Advanced Synthesis & Catalysis

Accepted Article

Title: Regio- and Stereoselective Synthesis of Enynyl-Aryl Ethers Enabled by Copper/Iodide Tandem Catalysis

Authors: Yun-Bin Wu, Lin Xiao, Chun-Li Mao, Zhong-Lin Zang, Cheng-He Zhou, and Gui-Xin Cai

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201900626

Link to VoR: http://dx.doi.org/10.1002/adsc.201900626

10.1002/adsc.201900626

COMMUNICATION

DOI: 10.1002/adsc.201######.

Regio- and Stereoselective Synthesis of Enynyl-Aryl Ethers Enabled by Copper/Iodide Tandem Catalysis

Yun-Bin Wu,[a] Lin Xiao,[a] Chun-Li Mao,[a] Zhong-Lin Zang,[a] Cheng-He Zhou*,[a] and Gui-Xin Cai*,[a,b]

[a] Key Laboratory of Applied Chemistry of Chongqing Municipality, Institute of Bioorganic & Medicinal Chemistry, School of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, China
E-mail of corresponding author: gxcai@swu.edu.cn; zhouch@swu.edu.cn.
[b] Beijing National Laboratory for Molecular Sciences, Beijing 100190, China

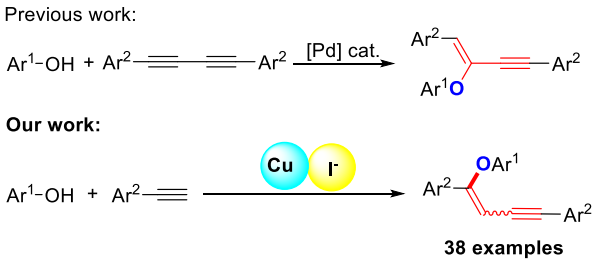
Received:######.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

Abstract: An approach to preparing enynyl-aryl ethers from phenols and phenylacetylenes is described. This method without extra ligands, overcoming the favored Glaser−Hay dimerization of alkyne, features a wide substrate scope (38 examples including endofolliculina and indole) and the merits of high atom and step economy, good regio- and stereoselectivity (*Z*-isomers major) in moderate to good isolated yields. Mechanistic studies show that the reaction is enabled by distinctive copper/iodide tandem catalysis.

Keywords: copper/iodide tandem catalysis; enynyl-aryl ethers; regio- and stereoselectivity; cross-electrophile coupling

Enynyl-aryl ether derivatives possessing conjugated double and triple bonds are valuable and privileged scaffolds widely embedded in organic materials, pharmaceuticals and agrochemicals.[1,2d] Great efforts have been made to gain access to this intriguing structural unit. Published synthetic methods include the addition of phenols to conjugated diynes[2a], Sonogashira couplings[2b-2d] and multistep procedures[2e-2i]. Although the chemical community has made significant progress in this field, current methods still suffer from various challenges, such as the limited substrate scope, expensive catalysts, prefunctionalized starting materials and/or the requirement of multistep procedures. Ideally, employing the commercially available and cheap phenols and phenylacetylenes to directly construct C(sp^2)−O/C(sp^2)−C(sp) bonds can effectively avoid the separation of halides, and therefore promoting the elegance of synthesis. However, major challenges happen, due to the high reactivity of phenols and alkynes[3], especially the oxidation of phenols and unsaturated C−C bonds by high-valent iodine reagents[4] along with the homo-/heterocoupling of phenylacetylenes in the presence of transition metals[5], and straightforward methods for the efficient synthesis of enynyl-aryl ether compounds are still scarce. Copper catalysis, owing to the low toxicity and cost-effective nature of copper, has witnessed significant momentum since its emergence[3a,6]. But the success of these protocols generally relies on the auxiliary of extra ligands[6,7], in particular of nitrogen- and oxygen-carrying compounds, and the study of other factors boosting copper catalysis is underdeveloped. Although organic transformations involving iodine reagents are quite elegant and particularly useful[8], a limited knowledge has been acquired when employing the copper/iodide combination for tandem catalysis without additional ligands. Thus, driven by our previous works constructing the scaffold of aryl alkenyl ether[9] and copper-catalyzed tandem reactions[10] promoted by equivalent iodides[11], we herein report a regio- and stereoselective route using unactivated phenols and phenylacetylenes via the copper/iodide tandem catalysis[12] without extra ligands to efficiently prepare enynyl-aryl ether compounds (Scheme 1).



Scheme 1. Synthetic strategies of enynyl-aryl ethers.

