# LDA-Mediated Synthesis of Triarylmethanes by Arylation of Diarylmethanes with Fluoroarenes at Room Temperature

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S *Supporting Information*

ABSTRACT: A practical and convenient approach for the secondary C(sp^3)−H arylation of diarylmethanes with various fluoroarenes is described. The reaction proceeds smoothly in the presence of LDA (lithium diisopropylamide) at room temperature and affords triarylmethanes in moderate to high yields.
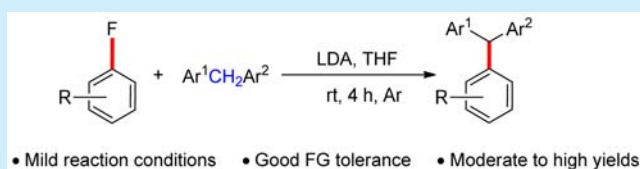
riarylmethanes (TAMs) are often found as structural frameworks in pharmaceuticals and polymers, especially in leuco dyes due to their special photochemical and photophysical properties.[1] Because of their importance in organic synthesis, considerable attention has been devoted to the development of efficient methods for the synthesis of triarylmethane derivatives.[2] The traditional method for the synthesis of triarylmethane derivatives is Friedel−Crafts arylation of diarylmethanols in the presence of different Lewis acids.[3] In recent years, a number of novel approaches toward triarylmethanes have been reported (Scheme 1, a−e).[4]

Scheme 1. Recent Methods for the Synthesis of Triarylmethanes
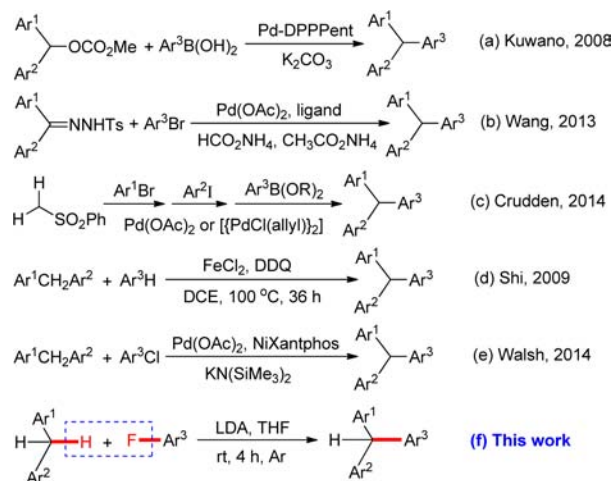
Although these reported methodologies are facile and straightforward, the limitations of these approaches include the use of an expensive ligand, an expensive palladium salt, the limited diversity of the starting materials, and harsh reaction conditions with regard to temperature and acidity.[5] Hence, the development of environmentally benign and

practical methods for the synthesis of triarylmethanes is an important goal of organic synthesis.

The cleavage and functionalization of carbon−fluorine bonds have attracted considerable attention from many chemists because of their important application in practical organic synthesis.[6] The replacement of fluorine atom on the electron-deficient fluoroaromatics via nucleophilic aromatic substitution (S$_N$Ar) with nucleophiles is a traditional method for the functionalization of aryl fluorides.[7] However, aryl fluorides with an electron-donating group would deactivate the S$_N$Ar reaction, and rather higher reaction temperature and prolonged reaction time are required to ensure a smooth reaction.[8]

The transition-metal-catalyzed cross-coupling of fluoroarenes with organometallics such as Grignard, organozinc reagents, and organoboron compounds,[9] which involve the activation of the C−F bond, has become a powerful tool for the functionalization of fluoroarenes. However, the methodology suffers from the use of toxic nickel catalyst, expensive palladium catalyst, and complicated ligands.[10]

Defluorination of fluoroarenes via arynes in the presence of strong base, although known as a simple alternative for the cleavage of carbon−fluorine bonds, has not attracted enough attention in fluorine and organic chemistry.[11] To date, only a few limited reports have been found in the literature.[12] The obvious drawback of this method is the use of very low reaction temperatures, typically −78 °C, thus limiting the scope and generality of the protocol.[13] In continuation of our interest in the cleavage and functionalization of carbon−fluorine bonds,[14] we herein report an efficient and mild method for the synthesis of triarylmethanes by arylation of diarylmethanes with fluoroarenes in the presence of LDA (lithium diisopropylamide) at room temperature (Scheme 1, f).

Initially, diphenylmethane **1a** and fluorobenzene **2a** were used as model reactants for the optimization of the arylation reaction conditions, and the results are shown in Table 1.

