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Copper-Catalyzed Regioselective Reaction of Internal Alkynes and Diaryliodonium Salts

Ze-Feng Xu, Chen-Xin Cai, and Jin-Tao Liu*

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry,
Chinese Academy of Science, Shanghai 200032, China

jtliu@sioc.ac.cn

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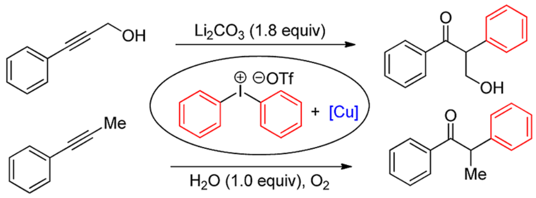
ABSTRACT



The copper-catalyzed highly regioselective reaction of internal alkynes with diaryliodonium salts was achieved for the first time. α-Arylketones were obtained in moderate to good yields from arylpropargylic alcohols or aryl alkyl alkynes under mild conditions. It was found that the two kinds of substrates underwent two different arylation–oxygenation pathways under different reaction conditions based on deuterated experiments, controlling experiments, and spectroscopic analysis of reaction intermediates.

Carbonyl compounds, especially α-aryl carbonyl compounds, are of particular importance in organic and pharmaceutical chemistry, and Markovnikov hydration of alkynes is an ideal method for their synthesis. Mercury(II) salts combined with acids, such as HgO/H_2SO_4 and HgO/BF_3, although of potential toxicity, are reliable catalytic systems for this transformation and are widely used.[1] Alternative transition metallic catalysts have been sought in recent years, such as Pt, Fe, Pd, Ir, Ag, Sn–W, and Co.[2] Recently, it has been found that gold complexes can efficiently catalyze the transformation of alkynes to ketones (Scheme 1A).[3] Among some recent significant studies, Zhang's group made a major contribution to the gold-catalyzed transformations of propargylic esters to eneketons, and a $Au^{I/III}$ catalysis cycle was established to synthesize α-arylketones utilizing boronic acids as the coupling partners and selectfluor as an oxidant to transfer

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10.1021/ol4003543

Scheme 1

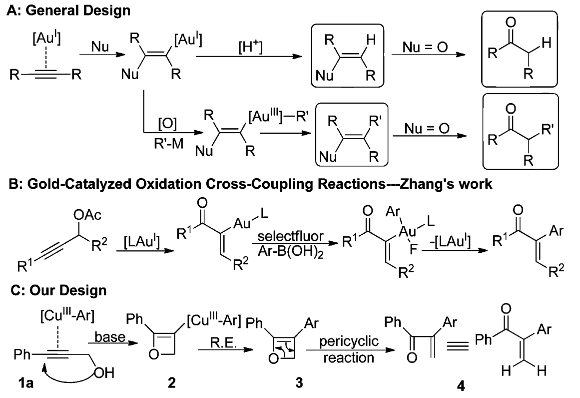
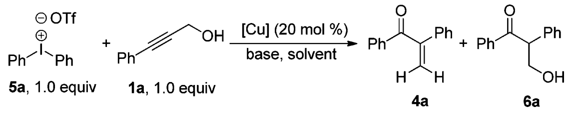


Table 1. Optimization of Reaction Conditions



entry	[Cu]	solvent	base (equiv)	temp (°C)	t (h)	yield (%)[a] 4a	6a
1	CuI	DCE	–	60	24	–	–
2	CuI	DCE	Li_2CO_3 (2.0)	60	24	21	–
3	–	DCE	Li_2CO_3 (2.0)	60	24	–	–
4	CuI	DCE	Na_2CO_3 (2.0)	60	24	4	–
5	CuI	DCE	K_2CO_3 (2.0)	60	24	–	–
6	CuI	DCE	Li_2CO_3 (1.8)	60	24	28	–
7	CuI	DCE	Li_2CO_3 (1.8)	70	24	32	–
8	CuI	DCE	Li_2CO_3 (1.8)	80	24	3	50
9	CuI	DCE	Li_2CO_3 (1.8)	70	72	6	50
10	CuCl	DCE	Li_2CO_3 (1.8)	70	24	<2	57
11	CuBr	DCE	Li_2CO_3 (1.8)	70	24	<2	61
12	CuCN	DCE	Li_2CO_3 (1.8)	70	24	<2	52
13	Cu(OTf)$_2$	DCE	Li_2CO_3 (1.8)	70	24	18	–
14	CuCl	DCM	Li_2CO_3 (1.8)	70	24	–	51
15	CuI	DCM	Li_2CO_3 (1.8)	70	24	3	87
16[b]	**CuI**	**DCM**	**Li_2CO_3 (1.8)**	**70**	**18**	**6**	**87**
17[c]	CuI	DCM	Li_2CO_3 (1.8)	70	24	12	46

[a] Determined by ^{1}H NMR with MesH as an internal standard. [b] 1.1 equiv of Ph$_2$IOTf was utlized. [c] 1.0 equiv of H$_2$O was added.

