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Alcohol assisted C–C bond breaking: copper-catalyzed deacetylative α-arylation of β-keto esters and amides†

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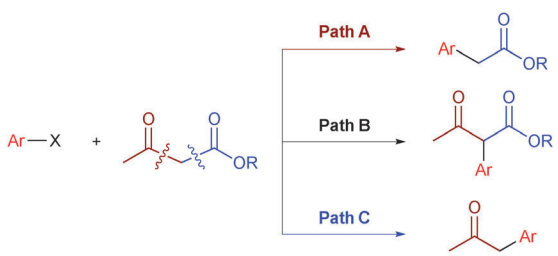
Jie Ke,‡[a] Chuan He,‡[a] Huiying Liu,[a] Huan Xu[a] and Aiwen Lei*[ab]

A method of alcohol-assisted copper-catalyzed highly selective deacetylative α-arylation of β-keto esters and amides has been demonstrated, which illustrated an efficient example of achieving α-aryl esters and amides. From the synthetic point of view, this arylation protocol is general and practical, representing a simple way to produce α-arylated carbonyl compounds from basic starting materials at low cost.

α-Arylated carbonyl compounds are important motifs in many natural products, pharmaceuticals and bioactive molecules, which have always drawn chemists' attention in organic synthesis.[1] In particular, α-aryl esters and their derivatives are found at the core of numerous important analgesic, non-steroidal anti-inflammatory drugs (NSAIDs), and phytohormonal growth regulators. During the past several decades, although a number of efforts have been made,[2] there still remains a great challenge for the synthesis of these interesting structural moieties with high efficiency and selectivity from basic chemical materials. Pioneered by Buchwald, Hartwig and Miura, the palladium-catalyzed arylation of various enolates of carbonyl compounds using aryl halides as electrophiles has been well developed, which has become an efficient synthetic method for the C_{sp^2}–C_{sp^3} bond formation.[2c,3] However, Pd is used as the catalyst and some special phosphine ligands and strong bases are also needed in this protocol. Meanwhile, some other approaches, including the copper-catalyzed direct α-arylation of benzyl phenyl ketones,[4] the umpolung α-arylation by the coupling of α-halocarbonyl compounds with aryl-metal-reagents,[5] and the α-arylation using diaryliodonium salts,[6] have also achieved the same goal.

As an alternative approach, transition-metal-catalyzed deacetylative or decarboxylative arylation could also provide α-arylated carbonyl compounds *via* C–C bond breaking. Transition-metal-catalyzed selective cleavage of C–C bonds is always of great significance and challenge both in the fundamental scientific interest and organic synthesis.[7] Among those bond activation patterns, the direct cleavage of unstrained C–C bonds is the most difficult process due to the inertness of C–C bonds. Accordingly, application of this approach to achieve cross-coupling reaction/α-arylation is especially attractive. Recently, copper-catalyzed deacetylative arylation of 1,3-dicarbonyl compounds *via* C–C bond activation has been realized, which efficiently led to the formation of α-arylation products under mild conditions.[8] However, the deacetylative arylation of α-keto esters suffered from the problems of selectivity and conversion, and the substrate scope was also not well-established.[8a,9] Obviously, these inherent problems limit the general application of this synthetic method, because at least three types of arylation products could be obtained (Scheme 1). Usually, the direct arylation (Path B)[2c,10] and dealkoxycarbonylative arylation[11] or decarboxylative arylation[12] (Path C) processes are relatively easy to be achieved under Pd- or Cu-catalyzed conditions. However, rare examples for the highly selective deacetylative arylation (Path A) have been addressed in the literature.[8a,c,9,13] As mentioned before, α-aryl ester and amide products corresponding to Path A are more important and of high interest to the pharmaceutical industry. Herein, we communicate our results from alcohol-assisted copper-catalyzed highly selective deacetylative α-arylation of β-keto esters and amides. In the presence of alcohol, both selectivity and conversion could be enhanced satisfactorily.

Our initial efforts were focused on the reaction of iodobenzene **1a** and ethyl acetoacetate **2a** by using CuI as the catalyst. The desired deacetylative arylation product **3aa** could be observed in the presence of base in DMSO (Table 1, entries 1–3). Unfortunately, the selectivity and conversion problems were also encountered in these reactions. Most of the starting material **1a** remained intact,



Scheme 1 Selectivity problem in the copper-catalyzed α-arylation of β-keto esters.

