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The Friedel–Crafts acylation of aromatic compounds with carboxylic acids by the combined use of perfluoroalkanoic anhydride and bismuth or scandium triflate

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Abstract—Aromatic ketones were synthesized by solventless Friedel–Crafts acylation of anisole, mesitylene, xylenes, and toluene with acetic acid and benzoic acid in the presence of trifluoroacetic anhydride by use of bismuth or scandium triflate at 30 °C. Toluene, benzene, and even deactivated substrate such as chlorobenzene were benzoylated by the combined use of heptafluorobutyric anhydride and bismuth triflate at 75–100 °C. The catalyst could be easily recovered and reused repeatedly for the reaction.
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The Friedel–Crafts acylation of aromatic compounds with acyl halides, which is an important process for the preparation of pharmaceuticals, perfumes, and polymers, has been performed with at least a stoichiometric amount of Lewis acids.[1,2] Aromatic ketones have been also prepared by dehydrative acylation reactions of aromatic compounds with carboxylic acids catalyzed by various types of acid such as methanesulfonic acid,[3] trifluoromethanesulfonic acid (TfOH),[4] Nafion-H,[5] zeolite,[6] and heteropoly salt.[7] However the acid catalysts are generally used in excess of molar amounts. Recently, Kobayashi et al. reported the direct acylation of phenol and naphthol derivatives with carboxylic acids using a catalytic amount of metal triflate such as Hf(OTf)$_4$, Zr(OTf)$_4$, or Sc(OTf)$_3$.[8] Furthermore, Shimada's group reported both the intramolecular reaction of 3-arylpropionic acids in the presence of Tb(OTf)$_3$[9] and the intermolecular reaction of anisole and alkylbenzenes with carboxylic acids in the presence of Eu(NTf$_2$)$_3$.[10] However, drastic conditions at high temperature are 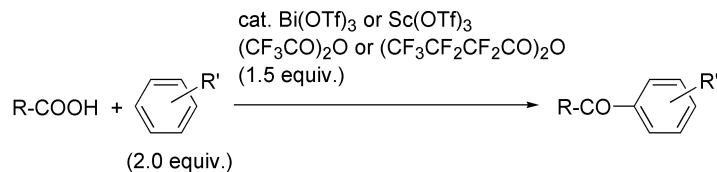needed and/or applicable substrate range is limited on the direct dehydration reactions. On the other hand, the Friedel–Crafts acylation via mixed anhydrides prepared in situ from carboxylic acids has been achieved by the combined use of an activating agent and a catalyst, for example, p-trifluoromethylbenzoic anhydride and SiCl$_4$–AgClO$_4$,[11] trifluoroacetic anhydride (TFAA) and H$_3$PO$_4$,[12,13] or TFAA and AlPW$_{12}$O$_{40}$.[14] The mixed anhydride methods are advantageous in terms of the mild conditions employed and the easily availability of carboxylic acids, however, the substrates are limited to activated benzenes such as anisole, xylene, and toluene. Development of more efficient activating agents and/or catalysts is still demanded. In this paper we report an facile and efficient method for preparation of aromatic ketones by solventless Friedel–Crafts acylation of aromatic compounds with carboxylic acids in the presence of perfluoroalkanoic anhydride such as TFAA or heptafluorobutyric anhydride (HFBA) by use of Bi(OTf)$_3$ or Sc(OTf)$_3$ as a catalyst (Scheme 1).

We first examined the effect of catalysts such as Nafion-H[15] (Nafion NR-50 beads), TfOH,[16] Bi(OTf)$_3$[17] and Sc(OTf)$_3$[18] on the Friedel–Crafts acetylations of aromatic compounds with acetic acid in the presence of 1.5 equiv of TFAA at 30 °C (Scheme 2). The time courses for production of acetophenones **1**–**5** were followed by GC.
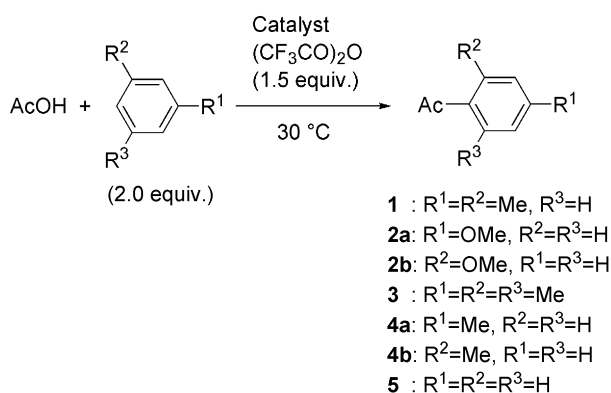
Figure 1 shows the results for m-xylene. The acetylation of m-xylene proceeded very slowly without the catalyst.

