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Synthesis of difluoromethylated diarylmethanes via Fe(OTf)$_3$-catalyzed Friedel–Crafts reaction of 2,2-difluoro-1-arylethyl phosphates

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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The Fe(OTf)$_3$-catalyzed Friedel–Crafts reaction of 2,2-difluoro-1-arylethyl phosphates with electron-rich (hetero)arenes afforded difluoromethylated diarylmethanes. Control experiments showed that Fe(OTf)$_3$ behaves as the Lewis acid, and that the phosphate leaving group and *o*- or *p*-alkoxy substituents on the substrates are necessary for the Fe(OTf)$_3$-catalyzed reaction to proceed under mild conditions.

Diarylmethane is an important structural motif found in a diverse range of biologically active molecules (Figure 1a).[1] Therefore, numerous synthetic methods have been developed for the efficient synthesis of 1,1-diarylmethanes.[2] On the other hand, fluoroalkyl groups have attracted much attention in medicinal chemistry because they can improve the intrinsic potency, metabolic stability, and bioavailability of the constituent drug molecules.[3] There have been several reports on efficient synthetic strategies, including enantioselective methods, for trifluoromethylated diarylmethanes.[4] In addition, synthetic methods for their difluoromethyl (CF_2H) analogs are developed (Figure 1b),[4a,f,g] because the CF_2H group has significant properties distinct from those of the trifluoromethyl group; the CF_2H group functions as a lipophilic bioisostere of hydroxy (OH) and mercapto (SH) groups.[5] However, the scope of difluoromethylated diarylmethanes has been relatively narrow. This is partly because of the inefficiency in the preparation of CF_2H-substituted benzylic precursors and the requirement of an expensive difluoromethylating agent. Therefore, a novel strategy for the synthesis of difluoromethylated diarylmethanes is sought.

We have previously reported the efficient preparation of allylic phosphates from cycloalkenones via the addition of a lithiated difluorophosphonate and subsequent phospha-Brook rearrangement (Scheme 1a).[6] The obtained phosphates were successfully transformed into (difluoromethyl)alkenes via an S_N2'-type substitution reaction using organocuparates. As a continuation of this work, we investigated the Friedel–Crafts (F–C) reaction of CF_2H-substituted benzyl phosphates, which can be readily prepared from the corresponding benzaldehydes via the addition of $LiCF_2PO(OEt)_2$ and subsequent phospha-Brook rearrangement using K_2CO_3 as a base in wet DMF (Scheme 1b). Although the synthesis of diarylmethanes via cross-coupling

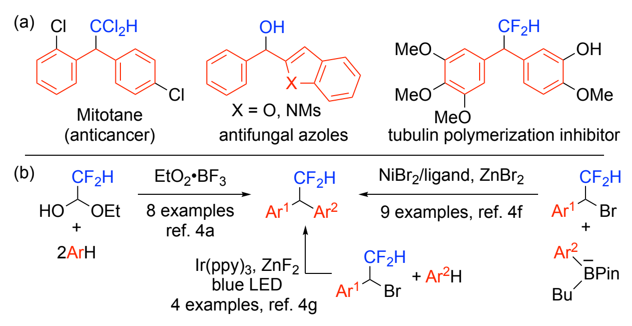
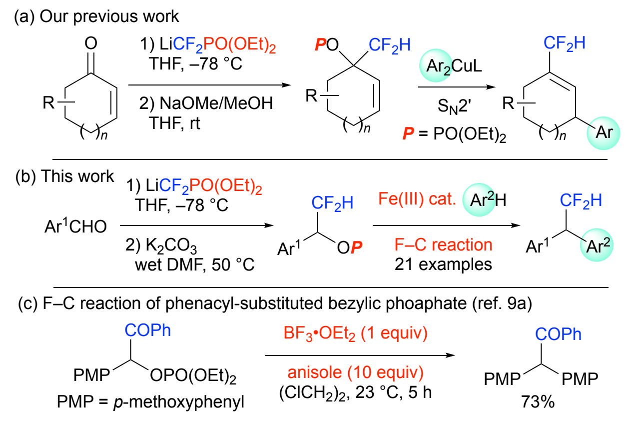


Fig. 1 (a) Biologically active compounds containing diarylmethane motif and (b) previous synthesis of difluoromethylated diarylmethanes.



Scheme 1 (a,b) Synthesis of difluoromethylated phosphates via phospha-Brook rearrangement and subsequent arylation, and (c) F–C reaction of phenacyl-substituted benzylic phosphate.

