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Acid-mediated intermolecular C–F/C–H cross-coupling of 2-fluorobenzofurans with arenes: synthesis of 2-arylbenzofurans†

Takeshi Fujita,* Ryutaro Morioka, Takuya Fukuda, Naoto Suzuki and Junji Ichikawa*

Transition-metal-free acid-promoted biaryl construction was achieved *via* intermolecular C–F/C–H cross-coupling. By treating 2-fluorobenzofurans with arenes in the presence of $AlCl_3$, 2-arylbenzofurans were obtained. This protocol was successfully applied to the short-step orthogonal synthesis of a bioactive 2-arylbenzofuran natural product, which allows independent transformations of C–F and C–Br bonds. Mechanistic studies indicated that α-fluorine-stabilized carbocations, generated *via* the protonation of 2-fluorobenzofurans, served as key intermediates. The Friedel–Crafts-type C–C bond formation between the α-fluorocarbocations and arenes, followed by hydrogen fluoride elimination, afforded 2-arylbenzofurans.

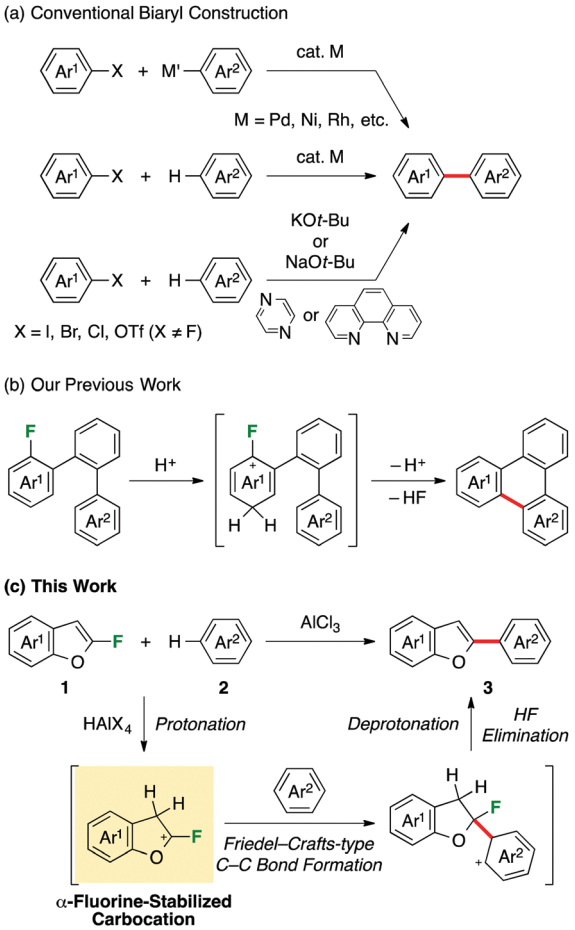
For a long time, biaryl construction through intermolecular cross-coupling *via* $C(sp^2)$–$C(sp^2)$ bond formation has been one of the most important studies in synthetic organic chemistry. For the past half-century, a wide variety of transition-metal-catalyzed cross-coupling reactions typically between aryl halides (Ar^1X) and arylmetal species (Ar^2M') have been developed to provide tremendous support for pharmaceutical and material sciences (Scheme 1a, top).[1] Among the transition-metal-catalyzed cross-coupling reactions, the intermolecular direct arylation of aryl halides (Ar^1X) with arenes (Ar^2H) *via* C–H bond cleavage has been exponentially studied (Scheme 1a, middle).[2] This protocol allows an improved atom-economical alternative for biaryl construction because Ar^2H instead of Ar^2M' can be used. More recently, the transition-metal-free cross-coupling of Ar^1X with Ar^2H in an intermolecular fashion has also been reported (Scheme 1a, bottom).[3] In these reactions, nitrogen-containing substrates or additives were often combined with metal *tert*-butoxide to generate aryl radical species from Ar^1X, which undergo C–C bond formation with Ar^2H. Although this approach is an improved alternative to the aforementioned methods for intermolecular cross-coupling, the aryl (pseudo)halide substrates have been limited to aryl iodides, bromides, chlorides, or sulfonates. Aryl fluorides have never been applicable to this type of reaction, presumably because aryl radical species are difficult to generate *via* the homolytic cleavage of C–F bonds, which exhibit higher dissociation energy.