$$\text{R-COOH} + \underset{(2.0 \text{ equiv.})}{\overset{\text{R'}}{\bigodot}} \xrightarrow[\text{(1.5 equiv.)}]{\substack{\text{cat. Bi(OTf)}_3 \text{ or Sc(OTf)}_3 \\ (CF_3CO)_2O \text{ or } (CF_3CF_2CF_2CO)_2O}} \text{R-CO}\overset{\text{R'}}{\bigodot}$$

Scheme 1.

$$\text{AcOH} + \underset{(2.0 \text{ equiv.})}{\overset{R^2}{\underset{R^3}{\bigodot}}R^1} \xrightarrow[30\,°C]{\substack{\text{Catalyst} \\ (CF_3CO)_2O \\ (1.5 \text{ equiv.})}} \text{Ac}\overset{R^2}{\underset{R^3}{\bigodot}}R^1$$

1 : R^1=R^2=Me, R^3=H
2a: R^1=OMe, R^2=R^3=H
2b: R^2=OMe, R^1=R^3=H
3 : R^1=R^2=R^3=Me
4a: R^1=Me, R^2=R^3=H
4b: R^2=Me, R^1=R^3=H
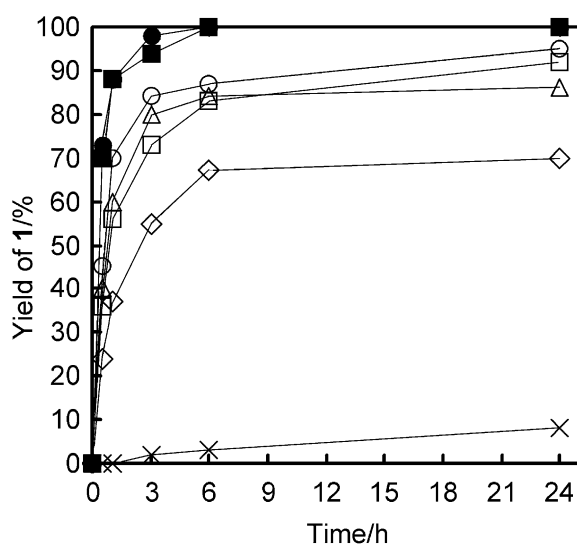**5** : R^1=R^2=R^3=H

Scheme 2.

Figure 1. Time courses of the Friedel–Crafts acetylation of *m*-xylene (2 mmol) with acetic acid (1 mmol) in the presence of TFAA (1.5 mmol) at 30 °C by use of several catalysts: none (×), 10 mol% Nafion-H (◇), 10 mol% TfOH (△), 3.3 mol% Bi(OTf)$_3$ (○), 3.3 mol% Sc(OTf)$_3$ (□), 10 mol% Bi(OTf)$_3$ (●), and 10 mol% Sc(OTf)$_3$ (■). Yield of **1** was determined based on acetic acid by GC: conditions; detector, FID; column: OV-17 (3.2 mm, 2 m); carrier gas, N$_2$; temp 100–280 °C (10 °C/min); internal standard, tridecane.

The addition of 10 mol% Nafion-H (Nafion NR-50 beads) or 10 mol% TfOH promoted the reaction, and the yield of **1** was 70% for Nafion-H and 86% for TfOH after 24 h. The catalytic activity of 10 mol% TfOH was almost equal to those of 3.3 mol% Bi(OTf)$_3$ and 3.3 mol% Sc(OTf)$_3$. When using 10 mol% Bi(OTf)$_3$ or 10 mol% Sc(OTf)$_3$, the reaction was complete in 6 h. Dubac's group already elucidated that metal triflates had the same activity as triplicate amount of TfOH on

the reaction of toluene with benzoyl chloride and the real catalyst was TfOH formed from the metal triflates by ligand exchange reaction.[19b] The present activity tendency of the catalysts coincides with that described by them. Since Nafion-H, Bi(OTf)$_3$, and Sc(OTf)$_3$ can be more easily recovered than TfOH from the reaction mixture, we decided to use these catalysts on the following reactions.