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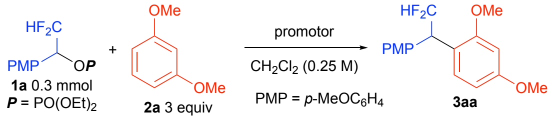
Electronic Supplementary Information (ESI) available: [experimental details and NMR charts]. See DOI: 10.1039/x0xx00000x

reactions of benzyl phosphates with aryl nucleophiles has been reported by several research groups, the existing methods are limited to the use of primary benzyl phosphates.[7] Moreover, the F–C reaction of benzyl phosphates has rarely been investigated.[8,9] Smith and Johnson demonstrated the F–C reaction of phenacyl-substituted benzyl phosphates as challenging substrates bearing an electron-withdrawing group at the benzylic position, although a stoichiometric amount of the Lewis acid and 10 equivalents of arenes were required (Scheme 1c).[9a] In addition, Pallikonda and Chakravarty performed catalytic F–C reactions of benzyl phosphates using trifluoromethanesulfonic acid (TfOH) as the Brønsted acid catalyst under neat conditions.[9b] Recently, Yurino, Ohkuma, and coworkers reported that $Al(OTf)_3$ efficiently catalyzed the F–C reaction of primary benzylic phosphates, albeit at a high temperature (100 °C).[9c] Thus, we assumed that CF_2H-substituted benzyl phosphates are potential substrates for the F–C reaction. Nevertheless, the development of an efficient protocol to catalyze the F–C reaction of benzylic phosphates deactivated by the electron-withdrawing CF_2H group under mild conditions is a formidable challenge.[10] Herein, we report our successful implementation of the synthesis of CF_2H-substituted diarylmethanes via the iron-catalyzed F–C reaction of 2,2-difluoro-1-arylethyl phosphates.[11]

At the outset, the reaction of known phosphate **1a** with 1,3-dimethoxybenzene (**2a**) was performed under various conditions to identify the optimal promoter (Table 1). According to the report by Smith and Johnson,[9a] $Et_2O•BF_3$ was tested as a Lewis acid promoter. In a dry CH_2Cl_2 solution (0.25 M), **1a** and **2a** (3 equiv) were treated with $Et_2O•BF_3$ (1.5 equiv) at 0 °C for 3 h to afford the desired product **3aa** in 86% yield (entry 1). The reaction was repeated with decreased amounts of **2a** (1.5 equiv) to afford **3aa** in a slightly lower yield (74%) along with small amounts of a 2:1 adduct as a mixture of diastereomers (entry 2). When 0.5 equiv of $Et_2O•BF_3$ was used, the reaction did not complete within 5 h and **3aa** was obtained in 39% yield along with 45% recovery of **1a** (entry 3). Next, TfOH was tested as a Brønsted acid promoter.[9b] The reaction proceeded smoothly in the presence of 1.0 equiv of TfOH at 0 °C for 2 h, affording **3aa** in 83% yield along with small amounts of the 2:1 adduct (entry 4). Although, a similar result was obtained with 0.5 equiv of TfOH (entry 5), the reaction did not proceed to completion even in 5 h when the amount of TfOH was further reduced to 0.2 equiv (entry 6).

Table 1 F–C reaction of **1a** with **2a** under various conditions.



Entry	Conditions	Yield/%[a]
1	$Et_2O•BF_3$ (1.5 equiv), 0 °C, 3 h	86
2[b]	$Et_2O•BF_3$ (1.5 equiv), 0 °C, 3 h	74[c]
3	$Et_2O•BF_3$ (0.5 equiv), 0 °C, 5 h	39 (45)
4	TfOH (1.0 equiv), 0 °C, 1.5 h	83[c]
5	TfOH (0.5 equiv), 0 °C, 1.5 h	85[c]
6	TfOH (0.2 equiv), 0 °C, 5 h	34 (40)
7	$Fe(OTf)_3$ (0.2 equiv), 0 °C, 5 h	68 (19)
8	$Fe(OTf)_3$ (0.2 equiv), 20 °C, 2.5 h	82[c]
9	$Cu(OTf)_2$ (0.2 equiv), 20 °C, 5 h	46 (44)
10	$Al(OTf)_3$ (0.2 equiv), 20 °C, 5 h	82 (trace)[c]
11[d]	$Fe(OTf)_3$ (0.1 equiv), 20 °C, 1 h	87[c]
12[d,e]	$Fe(OTf)_3$ (0.05 equiv), 20 °C, 2 h	85
13	$FeCl_3•6H_2O$ (0.1 equiv), 20 °C, 5 h	81

[a] Isolated yields. Yields of recovered **1a** were indicated in parentheses. [b] **2a** (1.5 equiv). [c] Trace amounts of 2:1 adduct (<7%) was detected as a mixture of diastereomers. [d] Nitromethane was used as the solvent. [e] 1 mmol scale.