[a] College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, 430072, Hubei, P. R. China. E-mail: aiwenlei@whu.edu.cn
[b] State Key Laboratory for Oxo Synthesis and Selective Oxidation Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, 730000 Lanzhou, P. R. China

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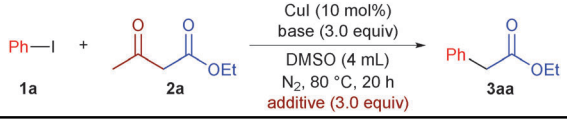
‡ These authors contributed equally to this work.

Table 1 Optimization of conditions for the reaction of **1a** with **2a**[a]

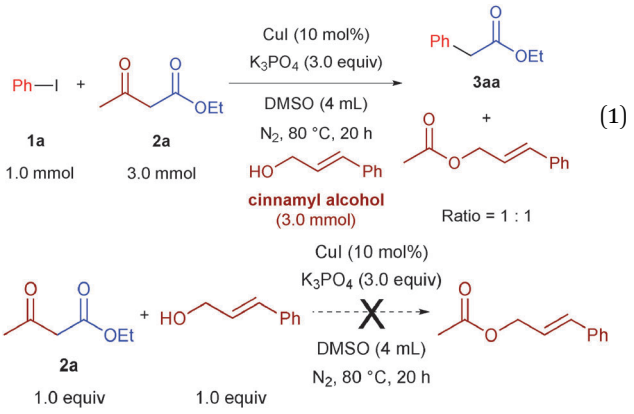


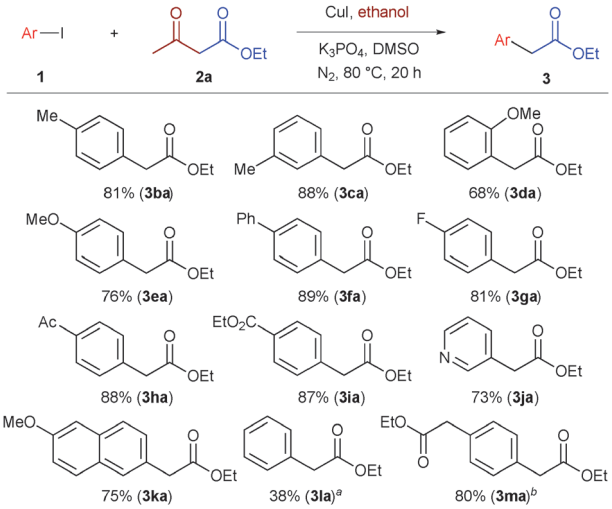
Entry	Base	Additive	Yield[b] (%)
1	K_3PO_4	None	41
2	$K_3PO_4·3H_2O$	None	25
3	K_3PO_4	H_2O	44
4	K_3PO_4	Cinnamyl alcohol	75 (66)
5	K_3PO_4	Ethanol	93 (82)
6[c]	K_3PO_4	Ethanol	0
7[d]	None	Ethanol	0

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (3.0 mmol), CuI (10 mol%), base (3.0 equiv.) in 4 mL of DMSO in N_2 at 80 °C for 20 h. [b] Yield determined by GC analysis with naphthalene as the internal standard; isolated yields for entries 4 and 5 in the parentheses. [c] Without CuI. [d] Without base.

and both the direct arylation product and deacetylative arylation product could be afforded under the current conditions. In the previous work, H_2O was demonstrated to be a good promoter in assisting the C–C bond activation process in the reaction.[8b] We envisioned that some other additives might be effective for the C–C bond breaking. After some efforts, alcohol was found to be the best additive, which played a crucial role in promoting the deacetylative arylation process, both in selectivity and conversion (Table 1, entries 4 and 5). In the presence of ethanol, perfect selectivity and 93% yield of **3aa** could be produced under the similar mild conditions (Table 1, entry 5). Without either copper catalyst or base, no reaction occurred under the standard conditions (Table 1, entries 6 and 7).

It is noteworthy that when cinnamyl alcohol was employed as the additive, cinnamyl acetate could be observed along with the formation of deacetylative arylation product **3aa** in a 1 : 1 ratio (eqn (1)) (Table 1, entry 4). This interesting result indicated that alcohol not only assisted the C–C bond breaking, but also *in situ* captured the leaving -Ac group to form acetate during the deacetylative arylation process. Meanwhile, a blank experiment has also been carried out under the same conditions without adding aryl iodide **1a**. As shown in eqn (2), no cinnamyl acetate was observed, which indicated that the C–C bond activation occurred along with the arylation process. Notably, when ethanol was used as the additive, only ethyl acetate was produced as the byproduct, which could be easily removed after the reaction (Table 1, entry 5).

