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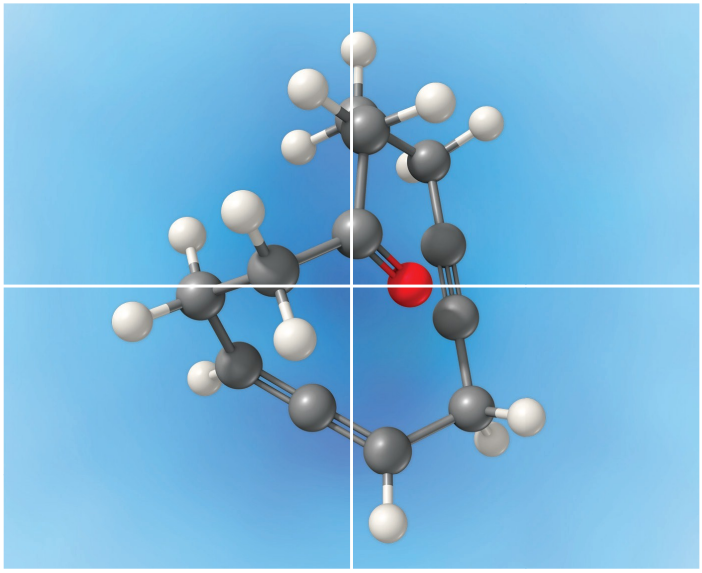

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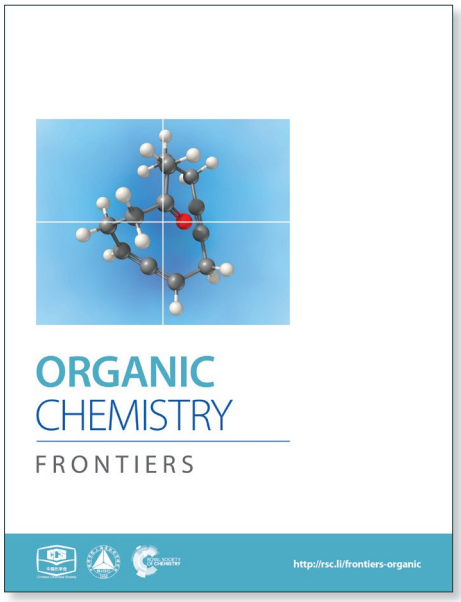

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Copper-catalyzed tandem A^3-coupling–isomerization–hydrolysis reactions of aldehydes and terminal alkynes leading to chalcones

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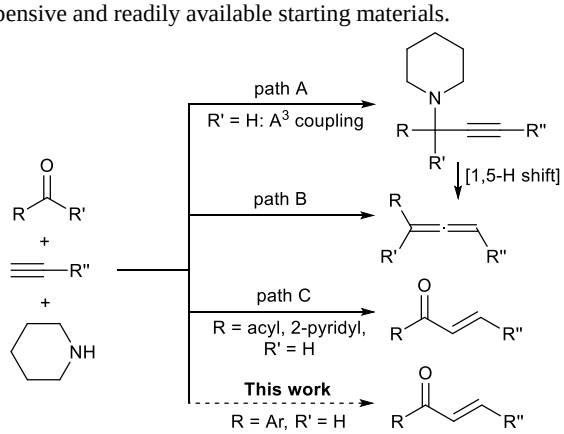
Catalyzed by simple copper salt, the reaction of an aryl aldehyde and a terminal alkyne in the presence of piperidine delivers the valuable chalcone products, which were rarely found in previous A^3 coupling reactions. This reaction can be applied to a wide range of substrates. Mechanistic studies indicate that this reaction experiences tandem process containing A^3 coupling, copper assisted isomerization of propadienamine to allenylamine and subsequent hydrolysis.

