Fluorenes as new molecular scaffolds for carbon–carbon σ-bond cleavage reaction: acylfluorenylation of arynes†

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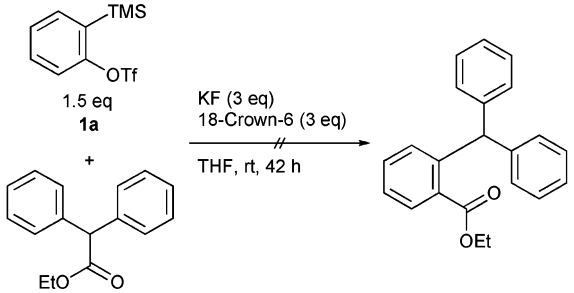
Acyl and fluorenyl moieties are facilely installed into neighbouring positions of aromatic skeletons *via* C–C bond cleavage reaction using arynes.

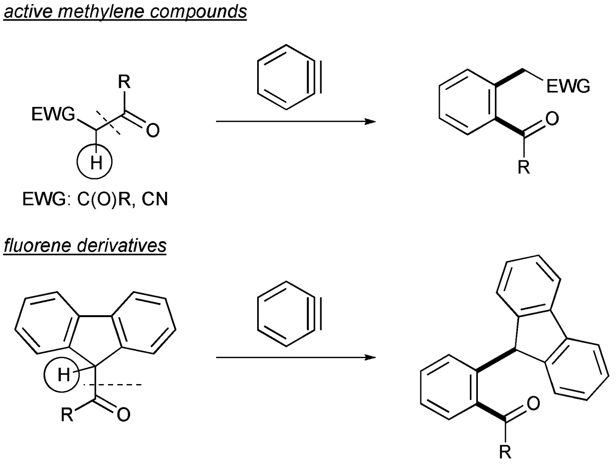
Direct installation of two carbon units (C^1 and C^2) into carbon–carbon unsaturated compounds *via* C^1–C^2 bond cleavage has gained much attention, because it provides new organic transformations for constructing complex carbon frameworks in a straightforward manner.[1,2] In this context, Stoltz's[3] and our groups[4,5] have already disclosed insertion reactions of arynes into a C–C bond of β-dicarbonyl or α-cyanocarbonyl compounds, which offer facile approach to highly functionalized arenes, being hardly available by conventional methods, however, applicability of the reaction is totally restricted to active methylene compounds bearing two electron-withdrawing groups (EWG), to the best of our knowledge.[6] The key for the reaction to proceed would be smooth formation of a carboanionic species ($(EWG)_2C^-$) *via* rapid deprotonation induced by two EWGs,[3,4] and thus we envisaged that the use of another molecular scaffold having a C–H moiety of suitable acidity would result in a new C–C bond cleavage reaction. We report herein on acylfluorenylation of arynes using fluorene derivatives, where formation of a key carboanionic species is facilitated by its aromatic stabilization, allowing two carbon–carbon bond-forming processes (aryl–acyl and aryl–fluorenyl bonds) to occur at neighbouring positions of an aromatic skeleton all at once (Scheme 1).[7,8]

We initially conducted the reaction of benzyne (generated *in situ* from **1a**[9] and KF–18-Crown-6) with 9-fluorenyl isopropyl ketone (**2a**) in THF at room temperature and found that the methine–carbonyl bond added across benzyne to give a 97% yield of acylfluorenylation product **3aa** (Table 1, entry 1). Aryl fluorenyl ketones (**2b** or **2c**) could also participate in the reaction to give the products (**3ab** or **3ac**) in 90 or 74% yield (entries 2 and 3), and the reaction using cyclopropyl (**2d**) or cyclobutyl (**2e**) ketone furnished **3ad** or **3ae**, whose strained cyclic structure remained intact (entries 4 and 5). Although the yields were somewhat lower than those described above, the C–C bond of heteroaryl (**2f**) or sterically-congested (**2g** or **2h**) ketones underwent the insertion of benzyne (entries 6–8). Furthermore, the reaction was applicable to esters of fluorenecarboxylic acid (**2i** or **2j**), providing high yields of **3ai** or **3aj** (entries 9 and 10). A fluorenyl moiety plays a vital role in enabling the present C–C cleavage reaction to proceed, and thus, no trace of the desired product was formed in the reaction using ethyl diphenylacetate despite its structural resemblance to **2i** (eqn (1)).



