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Synthesis of Diverse Aromatic Ketones through C–F Cleavage of Trifluoromethyl Group

Mai Ikeda, Tsubasa Matsuzawa, Takamoto Morita, Takamitsu Hosoya, and Suguru Yoshida*

Abstract: An efficient synthetic method of aromatic ketones through C–F cleavage of trifluoromethyl group is disclosed. The high functional group tolerance of the transformation and the remarkable stability of trifluoromethyl group in various reactions enabled multisubstituted aromatic ketone synthesis in an efficient route involving useful transformations such as *ortho*-lithiation, aryne chemistry, and cross-couplings.

Aromatic ketones are of great importance in a wide range of disciplines including photochemistry, materials chemistry, pharmaceutical sciences, and chemical biology.[1] Despite enormous efforts to develop facile synthetic methods of aromatic ketones, it is not easy to prepare highly functionalized aromatic ketones in a multi-step manner due to the electrophilic carbonyl group. In particular, accessible ketones are quite limited in the conventional Friedel–Crafts reaction owing to the harsh conditions and the low functional group tolerance in the preparation of reactive acyl chlorides (Figure 1A).[1] Recent significant achievements have expanded the available aromatic ketones by virtue of the significant accessibility of starting materials and mild conditions.[2] For instance, a palladium-catalyzed diaryl ketone synthesis using esters and arylboronic acids developed by Newman, Houk, and coworkers enhanced the accessibility of aromatic ketones (Figure 1B).[2d] However, a multi-step synthesis involving these transformations toward highly functionalized ketones still require protecting groups or functional group transformations into the carbonyl group to avoid undesired bond formations at the electrophilic carbonyl carbon. Thus, a facile method to prepare aromatic ketones using a robust C1 unit is expected to achieve the synthesis of highly functionalized aromatic ketones in an efficient synthetic route involving reactive intermediates such as carbanions. Herein, we describe an efficient method to prepare aromatic ketones through C–F cleavage of the trifluoromethyl group (Figure 1C).

Since trifluoromethyl group is a robust functional group in the presence of a broad range of compounds such as acids or nucleophiles, the C–F transformation of the trifluoromethyl group is a challenging issue in synthetic organic chemistry.[3–6] The synthesis of highly functionalized aromatic ketones from benzotrifluorides is not easy owing to the harsh conditions using a strong Lewis or Brønsted acid. On the basis of recent our study for the mild C–F transformation,[6] we at first envisioned that an arylation and carbonyl formation of the trifluoromethyl group of benzotrifluorides will furnish aromatic ketones. The transformation of trifluoromethyl group as a robust C1 unit under the mild reaction conditions would allow for an efficient synthetic route involving useful transformations such as *ortho*-lithiation, aryne chemistry, and cross-couplings. Considering the good affinity between boron and fluorine and the gentle reactivity of boron tribromide used in various natural product synthesis,[7] we attempted a reaction between 4-methylbenzotrifluoride (**1a**) and mesitylene (**2a**) using boron tribromide at 25 °C (Figure 1D). As a result, we found that the reaction followed by adding methanol provided diaryl ketone **3a** in high yield through the cleavage of three C–F bonds.[8] When water was used instead of methanol, the desired ketone **3a** was not obtained.