Tandem reactions, in which multiple reactions are combined into one synthetic operation, have been extensively studied in synthetic chemistry in recent years.[1] Three-component tandem reaction of an aldehyde, a terminal alkyne and an amine, often catalyzed by transition-metals and widely known as A^3-coupling, generally leads to the formation of a propargylamine[2] (Scheme 1, path A). Commonly, such structure is stable under typical A^3-coupling reaction conditions if there is no additional nucleophilic center[3] on the substrate structure. An alternative reaction pathway is the generation of allenes via hydride shifting (1,5-H shift) of propargylamine along with the elimination of amine, which was firstly developed by Crabbe and later modified by Ma's group, et al. Formaldehyde,[4] aldehydes,[5] and ketones[6] can be applied for corresponding allene formations using this strategy (Scheme 1, path B). In conjunction with our current interest on copper catalyzed coupling reactions with alkynes,[7] we unexpectedly discovered that these components could lead to valuable α,β-unsaturated ketones. So far, only two special instances, namely glyoxal-[8] or pyridine-2-carbaldehyde-like[9] substrates could achieve such products via alkyne-allene isomerization and subsequent hydrolysis, mainly due to the fact that presence of the electron-withdrawing group in the propargylamine structure will promote the deprotonation (Scheme 1, path C). Meanwhile, expensive Au catalyst or special supported copper nanoparticles were prerequisite to the success of the above transformations, therefore it severely hinders their application in synthesis.

Our study showed that such limitation above could be conquered by using simple and environmental benign copper salt as catalyst in DMSO. The typical A^3 starting materials with a broad scope of aryl alkynes and aldehyde could lead to the formation of chalcones. Although many strategies have been known for chalcone synthesis such as classical Claisen–Schmidt condensation[10], catalyzed cross coupling[11a,c], Meyer-Schuster rearrangements[11b], carbonylation[11f] and hydroacylation[11h], our method is a new strategy for the synthesis of such important biologically active building blocks[12] from inexpensive and readily available starting materials.

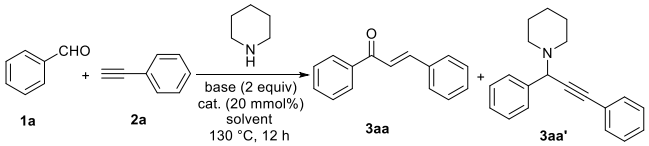


Scheme 1 Three-component reaction of an aldehyde/ketone, a terminal alkyne and an amine

We began our study on the traditional A^3 coupling reaction by using benzaldehyde (**1a**), phenylacetylene (**2a**), and piperidine as starting materials. Initially, catalyzed by $Cu(OAc)_2$, the reaction was carried out in DMSO in the presence of pyridine as base at 100 °C for 12 h. Unsurprisingly, the A^3 product propargylamine (**3aa′**) was obtained in 27% GC yield as the major product. In addition, the unexpected product chalcone (**3aa**) was formed in 11% yield (Table 1, entry 1). We then decided to optimize the reaction conditions to

make **3aa** as the main product. To our delight, raising the reaction temperature to 130 °C efficiently reversed the product distribution (Table 1, entry 2). Solvent obviously played an important role in the selectivity of this reaction and DMSO was the only one among all solvents we screened which could lead to the formation of chalcone as the main product (Table 1, entries 3-7). Further screening on bases showed that pyridine was the optimal one (Table 1, entries 8-9). Interestingly, under pyridine-free condition, only slight decreasing on chalcone formation was observed (Table 1, entry 10), which suggested that pyridine might not act as a base but a ligand in this transformation. The reactions performed under solvent free conditions did not lead to satisfied results, showing the important role that DMSO played (Table 1, entries 11-12).