In contrast, we have already developed a strategy for acid-mediated intramolecular cross-coupling *via* aromatic C–F bond activation involving $C(sp^2)$–$C(sp^2)$ bond formation (Scheme 1b).[4] In our strategy, the initial protonation of Ar^1F generated intermediary arenium ions, which were stabilized by the fluorine substituent.[5] The arenium ions reacted with nucleophilic Ar^2H units *via* the intramolecular Friedel–Crafts-type C–C bond formation. Subsequent hydrogen fluoride elimination afforded a benzene-fused aromatic system. As the next challenge of our formal cross-coupling reactions, we explored acid-mediated C–F/C–H coupling of aryl fluorides with arenes in an intermolecular fashion, which is considered more difficult entropically. In this study, we chose 2-fluorobenzofurans **1**[6] as substrates because intermediary arenium ions would be readily generated through double stabilization by the fluorine and oxygen substituents. We discovered that $AlCl_3$ was effective in promoting the intermolecular coupling of **1** with Ar^2H **2**, resulting in the synthesis of 2-arylbenzofurans **3** (Scheme 1c). Although defluorinative $C(sp^2)$–$C(sp^2)$ coupling by silylium ions[7] or γ-Al_2O_3[8] have recently been reported, these are limited to intramolecular reactions or require silyl groups on the fluorine-containing substrates because they proceed *via* extremely unstable aryl cation(-like) species.

First, we investigated this intermolecular C–F/C–H coupling reaction using 2-fluorobenzofuran (**1a**) and 5 equiv. of *p*-xylene (**2a**) as model compounds (Table 1). Although no coupling product was obtained in the presence of acetic acid or *p*-toluenesulfonic acid (Table 1, entries 1 and 2), the use of trifluoromethanesulfonic acid in CH_2Cl_2 at −20 °C afforded the expected defluorinated coupling product, 2-xylylbenzofuran (**3aa**), in an 8% yield (Table 1, entry 3). Among the Lewis acids screened (Table 1, entries 4–6), $AlCl_3$ was found to be the best, affording **3aa** in a 63% isolated

Division of Chemistry, Faculty of Pure and Applied Sciences, University of Tsukuba, Tsukuba, Ibaraki 305-8571, Japan. E-mail: fujita@chem.tsukuba.ac.jp, junji@chem.tsukuba.ac.jp

† Electronic supplementary information (ESI) available: Experimental procedures and characterisation data of new compounds. CCDC 2075144. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc03453g

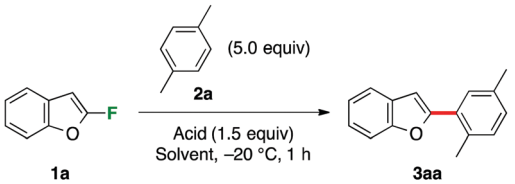


Scheme 1 Cross-coupling *via* C(sp^2)–C(sp^2) bond formation.

yield (Table 1, entry 6). The cross-coupling was sluggish in the presence of molecular sieves, to afford **3aa** in a 34% yield (Table 1, entry 7).[9] To improve the yield of **3aa**, we screened the solvents. Out of the several solvents that were examined (Table 1, entries 6 and 8–11), CH_2Cl_2 was found to be an exceptionally effective solvent. Oxygen- or nitrogen-containing solvents probably coordinate to $AlCl_3$ to retard the reaction. When the reaction was conducted with 20 equiv. of **2a** without any solvent, **3aa** was obtained in a 91% isolated yield (Table 1, entry 12). Based on these results, we concluded that two types of conditions are suitable: one can suppress the amount of Ar^2H used (Table 1, entry 6; Method A) and the other does not use any solvent (Table 1, entry 12; Method B).

The coupling reactions of a variety of substituted **1** with several arenes **2** were investigated using Method A and/or Method B mentioned above (Table 2).[10,11] Relatively electron-rich Ar^2H, such as **2a**, *m*-xylene (**2b**), thiophene (**2c**), phenol (**2d**), 1,3-dimethoxybenzene (**2e**), and 1,4-dimethoxybenzene (**2f**), were successfully coupled with unsubstituted and substituted **1**. Notably, C–C bond formation, rather than C–O bond formation, occurred exclusively in the case of the reaction with **2d** to produce **3ad**, despite substantial nucleophilicity of the hydroxyl group. To afford **3ba–3bc**, **3bf**, **3ca**, and **3da**, 2-fluorobenzofurans **1b–1d** bearing an alkyl or an aryl group at the 3-position underwent defluorinative coupling. Using

