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ARTICLE TYPE

Cu-Catalyzed Intramolecular Hydroarylation of Alkynes

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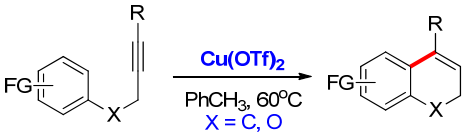
An efficient Cu-catalyzed intramolecular hydroarylation reaction of alkynes has been developed. The reaction is accomplished under mild conditions and shows good tolerance to both of electron-rich and electron-deficient aryl nucleophiles. A series of aryl, heteroaryl, alkyl, and even the N-group attached alkynes are all suitable substrates for the intramolecular hydroarylation.

Introduction

Transition metal-catalyzed hydroarylation of alkynes represents a practical and atom-economical method to form new C(sp^2)-C(sp^2) bonds via aromatic C-H activation.[1-2] In addition, the intramolecular hydroarylation reaction has been recognized as an efficient approach to construct polycyclic aromatic frameworks. Many groups have studied this reaction. For instance, Pd, Pt, Au, Ru, and others precious-metal catalysts catalyzed intramolecular hydroarylation reaction of alkynes have been reported in the past decades.[3] Nonetheless, some problems remained to be solved with these reactions. Expensive and/or poisonous catalysts were normally used to promote the reaction in previous studies, which limited the development of large-scale application. The selectivity of *exo*- and *endo*-type cyclization products still needs to be controlled. Recently, the Fe-catalyzed intramolecular hydroarylation of alkynes have also been reported,[4] but there are still limitations in the types of substrates. For instance, electron-rich aryl nucleophiles are necessary for the intramolecular hydroarylation in Campagne's work.[5] On the other hand, the electron-rich aryl nucleophiles underwent the transformation with a very low yield (4-MeO and 2-MeO, 19% and 13%) in Takaki's work.[6] Besides, the aryl attachment on the alkyne terminal plays an essential role in above reactions. Therefore, the development of a nontoxic and inexpensive catalyst system with universal functional group compatibility is an interesting challenge.

Herein, we describe an general and efficient Cu-catalyzed intramolecular hydroarylation reaction of alkynes under mild conditions (Scheme 1).[7] Both of electron-rich and electron-deficient aryl nucleophiles are well tolerated in the reaction to give the 6-*endo* products in moderate to good yields. Not only the aryl, alkyl, but also the N-group attached alkynes are suitable substrates for the Cu-catalyzed intramolecular hydroarylation. Meanwhile, polycyclic dihydronaphthalenes and chromenes derivatives, which are valuable organic skeleton,[8] can be synthesized by present protocol.

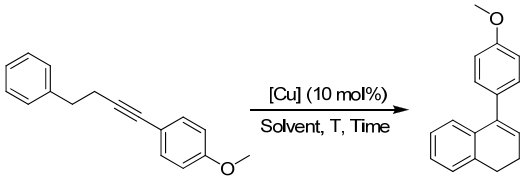
We began our study by examining the intramolecular hydroarylation of 1-methoxy-4-(4-phenylbut-1-ynyl)benzene (**I**). First, different copper catalysts (entries 1-8) were examined in DCE under 80 °C. As a uniquely effective catalyst, $Cu(OTf)_2$ showed commendable catalytic effect, and the target product was obtained in 22% yield (Table 1, entry 6). Other copper catalysts



R = aryl, alkyl, heterocycle
FG = electron-rich and electron-deficient groups

Scheme 1 Cu-catalyzed intramolecular hydroarylation reaction of alkynes

Table 1. Optimization of the Reaction Conditions[a]



I II

Entry	CuX	Solvent	T (°C)	Time (h)	Yield (%)[b]
1	Cu	DCE	80	12	NR
2	CuCl	DCE	80	12	trace
3	CuI	DCE	80	12	NR
4	$CuCl_2$	DCE	80	12	NR
5	$Cu(OAc)_2$	DCE	80	12	NR
6	$Cu(OTf)_2$	DCE	80	12	22
7	$Cu(OTf)_2$	MeOH	80	12	5
8	$Cu(OTf)_2$	DCE/MeOH (1:1)	80	12	48
9	$Cu(OTf)_2$	DCE/MeOH[c]	80	12	87
10	$Cu(OTf)_2$	$MeNO_2$	80	12	18
11	$Cu(OTf)_2$	$PhCH_3$	80	12	95
12	$Cu(OTf)_2$	1,4-dioxane	80	12	trace
13	$Cu(OTf)_2$	$PhCH_3$	60	12	94
14	$Cu(OTf)_2$	$PhCH_3$	30	12	7
15	$Cu(OTf)_2$	$PhCH_3$	60	1	6
16	$Cu(OTf)_2$	$PhCH_3$	60	3	63
17	**$Cu(OTf)_2$**	**$PhCH_3$**	**60**	**4**	**94 (89)[d]**
18[e]	$Cu(OTf)_2$	$PhCH_3$	60	12	trace
19	---	$PhCH_3$	60	12	NR