Next, acetic acid was allowed to react with several benzenes (Table 1). In the absence of the catalyst, the acetylations of anisole and mesitylene proceeded faster than that of *m*-xylene: Acetophenones **2a,b** and **3** were obtained in 86% and 95% yields after 24 h, respectively. Although Nafion-H, Bi(OTf)$_3$, and Sc(OTf)$_3$ promoted the acetylation of anisole, the elongation of the reaction time led to the decrease in the yield of **2a,b**. Hydroxy-acetophenones were isolated as minor products in the reaction mixture after 24 h, and are probably produced from **2a,b** by cleavage of O–Me bond. Bi(OTf)$_3$ and Sc(OTf)$_3$ were more effective than Nafion-H on the acetylation of mesitylene. The acetylation of toluene using 10 mol% Bi(OTf)$_3$ or 10 mol% Sc(OTf)$_3$ gave **4a,b**, while no reaction took place without the catalyst. Bi(OTf)$_3$ was more effective than Sc(OTf)$_3$. No or little acetylation of benzene occurred both in the absence and in the presence of Bi(OTf)$_3$. Bi(OTf)$_3$ and Sc(OTf)$_3$ are found to be more active on the TFAA-mediated acetylation than AlPW$_{12}$O$_4$[14] as the catalyst, and be almost comparable with H$_3$PO$_4$.[12,13]

The acetylations of aromatic compounds at higher temperature were carried out in the presence of HFBA (bp 108–109 °C) instead of TFAA (bp 39.5–40 °C) and the results are shown in Table 2. Under the conditions at 100 °C without the catalyst, both anisole and mesitylene gave the corresponding acetophenones in high yields for 3 h, and *m*-xylene gave **3** in 60% yield for 24 h. The reaction of *m*-xylene using 3.3 mol% Bi(OTf)$_3$ was complete in 3 h. The reaction of toluene at 100 °C without the catalyst was very slow, while that with 10 mol% Bi(OTf)$_3$ gave **4a,b** in 32% yield. Decreasing yield of **4a,b** with the elapse of the reaction time suggests that **4a,b** gradually decompose during the reaction. (The decomposed products was not yet determined.) Benzene could be acetylated in low yield in the presence of 10 mol% Bi(OTf)$_3$ at 75 °C.

The benzoylations of aromatic compounds were attempted in the presence of TFAA or HFBA (Scheme 3). Table 3 summarizes the results. The TFAA-mediated benzoylations of anisole and mesitylene without the catalyst at 30 °C afforded **6** and **7**, respectively, in 41% and 36% yields after 12 h. When HBFA was used at

Table 1. The Friedel–Crafts acetylations of aromatic compounds with acetic acid in the presence of TFAA at 30 °C[a]

Entry	Substrate	Catalyst (mol%)	Product	Yield/% (isomer distribution/**a**:**b**)[b]		
				3 h	6 h	24 h
1	Anisole	None	**2a,b**	51 (96:4)	71 (96:4)	86 (98:2)
2	Anisole	Nafion-H (10)	**2a,b**	84 (98:2)	82 (98:2)	75 (99:1)
3	Anisole	Bi(OTf)$_3$ (3.3)	**2a,b**	73 (96:4)	72 (98:2)	65 (98:2)
4	Anisole	Sc(OTf)$_3$ (3.3)	**2a,b**	76 (98:2)	71 (98:2)	68 (98:2)
5	Mesitylene	None	**3**	17	28	95
6	Mesitylene	Nafion-H (10)	**3**	40	63	100
7	Mesitylene	Bi(OTf)$_3$ (3.3)	**3**	92	100	100
8	Mesitylene	Sc(OTf)$_3$ (3.3)	**3**	100	100	100
9	Toluene	None	**4a,b**	0	0	0
10	Toluene	Bi(OTf)$_3$ (10)	**4a,b**	38 (94:6)	43 (94:6)	46 (95:5)
11	Toluene	Sc(OTf)$_3$ (10)	**4a,b**	25 (96:4)	27 (96:4)	30 (96:4)
12	Benzene	None	**5**	0	0	0
13	Benzene	Bi(OTf)$_3$ (10)	**5**	1	1	1
14	Benzene	Sc(OTf)$_3$ (10)	**5**	0	0	0