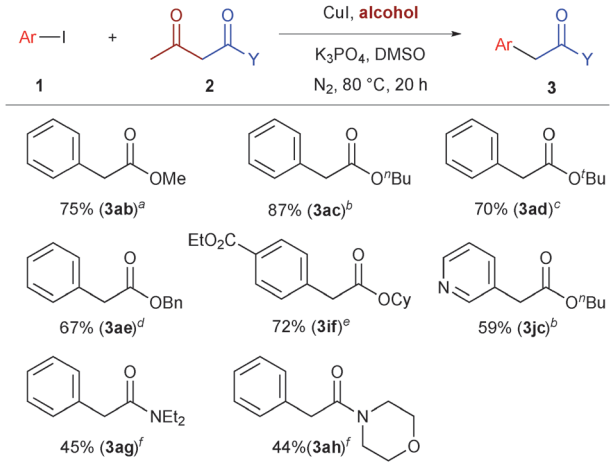




Scheme 2 Substrate scope for the deacetylative arylation of aryl halide **1** with **2a**. *Reaction conditions*: **1** (1.0 mmol), **2a** (3.0 mmol), CuI (10 mol%), K_3PO_4 (3.0 mmol), ethanol (3.0 mmol) in 4 mL of DMSO in N_2 at 80 °C for 20 h, isolated yields; [a]**1l** bromobenzene was used, and picolinic acid (20 mol%) as the ligand. [b]**1m** (1.0 mmol), **2a** (6.0 mmol), CuI (0.2 mmol), K_3PO_4 (6.0 mmol), ethanol (6.0 mmol) in 8 mL of DMSO.

Consequently, this alcohol-assisted copper-catalyzed highly selective deacetylative α-arylation protocol encouraged us to further examine the feasibility to the efficient α-aryl esters and amides synthesis. Promoted by ethanol, various aryl iodides were found to be effective for the deacetylative arylation under the standard conditions (Scheme 2). Both electron-donating and -withdrawing substituted groups were well tolerated, such as Me, OMe, Ph, F, Ac, and COOEt groups (**3ba–3ia**). Aryl iodides bearing substituted groups at *para*, *meta*, and *ortho* positions could all react smoothly in good yields. Heteroaryl iodides such as 3-iodopyridine **1j** could also be compatible to give the desired product **3ja** in good yield. 2-Iodo-6-methoxynaphthalene **1k** was also suitable for this transformation in 75% yield (**3ka**). In addition, aryl bromide **1l** could be readily introduced in the reaction in the presence of picolinic acid ligand, but with lower yield (**3la**). Moreover, the reaction of 1,4-diiodobenzene **1m** with **2a** resulted in the corresponding difunctionalized product **3ma** in 80% yield.

Furthermore, a variety of β-keto esters and amides **2** were also considered as suitable partners with aryl iodides **1** to access the α-aryl esters and amides (Scheme 3). It is noteworthy that, when ethanol was employed as the additive for the deacetylative arylation of different β-keto esters, the transesterification byproducts could be observed in the reactions. To avoid the side reaction, the corresponding alcohol was used as the additive for different β-keto esters. As shown in Scheme 3, methyl, *n*-butyl, *t*-butyl, benzyl, cyclohexyl acetoacetates were all allowed to react with aryl iodides smoothly providing the desired products in good yields (**3ab–3ae** and **3if**). Pyridine moieties could also be employed to react with butyl 3-oxobutanoate **2c** without any difficulties (**3jc**). Moreover, 1,3-dicarbonyl compounds bearing amide groups **2g** and **2h** were also effective in the reaction with **1a** and to afford the α-aryl amides **3ag** and **3ah** in moderate yields.



Scheme 3 Substrate scope for the deacetylative arylation of aryl iodide **1** with β-keto esters and amides **2**. *Reaction conditions*: **1** (1.0 mmol), **2** (3.0 mmol), CuI (10 mol%), K_3PO_4 (3.0 equiv.), alcohol (3.0 mmol) in 4 mL of DMSO in N_2 at 80 °C for 20 h, isolated yields; [a]MeOH was used, GC yield 90%; [b]*n*BuOH was used; [c]EtOH was used, GC yield 79%; when *t*BuOH was used, only trace yield; [d]BnOH was used; [e]EtOH was used; when CyOH was used, only 13% yield; [f]EtOH was used.

In conclusion, we have developed a novel method of alcohol-assisted copper-catalyzed highly selective deacetylative α-arylation of β-keto esters and amides, which illustrated an efficient example of achieving α-aryl esters and amides under mild conditions. Assisted by the crucial alcohol, both selectivity and conversion could be enhanced satisfactorily. From the synthetic point of view, this arylation protocol is general and practical, representing a simple way to produce α-arylated carbonyl compounds from basic starting materials at low cost. Further mechanistic studies on this alcohol-assisted deacetylative arylation transformation are currently underway in our laboratory.

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