

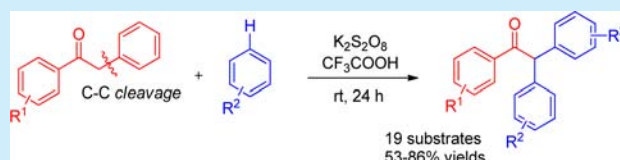
Aerobic Dehydrogenative α -Diarylation of Benzyl Ketones with Aromatics through Carbon–Carbon Bond Cleavage

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Supporting Information

ABSTRACT: Substituted benzyl ketones reacted with aromatics in the presence of $K_2S_2O_8$ in CF_3COOH at room temperature, yielding α -diaryl benzyl ketones through a carbon–carbon bond cleavage. In the reaction, two new carbon–carbon bonds were formed and one carbon–carbon bond was cleaved. It is very interesting that two different nucleophiles such as benzyl ketones and aromatics were coupled together without metal, which is unusual in organic synthesis.



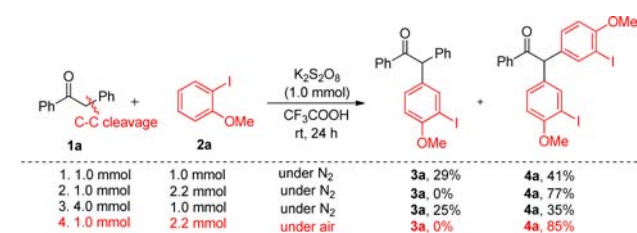
Substituted α -arylketones are synthetically useful organic compounds which are found in various natural products, dye precursors, and materials.¹ In addition, α -arylketones exhibit interesting pharmacological and biological activities.² Transition-metal-catalyzed α -arylation of substituted ketones with aromatic halides or organometallic reagents is a unique method to synthesize α -arylketones in a highly efficient manner.³ Several research groups have paid tremendous attention to develop efficient methods to synthesize α -arylketones from substituted ketones in the presence of metal catalysts and specially designed ligands.³ In these reactions, mostly aromatic halides or organometallic reagents are used as an aryl source. Instead of using a preactivated coupling partner such as a C–X or C–M moiety, if the same reaction is performed by the C–H bond of aromatics, it would be even more useful in organic synthesis. In the meantime, preparation of aryl coupling partners takes more number of steps and requires tedious reaction procedure.

Similar to α -arylketones, several ways exist to synthesize α -diarylketones. Generally, α -diarylketones are prepared by two ways: (a) SeO_2 -mediated addition of acetophenones with electron-rich aromatics in the presence of $BF_3 \cdot Et_2O$ ^{4a} and (b) metal-catalyzed cross-coupling of acetophenones or α -aryl acetophenones with aromatic electrophiles in the presence of a specially designed ligand.^{3,4b} In both methods, metals such as a stoichiometric amount of SeO_2 and a catalytic amount of metal catalyst and ligand were used.

Recently, oxidative dehydrogenative cross-coupling reaction such as coupling of two different moieties of sp^2 – sp^2 or sp^2 – sp^3 or sp^3 – sp^3 C–H bonds has gained tremendous attention in organic synthesis.⁵ This type of reaction is highly atom economical and environmentally friendly. However, this type of coupling reaction is very challenging, and several side reactions are possible. Metal-catalyzed dehydrogenative cross-coupling of sp^2 – sp^2 C–H bonds has been reported in the literature.⁵ Meanwhile, a metal-free cross-coupling of sp^3 – sp^3 C–H bonds has also been demonstrated in the literature,^{6,7} but the cross-coupling of sp^2 – sp^3 C–H bonds has not been well

explored in the literature. In the meantime, mostly for α -arylation of substituted ketones, only aromatic halides or organometallic reagents are used.

With the existing background, we have tried to do the α -arylation of substituted ketones with aromatics instead of using aromatic halides or organometallic reagents via C–H bond activation without metal catalyst. Basically, we would like to do the direct coupling of two nucleophiles such as the sp^3 C–H bond of substituted ketones and the sp^2 C–H bond of aromatics. For this coupling reaction, a substituted ketone such as benzyl phenyl ketone was taken as a model substrate. Initially, the oxidative coupling of benzyl phenyl ketone (**1a**) (1.0 equiv) with 2-iodoanisole (**2a**) (1.0 mmol) in the presence $K_2S_2O_8$ (1.0 mmol) in CF_3COOH at room temperature for 24 h under N_2 was examined (Scheme 1, entry 1). In the reaction,

