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I_2–CF_3SO_3H Synergistic Promoted sp^3 C–H Bond Diarylation of Aromatic Ketones

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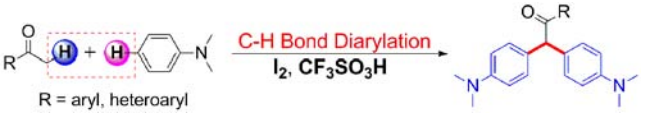
ABSTRACT

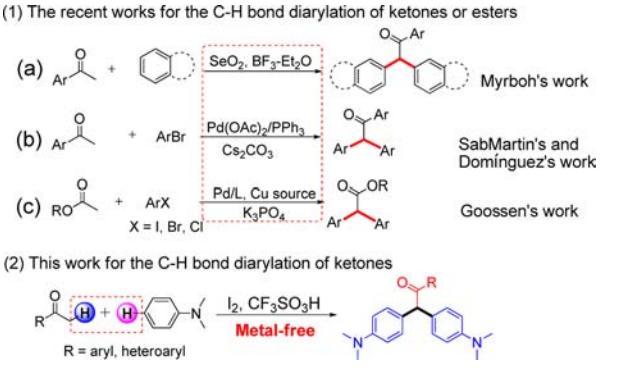


An I_2–CF_3SO_3H synergistic promoted sp^3 C–H bond diarylation protocol was developed for the synthesis of 2,2-bis(4-(dimethylamino)phenyl)-1-aryl ethanones. The reaction performed well in the absence of any metal and ligand. It integrated three reactions with different mechanisms (iodination, Kornblum oxidation, and hydroarylation) in a single reactor.

Diarylmethane derivatives are important substructures and widely exist in natural products, dye precursors, histological stain agents, and materials science.[1] Many compounds containing a diarylmethane motif exhibit potent biological activities and medicinal significance in antitubercular, anticancer, and antiproliferative agents.[2] Consequently, many synthetic methods have been reported for the synthesis of diarylmethane derivatives. The most common methods involve condensation of electron-rich arenes with aldehydes/ketones or imines.[3] Transition-metal catalyzed coupling methods have also been developed.[4]

Direct arylation of the C–H bond has been considered as one of the most fundamental strategies to construct C–C bonds. Many impressive results have been achieved through this method.[5] However, few methods have been developed for diarylation of the C–H bond in ketones and esters. Recently, Myrboh and co-workers proposed a graceful regioselective diarylation of aromatic ketones in the presence of SeO_2 and BF_3–Et_2O (Scheme 1, (a)).[6] SabMartin and Domíguez also demonstrated an interesting regioselective diarylation of ketone enolates by a homogeneous and heterogeneous catalysis strategy (Scheme 1, (b)),[7] whereas, Goossen developed an elegant palladium/copper cocatalyzed strategy for diarylation of acetic acid esters (Scheme 1, (c)).[8]

Scheme 1. Protocols for sp^3 C–H Bond Arylation



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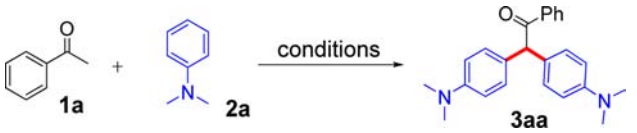
Recently, metal-free C−H coupling has attracted much attention.[9] However, the development of a metal-free protocol for diarylation of aromatic ketones remains very desirable. In a recent project, we developed a molecular iodide promoted di(hetero)arylation of aromatic ketones with indoles.[10] However, the electron-rich arenes were not tolerant for this method. Following up on this work, we herein reported an I_2−CF_3SO_3H synergistic promoted protocol for the diarylation of aromatic ketones with electron-rich arenes such as *N*,*N*-dialkylanilines, *N*-methylpyrrole, and anisole derivatives (Scheme 1, (2)).

Initially, the reaction of aryl methyl ketone (**1a**) and *N*,*N*-dimethylaniline (**2a**) was selected as a model reaction for optimization of the conditions. First, we screened a series of Lewis acids, such as Ti(*i*-PrO)$_4$, $AlCl_3$, $ZnCl_2$, $FeCl_3$, $InCl_3$, and $NbCl_5$, for this reaction, but none of the desired product **3aa** was obtained (Table 1, entries 1−5). We then screened various Brønsted acids and found $MeSO_3H$ and CF_3SO_3H were particularly effective catalysts (Table 1, entries 8 and 9). But, other Brønsted acids, such as H_2SO_4, HOAc, PTSA, and TFA, could not promote the reaction. In addition, the reaction could not perform without I_2 (Table 1, entry 13). After several experimental optimizations, we found that **1a** (1.0 mmol) reacted with I_2 (1.5 mmol) in DMSO at 100 °C for 1−2 h, which was followed by the addition of **2a** (2.0 mmol) and CF_3SO_3H (50 mol %) for another 1 h. The desired product was afforded in 68% yield (Table 1, entry 14).