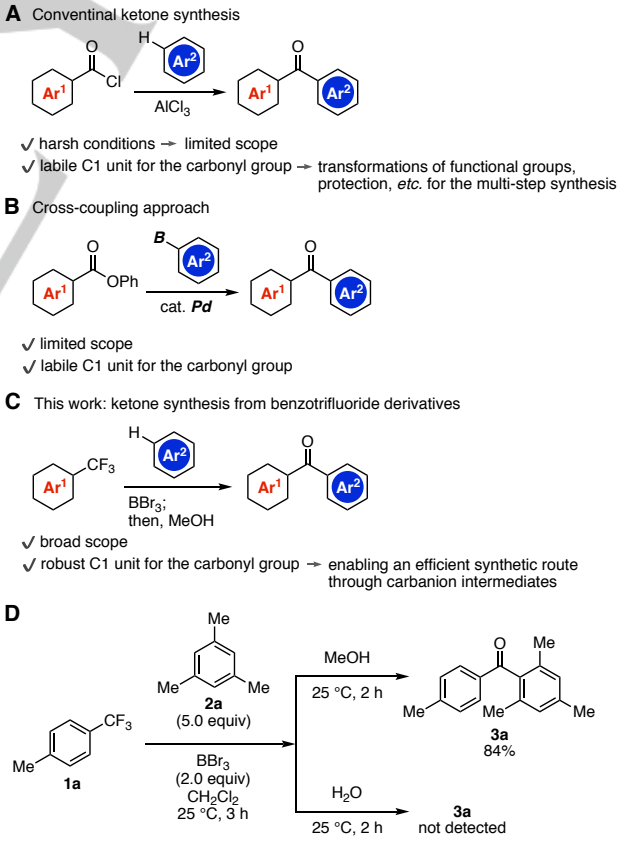

Figure 1. Ketone syntheses. (A) Conventional methods. (B) Ketone synthesis from esters. (C) This work. (D) Initial attempts.

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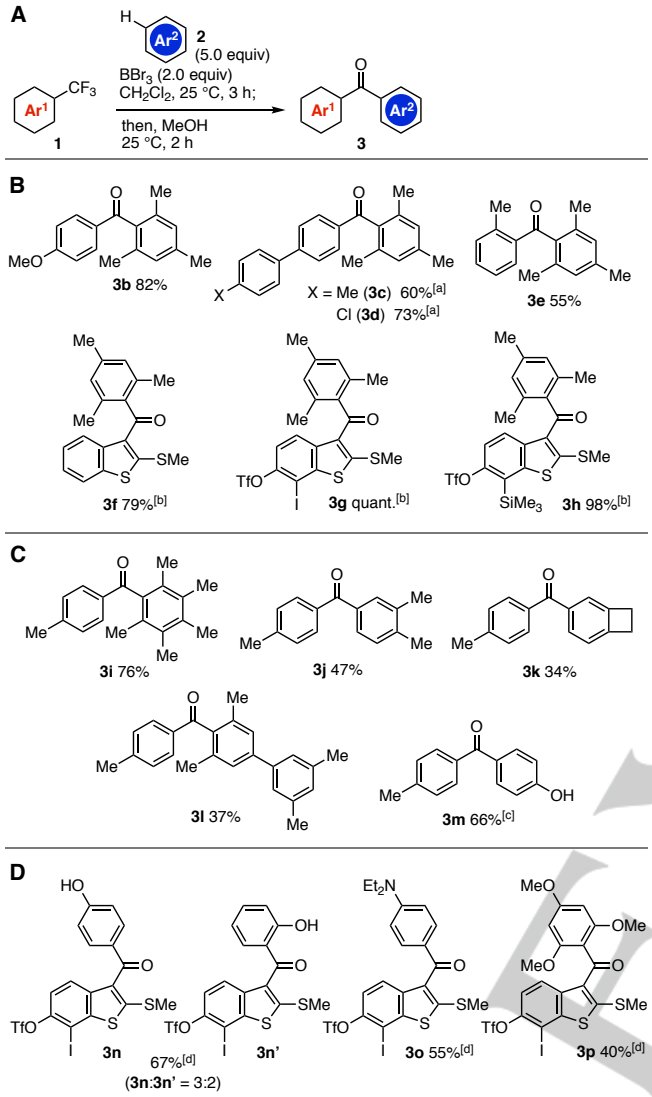

Figure 2. Synthesis of diaryl ketones **3** from benzotrifluoride derivatives **1**. See, the Supporting Information for the structures of **1** and **2**. (A) General scheme. (B) Reactions between various benzotrifluoride derivatives **1** with **2a**. (C) Reactions between **1a** with various arenes **3**. (D) Synthesis of various benzo[*b*]thiophenes **3n**–**3p**. [a] Reaction time for the first step was 12 h. [b] Reaction time for the first step was 21 h. [c] The procedure was changed as follows: 1. **1** (1.0 equiv), BBr_3 (2.0 equiv), CH_2Cl_2, 25 °C, 3 h; 2. **2** (5.0 equiv), 25 °C, 2 h; 3. MeOH, 25 °C, 2 h. [d] The procedure was changed as follows: 1. **1** (1.0 equiv), BBr_3 (2.0 equiv), CH_2Cl_2, 25 °C, 21 h; 2. **2** (5.0 equiv), 25 °C, 2 h; 3. MeOH, 25 °C, 2 h.