Au^I to Au^{III}, which was able to undergo a transmetalation reaction and the following reductive elimination reaction to produce the products and regenerate the Au^I catalyst (Scheme 1B).[4]

Recently, the direct copper-catalyzed arylation of various compounds with iodonium salts has been extensively studied.[5] Iodonium salts are indeed extremely appealing as they are air- and moisture-stable and can be easily prepared in one step from commercially available materials.[6] Gaunt's research group has demonstrated that, in the presence of copper and diaryliodonium salts, a Cu^{III}-aryl intermediate formed, and as bearing a d^8-configuration, it was a highly electrophilic metal species.[5c] The selective Cu-catalyzed arylation of indoles,[5j] aromatic compounds,[5g−i] and alkenes[5c] was also reported with the combination of copper salt and hyperiodonium by his group. MacMillan et al. described an elegant Cu-catalyzed enantioselective α-arylation[5d,f] of carbonyl groups.

Inspired by these significant works, we envisioned that the Cu^{III}-aryl intermediate, as highly electrophilic metal species, may also coordinate with the C−C triple bond as in the Au^I species. Then the nucleophilic attack on the activated triple bond would result in the formation of a new Cu^{III} species, which undergoes reductive elimination to give the coupling product. Accordingly, we designed the following transformations: propargyl alcohol **1a** coordinated first with the Cu^{III}-aryl species, then the intramolecular nucleophilic attack by oxygen produced intermediate **2**, reductive elimination of **2** gave the 2*H*-oxete derivative **3**,[7] and the final product, α,*β*-unsaturated ketone **4**, was formed through the pericyclic reaction of **3** (Scheme 1C).

Herein we describe the successful execution of the above design via a Cu$^{I/III}$ catalytic cycle, which provides a highly regioselective synthesis of arylketones from propargylic alcohols. Furthermore, a similar transformation of aryl alkyl alkynes was also achieved without a base.

At the outset of the study, 3-phenylprop-2-yn-1-ol (**1a**) and diphenyliodonium triflate (**5a**) were chosen as model substrates to establish the optimized reaction conditions (Table 1). The reaction was first examined in 1,2-dichloroethane (DCE) at 60 °C using 20 mol % CuI as a catalyst, but no desired product was formed and **1a** decomposed (Table 1, entry 1). When 2.0 equiv of Li_2CO_3 was added, **4a** was formed in 21% yield (entry 2). The copper catalyst was necessary for the reaction, and **1a** remained unchanged in the absence of CuI (entry 3). Further screening of bases and their equivalents (entries 4−7) showed that a better result was obtained when the reaction was carried out at 70 °C using 1.8 equiv of Li_2CO_3 (entry 7), but the yield was still very low. When a higher temperature (80 °C, 24 h) or a prolonged reaction time (70 °C, 72 h) was utilized, the hydrated product (**6a**) was formed in moderate yields (entries 8 and 9). Using other Cu sources gave almost the same results (entries 10−12) or a low yield of **4a** (entry 13). Using dichloromethane (DCM) instead of DCE as solvent did not improve the yield of **6a** in the case of CuCl (entry 14). To our delight, when the reaction was carried out in DCM using CuI as a catalyst, an 87% yield of **6a** was achieved (entry 15). It was also found that a shorter reaction time was required when a slight excess of **5a** was used (entry 16). Residual H_2O in starting materials was

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(6) For recent reviews, see: (a) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052. (b) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924. For synthesis of diaryliodonium salts, see also: (c) Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem.* **2008**, *73*, 4602. (d) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610. (e) Kitamura, T.; Matsuyuki, J.; Nagata, K.; Furuki, R.; Taniguchi, H. *Synthesis* **1992**, 945.

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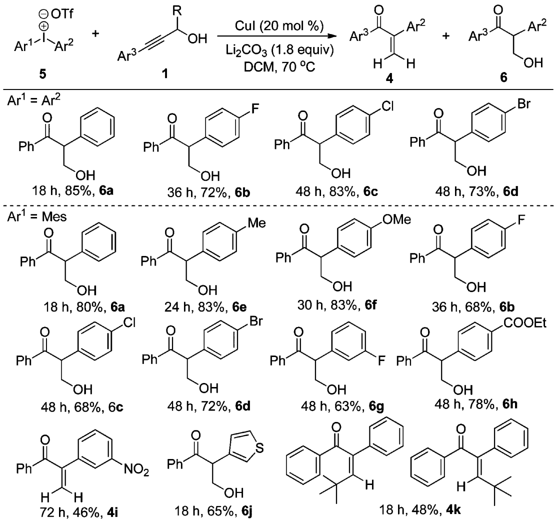
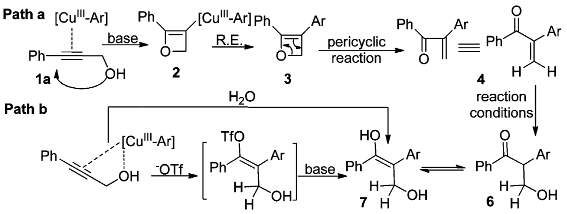
Scheme 2. Scope of the Substrates



enough for the transformation, and the addition of water resulted in a lower yield (entry 17). Finally, the optimized reaction conditions were established as indicated in entry 16.