Table 1 Screening of the conditions for C–F/C–H cross-coupling of **1a** with **2a**



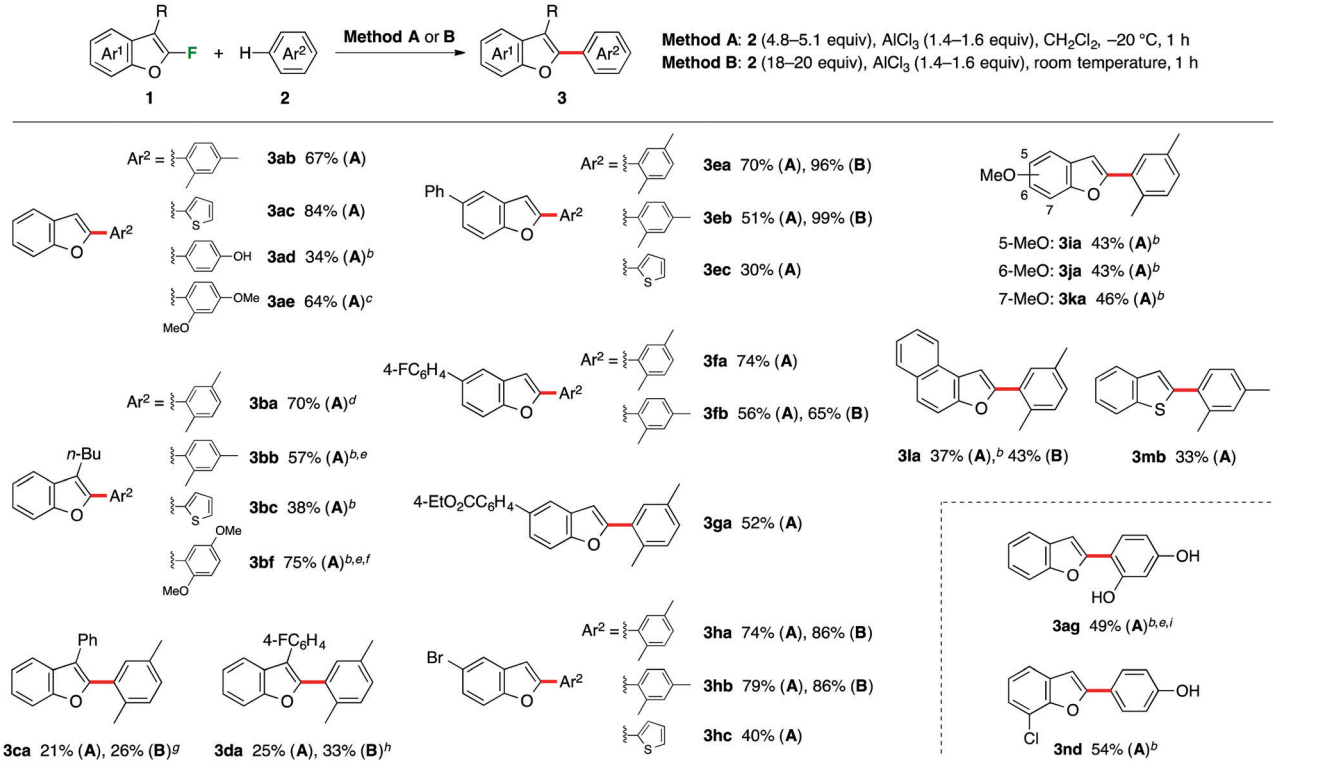
Entry	Acid	Solvent	**3aa**[a] (%)
1	AcOH	CH_2Cl_2	N.D.[b]
2	TsOH	CH_2Cl_2	N.D.[b]
3	TfOH	CH_2Cl_2	8
4	$FeCl_3$	CH_2Cl_2	N.D.[b]
5	$BF_3{\cdot}OEt_2$	CH_2Cl_2	N.D.[b]
6	$AlCl_3$	CH_2Cl_2	68 (63)[c]
7[d]	$AlCl_3$	CH_2Cl_2	34
8	$AlCl_3$	THF	N.D.[b]
9	$AlCl_3$	MeCN	N.D.[b]
10	$AlCl_3$	$MeNO_2$	N.D.[b]
11[e]	$AlCl_3$	$(CF_3)_2CHOH$	Trace
12[f]	$AlCl_3$	None	96 (91)[c]

[a] Yield was determined by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard. [b] N.D. = not detected. [c] Isolated yield. [d] Molecular sieves 4 A (250 wt%) was added. [e] 0 °C. [f] Reaction was conducted at room temperature using **2a** (20 equiv.).