[a] Reaction conditions: **I** (0.01mmol), [Cu] (10 mol%), solvent (1 mL) under Ar atmosphere. [b] Yield determined by GC. [c] 10 equiv of MeOH in DCE. [d] Isolated yield. [e] In air.

gave inferior results (Table 1, entries 1-5). In order to improve the product yield, a series of organic solvents were tested (entries 7-13). The mixed solvent of DCE/MeOH showed a better result than either DCE or MeOH (entry 8). When 10 equiv of MeOH was added in DCE as the reaction solvent, the product yield was improved to 87% (entry 9).[9] Surprisingly, $PhCH_3$ showed the best efficiency for this reaction, and the yield of desired product was further increased to 95% (entry 11). In addition, it was our goal to achieve this reaction under milder conditions. It was delighted that when we reduced the temperature to 60 °C, the yield of product was not significantly reduced (entry 13). However, the reaction at 30 °C showed a much low activity under the same

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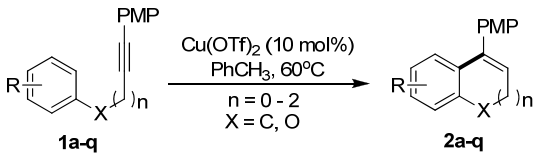
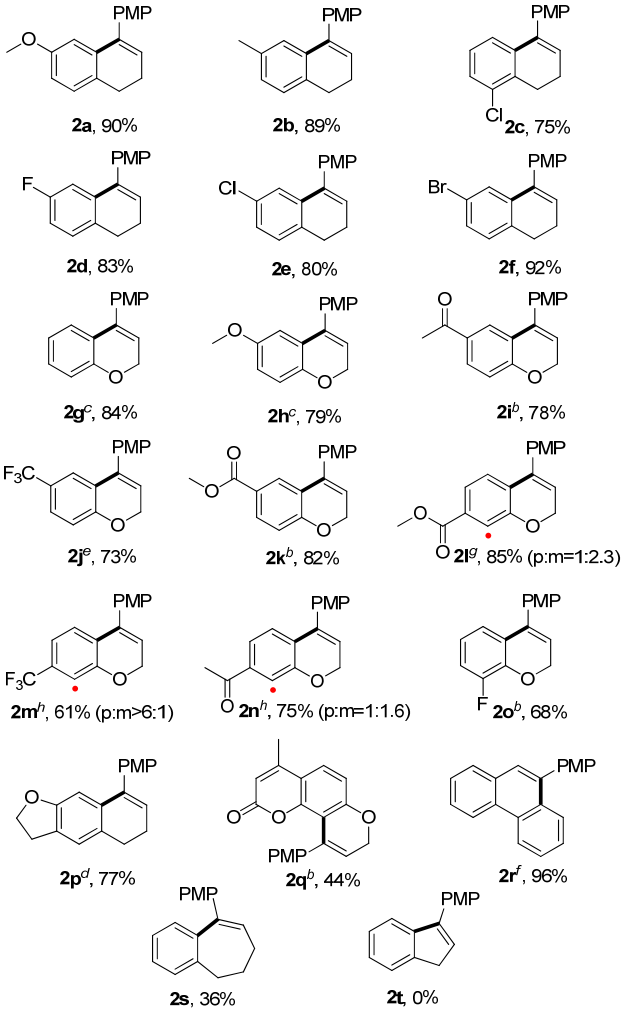
Table 2. Scope of aryl nucleophiles[a]