Table 1 Optimization of the Reaction Conditions [a]

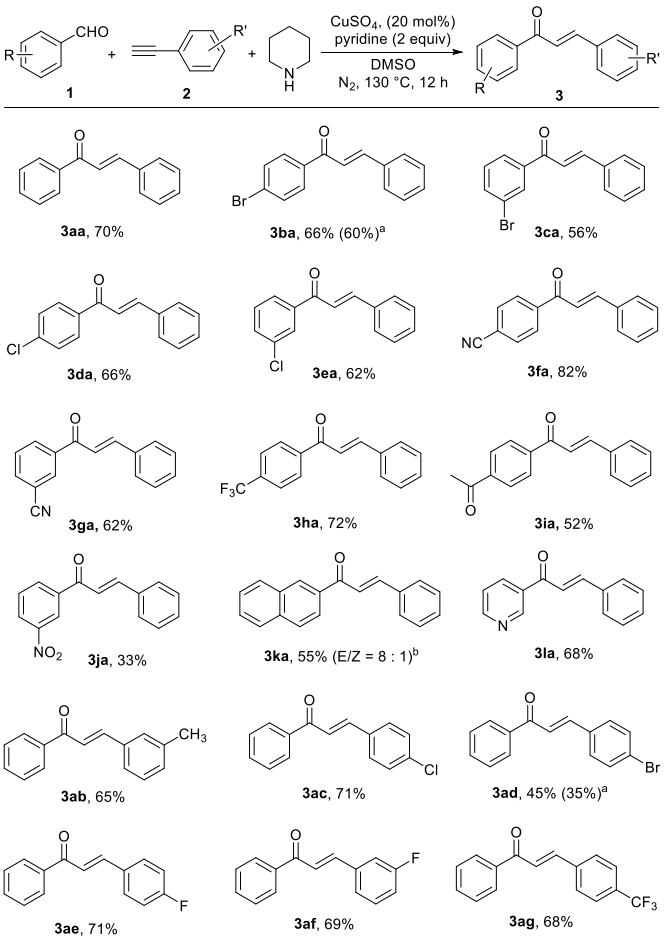


Entry	Cat.	base	solvent	**3aa** (%)[b]	**3aa′** (%)[b]
1[c]	$Cu(OAc)_2$	pyridine	DMSO	11	27
2	$Cu(OAc)_2$	pyridine	DMSO	50	5
3	$Cu(OAc)_2$	pyridine	toluene	trace	72
4	$Cu(OAc)_2$	pyridine	*o*-xylene	4	78
5	$Cu(OAc)_2$	pyridine	*t*-AmOH	0	88
6	$Cu(OAc)_2$	pyridine	dioxane	trace	74
7	$Cu(OAc)_2$	pyridine	NMP	16	35
8	$Cu(OAc)_2$	Et_3N	DMSO	35	9
9	$Cu(OAc)_2$	DABCO	DMSO	38	1
10	$Cu(OAc)_2$	-	DMSO	45	7
11	$Cu(OAc)_2$	pyridine	-	25	32
12	$Cu(OAc)_2$	-	-	27	5
13	-	pyridine	DMSO	0	0
14	CuBr	pyridine	DMSO	42	8
15	$CuBr_2$	pyridine	DMSO	43	17
16	CuCl	pyridine	DMSO	55	10
17	$CuCl_2$	pyridine	DMSO	39	6
18	CuI	pyridine	DMSO	33	7
19	$Cu(TFA)_2$	pyridine	DMSO	28	21
20	$CuSO_4$	pyridine	DMSO	76 (70)[d]	1
21	$Cu(OTf)_2$	pyridine	DMSO	46	2
22	$AuCl_3$	pyridine	DMSO	39	4
23	AgOTf	pyridine	DMSO	32	4