Scheme 1. Reaction of Benzyl Phenyl Ketone (**1a**) with **2a**

two different arylation products, such as α -monoarylated ketone **3a** in 29% yield and α -diarylated ketone **4a** in 41% yield, were observed. Surprisingly, in the α -diarylated compound **4a**, two 2-iodoanisole moieties were incorporated at the methene sp^3 carbon of **1a**, and the Ph group adjacent to methene of **1a** was cleaved. It is very important to note that the reaction is highly regioselective, and only the *para* C–H bond of the methoxy substituent of **2a** was added to the methene

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carbon of **1a**. In the reaction, two new carbon–carbon bonds were formed and one carbon–carbon bond was cleaved. It is important to mention that, in the present reaction, two nucleophiles such as substituted ketones and electron-rich aromatics were coupled without any metal, which is unusual in organic synthesis.

Further, the same reaction was performed without $K_2S_2O_8$ and only in CF_3COOH under N_2 . However, in the reaction, no products **3a** and **4a** were observed. This result clearly revealed that $K_2S_2O_8$ is highly important for the reaction. Further, the same reaction was tested in the presence of an excess amount of **2a** (2.2 mmol) in the presence of $K_2S_2O_8$ under N_2 . In the reaction, only product **4a** was observed in 77% yield (Scheme 1, entry 2). In the meantime, the arylation reaction of **2a** (1.0 mmol) with an excess amount of **1a** (4.0 mmol) was also tested. In the reaction, products **3a** and **4a** were observed in 25 and 35% yields, respectively (Scheme 1, entry 3). It seems α -diarylated ketone **4a** cannot be suppressed, but α -monoarylated ketone **3a** can be suppressed by altering the ratio of reactants.

The reaction was tested with other oxidants (1.0 mmol) such as DDQ, Ag_2O , $PhI(OAc)_2$, benzoquinone, $Cu(OAc)_2$, $(NH_4)_2S_2O_8$, and oxone instead of $K_2S_2O_8$ in CF_3COOH . Among them, oxidant $(NH_4)_2S_2O_8$ produced product **4a** in 70% isolated yield. Remaining oxidants were not effective. Next, the catalytic reaction was tested with various solvents such as CH_3COOH , MeOH, pivalic acid, toluene, benzene, THF, DMF, DCE, *tert*-BuOH, CF_3SO_3H , and CF_3COOH in the presence of $K_2S_2O_8$. Among them, CF_3COOH was very effective, giving product **4a** in 77% isolated yield. CF_3SO_3H was slightly less effective, providing **4a** in 70% isolated yield. The other solvents were totally ineffective. Next, the reaction of **1a** and **2a** was examined under air. Surprisingly, the reaction worked very well, yielding product **4a** in 85% isolated yield (Scheme 1, entry 4). Then, the same reaction was tested without $K_2S_2O_8$ under air. In the reaction, product **4a** was observed only in 45% yield. It seems that $K_2S_2O_8$ plays an important role in increasing the yield of product **4a** drastically under air. On the basis of these optimization studies, we have concluded that $K_2S_2O_8$ is the better oxidant and CF_3COOH is the better solvent for the reaction under air for 24 h at room temperature. It is important to note that starting material α -aryl acetophenones **1** can be easily prepared by the Friedel–Crafts acylation of substituted aromatics with substituted phenylacetyl chlorides in the presence of $AlCl_3$.⁸ In addition, in the present reaction, α -diarylketones **4** were prepared by using easily affordable reagents $K_2S_2O_8$ and CF_3COOH without any metal.

The scope of the α -bisarylation reaction was examined with substituted aromatics (Table 1). The reaction of benzyl phenyl ketone (**1a**) with anisole (**2b**) gave a mixture of α -diarylketones **4b** and **4b'** in 39 and 18% yields, respectively (entry 1). In product **4b**, the *para* C–H bond of two moieties of anisole was added at the methene carbon of **1a**, whereas in product **4b'**, a *para* C–H bond of anisole and an *ortho* C–H bond of anisole were added at the methene carbon of **1a**. 2-Methylanisole (**2c**) and 3-methylanisole (**2d**) yielded α -diarylketones **4c** and **4d** in 68 and 72% yields, respectively (entries 2 and 3). In the reaction, *para* C–H of the methoxy group of **2c** and **2d** was involved, whereas, in the reaction of 4-methylanisole (**2e**) with **1a**, the *ortho* C–H bond of the methoxy group of **2e** was added at the methene carbon of **1a**, yielding α -diarylketone **4e** in 71% yield (entry 4). The structure of compound **4e** was confirmed by single-crystal X-ray diffraction (see Supporting Information). Similarly, 1,4-dimethoxybenzene (**2f**) afforded α -diarylketone

