; (3) LiBr (5.21 g, 60 mmol), Selectfluor (7.08 g, 20 mmol), Et_3N (2.02 g, 20 mmol), dry THF (30 mL), 30 min. Isolated yields.

It is worth mentioning that α-bromo-α-fluoro-2-indolones **2q**−**2s** have been first synthesized through this strategy in good yields since α-fluoro-2-indolones are key structures found in numerous nature products and pharmaceuticals (Figure 1),

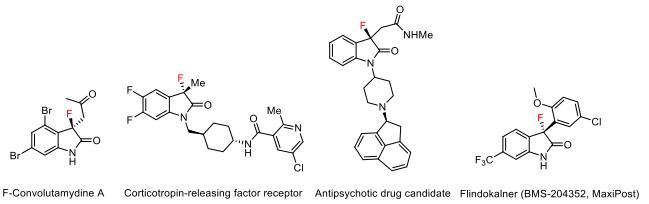


Figure 1. Examples of bioactive compounds containing a 3-fluorooxindole unit.

such as F-convolutamydine A, corticotropin-releasing factor receptor, antipsychotic drug candidate, and flindokalner (BMS 204352, MaxiPost).[16] The product **2s** could be used as building block to prepare the potassium channel activator flindokalner via coupling reaction. Furthermore, we have synthesized bromofluorinated paeonol derivative **2t**. Paeonol is a compound found in some traditional Chinese medicine remedies and shows some biological activity.[17] The fluorinated agent **2t** could serve as a fluorinated synthon for the modification of the paeonol structure.

With the monofluorinating agents **2** in hand, we sought to explore their application in organic synthesis. Therefore, 2-bromo-2-fluoro-1-phenylethan-1-one **2a** and phenylboronic acid **3a** were selected as model substrates to optimize the Suzuki coupling reaction conditions. Initially, the reaction was performed in the presence of 5 mol % of $Ni(OTf)_2$ without any ligand, leading to no formation of the desired coupling product (Table 2, entry 1). Then a variety of diamine ligands were examined in the model reaction. We observed that 1,10-phenanthroline (**L6**) showed highest activity, providing the desired coupling product **4a** in 92% yield (Table 2, entry 7). Other bipyridine (bpy) and bpy-based ligands **L1**−**L5** also could afford the product **4a**, but in relatively lower yields (Table 2, entries 2−6). Furthermore, a careful survey of nickel catalysts (Table 2, entries 8−11) and solvents (entries 12−15) was then performed, which showed the combination of $Ni(OTf)_2$ and 1,4-dioxane was the best choice (Table 2, entry 7). Decreasing the reaction temperature from 80 to 70 °C resulted in a lower yield (Table 2, 57%; entry 16). The control experiment indicated that the yield of **4a** was greatly reduced under air atmosphere (Table 2, 43%, entry 17). Finally, an optimization of the amount of phenylboronic acid (Table 2, entries 18 and 19) revealed that product **4a** could be obtained in the highest yield when the reaction of **2a** was conducted with 1.5 equiv of phenylboronic acid **3a** catalyzed by 5 mol % of $Ni(OTf)_2$ and 1,10-phenanthroline (phen) in 1,4-dioxane at 80 °C under N_2 atmosphere (Table 2, entry 7).

With the optimized reaction conditions in hand (Table 2, entry 7), we next examined the scope of this nickel-catalyzed monofluoroacylation of phenylboronic acid **3a** by using structurally diverse α-bromo-α-fluoroketones **2** (Table 3). Overall, the monofluorinating building blocks bearing electron-donating or electron-withdrawing groups on the benzene ring are compatible with the reaction conditions, thus providing the products **4a**−**4i** in high yields. 2-Bromo-2-fluoro-1-(naphthalen-2-yl) ethanone **2k** and 2-bromo-2-fluoro-1-(thiophene-2-yl)ethanone **2l** were also suitable monofluorinating agents for