A wide range of diaryl ketones were synthesized from various benzotrifluorides and aromatic compounds (Figures 2A and 2B). Indeed, 4-anisyl mesityl ketone (**3b**) was obtained through the C–F cleavage of 4-methoxybenzotrifluoride without demethylation of the methoxy group. Ketones **3c** and **3d** were also prepared by treating 4-trifluoromethylbiphenyl derivatives. The reaction using bulky 2-methylbenzotrifluoride uneventfully took place to afford mesityl 2-tolyl ketone (**3e**) in moderate yield. Since benzo[*b*]thiophenes having a trifluoromethyl group participated in synthesizing ketones **3f**–**3i** without damaging various functional groups, an advantage of this synthetic method was clearly shown. For example, the ketone synthesis using CF_3-substituted benzo[*b*]thiophenes, prepared from CF_3-substituted ketene dithioacetal monoxide with triflic anhydride,[9] successfully underwent to furnish **3f**–**3h** in good to excellent yields leaving reactive methylthio, iodo, silyl, and triflyloxy groups untouched. On the other hand, transformations of the benzo[*b*]thiophene having various functional groups under reported Lewis or Brønsted acid conditions resulted in failure.[10]

A broad range of aromatic compounds were applicable to the diaryl ketone synthesis (Figures 2A and 2C). For example, 2,3,4,5,6-pentamethylphenyl 4-tolyl ketone (**3i**) was efficiently prepared by treatment of benzotrifluoride **1a** and 1,2,3,4,5-pentamethylbenzene with boron tribromide followed by addition of methanol. In addition, the reactions of **1a** with *o*-xylene, cyclobutabenzene, and 3,3',5,5'-tetramethylbiphenyl also took place to afford the corresponding diaryl ketones **3j**–**3l** in moderate yields. Furthermore, 4-hydroxyphenyl 4-tolyl ketone (**3m**) was synthesized from benzotrifluoride **1a** and phenol with a modified procedure.[8] It is worth noting that the synthesis of highly functionalized benzo[*b*]thiophenes **3n**–**3p** was accomplished by the reaction of 7-iodo-2-methylthio-3-trifluoromethyl-6-(triflyloxy)benzo[*b*]thiophene with boron tribromide followed by adding phenol, *N*,*N*-dimethylaniline, and 1,3,5-trimethoxybenzene with methanol (Figure 2D).[11] Compared to the defluoroarylation using aromatic compounds as a solvent reported by Hu and coworkers,[5d] the broad scope is a benefit of our method.

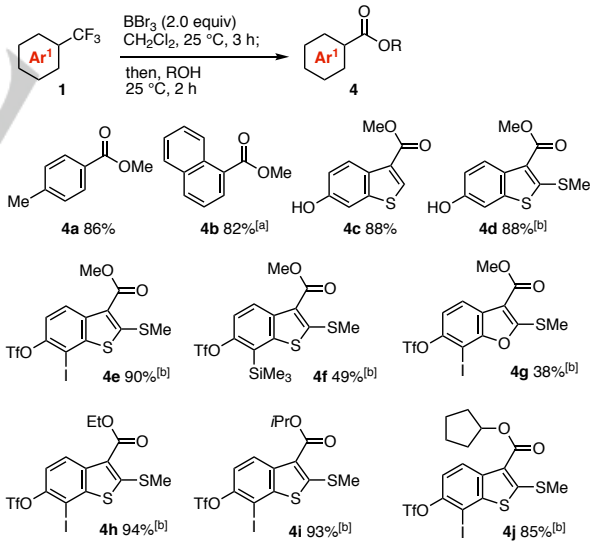

Figure 3. Synthesis of esters from benzotrifluoride derivatives **1**. See, the Supporting Information for the structures of **1**. [a] The procedure was changed as follows: 1. **1** (1.0 equiv), BBr_3 (2.0 equiv), CH_2Cl_2, 50 °C, 3 h (sealed tube); 2. MeOH, 50 °C, 2 h. [b] Reaction time for the first step was 21 h.