[a] Acetic acid (1 mmol) was allowed to react with aromatic compounds (2.0 mmol) in the presence of TFAA (1.5 mmol) by use or no use of the catalyst (3.3 or 10 mol%) at 30 °C.
[b] Determined by GC using decane for toluene, tridecane for mesitylene, or tetradecane for anisole and benzene as an internal standard under the same conditions as described in Figure 1.

Table 2. The Friedel–Crafts acetylations of aromatic compounds with acetic acid in the presence of HFBA[a]
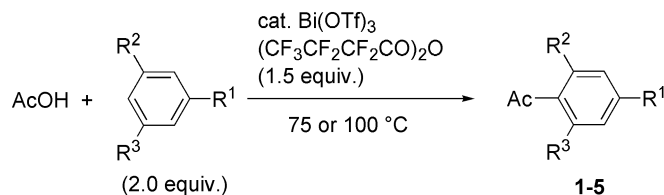
Entry	Substrate	Catalyst (mol%)	Temp/°C	Product	Yield/% (isomer distribution/**a**:**b**)[b]		
					3 h	6 h	24 h
1	Anisole	None	100	**2a,b**	89 (93:7)	85 (95:5)	73 (98:2)
2	Mesitylene	None	100	**3**	100	—[c]	—
3	*m*-Xylene	None	100	**1**	19	33	60
4	*m*-Xylene	Bi(OTf)$_3$ (3.3)	100	**1**	100	—	—
5	Toluene	None	100	**4a,b**	1 (100:0)	2 (100:0)	6 (86:14)
6	Toluene	Bi(OTf)$_3$ (10)	100	**4a,b**	32 (86:14)	22 (84:16)	16 (78:22)
7	Benzene	None	75	**5**	0	0	0
8	Benzene	Bi(OTf)$_3$ (10)	75	**5**	12	20	23

[a] Acetic acid (1 mmol) was allowed to react with aromatic compounds (2.0 mmol) in the presence of HFBA (1.5 mmol) by use or no use of the catalyst (3.3 or 10 mol%) at 75 or 100 °C.
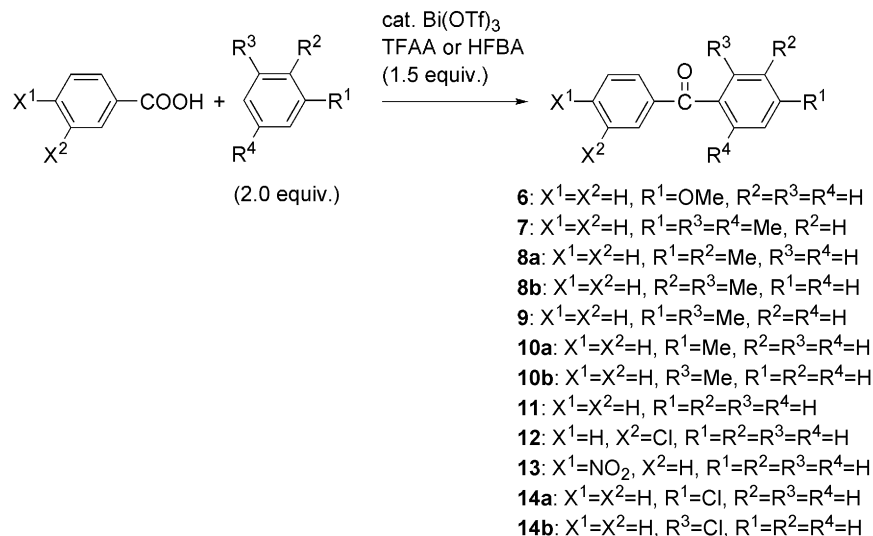[b] Determined by GC under the same conditions as described in Table 1.
[c] Not examined.