(1)

The scope of the reaction was further examined by using substituted arynes (Scheme 2). Such symmetrical arynes as 2,3-naphthalyne (from **1b**) or 4,5-dialkylated arynes (from **1c–1e**) smoothly reacted with **2a** to give the respective insertion products (**3ba–3ea**) in good yields. Perfect regioselectivities were observed in the reaction of 1,2-naphthalyne (from **1f**) or 3-methoxybenzyne (from **1g**), where the fluorenyl moiety was attached to the less congested site exclusively. In

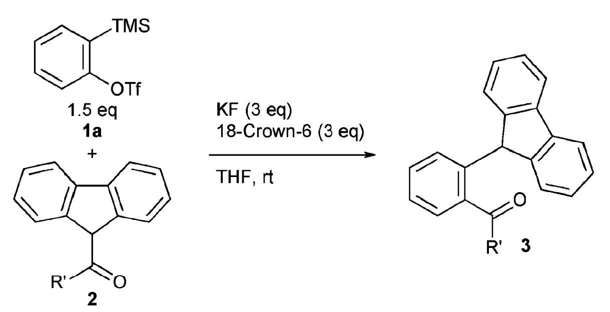


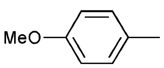
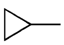
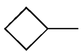
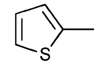
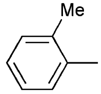
Scheme 1 Insertion reaction of arynes into C–C σ-bond.

Department of Applied Chemistry, Graduate School of Engineering, Hiroshima University, Higashi-Hiroshima 739-8527, Japan. E-mail: yhiroto@hiroshima-u.ac.jp; Fax: +81-82-424-5494; Tel: +81-82-424-7724

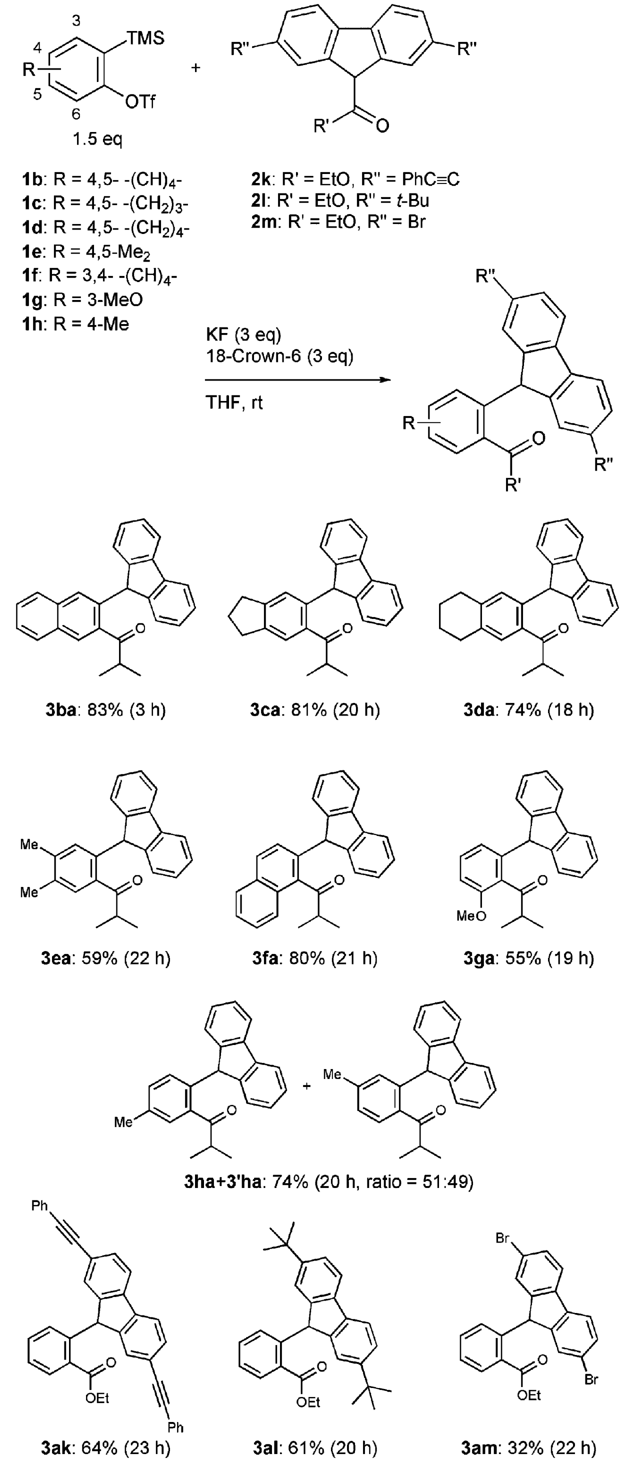
† Electronic supplementary information (ESI) available: Experimental procedure including spectroscopic and analytical data. See DOI: 10.1039/b814597k

Table 1 Acylfluorenylation of benzyne[a]



Entry	R′	**2**	*t*/h	Yield (%)[b]	**3**
1	*i*-Pr	**2a**	18	97	**3aa**
2	Ph	**2b**	26	90	**3ab**
3		**2c**	10	74	**3ac**
4		**2d**	15	71	**3ad**
5		**2e**	13	69	**3ae**
6		**2f**	20	58	**3af**
7		**2g**	17	63	**3ag**
8	*t*-Bu	**2h**	48	52	**3ah**
9	EtO	**2i**	12	93	**3ai**
10	*i*-PrO	**2j**	15	88	**3aj**

[a] The reaction was carried out in THF (10 mL) at rt using **1a** (0.30 mmol), **2** (0.20 mmol), KF (0.60 mmol) and 18-crown-6 (0.60 mmol). [b] Isolated yield based on **2**.