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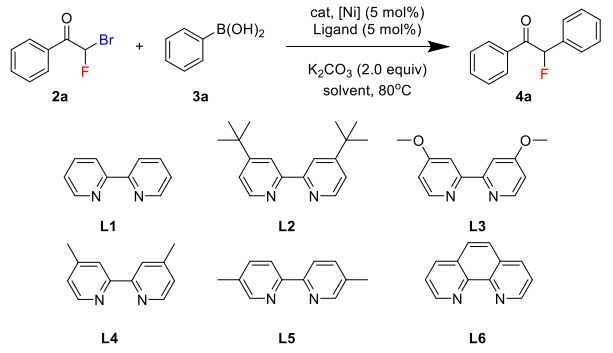
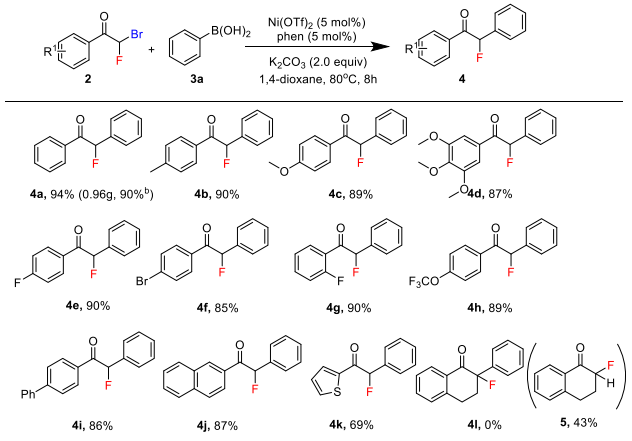
Table 2. Nickel-Catalyzed Monofluoromethylation of Phenylboronic Acid: Optimization of Reaction Conditions[a]



entry	Ni source	ligand	solvent	yield[b] (%)
1	$Ni(OTf)_2$		1,4-dioxane	NR
2	$Ni(OTf)_2$	**L1**	1,4-dioxane	45
3	$Ni(OTf)_2$	**L2**	1,4-dioxane	79
4	$Ni(OTf)_2$	**L3**	1,4-dioxane	87
5	$Ni(OTf)_2$	**L4**	1,4-dioxane	85
6	$Ni(OTf)_2$	**L5**	1,4-dioxane	73
7	$Ni(OTf)_2$	**L6**	1,4-dioxane	92
8	$NiBr_2$·DME	**L6**	1,4-dioxane	68
9	$Ni(acac)_2$	**L6**	1,4-dioxane	74
10	$Ni(NO_3)_2·6H_2O$	**L6**	1,4-dioxane	78
11	$NiCl_2$	**L6**	1,4-dioxane	trace
12	$Ni(OTf)_2$	**L6**	CH_3CN	46
13	$Ni(OTf)_2$	**L6**	Toluene	67
14	$Ni(OTf)_2$	**L6**	DME	83
15	$Ni(OTf)_2$	**L6**	DMF	trace
16[c]	$Ni(OTf)_2$	**L6**	1,4-dioxane	73
17[d]	$Ni(OTf)_2$	**L6**	1,4-dioxane	37
18[e]	$Ni(OTf)_2$	**L6**	1,4-dioxane	81
19[f]	$Ni(OTf)_2$	**L6**	1,4-dioxane	86

[a]Reaction conditions: **2a** (0.6 mmol, 1.0 equiv), **3a** (1.5 equiv), K_2CO_3 (2.0 quiv), 80 °C, 8 h, under N_2. [b]GC yields. [c]Performed at 70 °C. [d]Under air. [e]**3a** (1.2 equiv). [f]**3a** (2.0 equiv).

Table 3. Scope of α-Bromo-α-monofluoroketones[a]

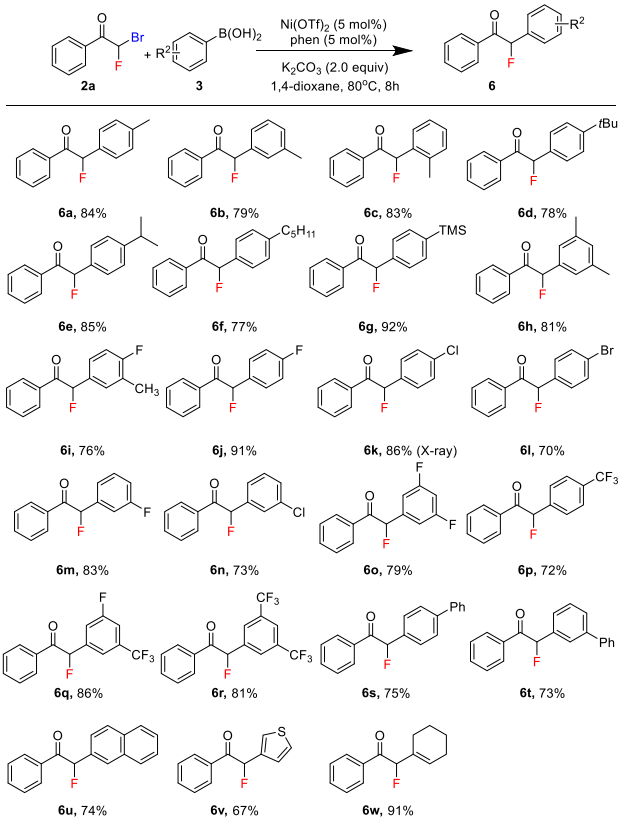


[a]Reaction conditions: **2** (0.6 mmol, 1.0 equiv), **3a** (1.5 equiv), $Ni(OTf)_2$ (5 mol %), phen (5 mol %), K_2CO_3 (2.0 equiv), 1,4-dioxane (2.0 mL), 80 °C, 8 h, under N_2. Isolated yields. [b]$Ni(OTf)_2$ (2 mol %), phen (2 mol %), reaction carried out on a gram scale.