Initially, we began our investigation by examining phenol (**1a**) and phenylacetylene (**2a**) as model substrates to optimize the reaction conditions (Table 1). Testing of **1a** and **2a** did lead to 30% isolated yield of enynyl-aryl ether products ***(Z)*-3aa/*(E)*-3aa'** with good *Z*:*E* selectivity (*Z*:*E* = 86:14) (Table 1, entry 1). In consideration of the auxiliary effect of ligands[6,7], we next investigated the commonly used *N*-donor ligand and unexpectedly, the ligand played a negative role in this transformation (Table 1, entry2). Then switching to

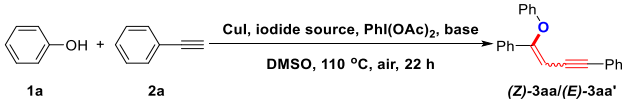
This article is protected by copyright. All rights reserved.

Accepted Manuscript

10.1002/adsc.201900626

other base revealed that Cs_2CO_3 was suitable one and a cheerful result could be achieved to deliver **3aa/3aa'** in 83% isolated yield (Table 1, entry 3). In comparison with TBAI, TBAB showed an analogous performance, whereas TBAC seemed to be much less effective (Table 1, entries 4-5). Finally, a slight decrease in yield was observed when the reaction was conducted at 100 °C, while the trace amount of products could be obtained at 90 °C (Table 1, entries 6-7). Further screening the reaction conditions including copper catalysts, oxidants, other iodide sources, bases and solvents has been shown in Supporting Information (SI) Table 1.

Table 1. Optimization of the reaction conditions[a].



entry	iodide source/additive	base	yield [%](*Z*:*E*) [b]
1	TBAI[c]	K_3PO_4	30 (86:14)
2[d]	TBAI	K_3PO_4	26 (82:18)
3	**TBAI**	**Cs_2CO_3**	**83 (86:14)**
4	TBAC[e]	Cs_2CO_3	42 (86:14)
5	TBAB[f]	Cs_2CO_3	74 (86:14)
6[g]	TBAI	Cs_2CO_3	72 (86:14)
7[h]	TBAI	Cs_2CO_3	trace

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.4 mmol), CuI (0.02 mmol), iodide source (0.02 mmol), $PhI(OAc)_2$ (1 equiv), base (2 equiv), DMSO (1 mL) in a sealed tube under air at 110 °C for 22 h.

[b] Isolated yields (*Z*-**3aa** isomer and *E*-**3aa** isomer can be completely separated by flash column chromatography, and the yield in Table 1 is the sum of the isolated yield of *Z*-**3aa** and that of *E*-**3aa**). The ratio of *Z* isomer to *E* isomer is calculated by the *Z* and *E* isomers' isolated yields.

[c] TBAI = tetrabutylammonium iodide.

[d] 1,10-Phenanthroline monohydrate (0.1 mmol) was added.

[e] TBAC = tetrabutylammonium chloride.

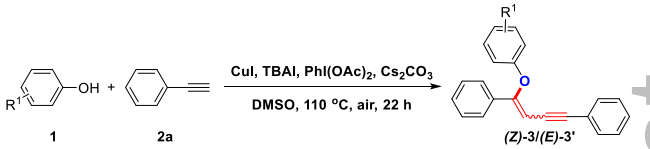
[f] TBAB = tetrabutylammonium bromide.

[g] 100 °C.

[h] 90 °C.

With the optimized protocol in hand, we next examined the substrate scope. First, phenols bearing various substituents on the phenyl ring were tested (Table 2). Pleasingly, both electron-rich and electron-deficient phenols undergo effective transformations and this reaction appears to be relatively insensitive to steric effects: *ortho*, *meta* and *para* substitution can be well-tolerated, except for the methoxyl group and the nitro group. Due to 2-methoxyphenol serving as a strong bidentate ligand on the copper catalyst[6], no desired product ***(Z)*-3ga** was observed in this transformation. And in the case of 4-methoxyphenol, only a very minor amount of the product ***(Z)*-3va** was formed. Notably, the structure of ***(Z)*-3wa** was confirmed by X-ray crystallography (Please refer to SI for details). [13] Naphthols were also compatible under the standard conditions, but the performance of naphthalen-2-ol was much better than that of naphthalen-1-ol (***(Z)*-3za** and ***(Z)*-3ya**, respectively). However, the success of this transformation could not be extended to phenols containing heterocycles such as pyridin-4-ol and quinolin-4-ol because of these heterocyclic phenols as strong bidentate ligands blocking the catalytic cycle of copper catalyst (not shown in Table 2).