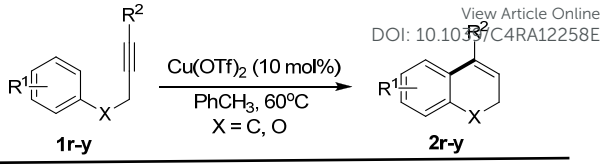


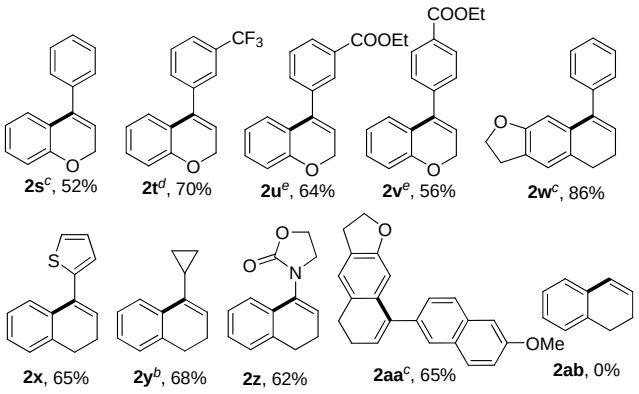
[a] Reaction conditions: **1** (0.01mmol), $Cu(OTf)_2$ (10 mol%), $PhCH_3$ (1 mL) at 60 °C for 4 h under Ar atmosphere. Isolated yield. PMP = p-methoxyphenyl. [b] the solvent is DCE. [c] DCE. 1 h. [d] 10 equiv of MeOH in DCE as the solvent. [e] DCE, 80°C [f] toluene, 80 °C.[g] DCE/ $PhCH_3$(1:1), 80°C. [h] DCE/ $PhCH_3$(1:4), 60°C, 8h.

optimized conditions (entry 14). Finally, the time of this reaction was also examined (entries15-17). Gratifyingly, the reaction was completed with an extremely high yield just in 4 hours (entry 17). Disappointedly, no detectable product was obtained when the reaction was underwent in air conditions (entry 18). Furthermore, in the absence of Cu-catalyst, we did not observe the desired product (entry 19).

With the optimized reaction conditions in hand, we next examined the substrate scope of aryl nucleophiles (Table 2). The O-tethered substrate bearing phenyl group afforded the cyclization product in 84% yield (**2g**). Not only the electron-rich aryl nucleophiles which commonly were used in previous works, were found to undergo the desired reaction in high efficiency, but also the electron-deficient aryl nucleophiles could give the products in moderate to good yields. Many synthetically important functional groups, including ether (**2a**, **2h**), methyl (**2b**), ketone (**2i**, **2n**), trifluoromethyl (**2j**, **2m**), ester (**2k**, **2l**), lactone (**2q**), were well-tolerated in the reaction.

Table 3. Scope of terminal alkyne attachments[a]

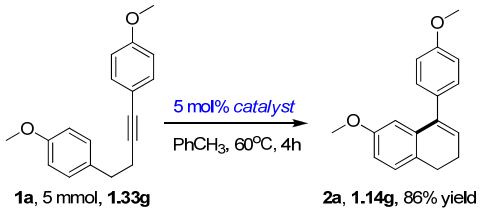




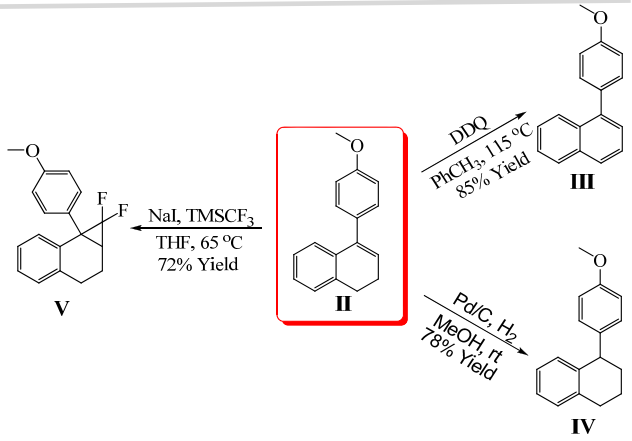
[a] Reaction conditions: **1** (0.01 mmol), $Cu(OTf)_2$ (10 mol%), $PhCH_3$ (1 mL) at 60°C for 4 h under Ar atmosphere. Isolated yield. [b] the solvent is DCE. [c] 10 equiv of MeOH in DCE as the solvent. [d] DCE, 100°C. [e] DCE/ $PhCH_3$(1:1), 80°C, 12 h.

Moreover, arene rings carrying fluoro-, chloro-, and bromo-substituents are compatible with the reaction, enabling additional modifications at the halogenated positions (**2c-2f**, **2o**). Notably, we found that the phenanthrene derivatives can also be achieved in high yield via the cyclization of *o*-alkynyl biaryls under present reaction conditions (**2r**). In addition, the successful synthesis of heterocyclic and polycyclic compounds (**2p**, **2q**) made the protocol be potentially used in late-stage intromolecular cyclization. Importantly, the intramolecular hydroarylation of the *meta*-substitutent substrate **1p** regioselectively gave the product **2p** in 77%. Furthermore, a seven-membered ring can also be formed by this reaction, albeit the yield is relatively lower (**2s**).[10] However, the five-membered ring indene derivative couldn't be formed (**2t**).