Various aromatic esters possessing functional groups were also synthesized through the C–F cleavage (Figure 3). For instance, esters **4a** and **4b** were efficiently prepared by treatment of 4-methylbenzotrifluoride and 1-trifluoromethylnaphthalene,

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respectively, with boron tribromide followed by addition of methanol.[12] When 6-methoxy-3-triflоromethylbenzo[*b*]thiophenes were used, esters **4c** and **4d** were obtained via the C–F cleavage and demethylation. Similar to the ketone synthesis, the good functional group tolerance achieved the preparation of benzo[*b*]thiophene **4e** or **4f** having *o*-iodo- or *o*-silylaryl triflate moiety. Benzo[*b*]furan-type ester **4g** was also synthesized in moderate yield. Furthermore, ester formation using a range of alcohols, that is, ethanol, 2-propanol, and cyclopentanol, took place smoothly to provide esters **4h**–**4j** in high yields without lacking iodo, triflyloxy, and methylthio groups.

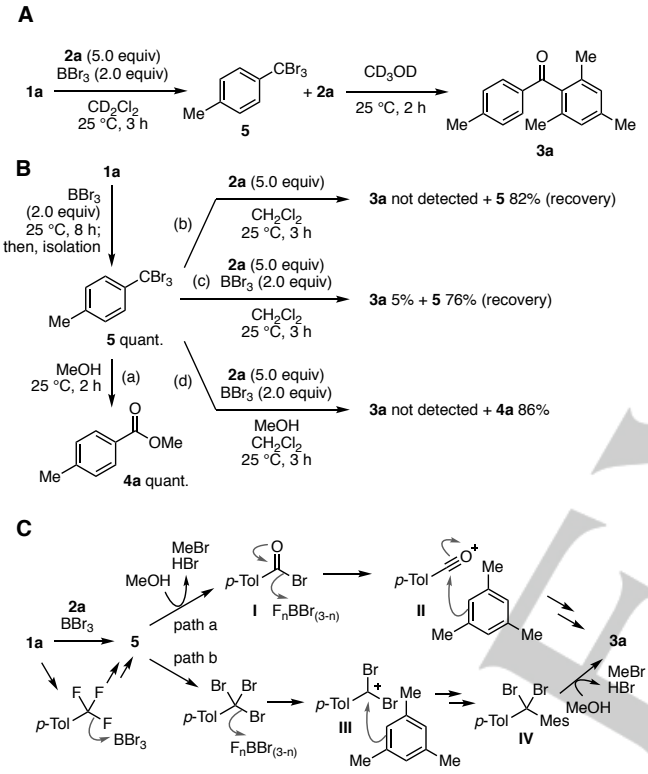

Figure 4. Control experiments to clarify the reaction mechanism. (A) NMR experiment. (B) Reactions using 4-(tribromomethyl)toluene (**5**). (C) Plausible reaction mechanisms.

