Versatile and Ligand-free Copper-catalyzed α-Arylations of Aromatic Ketones using diaryliodonium salts

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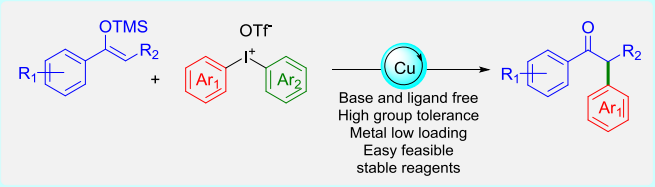
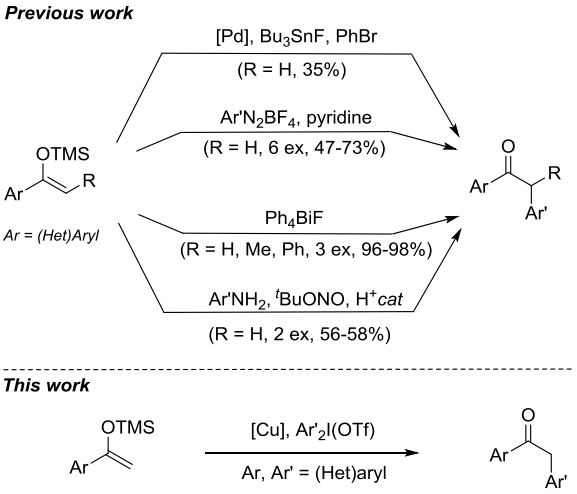
ABSTRACT: A ligand and base free copper catalyzed synthetic methodology for the efficient α-arylation of aromatic ketones has been developed. The reaction of the ketone-derived silyl enol ethers with diaryliodonium salts led to the intermolecular C-C coupling displaying high functional group tolerance with a low catalyst loading.



The α-arylation of aromatic ketones is a powerful synthetic tool in organic synthesis. As early as 1973, Semmelhack and co-workers reported the first nickel catalyzed intramolecular α-arylation of lithium enolates as a fundamental step in the total synthesis of synthetic intermediates of cephalotaxinone.[1] Since then, α-arylation reactions have found many applications, for examples, as the key step toward synthetic intermediates of active ingredients, such as Tamixofen or Oxcarbazepine.[2] The most widely used process to perform intermolecular α-arylations on aromatic ketones is the reaction of the corresponding enolate forms with aryl halides under palladium catalysis.[3] However, numerous other transition metal catalyzed or transition metal free α-arylation of enolizable aryl ketones have been disclosed.[4] Nevertheless, the high pKa of the α-proton of aromatic ketones (pKa = 25 in DMSO for acetophenone),[5] often requires the use of strong bases, complex ligands or harsh conditions, hence imposing certain limitations. In order to circumvent this issue, increased interest in the use of silyl enol ethers as starting compounds has emerged. Among the leading examples are the palladium or copper catalysed stereoselective α-arylation reactions of esters and imides using aryl halide,[Erreur ! Signet non défini.a] pseudo-halide[6b] or diaryliodonium salts as aryl source.[7] In contrast, for arylketone derived enolsilanes, only few examples of α-arylation reactions exist in the literature. Scheme 1 summarizes the sporadic attempts using silyl enol ethers of aromatic ketones reported so far. The presented methodologies use toxic reagents, provide modest yields in most cases and have very limited scope. The earliest example was reported in 1982 by Uribe and co-worker.[8] They generated *in-situ* an organotin species and performed the α-arylation, using aryl bromides under palladium catalysis. However, the organotin species was generated by a stochiometric amount of toxic tin fluoride reagent and gave only one low-yield example for acetphone with bromobenzene.



Scheme 1. α-Arylation using arylketone derived enolsilanes.

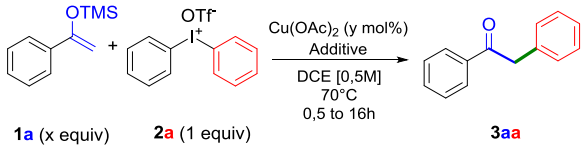
Later, Tanaka and co-worker disclosed a transition metal free version by using arene diazonium tetrafluoroborate.[9] This radical process is initiated by the interaction of the diazonium salt and pyridine, latter acting as reagent and solvent. Maruoka at al disclosed in 2003 an

efficient α-arylation of ketones with a tetraphenylfluorobismuth reagent.[10] Despite high yields with several enol substrates, the bismuth reagent had to be used in stochiometric amount, only one out of the four aryl groups was transferred and the scope was limited to the phenyl group. In 2014, the Gonzalez-Gomez group described a Brønsted acid catalyzed system.[11] They generated *in-situ* a diazonium salt from anilines as the aryl source. However this reaction required a huge excess of silyl enol ether and they reported only two examples from aromatic ketone derivatives.