3ba: 83% (3 h) **3ca**: 81% (20 h) **3da**: 74% (18 h)

3ea: 59% (22 h) **3fa**: 80% (21 h) **3ga**: 55% (19 h)

3ha+3′ha: 74% (20 h, ratio = 51:49)

3ak: 64% (23 h) **3al**: 61% (20 h) **3am**: 32% (22 h)

Scheme 2 Acylfluorenylation of arynes.

marked contrast, the reaction of 4-methylbenzyne (from **1h**) produced a mixture of two regioisomers in *ca.* 50 : 50 ratio. In addition, ethyl fluorene-9-carboxylate having phenylethynyl (**2k**)[10] or *tert*-butyl **2l**) substituent on its 2,7 positions also underwent the reaction facilely, whereas the use of 2,7-dibromofluorene **2m** resulted in a lower yield of the product.

Formation of fluorenyl anion **4** *via* deprotonation of **2** by a fluoride ion would trigger the acylfluorenylation as depicted in Scheme 3. Subsequent nucleophilic attack of **4** to an aryne that generates aryl anion **5**, followed by intramolecular nucleophilic substitution at a carbonyl moiety, gives acylfluorenylation product **3**. Owing to the aromatic stabilization of **4**, deprotonation of **2** takes place with greater facility than that of ethyl diphenylacetate, which would be responsible for the smooth reaction with **2**. The exclusive formation of **3fa** or **3ga** is ascribable to steric effects,[11] which prevent **4** from approaching the more congested site of 1,2-naphthalyne or 3-methoxybenzyne.[12]

In conclusion, we have demonstrated that a fluorene is an excellent molecular scaffold for C–C bond cleavage–dual C–C bond formation sequence, where the facile generation of a fluorenyl anion, being attributable to its aromatic stabilization, is the key to smooth progress. Based upon the present reaction, diverse multi-substituted arenes, which would otherwise be difficult to obtain, can be synthesized readily under extremely mild conditions. Further studies on constructing complex carbon frameworks of aromatic compounds *via* insertion reactions of arynes into a C–C bond are in progress in our laboratories.

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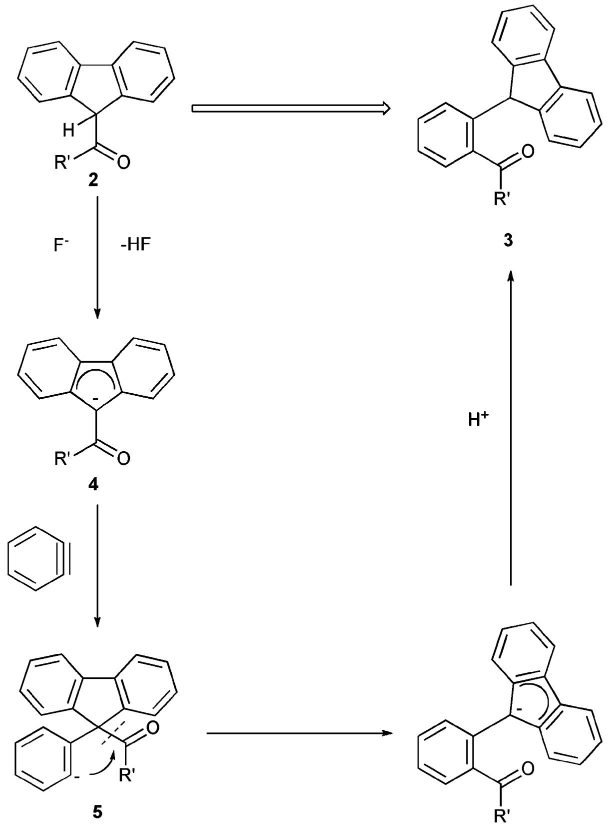

Scheme 3 Plausible pathway for acylfluorenylation.

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10 A 15% yield of ethyl 2,7-bis(phenylethynyl)-9-phenylfluorene-9-carboxylate was also produced as a by-product *via* a formal C–H bond cleavage reaction.

11 Inductive electron-withdrawing effect of a methoxy group in 3-methoxybenzyne also prefers nucleophilic attack at a *meta* position of the methoxy group.

12 Similar regioselectivities have been observed in the reaction of active methylene compounds. See ref. 4.