Metal triflates have been used as Lewis acid catalysts, and they often show Brønsted acid reactivity associated with the generation of TfOH under the reaction conditions.[12] Narasaka, Duñach, and coworkers investigated the effectiveness of metal triflates as catalysts for the reaction of unsaturated oximes.[13] They reported that $Al(OTf)_3$ selectively catalyzed the desired cyclization, while $Fe(OTf)_3$ and $Cu(OTf)_2$ caused the hydrolysis of the oxime moiety. With the expectation of the Lewis and Brønsted acid cooperative effect, several metal triflates were examined for use as promoters. Interestingly, the use of 20 mol% $Fe(OTf)_3$ instead of TfOH under the same conditions afforded **3aa** in an improved yield (68%) along with unreacted **1a** in 19% yield (entry 7). At an elevated temperature (20 °C), the reaction performed using 20 mol% $Fe(OTf)_3$ was complete within 2.5 h, affording **3aa** in 82% yield (entry 8). Other metal triflates were also tested; $Cu(OTf)_2$ gave much lower conversion in 5 h than that obtained when using $Fe(OTf)_3$, while $Al(OTf)_3$ led to near completion of the reaction in 5 h (entries 9 and 10). Therefore, $Fe(OTf)_3$ was demonstrated to be the most efficient promoter among the metal triflates examined in this study. Furthermore, when nitromethane was used as the solvent, the reaction was complete in 1 h even with a reduced amount of $Fe(OTf)_3$ (10 mol%), affording **3aa** in 87% yield (entry 11). When reaction was carried out with 5 mol% $Fe(OTf)_3$ at a 1 mmol scale for 2 h , **3aa** was obtained in 85% yield (entry 12). When $FeCl_3•6H_2O$ was used instead of $Fe(OTf)_3$, a longer reaction time (5 h) was required for the reaction completion, demonstrating the superior efficiency of $Fe(OTf)_3$ (entry 13). To the best of our knowledge, $Fe(OTf)_3$ has not been used as a catalyst for the F–C reaction of arenes with benzylic electrophiles.[11]

The scope of the F–C reaction of CF_2H-substituted benzyl phosphates with (hetero)aromatic compounds was investigated, and the obtained results are summarized in Figure 2. The reaction of **1a** with various arenes **2b–f** bearing alkoxy groups afforded the corresponding diarylmethanes **3ab–af** in good yields. Phenol derivative **2g** and indolinone derivative **2h** were also compatible with this protocol; the desired products **3ag** and **3ah** were obtained in 93% and 61% yields, respectively, although prolonged reaction times were required. In striking contrast, the less electron-rich *p*-chloroanisole failed to undergo the F–C reaction with **1a**, and the corresponding benzyl alcohol **4** (*vide infra*) was obtained in 54% yield as the major product. Electron-rich heteroarenes were also examined as coupling partners. 2-Methylfuran (**2i**) and benzofuran (**2j**) smoothly reacted with **1a** to afford the corresponding products **3ai** and **3aj** in high yields. The reaction with 7-methoxycoumarin (**2k**) occurred at the 3-position to afford natural product analog **3ak** in 51% yield.[14] In contrast, the reaction with indole did not proceed, and 88% of **1a** was recovered intact. This result implies that the basic indole behaves as a catalyst poison. Thus, the