To clarify the reaction mechanism of the diaryl ketone synthesis involving the C–F cleavage, we then conducted a reaction of benzotrifluoride **1a** with boron tribromide in the presence of mesitylene using dichloromethane-d_2 as a solvent (Figure 4A). As a result, we observed 4-(tribromomethyl)toluene with unreacted mesitylene (**2a**) in the ^{1}H NMR analysis of the resulting solution.[5c] Then, diaryl ketone **3a** was observed by the ^{1}H NMR analysis after an addition of methanol-d_4 to the reaction mixture. We then performed several control experiments using 4-(tribromomethyl)toluene (**5**) prepared from benzotrifluoride **1a** with boron tribromide (Figure 4B). While methanolysis of **5** quantitatively afforded ester **4a** (Figure 4B-a),[13] no direct reaction of **5** with mesitylene (**2a**) occurred (Figure 4B-b). When tribromide **5** was treated with boron tribromide in the presence of mesitylene (**2a**), only a small amount of diaryl ketone **3a** was obtained (Figure 4B-c).[14] Addition of mesitylene (**2a**), boron tribromide, and methanol to tribromide **5** in dichloromethane afforded ester **4a,** and diaryl ketone **3a** was not detected (Figure 4B-d).[15] These results in Figures 4A and 4B clearly showed that the synthesis of diaryl ketone **3a** was accomplished by the reaction between tribromide **5** and mesitylene (**2a**) with an in situ generated activator such as $F_nBBr_{(3-n)}$. Thus, we postulated a reaction mechanism shown in Figure 4C.[16] Firstly, a reaction between benzotrifluoride **1a** with boron tribromide provided tribromide **5** through the three-times defluorobromination. Then, transient generation of acyl bromide **I** by the reaction of tribromide **5** with methanol and Friedel–Crafts reaction between **I** and mesitylene (**2a**) triggered by the in situ generated $F_nBBr_{(3-n)}$ would furnish diaryl ketone **3a** (path a). Alternatively, the formation of dibromomethylene **IV** through the activation of C–Br bond by $F_nBBr_{(3-n)}$ and subsequent transformation into the diaryl ketone **3a** is also possible (path b).

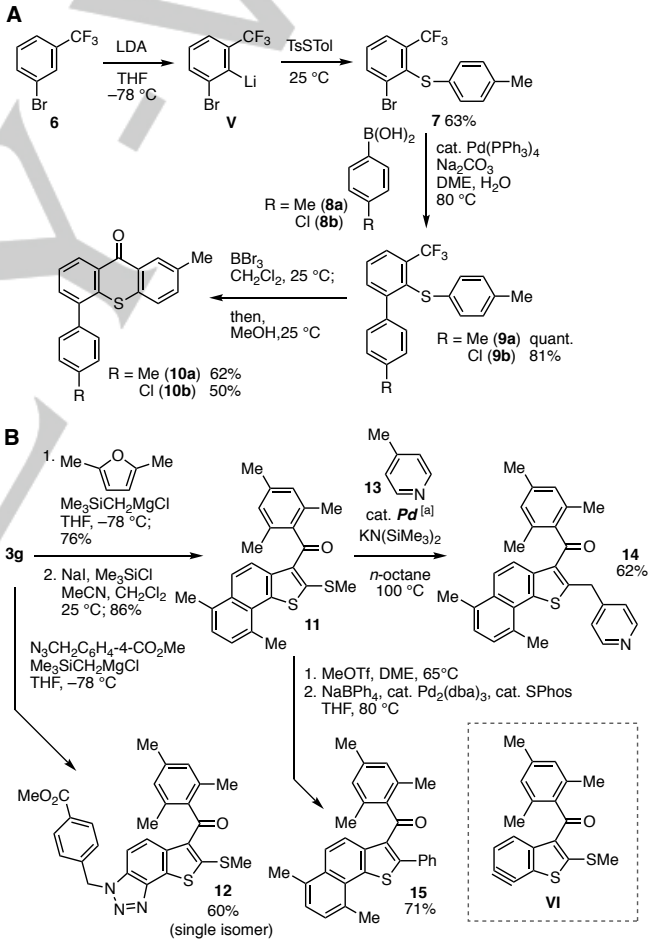

Figure 5. Multisubstituted aromatic ketone synthesis. (A) Synthesis of thioxanthones. (B) Synthesis of benzo[*b*]thiophenes. [a] ***Pd*** = SingaCycle-A1. See the Supporting Information for the details.