Under the optimal conditions, the scope of aryl methyl ketones was investigated. As shown in Scheme 2, the reaction demonstrated good compatibility with various aromatic ketones; both electron-donating and -withdrawing groups attached to the phenyl group of **1** could afford the corresponding products with moderate to good yields, such as Me, OMe, 2,4-(OMe)$_2$, Cl, Br, and NO_2 groups. And the electronic properties of aromatic ketones (**2e**−**2i**) had little influence on the efficiency of the reaction. Furthermore, the heteroaryl methyl ketones, such as furanyl (**1i**), thiophenyl (**1j, 1k**), benzofuryl (**1l**), and morpholinyl (**1o**), were investigated under the optimal conditions. To our delight, the corresponding products **3ia**−**3la** and **3oa** were also afforded in moderate yields (50%−63%). Meanwhile, 2-naphthyl and 1-naphthyl methyl ketones (**1m** and **1n**) also reacted with *N*,*N*-dimethylaniline **2a** to give satisfying results (75% and 71% yields). Furthermore, the target compounds **3ca** were further determined by X-ray crystallographic analysis (Figure 1).

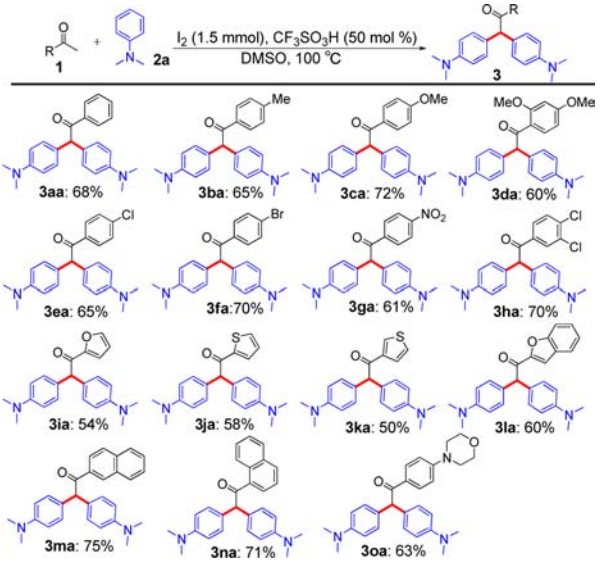
Table 1. Optimization Studies for the Synthesis of **3aa**[a,b]



entry	I_2 (mmol)	cat.	temp (°C)	time (h)	yield (%)[c]
1[a]	I_2 (1.0)	Ti(*i*-PrO)$_4$	100	12	n.r.
2[a]	I_2 (1.0)	$AlCl_3$	100	12	n.r.
3[a]	I_2 (1.0)	$FeCl_3$	100	12	n.r.
4[a]	I_2 (1.0)	$InCl_3$	100	12	n.r.
5[a]	I_2 (1.0)	$NbCl_5$	100	12	n.r.
6[a]	I_2 (1.0)	H_2SO_4	100	12	n.r.
7[a]	I_2 (1.0)	HOAc	100	12	n.r.
8[a]	I_2 (1.0)	$MeSO_3H$	100	4	55
9[a]	I_2 (1.0)	CF_3SO_3H	100	4	58
10[a]	I_2 (1.0)	PTSA	100	6	n.r.
11[a]	I_2 (1.0)	TFA	100	10	n.r.
12[b]	I_2 (1.0)	CF_3SO_3H	100	2	62
13[a]	–	CF_3SO_3H	100	12	n.r.
14[b]	I_2 (1.5)	CF_3SO_3H	100	2	68
15[b]	I_2 (2.0)	CF_3SO_3H	100	3	67
16[b]	I_2 (1.5)	CF_3SO_3H	110	3	62

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), I2 (1.0 mmol) catalyst (0.5 mmol, 50 mol %), heated in 3 mL of DMSO. [b] Reaction conditions: **1a** (1.0 mmol) and I_2 in DMSO at 100 °C for 1−2 h. To this reaction mixture were added **2a** (2.0 mmol) and CF_3SO_3H (0.5 mmol) at 100 °C, until the disappearance of **2a**, monitored by TLC. [c] Isolated yield.