The scope of this reaction was then promptly investigated. The results are shown in Scheme 2. In general, symmetrical diaryliodonium salts (Ar^1 = Ar^2) were successfully employed, and both electron abundant and deficient aryls were found to be suitable for this reaction, affording the corresponding α-arylketones in good yields (Scheme 2, upper section, **6a**–**d**). Unsymmetrical diaryliodonium salts containing a usual aryl group and a more steric aryl unit (Ar^1 = Mes) that would transfer inefficiently in the Cu-catalyzed process[5j,8] were also studied. Diaryliodonium salts containing an electron abundant aryl gave the desired products in good yields (Scheme 2, bottom section, **6a**, **6e**–**f**). A slightly lower yields were obtained with electron-deficient ones (Scheme 2, bottom section, **6b**–**d**, **6g**–**h**). The reaction was also successfully applied to the diaryliodonium salt containing a heteroaromatic ring (**6j**). However, α,*β*-unsaturated ketones were obtained as the major products in the case of the diaryliodonium salt with a *m*-NO$_2$ substituted group (**4i**).

Scheme 3. Proposed Mechanism for the Formation of **6**

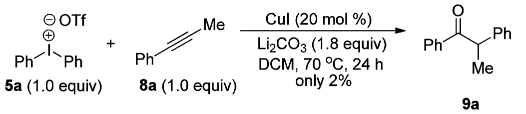


To further enlarge the scope of the reaction, several propargyl alcohols were next investigated. In the case of Ar^3 = Ph, R = ^{t}Bu, the unhydrated product **4k** was obtained in 48% yield, and when R = ^{i}Pr or 4-Cl-C$_6$H$_4$, complex mixtures were obtained and could not be separated by flash column chromatography or even preparative TLC. For alcohols with two alkyl substituents at the α-carbon, ene-ynes were formed as major products (Supporting Information (SI)).

The regioselectivity of the above reaction was excellent, and no methyl ketones were observed. Both electron-donating and -withdrawing groups on the aromatic ring in diaryliodonium salts were tolerated. This made it possible to further functionalize these products, demonstrating the potential of this protocol.

Regarding the mechanism for the formation of **6**, two possible pathways might be involved (Scheme 3). In path **a**, a Cu^{III}-aryl species and the 2*H*-oxete **3** were formed as the crucial intermediates as we assumed in our design (Scheme 1C). Under the reaction conditions, the desired product **4** was hydrated to give **6** as the final product. In path **b**, after the coordination of the Cu^{III}-aryl species with the substrate, water or TfO$^-$ rather than the hydroxyl group might attack the activated triple bond, followed by reductive elimination, hydrolysis, and tautomerism, to give the product **6.**

Careful study showed that **4** was always formed prior to **6** at the beginning of the reaction by ^{1}H NMR, and **4** could be easily converted to **6** under the reaction conditions, whereas the reverse transformation did not occur. Furthermore, when 1-phenyl-1-propyne (**8a**) was used to react with **5a** under the same conditions, only 2% of the desired product **9a** was obtained (eq 1, also entry 1 in Table S1 (SI)). Therefore it is reasonable to infer that the reaction took place through path **a**.



(1)

It was interesting to find that the α-arylketone **9a** with the main byproduct propiophenone **10** was formed regioselectively when the reaction of **8a** with **5a** was carried out in the absence of base under conditions similar to those for eq 1 (entry 2, Table S1 (SI)). To improve the yield of **9a**, the reaction conditions were further investigated. As shown in Table S1 (SI), the best result was obtained when the reaction was carried out in DCM at 80 °C in the presence of 1.0 equiv of water using Cu(OAc)$_2$ as the catalyst under an oxygen atmosphere entry 18, Table S1 (SI), also the equation in Scheme 4.