Herein, we describe a ligand-free copper-catalyzed α-arylation of aryl ketones under their silyl enol ether using diaryliodonium salts as aryl source.

For our first trials, we chose the following readily available substrates: the silyl enol ether of acetophenone **1a** (3 equiv) and diphenyliodonium triflate **2a** (1 equiv)**.** Using copper(II) acetate (10 mol%) as precatalyst, phenantroline (10 mol%) as additives and 1,2-dichloethane (DCE) (0.25 M) as solvent, we obtained 53% of excepted product **3aa** (Table 1, entry **1**) at 25 °C and 80% at 70 °C (entry **2**).

Table 1. Copper catalyzed α-arylation of 1-phenyl-1-trimethylsiloxyethylene **1a** with diphenyliodonium triflate **2a**: reaction conditions.[a][b]



1a (x equiv) **2a** (1 equiv) **3aa**

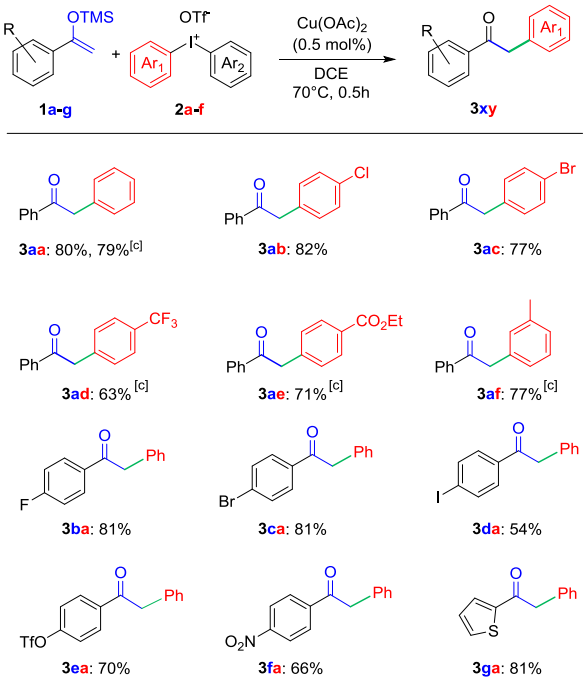
Entry	1a (equiv)	[Cu] (mol%)	t (h)	Yields (%)
1[c][d]	3	10	16	52
2[d]	3	10	16	80
3	3	10	16	82
4	3	0	16	2
5[e]	3	10	16	60
6[f]	3	10	16	73
7	3	10	16	82
8	3	5	2	84
9	3	0.5	2	84
10	3	0.25	2	49
11	1.5	0.5	2	70
12	1.5	0.5	0.5	84 (80)[g]

a) Reaction conditions: **1a** (0,4 to 0.75 mmol), **2a** (0.25 mmol), $Cu(OAc)_2$ (0.0013 to 0.025 mmol) and 1,2-dichloroethane (DCE) (0.5 mL) for 0.5 to 16h at 25 to 70°C under an argon atmosphere. b) NMR yields using trichloroethylene as an internal standard; c) reaction performed at 25°C. d) Reaction performed with phenantroline (10 mol%, 0,02 mmol). e) Reaction performed under air atmos. f) Hexafluorophosphate as counter anion. g) Isolated yield.

Ligand free conditions allowed the formation of **3aa** with similar yield (entry **3**), whatever the copper source ($Cu(OTf)_2$, CuI or CuBr) (see Supporting Information). The copper-free conditions gave traces of product and pointed out the crucial role of metal (entry **4**). Under aerobic conditions, the formation of **3aa** was observed but the process was less effective (entry **5**). The change of the counter anion of diphenyliodonium from triflate to hexafluorophosphate induced slightly lower yield (entry **6**), while reducing the reaction time from 16 h to 2 h did not modify the formation of **3aa** (entry **7**). We then studied the copper loading which could be reduced to 0.5 mol% (entry **8** to **9**) without affecting the yield, whereas an even lower copper loading (0.25 mol%) gave only a fair 49% of **3aa** (entry **10**). Reducing the amount of **1a** from 3 to 1.5 equivalents, slightly decreased the yield (entry **11**). However, surprisingly, additional shortening of the reaction time to 0.5 h afforded 84% of **3aa** (entry **12**).

