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Copper Catalyzed Arylation/C−C Bond Activation: An Approach toward α-Aryl Ketones

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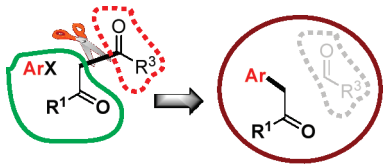
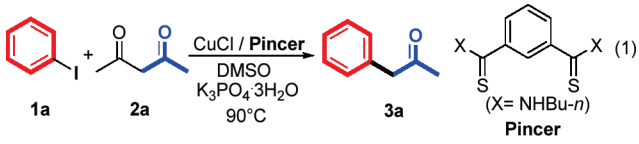
Transition-metal-catalyzed selective C−C bond activation (cleavage) currently fascinates organometallic chemists, due to not only its fundamental scientific interest but also its potential usage in organic synthesis.[1−4] Because of the inertness of C−C bonds, only a few examples of the catalytic activation of C−C bonds have been reported before 2000.[3,5] In recent years, significant progress has been achieved, which involved some effective strategies to activate the C−C bonds, such as employing the strained ring systems,[6−13] directing by chelation groups,[14−18] or by other means.[19−35] Due to an interest in the copper-catalyzed C−C bond formation/α-arylation of carbonyl compounds, we accidentally discovered a C−C bond activation, which meanwhile led to an efficient approach toward α-aryl ketones under mild conditions (Scheme 1).

Scheme 1. Approach to the α-Aryl Ketones



The α-aryl carbonyl compounds are important components of many pharmaceuticals and bioactive molecules. Buchwald and Hartwig have pioneered the palladium-catalyzed arylation of a variety of carbonyl compounds using aryl halides as electrophiles.[36,37] Fu and Lei employed an alternative arylation strategy by using α-halocarbonyl compounds and ArM to achieve the same goal.[38,39] Because of the economic attractiveness and good functional group tolerance, copper catalysts are remarkably advantageous in chemical syntheses. Buchwald,[40] Ma,[41] and Kwong[42] et al. have reported the efficient arylations of β-dicarbonyl compounds catalyzed by copper salts. To the best of our knowledge, no examples have been described in literature of α-aryl ketones being prepared using a copper catalyst from the direct arylation of simple ketones. As shown in Scheme 1, we communicated herein our finding in arylation/C−C bond activation, which illustrated an efficient example of achieving α-aryl ketones using a simple copper salt as the catalyst without ligands.



Our initial efforts focused on the direct coupling between aryl halides **1a** and β-diketone compounds **2a** by using the (pincer thioamide)-Cu complex as the catalyst precursor (eq 1) (see more details in the Supporting Information). It was unexpected that the direct arylation product 3-phenylpentane-2,4-dione **4a** was not the final product but the α-phenyl ketone **3a** was produced instead, in which an acyl group was cleaved.

Table 1. Reaction Parameters of **1a** with **2a**[a]

entry	catalyst	base	solvent	yield (%)[b]
1	Pincer CuCl	K_2CO_3	DMSO	60
2	Pincer CuCl	Cs_2CO_3	DMSO	71
3	Pincer CuCl	$K_3PO_4·3H_2O$	DMSO	87
4	**CuI**	**$K_3PO_4·3H_2O$**	**DMSO**	**98**
5	$CuCl_2$	$K_3PO_4·3H_2O$	DMSO	91
6	$Cu(OAc)_2·H_2O$	$K_3PO_4·3H_2O$	DMSO	92
7	none	$K_3PO_4·3H_2O$	DMSO	NR
8	CuI	none	DMSO	NR
9[c]	CuI	$K_3PO_4·3H_2O$	DMSO	NR
10	CuI	$K_3PO_4·3H_2O$	DMF	82
11	CuI	$K_3PO_4·3H_2O$	DMA	48
12	CuI	$K_3PO_4·3H_2O$	toluene	NR
13	CuI	$K_3PO_4·3H_2O$	dioxane	NR
14[d]	CuI/TMEDA	$K_3PO_4·3H_2O$	DMSO	42
15[e]	CuI/DMEDA	$K_3PO_4·3H_2O$	DMSO	46

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (3.0 mmol), base (3 equiv), copper catalyst (10 mol %) in DMSO at 90 °C for 20 h. [b] GC yields. [c] At 60 °C. [d] TMEDA (20 mol %) was added. [e] DMEDA (20 mol %) was added.