this transformation, and **2l** was less effective in the coupling reaction, affording the product **4k** in 69% yield. However, when the monofluorinating agent **2o** was subjected to the reaction, no coupling product was observed and the reduction product **5** was obtained instead. Meanwhile, we also carried out a gram-scale reaction which gave product **4a** in a high yield of 90%. This result could be achieved by reducing the amount of nickel catalyst to 2 mol % of substrate **2a**.

Encouraged by the excellent radical reactivity of α-bromo-α-fluoroketones **2**, we then investigated the scope of the monofluoroacylation by testing various aryl boronic acids in reaction with **2a**. As shown in Table 4, aryl boronic acids with

Table 4. Scope of Substituted Aryl Boric Acid Substrates[a]



[a]Reaction conditions: **2a** (0.6 mmol, 1.0 equiv), **3** (1.5 equiv), $Ni(OTf)_2$ (5 mol %), phen (5 mol %), K_2CO_3 (2.0 equiv), 1,4-dioxane (2.0 mL), 80 °C, 8 h, under N_2. Isolated yields.

various substituents on the aryl ring, both electron-donating and electron-withdrawing groups, are all suitable cross-coupling partners for the transformation, no matter where the substituent is located, affording the corresponding fluoromethylated arenes **6a**–**6r** in good yields. The structure of compound **6k** was confirmed by X-ray diffraction analysis (see the SI). Additionally, boronic acids derived from polycyclic and heterocyclic arenes, such as *p*-biphenyl, *m*-biphenyl, 2-naphthyl, and thiophene, reacted smoothly with **2a** to give the compounds **6s**, **6t**, **6u**, and **6v** in satisfactory yields. Most remarkably, cyclohexene-1-boronic acid was also compatible with the reaction condition, giving the product **6w** in a high yield (91%).

To further probe the generality of the new reaction, the treatments of several α-bromo-α-monofluoroketones **2** with different boronic acids **3** were performed under the same reaction conditions (Table 5). Gratifyingly, all reactions

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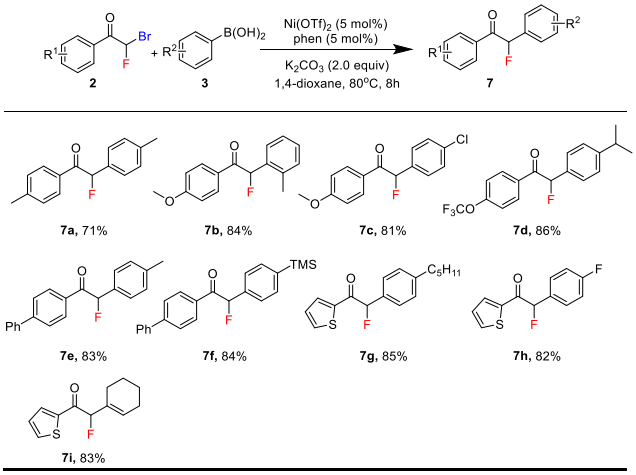
Table 5. Scope of α-Bromo-α-monofluoroketones and Substituted Aryl Boric Acid Substrates[a]

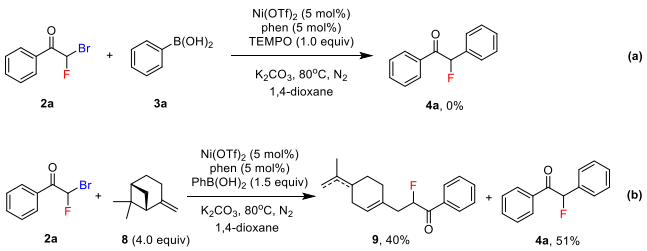


[a]Reaction conditions: **2** (0.6 mmol, 1.0 equiv), **3** (1.5 equiv), $Ni(OTf)_2$ (5 mol %), phen (5 mol %), K_2CO_3 (2.0 equiv), 1,4-dioxane (2.0 mL), 80 °C, 8 h, under N_2. Isolated yields.

proceeded smoothly to give the target compounds **7a**–**7i** in high yields, which proved the universal applicability of the reaction in the preparation of diverse monofluoroketones.