30 °C instead of TFAA for the reactions of anisole and mesitylene, the yields of **6** and **7** were 24% and 10%, respectively (data not shown in Table 3): A reason of the low yields is likely that the reaction mixture is heterogeneous because neither anisole nor mesitylene is soluble in HBFA at 30 °C. On the other hand, when HFBA alone was used at 100 °C, anisole and mesitylene were rapidly converted into the corresponding ketones in high yields. Bi(OTf)$_3$ was effective not only for the TFAA-mediated benzoylations at 30 °C of anisole, mesitylene, xylenes, and toluenes but also for the HFBA-mediated acylations at 75 °C of toluene and benzene with benzoic acid, *m*-chlorobenzoic acid, or *p*-chlorobenzoic acid. Chlorobenzene, one of the deactivated benzenes, was also benzoylated by the combination use of Bi(OTf)$_3$ and HFBA at 100 °C. It has been reported that less

reactive substrates such as toluene, benzene, and chlorobenzene were acylated with acyl chlorides or acyl anhydrides by a catalytic amount of metal perfluoroalkylsufonates, for example, Bi(OTf)$_3$,[19] Hf(OTf)$_4$–TfOH,[20] Hf(OTf)$_4$ in LiClO$_4$–MeNO$_2$,[21] Cu(OTf)$_2$,[22] B(OTf)$_3$,[23] Al(OTf)$_3$,[23] Ga(OTf)$_3$,[23] and Ga(OSO$_2$CF$_2$CF$_2$CF$_3$)$_3$.[24] However, the catalytic acylation of benzene and chlorobenzene with free carboxylic acid via mixed anhydride generated in situ was not reported, as far as we know. It is noteworthy that toluene, benzene, and especially deactivated substrate such as chlorobenzene are benzoylated in the present conditions.

Finally, we tried recovery and reuse of the catalyst on the Bi(OTf)$_3$-catalyzed benzoylation of *m*-xylene with benzoic acid in the presence of TFAA (Table 4). The

6: $X^1=X^2=H$, $R^1=OMe$, $R^2=R^3=R^4=H$
7: $X^1=X^2=H$, $R^1=R^3=R^4=Me$, $R^2=H$
8a: $X^1=X^2=H$, $R^1=R^2=Me$, $R^3=R^4=H$
8b: $X^1=X^2=H$, $R^2=R^3=Me$, $R^1=R^4=H$
9: $X^1=X^2=H$, $R^1=R^3=Me$, $R^2=R^4=H$
10a: $X^1=X^2=H$, $R^1=Me$, $R^2=R^3=R^4=H$
10b: $X^1=X^2=H$, $R^3=Me$, $R^1=R^2=R^4=H$
11: $X^1=X^2=H$, $R^1=R^2=R^3=R^4=H$
12: $X^1=H$, $X^2=Cl$, $R^1=R^2=R^3=R^4=H$
13: $X^1=NO_2$, $X^2=H$, $R^1=R^2=R^3=R^4=H$
14a: $X^1=X^2=H$, $R^1=Cl$, $R^2=R^3=R^4=H$
14b: $X^1=X^2=H$, $R^3=Cl$, $R^1=R^2=R^4=H$

Scheme 3.

Table 3. The Friedel–Crafts acylations of aromatic compounds with benzoic acids in the presence of TFAA or HFBA[a]