This arylation/C−C activation prompted us into investigating the reaction parameters. Selected results were compiled in Table 1. Compared with K_2CO_3 and Cs_2CO_3, $K_3PO_4·3H_2O$ was the best base in promoting this reaction (Table 1, entries 1−3). Interestingly, CuI alone gave the best results, in which the yield was up to 98% (Table 1, entry 4). Cu(I) and Cu(II) salts showed similar efficiency (Table 1, entries 4−6). When the reaction temperature was lowered to 60 °C, no reaction occurred (Table 1, entry 9). In DMF and DMA, the reactions gave the desired products in low yields (Table 1, entries 10−11), while no reactions occurred in toluene and dioxane (Table 1, entries 12−13). Addition of TMEDA or DMEDA inhibited the reaction (Table 1, entries 14−15).

The substrate scope toward this arylation/C−C bond activation was further investigated, and the results were listed in Table 2. A wide array of aryl iodides were examined in the reaction with diketone **2a**, and moderate to excellent yields were obtained in producing the corresponding α-aryl ketones (Table 2). Iodobenzene derivatives, which bear substituted groups such as methyl, *i*-propyl, methoxyl, chloro, fluoro, alkoxycarbonyl, nitro, phenyl, etc. at *para* positions, all reacted smoothly with **2a** to afford the desired corresponding products (Table 2, entries 2, 4−8, 10−11). It is noteworthy that the free COOH group in 4-iodobenzoic acid **1i** was fairly compatible with these conditions to afford 82% of product

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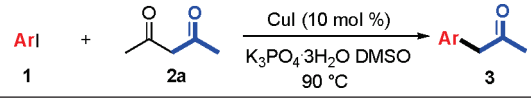
3i (Table 2, entry 9). 1-Iodo-3-methylbenzene **1c** also reacted smoothly in good yield (Table 2, entry 3). However, iodobenzene derivatives with a functional group substituted at *ortho* positions could not react with **2a**.

Table 2. Reactions of **2a** with Various Aryl Iodides **1**[a]

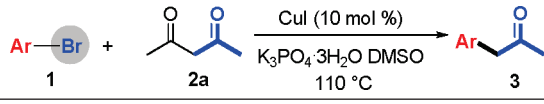


entry	1		3	yield (%)[b]
1	Ar = Ph	**1a**	**3a**	75
2	Ar = *p*-Me-C_6H_4	**1b**	**3b**	74
3	Ar = *m*-Me-C_6H_4	**1c**	**3c**	71
4	Ar = *p*-*i*-Pr-C_6H_4	**1d**	**3d**	74
5	Ar = *p*-MeO-C_6H_4	**1e**	**3e**	89
6	Ar = *p*-Cl-C_6H_4	**1f**	**3f**	67
7	Ar = *p*-F-C_6H_4	**1g**	**3g**	79
8	Ar = *p*-COOEt-C_6H_4	**1h**	**3h**	91
9	Ar = *p*-COOH-C_6H_4	**1i**	**3i**	82
10	Ar = *p*-NO_2-C_6H_4	**1j**	**3j**	56
11	Ar = *p*-Ph-C_6H_4	**1k**	**3k**	81

[a] Reaction conditions: **1** (1.0 mmol), **2a** (3.0 mmol), $K_3PO_4 \cdot 3H_2O$ (3 equiv), CuI (10 mol %) in DMSO at 90 °C for 20 h. [b] Isolated yields.

To our delight, aryl bromides could also react with **2a** smoothly at 110 °C, and the results were listed in Table 3. Similarly, the reactions of bromobenzene dervatives substituted at *para* positions with various functional groups also took place smoothly with **2a**. The substrate 2-bromonaphthalene **1s** also displayed good selectivity to afford 64% of the product (Table 3, entry 8).