In order to gain some insight into the reaction mechanism, two control experiments were then carried out (Scheme 2).

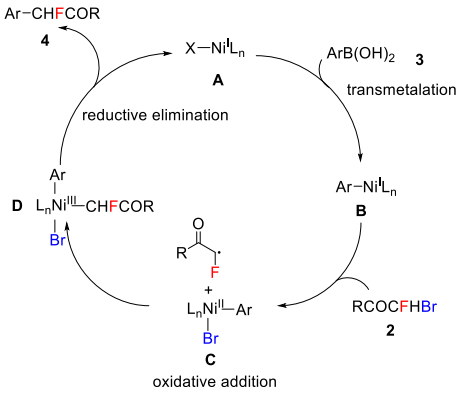
Scheme 2. Radical-Trapping Experiment



The reaction was completely suppressed when 1.0 equiv of TEMPO (2,2,6,6-tetramethyl-1-oxylpiperidine) was added into the reaction system (Scheme 2a), which shows that a radical may be involved in the reaction pathway. We were able to trap the PhCOCHF• radical using (1*S*)-(−)-*β*-Pinene **8** under our standard conditions, giving the ring-opened diene **9** in 40% yield accompanied by 51% yield of the coupling product **4a** (Scheme 2b), which further implicated the generation of the PhCOCHF• radical in the reaction process. On the basis of the control experiment and literature data, we proposed a plausible reaction mechanism shown in Scheme 3. As depicted, the Ni^{I} species **A** may be produced through the comproportionation reaction of in situ generated Ni^{0} and the remaining Ni^{II} species.[4h,18] The transmetalation between species **A** and aryl boronic acid **3** could afford Ni^{I}–Ar species **B**, which subsequently reacted with **2** to form monoaluoroalkyl radical and Ni^{II} intermediate **C** through an bromine atom transfer process. The intermediate **C** is then went through an oxidative radical addition to give Ni^{III} species **D** followed by reductive elimination to form the final monofluorinated product **4** while regenerating Ni^{I} species **A**.

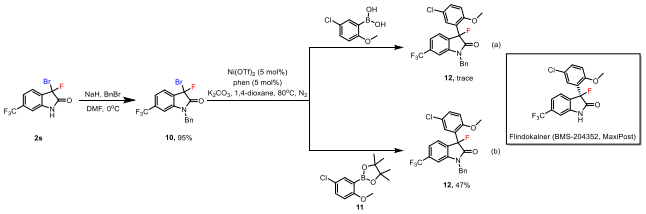
Finally, we anticipated that the potassium channel activator flindokalner would be prepared via this reported coupling

Scheme 3. Proposed Reaction Mechanism



reaction by using compound **2s** as a monofluorinated building block. First, the amino group in the agent **2s** was protected with a benzyl group to afford the intermediate **10**, which then reacted with 5-chloro-2-methoxybenzeneboronic acid under the standard reaction conditions. However, only a trace yield of the target compound **12** was observed (Scheme 4a). Next,

Scheme 4. Synthesis of Benzyl-Protected BMS-204352 (Racemate)



2-(5-chloro-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **11** was used to react with **2s** under the same reaction conditions. Gratifyingly, the desired compound **12** was obtained in 47% yield, which could be used as an important medical intermediate to further prepare flindokalner (Scheme 4b). This method is more efficient and easier compared with the traditional synthetic route for flindokalner.[16d]

In summary, we have developed a novel method for the preparation of α-bromo-α-fluoroketones by a trifluoroacetate release protocol. A series of α-bromo-α-fluoroketones including α-bromo-α-fluoro-2-indolones were synthesized in good yields. The coupling reactions between α-bromo-α-fluoroketones and arylboronic acids occurred efficiently in the presence of $Ni(OTf)_2$, phen, and K_2CO_3 with high yields. This method demonstrated broad scope and high efficiency. Mechanistic investigation indicated that a monofluoroalkyl radical is involved in the coupling reaction pathway. Moreover, an important medical intermediate of flindokalner **12** was obtained via a nickel-catalyzed coupling reaction of 3-bromo-3-fluoro-6-(trifluoromethyl)indolin-2-one **2s** and 2-(5-chloro-2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **11**. Further studies of the application of the monofluorinated agents **2** and the coupling reaction are still ongoing in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02474.

Experimental procedures, NMR spectra, and X-ray crystal data (PDF)

Accession Codes

CCDC 1897634, 1901373, and 1922967 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

The authors declare no competing financial interest.

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