Scheme 2. Scope of Aryl Methyl Ketones



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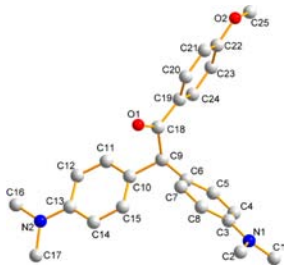
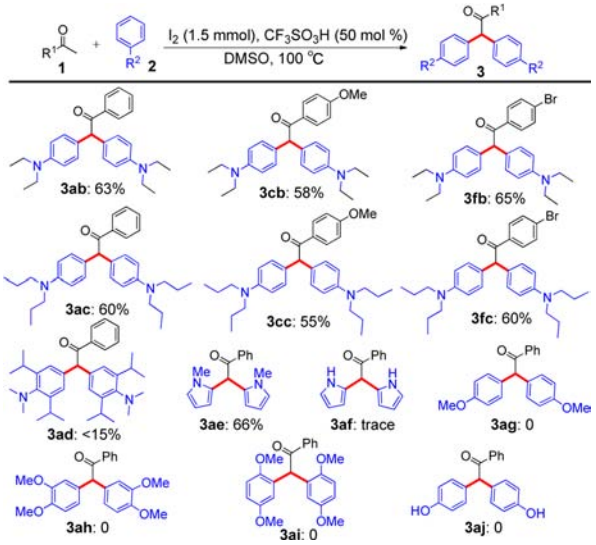


Figure 1. X-ray crystal structure of compound **3ca**.

To further expand the scope of the substrates, the diversity of electron-rich arenes was examined. Gratifyingly, *N*,*N*-diethylaniline **2b** and *N*,*N*-dipropylaniline **2c** could react smoothly with aryl methyl ketones to afford the corresponding products in moderate yields (Scheme 3, **3ab**−**3fc**). Moreover, the electronic properties of substrates **1** did not affect the reaction efficiency. However, when the substrate **2d** was used, the desired product **3ad** was only obtained in a very low yield, possibly due to the strong steric hindrance involved (< 15%). The *N*-methylpyrrole **2e** could also perform smoothly to afford the corresponding product under the conditions (Scheme 3, **3ae**, 66%). The reaction of pyrrole **2f** with acetophenone **1a** only gave a trace amount of the desired product. To our disappointment, the electron-rich arenes, such as anisole (**2g**), 1,2-dimethoxybenzene (**2h**), 1,4-dimethoxybenzene (**2i**), and phenol (**2j**), could not react with acetophenone **1a** to afford the desired products.

Scheme 3. Scope of Aryl Methyl Ketones and Electron-Rich Arenes



To further probe the reaction process, we monitored the reaction of **1a** (0.1 mmol) with **2a** (0.2 mmol) in the presence of I_2 (0.12 mmol) and CF_3SO_3H (50 mol %) by ^1H NMR spectroscopic studies (Figure 2). Through comparison with an authentic sample (see Figure S1), the signal at 4.6 ppm was assigned to the $-CH_2-$ group of α-iodo aryl methyl ketone **1aa** at 5−15 min.[11] In addition, the signals at 9.54 and 5.70 ppm were assigned to the phenylglyoxal aldehyde group (**1ac**) and the hemiacetal group (**1ab**).[12] With the addition of **2a** and CF_3SO_3H, the characteristic peaks of **1ac** and **1ab** were seen to disappear immediately. Meanwhile, the characteristic peaks of **3aa** were seen to appear (Ha, Hb, and $-N(Me)_2$ at δ = 8.08, 6.45, and 3.08 ppm). As shown in Figure 2, the reaction was achieved in 80 min with high conversion. These results demonstrated that phenacyl iodine (**1aa**) and phenylglyoxal (**1ac**) were important intermediates in the whole transformation.

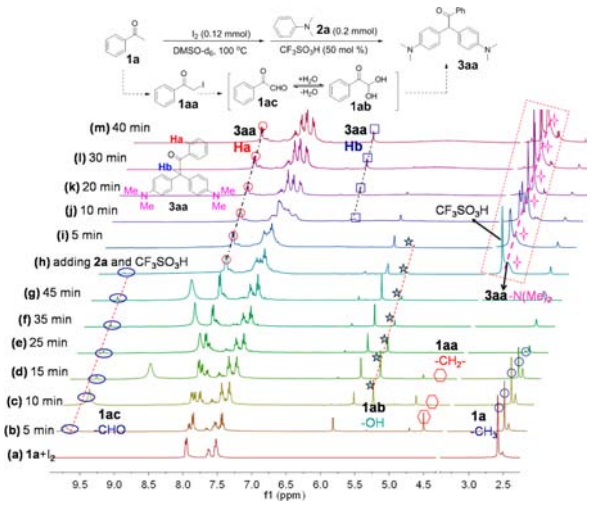


Figure 2. The reaction process of **1a** (0.1 mmol), **2a** (0.2 mmol), and I_2 (0.12 mmol) with CF_3SO_3H (50 mol %) at 100 °C was monitored by ^1H NMR spectroscopy (400 MHz, DMSO-d_6).