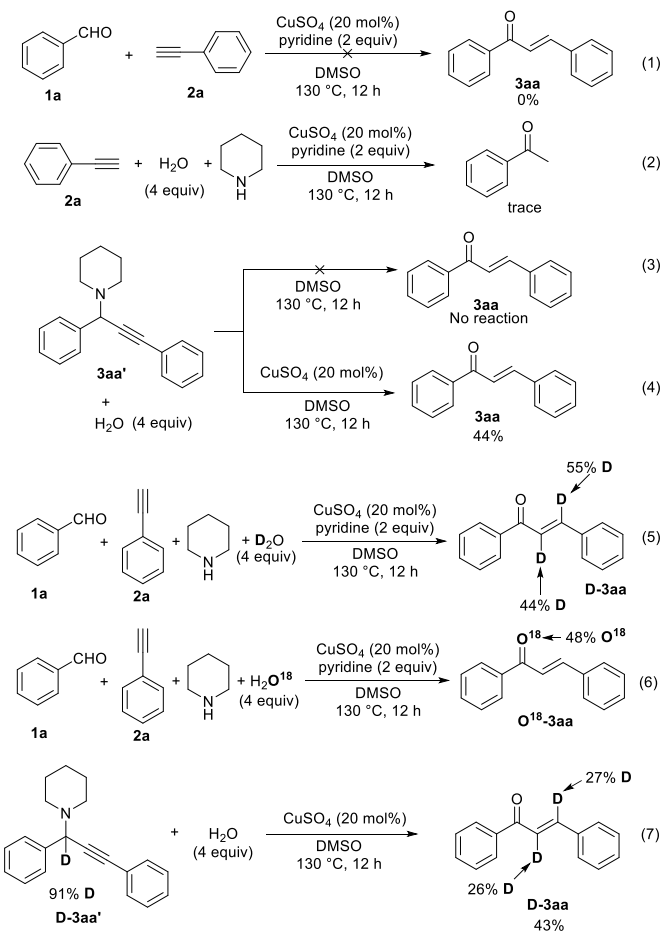
[a] Reaction conditions: benzaldehyde (**1a**) (52 μL, 0.5 mmol), phenylacetylene (**2a**) (75 μL, 0.75 mmol), piperidine (74 μL, 0.75 mmol), catalyst (0.1 mmol), base (1 mmol), solvent (1.5 mL), N_2 atmosphere. [b] Yields were based on GC analyses using *n*-dodecane as the internal standard. [c] The reaction was carried out at 100 °C. [d] Isolated yield.

Control experiment showed that no reaction occurred in the absence of a copper catalyst (Table 1, entry 13). As a result of catalyst screening (Table 1, entries 14-23), $CuSO_4$ exhibited the best reactivity and selectivity on chalcone formation (Table 1, entry 20). Other copper salts, either Cu(I) or Cu(II) gave low to medium yields. Notably, Au and Ag catalysts which were widely used in traditional A^3 couplings only gave inferior yields of chalcones under our conditions. We also used other secondary amines such as morpholine and pyrrolidine instead of piperidine, however, they were ineffective for this reaction (see Section 3.1 in Supporting Information).

Next, we explored the scope of this tandem reaction by using various aryl aldehydes **1** and terminal alkynes **2** under the optimized conditions and the results are summarized in Scheme 2. A wide range of chalcones could be readily obtained by this protocol. We first examined the reaction of phenylacetylene (**2a**) with a series of aryl aldehydes **1**. It could be seen that a wide range of substituents such as halo (Cl and Br), trifluoromethyl, cyano, acetyl and even the strong electron-withdrawing nitro group were all tolerated, affording corresponding chalcones (**3ba**-**3ja**) in moderate to high yields. 2-Naphthaldehyde (**1k**) and the heteroaromatic aldehyde (**1l**) could also be applied for this reaction. We then explored the scope of terminal alkynes **2**. Both electron-rich (**2b**) and electron-deficient (**2c**-**2g**) substituted phenylacetylenes exhibited good reactivity and the corresponding desired chalcones were obtained in moderate yields. All the reactions above had a clear preference for the *E* geometrical isomer demonstrating by a 15.5 Hz olefinic proton coupling constant. In very few cases a trace amount of the *Z* products (< 1 : 20) were detected. Exception is the reaction of 2-naphthaldehyde (**1k**), in which corresponding chalcone (**3ka**) was obtained as a mixture of isomers with the *E*/*Z* ratio of 8 : 1. Unfortunately, this reaction could not extend to strong electron-rich aldehydes, aliphatic aldehydes and aliphatic alkynes, wherein either A^3 coupling products were afforded or only starting material remained (for Me_2N- or AcHN-substituted benzaldehyde).