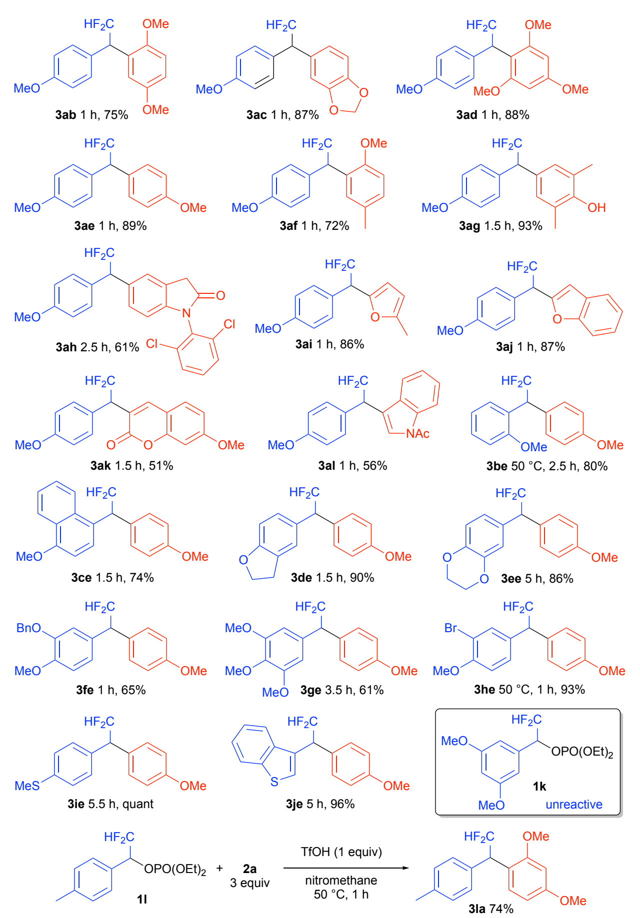


Fig. 2 The scope of Friedel–Crafts reaction of CF_2H-substituted benzyl phosphates with (hetero)aromatic compounds.

desired 3-benzylindole derivative **3al** was obtained in 56% yield when the less basic *N*-acetylindole (**2l**) was employed instead of the parent indole.

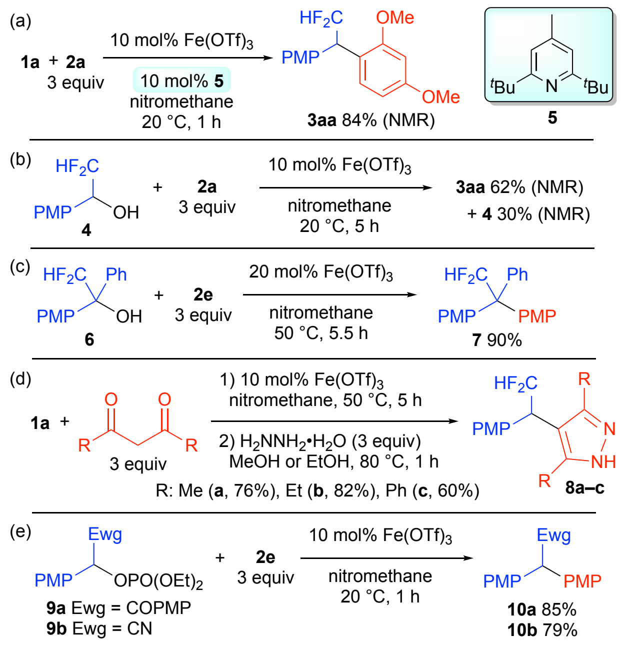
Next, several CF_2H-substituted benzylic phosphates were examined as substrates. *o*-Anisyl derivative **1b** was allowed to react with anisole (**2e**) under the standard conditions. As a result, **1b** was found to be less reactive than **1a**; the reaction was not complete in 5 h, and the expected product **3be** was obtained in a modest yield (58%) along with the recovered **1b** (32%). Complete conversion was achieved at 50 °C over 2.5 h to afford **3be** in 80% yield. The reactions of benzylic phosphates **1c**–**g** with **2e** delivered the corresponding products **3ce**–**ge** in moderate to high yields. The reaction of **1h**, which has the synthetically useful Br–C_{aryl} bond, was performed at 50 °C for 1 h to afford the corresponding product **3he** in 93% yield. Diarylmethanes **3ie** and **3je** were also obtained in high yields from *p*-(methylthio)phenyl- and benzothiophene-3-yl-substituted phosphates **1i** and **1j**, respectively. In contrast, 3,5-dimethoxyphenyl- and *p*-tolyl-substituted phosphates **1k** and **1l** failed to react with **2e** under the standard conditions, suggesting that the electron-donating ability of the aromatic substituents on the phosphate substrates plays a decisive role in their reactivity. These phosphates were subjected to the reaction with **2a** under harsher conditions. In nitromethane, **1l** and **2a** (3 equiv) were treated with TfOH (1 equiv) at 50 °C for 1 h, affording the expected product **3la** in 74% yield. In contrast, **1k** was unreactive under the same conditions. This result could be ascribed to the electron-withdrawing nature of the *meta* MeO groups.[10] Based on density functional theory calculations (Figure S1 and Table S1 in ESI), the stability of difluoromethyl-substituted benzyl cations with an *o*-, *m*-, or *p*-anisyl group decreases in the order ***para*-Int** (ΔG_{rel} = 0.0 kcal/mol) > ***ortho*-Int** (ΔG_{rel} = +5.4 kcal/mol) ≫ ***meta*-Int** (ΔG_{rel} = +13.7 kcal/mol). Thus, ***para*-Int** and ***ortho*-Int**, which have a quinone methide-type structure, are much more stable than ***meta*-Int**, and these computational data are in good agreement with the experimental results.