Entry	Carboxylic acid		Substrate	Anhydride	Catalyst (mol%)	Temp/°C	Time/h	Product	Yield/%[b] (isomer distribution/**a:b**)[c]
	$X^1 =$	$X^2 =$							
1	H	H	Anisole	TFAA	None	30	12	**6**	41
2	H	H	Anisole	TFAA	Bi(OTf)$_3$ (3.3)	30	12	**6**	98
3	H	H	Anisole	HFBA	None	100	3	**6**	95
4	H	H	Mesitylene	TFAA	None	30	12	**7**	36
5	H	H	Mesitylene	TFAA	Bi(OTf)$_3$ (10)	30	12	**7**	99
6	H	H	Mesitylene	HFBA	None	100	3	**7**	98
7	H	H	*o*-Xylene	TFAA	Bi(OTf)$_3$ (10)	30	12	**8a,b**	98 (97:3)
8	H	H	*m*-Xylene	TFAA	Bi(OTf)$_3$ (10)	30	12	**9**	98
9	H	H	Toluene	TFAA	Bi(OTf)$_3$ (10)	30	12	**10a,b**	72 (88:12)
10	H	H	Toluene	HFBA	Bi(OTf)$_3$ (10)	75	12	**10a,b**	96 (86:14)
11	H	H	Benzene	TFAA	Bi(OTf)$_3$ (10)	30	12	**11**	12
12	H	H	Benzene	HFBA	Bi(OTf)$_3$ (10)	75	12	**11**	90
13	H	Cl	Benzene	HFBA	Bi(OTf)$_3$ (10)	75	12	**12**	86
14	NO$_2$	H	Benzene	HFBA	Bi(OTf)$_3$ (10)	75	12	**13**	54
15	H	H	Chlorobenzene	HFBA	Bi(OTf)$_3$ (10)	100	12	**14a,b**	65 (94:6)

[a] Benzoic acid, *m*-chlorobenzoic acid, or *p*-chlorobenzoic acid (1 mmol) was allowed to react with aromatic compounds (2.0 mmol) in the presence of TFAA or HFBA (1.5 mmol) by use or no use of Bi(OTf)$_3$ (3.3 or 10 mol%) at 75 or 100 °C.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.

Table 4. Repeated use of Bi(OTf)$_3$ for the benzoylation of *m*-xylene[a]

Run	Isolated yield of **9**/%	Recovery of Bi(OTf)$_3$/%
1	98	95
2	96	96
3	97	96
4	96	95

[a] Benzoic acid (5 mmol) was allowed to react with *m*-xylene (10 mmol) in the presence of TFAA (7.5 mmol) and Bi(OTf)$_3$ (0.5 mmol) at 30 °C for 12 h.

reaction mixture was evaporated in vacuo in order to remove volatile TFAA, trifluoroacetic acid, and *m*-xylene. Hexane was added to the residue and the precipitate of Bi(OTf)$_3$ was collected by filtration. Bi(OTf)$_3$ was recycled and used repeatedly without loss of activity. Although metal triflates are usually recovered from the

aqueous layer after aqueous work-up, Bi(OTf)$_3$ is more easily recovered without post-treatment in our method.

In a typical procedure, to a mixture of benzoic acid (610 mg, 5.0 mmol), *m*-xylene (1.06 g, 10 mmol), and Bi(OTf)$_3$·4H$_2$O (364 mg, 0.5 mmol) in glass vial with Teflon-lined screw cap was added TFAA (1.06 cm^3, 7.5 mmol) at 0 °C, and the vial was sealed with the cap. The mixture was magnetically stirred at 30 °C for 12 h. After the reaction mixture has been evaporated in vacuo, 10 cm^3 of hexane was added to the gummy residue. The resulted solution was treated with ultrasonic cleaner bath (200 W) for 5 min: pale yellowish solid of Bi(OTf)$_3$ precipitated. The precipitate was filtered with suction, washed with hexane, and dried briefly in vacuo. Thus, 345 mg (95%) of Bi(OTf)$_3$ was recovered and reused on second run. On the other hand, the filtrate was evapo-

rated under the reduced pressure to give the almost pure **9** as colorless oil. Further purification was done by flash column chromatography on silica gel (25 g) with hexane/ Et$_2$O = 20/1 to give **9** (1.03 g, 4.90 mmol) in 98% yield.

In conclusion, the Friedel–Crafts acylation of aromatic compounds with carboxylic acids was successfully carried out by using Bi(OTf)$_3$ or Sc(OTf)$_3$ as the catalyst in the presence of perfluoroalkanoic anhydrides such as TFAA and HFBA under solventless and mild conditions, less reactive substrates such as benzene and chlorobenzene could be converted into the corresponding benzophenones. Further investigation to clarify the scope and limitation of the present reaction and to apply for synthesis of fine chemicals is now in progress.

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