Table 3. Reactions of **2a** with Various Aryl Bromides **1**[a]



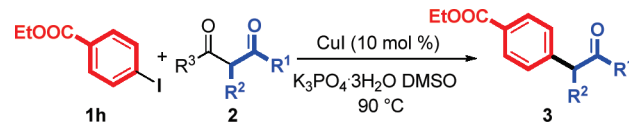
entry	1		3	yield (%)[b]
1	Ar = Ph	**1l**	**3a**	74
2	Ar = *p*-Me-C_6H_4	**1m**	**3b**	42
3	Ar = *m*-Me-C_6H_4	**1n**	**3c**	36
4	Ar = *p*-MeO-C_6H_4	**1o**	**3e**	50
5	Ar = *p*-Cl-C_6H_4	**1p**	**3f**	61
6	Ar = *p*-F-C_6H_4	**1q**	**3g**	55
7	Ar = *p*-CF_3-C_6H_4	**1r**	**3l**	72
8	Ar = *p*-Naphthyl-C_6H_4	**1s**	**3m**	64

[a] Reaction conditions: **1** (1.0 mmol), **2a** (3.0 mmol), $K_3PO_4 \cdot 3H_2O$ (3 equiv), CuI (10 mol %) in DMSO at 110 °C for 20 h. [b] Isolated yields.

The Cu-catalyzed arylation/C−C activation of various β-diketones was also investigated. When heptane-3,5-dione **2b** or nonane-4,6-dione **2c** was employed as the nucleophile to react with **1h**, the C−C activation was also observed, which produced the desired α-aryl ketones **3n** and **3o** in 70% and 58% yield, respectively (Table 4, entries 1−2). When R^2 was the methyl group, the corresponding arylation/C−C activation product **3p** was obtained in 35% yield (Table 4, entry 3). Interestingly, when unsymmetric β-diketones **2e** and **2f** were engaged in the system, the reactions exhibited excellent selectivities; only an acetyl group was cleaved from the β-diketones (Table 4, entries 4−5). No reaction occurred when **2g** was used as the nucleophile (Table 4, entry 6).

It is interesting for us to note that only a trace of C−C activation product formed while a 40% yield of direct arylation product **4a** was isolated when the reaction was carried out under anhydrous conditions (eq 2). In fact, Jiang et al. had described the reaction between aryl iodides and **2a** using CuI as a catalyst precursor in

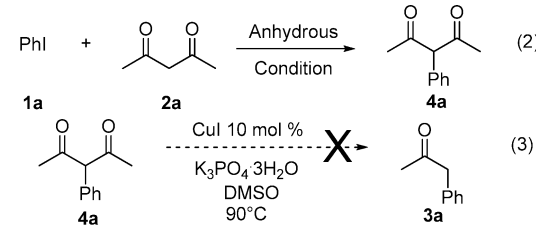
Table 4. Reactions of Various β-Diketones **2** with Aryl Iodide **1i**[a]



entry	R^1	R^2	R^3		3	yield (%)[b]
1	Et	H	Et	**2b**	**3n**	70
2	*n*-Pr	H	*n*-Pr	**2c**	**3o**	58
3	Me	Me	Me	**2d**	**3p**	35
4	Ph	H	Me	**2e**	**3q**	73
5	2-Naphthyl	H	Me	**2f**	**3r**	46
6	Ph	H	Ph	**2g**	**3s**	NR

[a] Reaction conditions: **1h** (1.0 mmol), **2** (3.0 mmol), $K_3PO_4 \cdot 3H_2O$ (3 equiv), CuI (10 mol %) in DMSO at 90 °C for 20 h. [b] Isolated yields.

the presence of L-proline as the ligand, which produced **4a** in a rather high yield.[43] Thus, we speculated that the presence of H_2O in our reaction system assisted the C−C activation process. Meanwhile, no C−C cleavage was observed when **4a** was subjected under the standard reaction conditions (eq 3).



Bunnett et al. had investigated the "nucleophilic" replacement of two halogens in dihalobenzenes without the intermediacy of monosubstitution products under irradiation (a classic diagnostic technique for the participation of radical anion intermediates).[44]

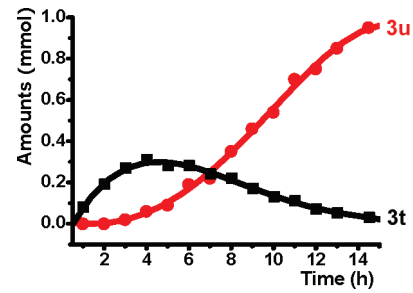
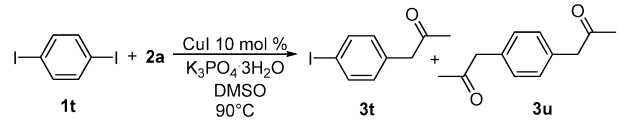