Table 1. Optimization of the Reaction Conditions[a,b]

entry	2a (equiv)	base (equiv)	solvent	yield[b] (%)
1	1.1	KHMDS (3.0)	THF	0
2	1.1	LiHMDS (3.0)	THF	0
3	1.1	NaHMDS (3.0)	THF	0
4	1.1	t-BuOK (3.0)	THF	0
5	1.1	Cs$_2$CO$_3$ (3.0)	THF	0
6	1.1	t-BuOLi (3.0)	THF	0
7	1.1	t-BuLi (3.0)	THF	0
8	1.1	LDA (3.0)	THF	64
9	1.5	LDA (3.0)	THF	93
10	2.0	LDA (3.0)	THF	89
11	1.5	LDA (2.5)	THF	86
12	1.5	LDA (2.0)	THF	61
13	1.5	LDA (1.5)	THF	35
14	1.5	LDA (3.0)	Et$_2$O	47
15	1.5	LDA (3.0)	hexane	36
16	1.5	LDA (3.0)	DMSO	0
17	1.5	LDA (3.0)	NMP	0
18	1.5	LDA (3.0)	DMF	0

[a]Reagents and conditions: **1a** (1.0 mmol), solvent (5 mL), 4 h. [b]Yields were determined by GC analysis and based on **1a**.

Among several bases tested, LDA turned out to be the only suitable base for the reaction, while other bases were totally ineffective and no product could be detected (entries 1−8). When the amount of fluorobenzene **2a** was increased to 1.5 equiv, diphenylmethane **1a** was successfully converted to the corresponding arylated product **3aa** in excellent yield (entry 9). Further increasing the amount of **2a** resulted in lower yield (entry 10). Moreover, the amount of LDA added has an important influence on the reaction yield. When the amount of LDA was reduced from 3.0 to 1.5 equiv of **1a**, the yield decreased sharply and only 35% of **3aa** was obtained (entries 11−13). Further screening of different solvents disclosed that THF proved to be effective for the reaction and provided the best results, while no reaction occurred in aprotic polar solvents such as DMSO, NMP, and DMF (entries 9 and 14−18).

To explore the substrate scope, we examined the reaction of a range of substituted fluorobenzenes with **1a** under the optimized reaction conditions (Table 1, entry 9). As shown in Scheme 2, in most cases, fluoroarenes **2a−l** proceeded smoothly and afforded the arylation products **3aa−al** in moderate to good yields. The fluoroarenes bearing electron-withdrawing groups or an electron-neutral group (**2a**) gave higher yields than those containing electron-donating groups on the aromatic rings (**2j** versus **2g**). Notably, fluoroarenes containing electron-donating groups provided a mixture of regioisomers (**3ab,ac,ad,ag**; the structures of the *ortho-*, *meta-*, and *para*-isomers were determined by their ¹H NMR spectra and the literature). These results implied that the reaction of

Scheme 2. Reactions of 1a with Various Substituted Fluorobenzenes 2a−l[a,b]
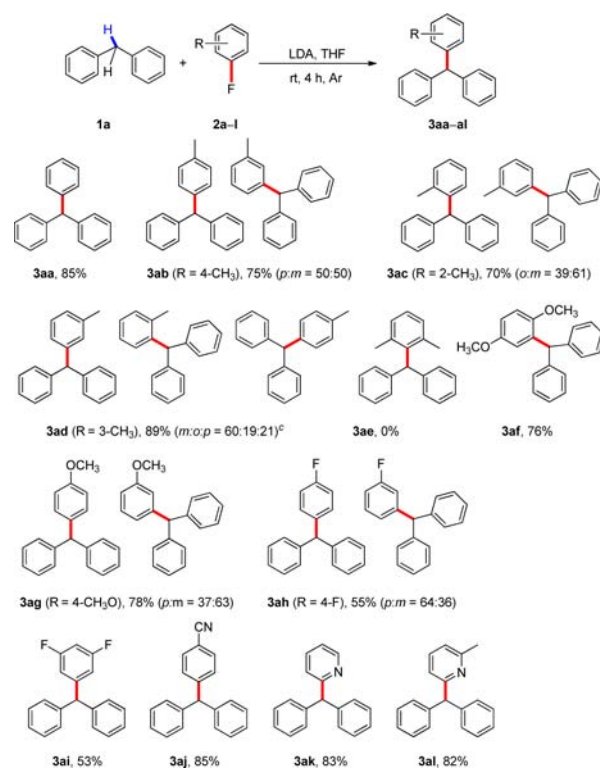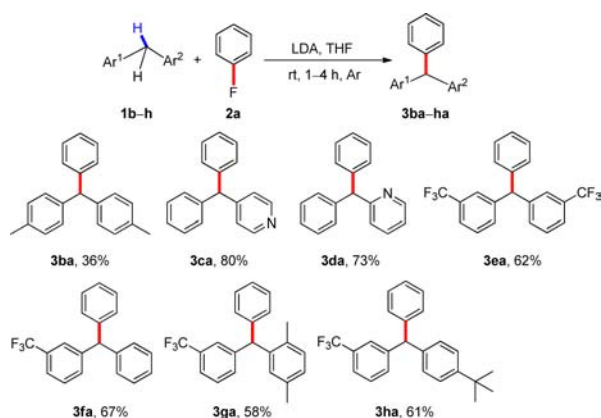