When the reaction of α-iodo ketone **1aa** (1.0 mmol) with dimethylaniline **2a** (2.0 mmol) in the presence of CF_3SO_3H (50 mol %) was performed in DMSO, the target product **3aa** was obtained in 69% yield (Scheme 4, (a)). The reaction of **1ab** and **2a** was treated with CF_3SO_3H (50 mol %) in DMSO at 100 °C, and the product **3aa** was subsequently obtained in good yield (82%). A competition experiment was also conducted, where acetophenone **1a** was treated with I_2 (1.2 mmol) in DMSO for 2 h and then **2a** (1.0 mmol), **2b** (1.0 mmol), and CF_3SO_3H (50 mol %) were added to the mixture for 1 h. The corresponding products **3aa** and **3ab** were obtained in 25% and 22% yields, respectively, and the crossed product **3aab** was afforded in 18% yield.

On the basis of the above results, a possible mechanism of the present reaction is depicted in Scheme 5. Initially,

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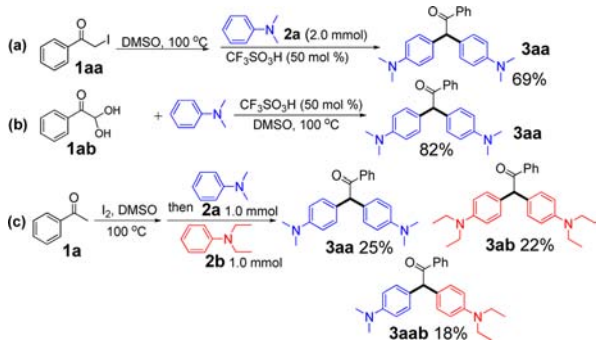
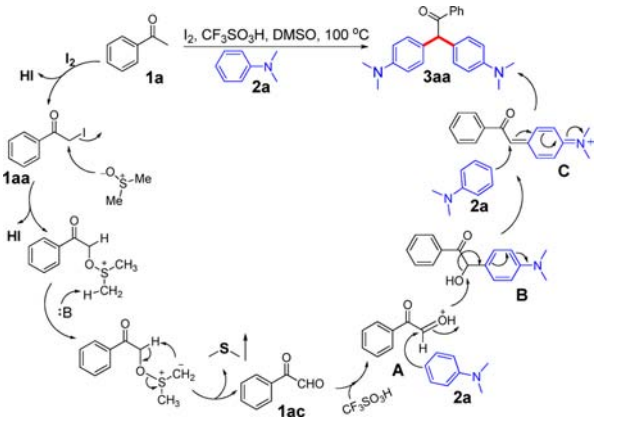
Scheme 4. Control Experiments



Scheme 5. Proposed Mechanism



molecular iodide promoted acetophenone **1a** to afford the intermediate α-iodo ketone **1aa**, which was subsequently converted into phenylglyoxal (**1ac**) by way of Kornblum oxidation in the presence of DMSO.[10] The aldehyde group of phenylglyoxal (**1ac**) was then activated by CF_3SO_3H to obtain activated intermediate **A**. Electron-rich *N*,*N*-dimethylaniline **2a** subsequently attacked the activated aldehyde group of phenylglyoxal (**1ac**) to give the intermediate **B**,[11] which underwent isomerization to afford the cation **C**. Finally, another *N*,*N*-dimethylaniline **2a** further trapped cation **C** to give the desired product **3aa**.

In conclusion, we developed an $I_2-CF_3SO_3H$ synergistic promoted sp^3 C−H bond diarylation protocol for the synthesis of 2,2-bis(4-(dimethylamino)phenyl)-1-aryl ethanones from simple and readily available aryl methyl ketones and *N*,*N*-dialkylanilines. It is notable that the reaction performed well in the absence of any metal and ligand. It therefore proved to be an efficient method for the diarylation of aromatic ketones. Further studies on the applications of this strategy will be reported in due course.

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Supporting Information Available. Spectrascopic data and general procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.