Method B, the yields of 2-arylated 5-phenylbenzofurans **3ea** and **3eb** were drastically improved up to 96% and 99% yields, respectively. The coupling of 2-fluorobenzofurans **1i–1k** bearing a methoxy group at the 5-, 6-, or 7-position proceeded regardless of the position of the substituent. Not only 2-fluorobenzofurans but also 2-fluoronaphtho-[2,1-*b*]furan (**1l**) and 2-fluorobenzothiophene (**1m**) participated in the reaction to afford the corresponding 2-arylated naphthofuran **3la** in a 43% yield (Method B) and benzothiophene **3mb** in a 33% yield (Method A), respectively. The one-step synthesis of 2-(2,4-dihydroxyphenyl)benzofuran (**3ag**, DHBF),[12] which possesses a bacterial biofilm formation inhibitory activity, was achieved through the $AlCl_3$-mediated coupling of **1a** with resorcinol (**2g**) in a CH_2Cl_2–$(CF_3)_2CHOH$ (10/1) mixed solvent system at room temperature. In addition, the coupling of 7-chloro-2-fluorobenzofuran (**1n**) with **2d** proceeded at room temperature to afford the corresponding benzofuran **3nd** in a 54% yield, which served as a cholinesterase inhibitor (ChEI).[13] It is noteworthy that bromine- and chlorine-bearing fluorobenzofurans **1h** and **1n** exclusively underwent defluorinative coupling without C–Br and C–Cl bond cleavage (**3ha–3hc** and **3nd**). Furthermore, even electron-withdrawing groups (CO_2Et **3ga**, Br, and Cl) on 2-fluorobenzofurans are not only tolerated in the reaction but also do not reduce the efficiency.

This protocol was successfully applied to the short-step synthesis of bioactive eupomatenoid 6 (**4**), which is a member of a family of naturally occurring 2-aryl-3-methyl-5-[(*E*)-prop-1-en-1-yl]benzofurans with antifungal, insecticidal, and antioxidant properties.[14] The strategy is based on the orthogonal coupling reaction using fluorine and bromine substituents on the benzofuran nucleus. In the presence of $AlCl_3$, the treatment of readily available 5-bromo-2-fluoro-3-methylbenzofuran (**1o**) with **2d** in 1,2-dichloroethane (DCE) at 80 °C afforded the corresponding coupling product **3od** in a 71% yield *via* the

Table 2 Synthesis of 2-arylbenzofurans **3**[a]

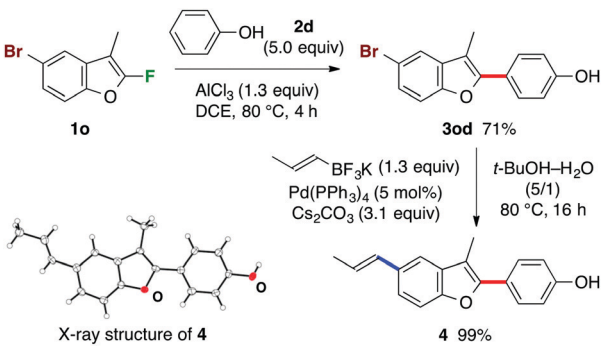


[a] Isolated yield. [b] Room temperature. [c] 40 °C, 24 h. [d] 3 h. [e] 2 h. [f] **2f** (2.0 equiv.). [g] $AlCl_3$ (2.0 equiv.), **2a** (26 equiv.). [h] **2a** (23 equiv.). [i] CH_2Cl_2–$(CF_3)_2CHOH$ (10/1).

exclusive C–F bond cleavage and C–C bond formation (Scheme 2). Subsequent Suzuki–Miyaura coupling of **3od** with potassium (*E*)-(prop-1-en-1-yl)trifluoroborate afforded **4** quantitatively. The unambiguous structural determination of **4** was achieved by X-ray crystallographic analysis (Scheme 2).