[a]Reaction conditions: **1a** (1.0 mmol), **2a−e,g−j** (1.5 mmol), **2f** (3.0 mmol), **2k** (1.2 mmol), LDA (3.0 mmol), THF (5 mL), rt, 1−4 h, Ar. [b]Isolated yield. [c]GC−MS yield.

electron-rich fluoroarenes might proceed via aryne intermediates. To further confirm this hypothesis, two additional experiments were performed. When the highly electron-rich aryl fluoride such as 2-fluoro-1,4-dimethoxybenzene was used as substrate, the reaction also proceeded smoothly and no regioisomer was observed (**3af**). However, when 2-fluoro-1,3-dimethylbenzene was used as substrate, no desired product was formed (**3ae**). These experiments clearly indicated that the arynes were generated in situ from the electron-rich fluoroarenes with LDA in the first step of the reaction.

The fluoroarene possessing mildly electron-withdrawing group gave the desired products in lower yield than those with electron-donating substituents, and a mixture of *para*- and *meta*-isomers was obtained (**3ah**). However, when fluoroarene having two mildly electron-withdrawing groups was subjected to the optimized reaction conditions, only a moderate yield of product was obtained (**3ai**) and no regioisomer was detected. Much to our delight, fluoroarenes bearing a strong electron-withdrawing group (**2j**) and fluoropyridine (**2k** and **2l**) afforded the arylated products in high yields without the formation of other isomers (**3aj**, **3ak**, and **3al**). On the basis of these experimental results, we assumed that the reaction of diphenylmethane **1a** with electron-poor aryl fluorides might proceed via a classical S$_N$Ar pathway.

Subsequently, the reactions of fluorobenzene **2a** with various diarylmethanes were investigated (Scheme 3). Despite the inertness of C−F bond of fluorobenzene, most of the reactions proceeded smoothly at room temperature. Generally,

Scheme 3. Reactions of 2a with Various Diarylmethanes 1b–h[a,b]

[a]Reaction conditions: **1b–h** (1.0 mmol), **2a** (1.5 mmol), LDA (3.0 mmol), THF (5 mL), rt, 1–4 h, Ar. [b]Isolated yield.

the electron-poor diarylmethanes gave good yields whereas the electron-rich diarylmethanes provided lower yield (**3ba**).

To evaluate the scope of the reaction further, several diarylmethanes, 9H-fluorene **1i** and 9H-xanthene **1j** were reacted with different fluoroarenes (Schemes 4–6). Generally,

**Scheme 4. Reactions of Diarylmethanes with Substituted Fluorobenzenes[a,b]**
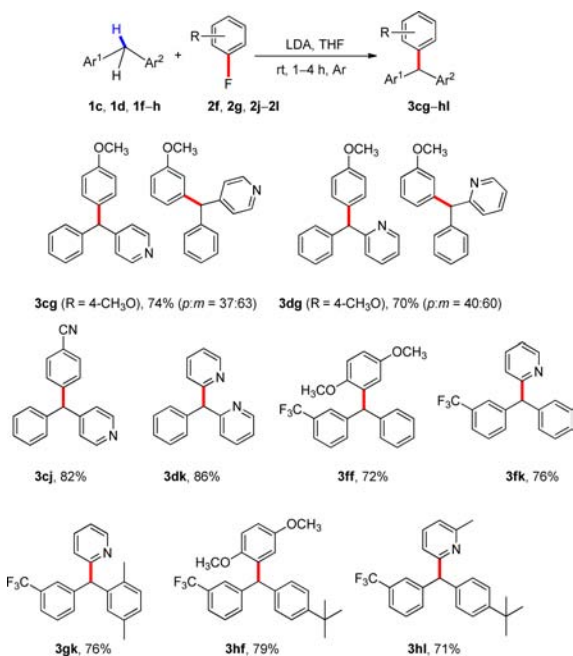
[a]Reaction conditions: **1c,d,f–h** (1.0 mmol); **2g,j–l** (1.5 mmol), **2f** (3.0 mmol), LDA (3.0 mmol), THF (5 mL), rt, 1–4 h, Ar. [b]Isolated yield.