Besides, the effect of terminal attachments R^2 in the substituent was investigated (Table 3). In addition to the PMP group, the simple phenyl group as terminal alkyne attachments was also sufficiently reactive, providing a moderate to good yield of the corresponding products (**2u**, **2y**). Compared with the previously developed cationic iron-catalyzed intramolecular hydroarylation alkyne,[6] the present method showed a better functional group compatibility, because the substrates with electron-deficient aromatic rings R^2 were difficult to obtain the desired products in Takaki's work. However, in our reaction, the R^2 group with strong electon-withdrawing CF_3 and ester substitued was also well-tolerated and give the product in excellent yield (**2v-2x**). The substrates with heterocyclic and polycyclic attachments on terminal alkyne, such as thiophene group, oxazolidinone group[11] and naphthalene groups, could undergo the hydroarylation reaction to get the product in good yield (**2z**, **2ab**, **2ac**). Note that the substrate of oxazolidinone-substituted could be tolerated successfully, which pave a route for the construction of more complex polycyclic aromatic compounds. Surprisingly, alkyne with terminal attachments was also achieved the reaction effectively to obtain the target product in 68% yield (**2aa**). Yet, there was no reaction occurred when the unsubstituted alkynes was used (**2ad**).

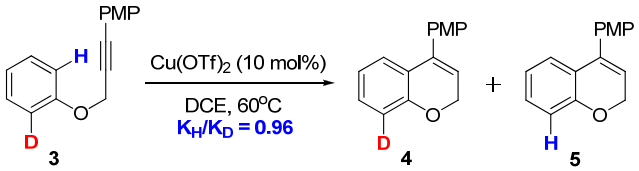


Scheme 2 Gram-scale reaction.



Scheme 3 Transformation of model product.

To probe the synthetic utility of this newly developed protocol, a scaled-up reaction was conducted with an aim on evaluating practical aspects. In this experiment, the hydroarylation of **1a** was conducted on 1.33 g scale, and product **2a** can be obtained in gram quantity with a satisfactory yield of 86% (Scheme 2).[12] Notably, a lower loading of Cu catalyst (5 mol %) was used in this gram-scale reaction. Besides, in order to further demonstrate the worth of the products, the further transformation of the model product was also studied (Scheme 3).[12] The product **II** was successfully oxidized by DDQ (1,2-dichloro-4,5-dicyanobenzoquinone) to a polyaromatic naphthalenes **III**. Then, the hydrogenation of product **II** can also be occurred smoothly (**IV**) with good yield. Next, the compound **V**, which may be an important difluorocyclopropanes derivatives in organofluorine chemistry,[13] was obtained by 1,1-difluorocyclopropanation of product **II**. A series of applications with model product provided a new method to construct the more complicated and valuable polycyclic derivatives.



Scheme 4 Isotope labeling experiment.

To better understand the reaction mechanism, we performed the kinetic isotope experiment (Scheme 4). The K_H/K_D values of intramolecular KIE (kinetic isotope experiments) indicated that the C-H cleavage is not the rate-determine step (K_H/K_D = 0.96). These results suggest that the present Cu-catalyzed cyclization may proceed via a Friedel-Crafts type process.[2h, 2u, 6, 14]

Conclusions

In summary, we have reported an efficient Cu-catalyzed intramolecular hydroarylation reaction of alkynes with good functional group tolerance. a nontoxic and inexpensive catalyst, $Cu(OTf)_2$, was successfully used in this hydroarylation reaction, and showed wonderful catalytic effect. Not only the aryl, but also the alkyl and N-group attached alkynes are suitable substrates for this reaction. Numerous *2H*-naphthalene and *2H*-chromene derivatives can be prepared in good to excellent yields via the straightforward, practically useful method.

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Experimental

General procedure for the synthesis of the Products.

A 10 mL over-dried Schlenk tube was charged with corresponding alkyne (0.1 mmol) (if solid), $Cu(OTf)_2$ (10 mol%, 3.62 mg). The tube was evacuated and backfilled with argon (this procedure was repeated three times). Under a counter flow of argon, corresponding alkyne (0.1 mmol) (if liquid) and solvent (1 mL) were added by syringe. The tube was sealed and the mixture was allowed to stir in a preheated oil bath at 60 °C for 4 h. The mixture was cooled to room temperature when the reaction was completed. Next, the organic solvent was concentrated under reduced pressure. The crude product was purified by chromatography on silica gel with petroleum ether/ethyl acetate to give the product **2**.

Acknowledgements

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Notes and references

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†Electronic Supplementary Information (ESI) available: Experimental details, characterization data, and ^1H and ^{13}C NMR spectra of products. See DOI: 10.1039/b000000x/

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9 Yields of **II** using various solvents: DCE (1 mL)/MeOH (10 equiv) (87%) > DCE (1 mL)/MeOH (20 equiv) (83%) > DCE (1 mL)/MeOH (5 equiv) (64%) > DCE (1 mL)/MeOH (2 equiv) (55%).

10 The yield of remainder material is 58%.

11 3,4-Dihydronaphthalen-1(2H)-one was got with the yield of 26%, when the reaction was accomplished.

12 The specific procedure of experiment. Please see supporting information.

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