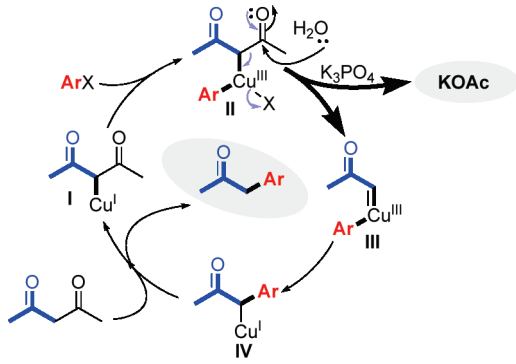
Figure 1. Distribution of bis-arylated **3t** and monoarylated **3u** with reaction time of the reaction of **1t** with **2a** (eq 4).

As shown in eq 4 and Figure 1, **3t** was clearly the intermediate for the *bis*-arylated product **3u**. This experimental data excluded the participation of radical intermediates in the C−C bond cleavage reaction.[45,46]



A putative reaction pathway was listed in Scheme 2. ArX could oxidatively add to the Cu(I) complex **I** to generate Cu(III) intermediate **II**. In the presence of H_2O, the C−C bond activation/cleavage occurred, which led to the formation of intermediate **III**

Scheme 2. Putative Mechanism of C−C Bond Activation (Cleavage) in the Arylation



and the release of KOAc. Reductive elimination of intermediate **III** could produce the other Cu(I) intermediate **IV**, which would finally produce the desired α-aryl ketones by reacting with the diketone and regenerate the Cu(I) intermediate **I** species for the next catalytic cycle. Another alternative pathway was discussed in the Supporting Information.

To probe the feasibility of the pathway and detect the formation of KOAc, we attempted to use *in situ* IR to monitor the reaction between **1a** and **2a**. We were delighted to see that the kinetic profiles clearly revealed not only the consumption of **2a** and the formation of **3a** but also a new species increasing at peak 1583 cm^{-1} (Figure 2A) which was unambiguously assigned as KOAc by comparison with an authentic sample of KOAc (Figure 2B).

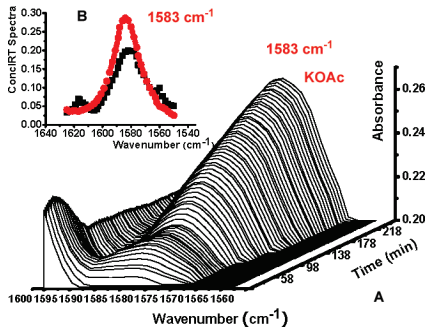
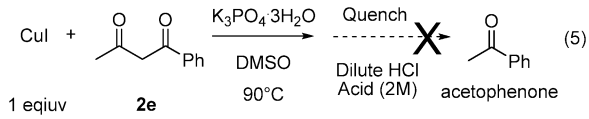


Figure 2. (A) 3D-FTIR profiles of the reaction of **1a** and **2a**. (B) ConcIRT spectra of the new component (black curve) and authentic sample of KOAc (red curve).

Stoichiometric reaction of **2e** with CuI was also investigated under the standard reaction conditions without adding ArI. No acetophenone was detected (eq 5), which revealed that the C−C activation did not occur in the Cu(I) intermediate **I** (Scheme 2).



In conclusion, we have revealed an efficient arylation/C−C activation process. *β*-Diketones and aryl halides (aryl iodides and aryl bromides) could undergo reaction smoothly in the presence of Cu(I) or Cu(II) salts in DMSO using $K_3PO_4 \cdot 3H_2O$ without ligands. The role of H_2O was unprecedented, which assisted the C−C activation. Various α-aryl ketones could be efficiently synthesized from this novel method. *In situ* monitoring of the formation of KOAc and experimentation relating to "a classic diagnostic technique for the participation of radical anion intermediates" revealed the preliminary mechanistic information for the reaction. This method is simple, general, and practical which complemented the classic method for the rapid construction of C−C bonds to a carbonyl moiety. The detailed mechanism is currently under investigation in our laboratory and will be reported in due course.

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Supporting Information Available: Experiment details and spectral data for all compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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