To gain mechanistic insight, we conducted control experiments using a deuterated substrate. In the presence of $AlCl_3$, the treatment of **1a** with fully deuterated **2a** (**2a-*d*$_{10}$**) afforded benzofuran ring-deuterated **3aa** (**3aa-*d***), which exhibited significant deuterium incorporation at the 3-position (56% D) and a low level of deuterium incorporation at the 4- and 6-positions (Scheme 3a). The source of the deuterium incorporated on the benzofuran ring should be the deuteron (D^+) generated not only *via* the elimination of the deuteron during the C–C bond formation but also *via* the H–D exchange of **2a-*d*$_{10}$** by residual protons. Thus, when nondeuterated product **3aa** was subjected to the same conditions, only a relatively small amount of deuterium incorporation was observed at the 3-position (25% D, Scheme 3b). The results of these experiments strongly suggest that substrates **1** are susceptible to protonation at the 3-position, which results in the generation of fluorine-stabilized carbocation intermediates[4,5] during the coupling process (Scheme 1c).

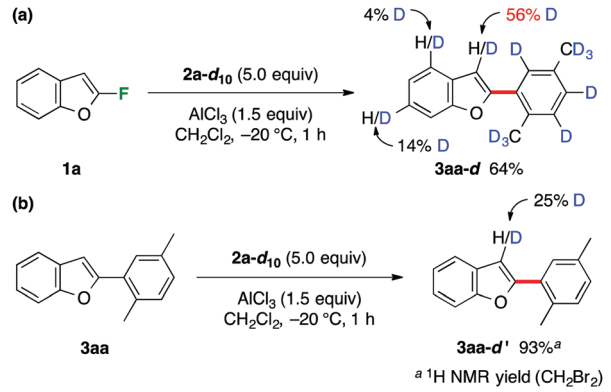
Furthermore, the effect of halogens on the 2-positions in benzofurans was investigated by reacting 2-halogenated benzofurans (**1a-Cl**: X = Cl; **1a-Br**: X = Br; **1a-I**: X = I) with **2a** in the



Scheme 2 Orthogonal synthesis of eupomatenoid 6 (**4**).

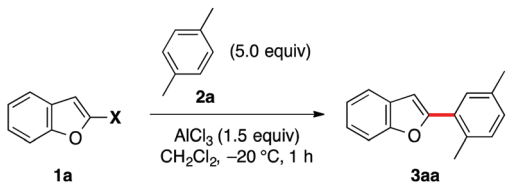
presence of $AlCl_3$ (Table 3). Compared to the fluorine substituent (**1a**: X = F, Table 3, entry 1), chlorine (**1a-Cl**), bromine (**1a-Br**), and iodine (**1a-I**) substituents hardly promoted the reaction (Table 3, entries 2–4). These results, along with those of the aforementioned control experiments (Scheme 3), clearly indicate that the fluorine substituent plays a crucial role in the stabilization of the intermediary carbocations,[4,5] resulting in an acceleration of the cation generation, that is, the rate-determining step in the Friedel–Crafts-type coupling reaction (Scheme 1c).

In summary, we developed an intermolecular cross-coupling reaction of 2-fluorobenzofurans with arenes *via* acid-mediated C–F bond activation. In this reaction, α-fluorocarbocations,



Scheme 3 Control experiments using deuterated **2a**.

Table 3 Effect of halogens on the 2-positions in benzofurans



Entry	1a	X	3aa[a] (%)
1	**1a**	F	68
2	**1a-Cl**	Cl	10
3	**1a-Br**	Br	3
4	**1a-I**	I	N.D.[b]

[a] Yield was determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. [b] N.D. = not detected.

which are generated from the treatment of 2-fluorobenzofurans with an acid, served as key intermediates. This renders our method significantly different from other methods for C–F bond arylation using transition metals.[15] This protocol allows coupling under mild conditions and enables the direct and efficient synthesis of 2-arylbenzofurans, which includes bioactive agents and a natural product. Furthermore, because of the difficulty in the cleavage (stability) of the C–F bonds, we expect this method to be useful for the orthogonal synthesis of complex molecules *via* late-stage C–F bond activation.

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Conflicts of interest

There are no conflicts to declare.

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10 Even when the yields of **3** were low, 2-fluorobenzofurans **1** were completely consumed, and the dimers and/or trimers of **1** were obtained by their self-coupling.
11 When the reactions were initiated at room temperature in Method A with smaller amounts of arenes **2**, the formation of the dimers and/or trimers of 2-fluorobenzofurans **1** increased. Thus, Method A was applied mainly at −20 °C.
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