the reaction proceeded smoothly at room temperature to yield arylated products, and the observed trend was the same as that seen for above-mentioned fluoroarenes and diaryl-methanes: electron-rich fluoroarenes tended to afford two regioisomers (**3cg,dg,ib,ig,jb**), whereas electron-poor fluoroar-enes afforded only one isomer (**3cj,dk,fk,gk,hl,ij,ik,im,jm**).

In summary, we have developed a facile and transition-metal-free synthesis of triarylmethanes by the secondary

Scheme 5. Reactions of 9H-Fluorene 1i with Substituted Fluorobenzenes[a,b]
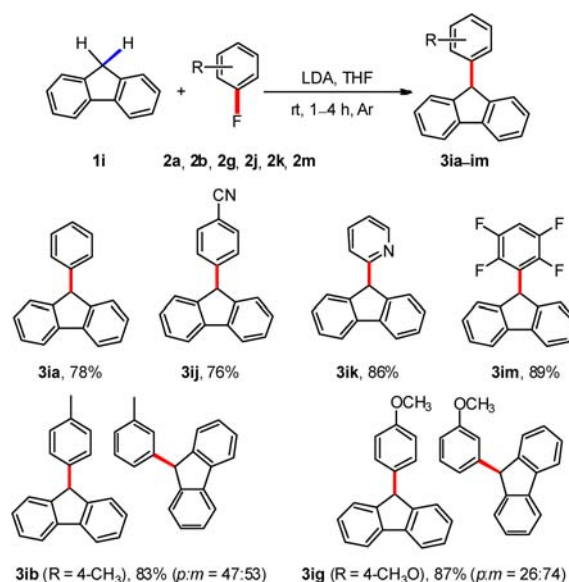
[a]Reaction conditions: **1i** (1.0 mmol), **2a, 2b, 2g, 2j, 2k, 2m** (1.5 mmol), LDA (3.0 mmol), THF (5 mL), rt, 1–4 h, Ar. [b]Isolated yield.

Scheme 6. Reactions of 9H-Xanthene 1j with Substituted Fluorobenzenes[a,b]
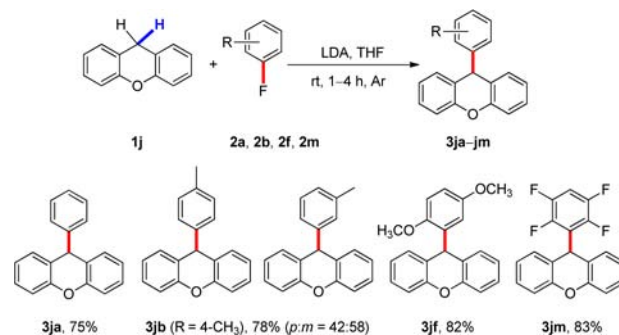
[a]Reaction conditions: **1j** (1.0 mmol), **2a,b,m** (1.5 mmol), and **2f** (3.0 mmol), LDA (3.0 mmol), THF (5 mL), rt, 1–4 h, Ar. [b]Isolated yield.

C(sp[3])−H arylation of diarylmethanes, 9H-fluorene, and 9H-xanthene with various readily available fluoroarenes. This direct arylation was promoted only by LDA. More importantly, with this protocol, both unreactive C−F bonds such as the C−F bond in **2f** and **2g** and reactive C−F bonds such as the C−F bond in **2j** could be readily cleaved in the presence of LDA at room temperature within short reaction times. The arylation of diphenylmethanes with electron-rich aryl fluorides proceeded via aryne intermediates, whereas electron-poor fluoroarenes proceed via a classical S$_N$Ar pathway. Furthermore, the arylation process exhibited good substrate scope and functional group tolerance, and a variety of triarylmethane derivatives were obtained in moderate to high yields. Further efforts to extend the applications of this method are underway in our laboratory.

ASSOCIATED CONTENT

ⓈSupporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02602.

> Experimental details and spectroscopic data for compounds **3** (PDF)

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Notes
The authors declare no competing financial interest.

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