An advantage of the diaryl ketone synthesis using the robust trifluoromethyl group as a C1 unit was showcased by the thioxanthone synthesis[17] through carbanion intermediates

(Figure 5A). Since the significant electron-withdrawing nature of the aromatic trifluoromethyl group enables *ortho*-lithiation with a base,[18] benzotrifluorides **9a** and **9b** were prepared by deprotonation of *m*-bromobenzotrifluoride (**6**) with lithium diisopropylamide (LDA) followed by thiolation with *S*-(*p*-tolyl) *p*-toluenethiosulfonate and cross-coupling reaction with arylboronic acids **8a** and **8b**. We then attempted an intramolecular diaryl ketone synthesis by treatment of benzotrifluorides **9a** and **9b** with boron tribromide followed by addition of methanol. As a result, thioxanthones **10a** and **10b** were successfully synthesized through the C–F cleavage and cyclization. The modular synthetic route from *m*-bromobenzotrifluoride, thiosulfonate, and arylboronic acids would serve in the construction of diverse thioxanthone library.

Since the diaryl ketone synthesis proceeded leaving a wide variety of transformable functional groups unreacted by virtue of mild reaction conditions, a wide variety of multisubstituted benzo[*b*]thiophenes **11**, **12**, **14**, and **15** were easily prepared through aryne reactions and C–S transformations (Figure 5A).[19] Indeed, we succeeded in the synthesis of naphthothiophene **11** and triazole-fused benzothiophene **12** via the generation of thienobenzyne **VI** at the *o*-iodoaryl triflate moiety and following [2+4] and [2+3] cycloadditions without damaging the carbonyl groups.[9b,9c,20,21] Furthermore, the remarkable transformability of the methylthio group accomplished C–C bond-forming reactions.[22,23] For example, diaryl ketone **14** was prepared by direct cross-coupling with 4-methylpyridine (**13**) using a palladium–NHC precatalyst.[23d] Additionally, *S*-methylation and palladium-catalyzed phenylation of the resulting sulfonium salt also proceeded to provide diaryl ketone **15** in good yield.[23b] These results clearly showed that diverse benzo[*b*]thiophenes can be synthesized by the combination of the diaryl ketone synthesis through the C–F cleavage, versatile transformations of aryne intermediates, and cross-coupling reactions.

In summary, we have developed a useful synthetic method of diary ketones from benzotrifluorides through C–F cleavage, where a variety of transformable functional groups were tolerated under mild conditions. Since the trifluoromethyl group is a robust electron-withdrawing C1 unit, the advantages of the diaryl ketone synthesis were shown by preparing highly functionalized thioxanthones and benzo[*b*]thiophenes in a modular synthetic manner. Further studies to clarify the detailed reaction mechanism and expand the scope of the diaryl ketones involving cyclic ketones via intramolecular reactions are currently underway.

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Keywords: C–F activation • fluorine • ketone • thioxanthone • benzothiophene

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[10] According to the conditions for C–C formation of trifluoromethyl group reported in refs. 5b and 5d, when the reaction of 7-iodo-2-methylthio-3-trifluoromethyl-6-triflyloxybenzo[*b*]thiophene using $AlCl_3$ or TfOH instead of BBr_3 was performed, a complex mixture of products was obtained along with recovery of the substrate. See the Supporting Information for the details.

[11] The treatment of a mixture of 7-iodo-2-methylthio-3-trifluoromethyl-6-triflyloxybenzo[*b*]thiophene and *N*,*N*-diethylaniline in dichloromethane with BBr_3 resulted in the recovery of the benzothiophene without ketone **3o**.

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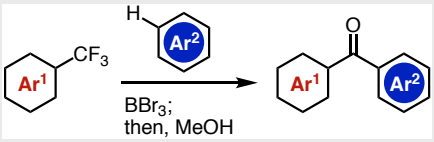

An efficient synthetic method of aromatic ketones through C–F cleavage of trifluoromethyl group is disclosed. The high functional group tolerance of the transformation and the remarkable stability of trifluoromethyl group in various reactions enabled multisubstituted aromatic ketone synthesis in an efficient route involving useful transformations such as *ortho*-lithiation, aryne chemistry, and cross-couplings.

*M. Ikeda, T. Matsuzawa, T. Morita, T. Hosoya, S. Yoshida**

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Synthesis of Diverse Aromatic Ketones through C–F Cleavage of Trifluoromethyl Group