With these optimized conditions in hand, we explored the scope for α-arylation of silyl ether enol **1a** with different diaryliodonium salts **2a-f** (Table 2). Symmetrical diaryliodonium salts were successfully employed. Halogen group on substrates **2b-c** (Cl and Br respectively) were found to be suitable and afforded the α-arylated product **3ab-ac** in good yields.

Table 2: Copper catalyzed α-arylation of several aryl silyl enol ethers **1a-g** and diaryliodonium triflates **2a-f**. [a][b])



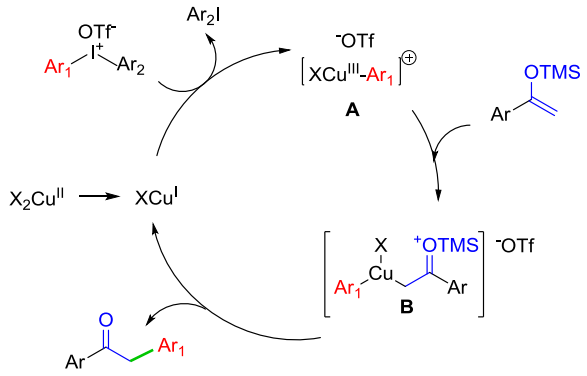
a) Reaction conditions: aryl silyl enol ether (0.375 to 0,625 mmol), symmetrical diaryliodonium salt (0.25 mmol), $Cu(OAc)_2$ (0.00125 mmol), DCE (0.5 mL) at 70 °C during 0.5 h. b) Isolated yield. c) Ar_2 = mesithyl (Mes).

Besides, we tested the mesitylaryliodonium salt strategy, in which the mesityl group would act as a dummy ligand due to its high steric hindrance in order to favor the addition of the other aryl group. In this case, mesitylaryliodonium triflate **2a'** gave the product **3aa** in 79% yield with 2 equiv of **1a** instead of 1.5 equiv. Then, mesitylaryliodonium salts bearing an electron withdrawing (EWG) group, such as trifluoromethyl **2d** or ethyl ester **2e** were engaged and formed **3ae-3ae** in moderate to good yields. A *meta*-methyl substituted diaryliodonium salt was compatible and afforded **3af** in good yield.

The scope of this α-arylation procedure was further explored with several functionalized aryl silyl enol ethers **1a-g** and diphenyliodonium triflate **2a** as aryl source (see Table 2). Halogens on silyl ether enol **1b-1d**, notably iodine, were well tolerated during the reaction and gave the corresponding products **3ba-3da** in good yields.

In the same way, the silyl enol ether with a triflate group **1e** was successfully engaged in this α-arylation process, affording the corresponding product **3ea** without any degradation. To the best of our knowledge, this is the first α-arylation process tolerating the triflate group as functional group on the ketone. Electron withdrawing groups on silyl enol ether such as the nitro-substituted **1f** induced a slight drop of the yield and gave **3fa** in 66% yield. Heteroaromatic silyl enol ether **1g**, bearing a thienyl group was employed and allowed the formation **3ga** in good yield.

Concerning the mechanism of the reaction, at this stage, we can exclude a radical-type reaction due to the good tolerance towards halogen substrates, including iodide. In accordance with previous reports in the literature,[12] a plausible intermediate for this reaction involves a Cu(III) species **A** resulting from the oxidative addition of Cu(I) into the Ar-I bond of the diaryliodonium salt (Scheme 2). This key intermediate **A** could then react with silyl enol ether to give the mixed copper(III)arylalkyl complex **B**. The latter would undergo a reductive elimination to regenerate the Cu(I) catalytic species and to yield the expected α-arylated ketone after the removal of the silyl group by the triflate anion.



Scheme 2. Mechanism proposal.

In summary, we have reported an efficient copper-catalyzed α-arylation of aromatic ketones under their silyl enol ether form using symmetrical diaryliodonium or mesitylaryliodonium salts as aryl source. This ligand and base-free process showed high tolerance toward sensitive functional groups such as triflate or iodine and was only limited by the available synthesis of diaryliodonium salt. Further studies focusing on the use of Cu(III) species are under investigation and will be reported in due course.

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Keywords: copper • catalysis • α-arylation • diaryliodonium • silyl enol ether •

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