Table 1. Arylation of **1a** with Aromatics **2a–l**^a

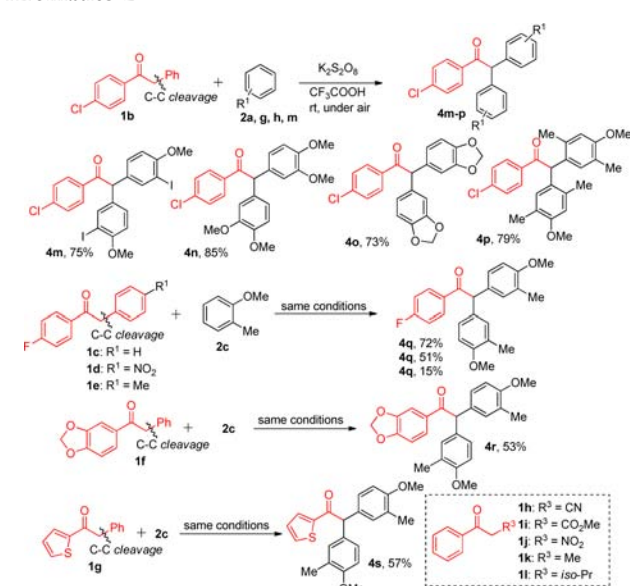
entry	2	product 4	yield (%) ^b
1			39+18 ^c
2			68
3			72
4			71
5			68
6			72
7			75
8			77
9			85
10			86
11			66

^aAll reactions were carried out using **1a** (1.0 mmol), **2c–l** (2.20 mmol), and $K_2S_2O_8$ (1.0 mmol) in CF_3COOH (1.0 mL) at room temperature under air for 24 h. ^bIsolated yield. ^c5.0 mmol of anisole was taken.

4f in 68% yield in which the *ortho* C–H bond of the methoxy group of **2f** participated in the reaction (entry 5). 1,2-Dimethoxybenzene (**2g**) was also efficiently involved in the reaction, affording α -bisarylketone **4g** in 72% yield in a highly regioselective manner (entry 6). Interestingly, a less electron-rich benzo[*d*][1,3]dioxole (**2h**) was nicely involved in the reaction, providing product **4h** in 75% yield (entry 7). In the reaction, the C-4 carbon of **2h** was inserted at the methene carbon of **1a**. Further, the reaction was examined with various trisubstituted benzenes **2i–l** (entries 8–11). Thus, the treatment of 2,3-dimethylanisole (**2i**) or 1,2-dimethoxy-4-methylbenzene (**2j**) with **1a** gave α -diarylketones **4i** and **4j** in 77 and 85% yields, respectively (entries 8 and 9). In these reactions, *para* C–H of the methoxy group of **2i–j** participated in the reaction. Surprisingly, mesitylene (**2k**) efficiently participated in the reaction, giving α -diarylketone **4k** in 86% yield (entry 10). In the reaction, a sterically hindered C–H bond of **2k** participated. Highly useful 5-bromobenzo[*d*][1,3]-dioxole (**2l**) reacted nicely with **1a**, affording α -diarylketone **4l** in 66% yield (entry 11). In the reaction, the *ortho* C–H bond of the bromo group of **2l** was involved. The arylation reaction was also performed with aromatics and heteroaromatics such as anilines, bromobenzene, fluorobenzene, nitrobenzene, indoles, and pyrroles. However, in these reactions, no arylation product was observed.

The α -diarylation was tested with substituted benzyl ketones **1b–g** (Scheme 2). When chloro-substituted benzyl phenyl

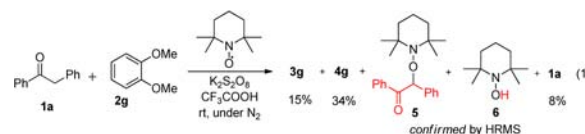
Scheme 2. Arylation of Substituted Ketones 1 with Aromatics 2



ketone **1b** was treated with 2-iodoanisole (**2a**), 1,2-dimethoxybenzene (**2g**), and benzo[*d*][1,3]dioxole (**2h**) under the optimized reaction conditions, α -diarylketones **4m–o** were observed in 75, 85, and 73% yields, respectively. Interestingly, trisubstituted aromatic 2-methoxy-1,4-dimethylbenzene (**2m**) also efficiently participated in the reaction, yielding product **4p** in 79% yield. Similarly, 2-methylanisole (**2c**) reacted efficiently with fluoro-substituted benzyl phenyl ketone **1c**, giving the corresponding α -diarylketone **4q** in 72% yield. NO₂ or Me substituent at benzyl group **1d** or **1e** yielded **4q** only in 51 and 15% yields, respectively. Further, benzo[*d*][1,3]dioxole group

substituted benzyl ketone **1f** reacted with **2c**, providing α -diarylketone **4r** in 53% yield. The arylation reaction was also compatible with heteroaromatic group substituted benzyl ketone **1g**. Thus, treatment of **1g** with 2-methylanisole (**2c**) gave α -diarylketone **4s** in 57% yield. Subsequently, the reaction was also tested with CN, CO₂Me, NO₂, and alkyls such as Me and *iso*-Pr **1h–l** instead of phenyl-substituted ketones. In these reactions, no α -arylation products were observed.