Under the optimized reaction conditions, the substrate scope of the reaction was screened next. The results were summarized in Scheme 4. Both symmetrical and unsymmetrical diaryliodonium salts could react with **8a** to give the corresponding α-arylketones in moderate to good yields. Usually, a shorter reaction time was required with unsymmetrical diaryliodonium salts containing an electron-abundant aryl (**9b**–**c**). Other alkynes such as 1-(*p*-ethylphenyl)-1-propyne, 1-(*p*-fluorophenyl)-1-propyne,

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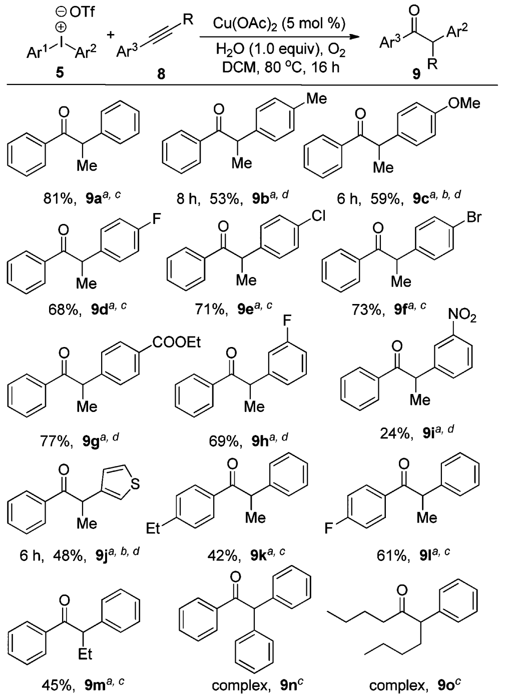
(8) (a) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (b) Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007**, *46*, 1924.

Scheme 4. Reaction of **8** with **5**[a]

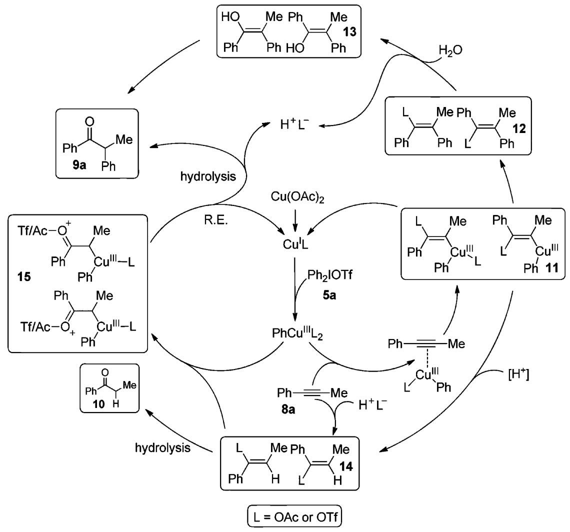


[a] Isolated yields. [b] 1.0 equiv of diaryliodonium salts were used. [c] $Ar^1 = Ar^2$. [d] Ar^1 = Mes.

and 1-phenyl-1-butyne were also examined. The corresponding products were obtained (**9k**–**m**), but the yields were lower.

According to several mechanism studies (SI), a plausible $Cu^{I/III}$ cycle was proposed for the above reaction (Scheme 5). The active species Cu^I would be initially formed through the disproportionation of Cu^{II}.[9,10] Oxidative addition of **5a** to the Cu^I species gave a strongly electrophilic Cu^{III}-aryl species, which could coordinate with **8a**. The resulting Cu^{III} complex then would undergo either an insertion reaction to the C–C triple bond or attack by nucleophiles to generate **11**. Reductive elimination of **11** may regenerate the active Cu^I species and the intermediates **12**, which would produce the final product **9** after hydrolysis and tautomerism accompanied with the generation of a proton. Meanwhile, another pathway may also occur in acidic conditions along with the accumulation of a proton. In the presence of a proton, **8a** may undergo an addition reaction to give intermediate **14**, which could also be formed through the protonation of **11**. Then an electrophilic metalation between the electron-abundant olefin **14** and the electrophilic Cu^{III}-aryl intermediate would produce the intermediate **15**. After reductive elimination and hydrolysis, the product **9** could be afforded along with the regeneration of a proton and the active Cu^I species. The byproduct **10** may be formed through the hydrolysis of intermediate **14**.

Scheme 5. Proposed Mechanism for the Reaction of **8a** with **5**



In summary, we have developed a new approach to the synthesis of α-arylketones by the Cu-catalyzed reaction of alkynes and diaryliodonium salts. The features of this protocol are as follows: (1) it is the first example of the Cu-catalyzed transformation of the C–C triple bonds to ketones, to our knowledge; (2) the reaction takes place under mild conditions with excellent regioselectivity; (3) unlike $Au^{I/III}$ catalyzed reactions in which an outer oxidant and a large excess of arylation reagent are needed, the iodonium salt acts as both an oxidant and arylation reagent in this reaction, and only 1.1–1.5 equiv of the iodonium salt is required; and (4) the reaction tolerates many functional groups, making it possible to further functionalize the products and synthesize more complicated compounds. These features demonstrate the potential of this protocol, and we believe that it will find many applications in organic synthesis.

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Supporting Information Available. Experimental details and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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