Scheme 2 Substrate scope. [a] In the absence of pyridine; [b] Based on GC.

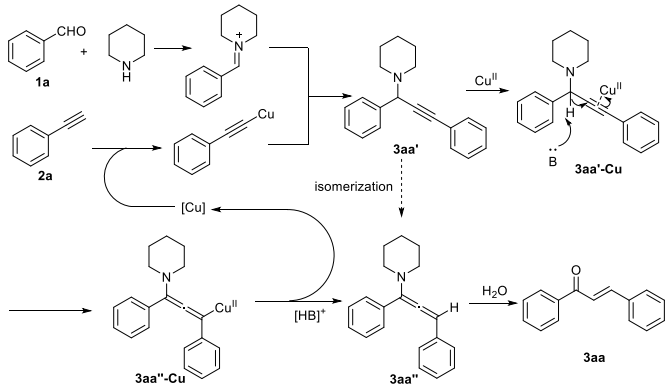


Scheme 3 Control experiments

To gain insight into the reaction mechanism, we initially carried out some control experiments. Firstly, when the reaction was performed in the absence of piperidine, no chalcone product was formed (Scheme 3, eq. 1). This result excludes the possible route containing the alkynylation of **1a** leading to the formation of propargylic alcohol (1,3-diphenylprop-2-yn-1-ol) and the subsequent isomerization via 1,3-H shift.[13] Next, the reaction of phenylacetylene (**2a**) with water under standard conditions afforded only trace of acetophenone, illustrating that our reaction was not proceed through the well-known Claisen–Schmidt condensation[10] (Scheme 3, eq. 2). These above experiments clearly supported the A^3 coupling was the first step. Therefore propargylamine **3aa'** was prepared and employed with water under different conditions. No reaction occurred when it was just heated at 130 °C in DMSO. Yet 44% of desired product **3aa** was obtained in the presence of $CuSO_4$, which suggested that $CuSO_4$ could promote chalcone formation in the absence of base (Scheme 3, eq. 3-4). Subsequently, our labeling experiment was conducted with D_2O and it was found that two deuterium atoms were incorporated into the final product **3aa** with 44% and 55% incorporation (Scheme 3, eq. 5). In ^{18}O labeling experiment, $H_2{}^{18}O$ was added to the reaction system under standard condition, resulting in the ^{18}O-labeled product **^{18}O-3aa** (Scheme 3, eq. 6). Finally, the A^3 product with the propargylic proton alpha to the amine being replaced by

deuterium (**D-3aa'**) was allowed to react with water. The low deuterated ratios in the product chalcone (**D-3aa**) indicated that this reaction is not proceeded via 1,2-hydride transfer.

On the basis of all above results, the reaction mechanism was postulated in Scheme 4. Initially, copper-catalyzed A^3 coupling results in the formation of propargylamine **3aa'**. Coordination of copper with the triple bond facilitates the deprotonation by a base, which is readily proceeded only in DMSO.[14] The existence of electron-withdrawing substituents is generally beneficial on enhancing the acidity of propargylic proton. Subsequent protonation affords allenylamine intermediate **3aa''**.[15] Hydrolysis of the enamine substructure then leads to the final product **3aa**, and the thermodynamically more stable *E* geometrical isomer is formed preferentially.



Scheme 4 Proposed mechanism.

Conclusions

In conclusion, we have developed a novel copper-catalyzed A^3-coupling–isomerization–hydrolysis tandem reaction to afford valuable chalcones from aryl aldehydes, terminal alkynes and piperidine, instead of stopping at the A^3-coupling step. Mechanistic study showed that copper catalyst might play dual roles in this transformation: facilitate the A^3 coupling as well as promote the isomerization of the propargylamine intermediate via coordination with the triple bond. Further research on understanding of this new reaction is ongoing in our laboratory.

Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental details and full spectroscopic data for all products]. See DOI: 10.1039/c000000x/

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