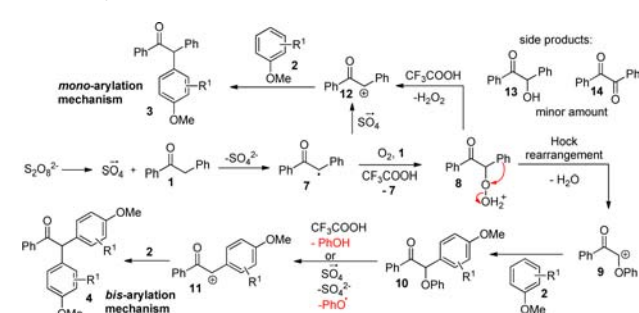
We strongly believe that the present arylation reaction proceeds via a radical mechanism. To support the mechanism, the following reaction was carried out (eq 1). The reaction of



1a with **2g** was tested in the presence of TEMPO free radical (1.0 equiv) and K₂S₂O₈ in CF₃COOH at rt for 24 h under N₂. In the reaction, α -monoarylketone **3g** and α -diarylketone **4g** were observed in 15 and 34% yields, respectively. In addition, TEMPO adducts **5** and **6** were also observed. The TEMPO adducts were confirmed by HRMS analysis. Meanwhile, 8% of starting material **1a** was recovered.

A possible reaction mechanism is proposed in Scheme 3. It is known that K₂S₂O₈ generates SO₄^{•−} radical anion, and the

Scheme 3. Possible Reaction Mechanism



corresponding anionic radical can abstract hydrogen from the acidic C–H bond of organic molecules.^{9a} In the present reaction, SO₄^{•−} abstracts hydrogen from the acidic methene carbon of **1a**, generating radical **7**. Further, a radical of intermediate **7** inserts into O₂ followed by abstracting hydrogen from another **1** and protonation in the presence of CF₃COOH producing intermediate **8**.^{6c} Intermediate **8** underwent an *ipso*-substitution rearrangement (Hock-type rearrangement), giving intermediate **9** and elimination of water (see cumene process).^{9b,c} Nucleophilic addition of aromatic **2** into intermediate **9** affords intermediate **10**.^{9c} Subsequently, intermediate **10** eliminates a phenoxy radical, providing cationic intermediate **11** in the presence of SO₄^{•−}.^{9d,e} It is also possible that the carbocation intermediate **11** may also form from intermediate **10** by a CF₃COOH-mediated ionic pathway with loss of PhOH in a cumene process.^{9b,c} Further, addition of aromatic **2** into intermediate **11** affords product **4**.^{9c} Monoarylated compound **3** was observed via nucleophilic addition of aromatic **2** into intermediate **12**.^{6c,l,m,9a,c} We have tried to trap a phenoxy radical. However, we were not able to trap it. It is known that a phenoxy radical spontaneously reacts themselves or with O₂, giving a mixture of phenol and quinone derivatives.^{9f} It is also highly possible that it could decompose

spontaneously under air and be very hard to trap.^{9f} In fact, we have observed a minor amount of phenol derivatives, which was confirmed by GC-MS. A loss of PhOH was anticipated in the ionic transformation of intermediates **10** to **11** mediated by acid. In fact, we have tried to isolate PhOH. However, we were not able to isolate it. It is well-known that PhOH rapidly converts into a phenoxy radical in the presence of a radical initiator under air or oxygen atmosphere.^{9f} The present reaction was also performed under an air atmosphere. Thus, we strongly believe that a phenoxy radical was formed from PhOH under the reaction conditions. In some of the reactions, a minor amount of side products **13** and **14** was observed. The observation of these products supports the reaction of oxygen into intermediate **7** and the formation of H₂O₂ which oxidizes **1** to **13** and **14**.^{6m}

In conclusion, we have shown a mild, simple, and regioselective synthesis of α -diarylketones by the reaction of benzyl ketones with aromatics. In the reaction, two new carbon–carbon bonds were formed and one carbon–carbon bond was cleaved.

■ ASSOCIATED CONTENT

■ Supporting Information

General experimental procedure and characterization details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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