To gain insights into the present $Fe(OTf)_3$-catalyzed F–C reaction, additional experiments were conducted, as shown in Scheme 2. 2,6-Disubstituted pyridines have been used to discriminate between the Lewis- and Brønsted-acid reactivity: they function as the proton scavengers to selectively inhibit Brønsted acid-mediated reaction.[15] The reaction of phosphate **1a** with 1,3-dimethoxybenzene (**2a**) was performed in the presence of 10 mol% $Fe(OTf)_3$ and 10 mol% 2,6-di(*tert*-butyl)-4-methylpyridine (**5**) in nitromethane at 20 °C for 1 h (Scheme 2a). As a result, **3aa** was obtained in 84% yield along with the remaining phosphate (**1a**, 8%), as confirmed by ^1H NMR analysis of the crude reaction mixture. Consequently, it is suggested that $Fe(OTf)_3$ promotes the F–C reaction of the difluoromethylated benzylic phosphates as a Lewis acid.

Next, benzylic alcohol **4** was subjected to the reaction with **2a** under the standard conditions in order to compare its reactivity with that of phosphate **1a** (Scheme 2b). Almost 30% of **4** remained even after the reaction was carried out for 5 h at 20 °C, and **3aa** was obtained in 62% yield, as suggested by ^1H NMR analysis of the crude reaction mixture. Therefore, this result clearly demonstrates the superiority of the phosphate leaving group in the $Fe(OTf)_3$-catalyzed F–C reaction. Nevertheless, benzhydrol **6** could be used as the substrate for $Fe(OTf)_3$-catalyzed F–C reaction. The reaction of **6** was performed in the presence of 20 mol% $Fe(OTf)_3$ at 50 °C for 5.5 h to afford triarylmethane **7** in 90% yield (Scheme 2c).

Recently, Yamazaki *et al.* reported the base-catalyzed substitution reaction of CF_3-substituted benzylic carbonates with 1,3-dicarbonyl compounds.[16] We also performed the reaction of phosphate **1a** with acetylacetone (3 equiv) in the presence of 10 mol% $Fe(OTf)_3$ at 50 °C for 5 h to afford the expected product **8** as an inseparable mixture with small amounts of alcohol **4** (Scheme 2d). The crude product was treated with hydrazine hydrate in methanol under reflux to afford pyrazole **8a** in 76% yield over two steps. Similarly, 3,5-heptanedione reacted with **1a** and the corresponding pyrazole **8b** was obtained in a higher yield (82%). Because the reaction using dibenzoylmethane afforded the corresponding intermediate as a solid, the subsequent condensation was performed in EtOH at 80 °C to give the desired product **8c**, albeit in a diminished yield (60%). Therefore, the nucleophile is not limited to (hetero)arenes in our $Fe(OTf)_3$-catalyzed reaction of CF_2H-substituted benzyl phosphates.

Finally, the present $Fe(OTf)_3$-catalyzed F–C reaction protocol could be applied to deactivated benzylic phosphates **9a** and **9b**,



Scheme 2 Control experiments and synthesis of triarylmethane **7** and pyrazole **8** (PMP = *p*-methoxyphenyl).

bearing a phenacyl or cyano group, respectively, to afford the expected products **10a** and **10b** in high yields (Scheme 2e).

In conclusion, we have successfully developed the Fe(OTf)$_3$-catalyzed F–C reaction of 2,2-difluoro-1-arylethyl phosphates with electron-rich (hetero)arenes toward the efficient synthesis of difluoromethylated diarylmethanes. The Fe(OTf)$_3$-catalyzed F–C reaction also proceeded in the presence of a proton scavenger, 2,6-di(*tert*-butyl)-4-methylpyridine, suggesting that Fe(OTf)$_3$ functions as a Lewis acid catalyst. The *p*-methoxybenzylic phosphate substrate was found to be superior to the corresponding alcohol. Moreover, Fe(OTf)$_3$ catalyzed the reaction of *p*-methoxybenzyl phosphate with 1,3-diketones, and the obtained products were converted into pyrazole derivatives through the condensation with hydrazine hydrate.

This research is partially supported by the Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS) from AMED under Grant Number JP20am0101099).

Conflicts of interest

There are no conflicts to declare.

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