Table 2. Substrate scope of phenols[a].



product		yield [%]	product		yield [%]
R^1 = H,	***(Z)*-3aa,**	71	R^1 = 3-CH_3,	***(Z)*-3na,**	43
	***(E)*-3aa',**	12		***(E)*-3na',**	10
= 2-F,	***(Z)*-3ba,**	52[b]	= 3-OCH_3,	***(Z)*-3oa,**	37
= 2-Cl,	***(Z)*-3ca,**	50[b]		***(E)*-3oa',**	8
= 2-Br,	***(Z)*-3da,**	49[b]	= 3-$C(CH_3)_3$,	***(Z)*-3pa,**	37[b]
= 2-I,	***(Z)*-3ea,**	42[b]	= 4-Cl,	***(Z)*-3qa,**	61
= 2-CH_3,	***(Z)*-3fa,**	35[b]		***(E)*-3qa',**	14
= 2-OCH_3,	***(Z)*-3ga,**	NP[c]	= 4-Br,	***(Z)*-3ra,**	58
= 2-$CH(CH_3)_2$,	***(Z)*-3ha,**	29[b]		***(E)*-3ra',**	14
= 3-F,	***(Z)*-3ia,**	69	= 4-I,	***(Z)*-3sa,**	53
	***(E)*-3ia',**	14		***(E)*-3sa',**	12
= 3-Cl,	***(Z)*-3ja,**	63	= 4-NO_2,	***(Z)*-3ta,**	NP[c]
	***(E)*-3ja',**	14	= 4-CH_3,	***(Z)*-3ua,**	21[b]
= 3-Br,	***(Z)*-3ka,**	62	= 4-OCH_3,	***(Z)*-3va,**	trace
	***(E)*-3ka',**	13	= 4-Ph,	***(Z)*-3wa,**	74
= 3-I,	***(Z)*-3la,**	56		***(E)*-3wa',**	14
	***(E)*-3la',**	12	= 4-CHO,	***(Z)*-3xa,**	42[b]
= 3-CF_3,	***(Z)*-3ma,**	44[b]	= 1-Naphthol,	***(Z)*-3ya,**	trace
			= 2-Naphthol,	***(Z)*-3za,**	27[b]

[a] Reaction conditions: **1** (0.4 mmol), **2a** (0.4 mmol), CuI (0.02 mmol), TBAI (0.02 mmol), $PhI(OAc)_2$ (1 equiv), Cs_2CO_3 (2 equiv), DMSO (1 mL) in a sealed tube under air at 110 °C for 22 h with isolated yields.

[b] Because the *E*-isomer is too little to separate and purify, only *Z*-isomer was isolated and analysed.

[c] NP = no desired product.

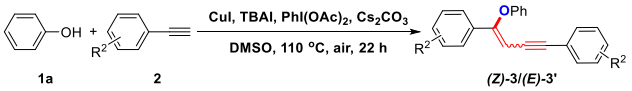
Phenylacetylenes bearing different substituents were also explored to further expand the substrate scope of our catalytic system (Table 3). Similarly, except for these functional groups including 2-OCH_3, 4-OCH_3 and 4-NO_2, a range of phenylacetylenes participated smoothly in this reaction and provided the corresponding products with high stereo-selectivity in moderate to good isolated yields. And the treatment with 2-ethynylthiophene and 3-ethynylpyridine proceeded well to obtain the desired products (***(Z)*-3aq/*(E)*-3aq'** and ***(Z)*-3ar/*(E)*-3ar'**) in moderate isolated yields, albeit in lower stereoselectivity. However, aliphatic alkyne such as 1-ethynylcyclohex-1-ene showed a poor performance giving a trace amount of the products.

Accepted Manuscript

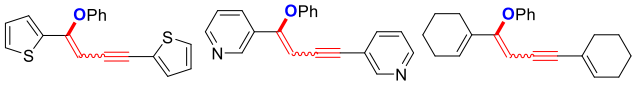
This article is protected by copyright. All rights reserved.

10.1002/adsc.201900626

Table 3. Substrate scope of phenylacetylenes[a].



product	yield [%]	product	yield [%]
R^2 = 2-Cl,	***(Z)*-3ab,** 48[b]	R^2 = 4-F,	***(Z)*-3ak,** 63
= 2-Br,	***(Z)*-3ac,** 43[b]		***(E)*-3ak',** 14
= 2-OCH_3,	***(Z)*-3ad,** NP[c]	= 4-Cl,	***(Z)*-3al,** 60
= 3-F,	***(Z)*-3ae,** 63[b]		***(E)*-3al',** 12
= 3-Cl,	***(Z)*-3af,** 55[b]	= 4-Br,	***(Z)*-3am,** 58
= 3-Br,	***(Z)*-3ag,** 51[b]		***(E)*-3am',** 13
= 3-CH_3,	***(Z)*-3ah,** 46[b]	= 4-CH_3,	***(Z)*-3an,** 44[b]
= 3-OCH_3,	***(Z)*-3ai,** 36[b]	= 4-$CH_2CH_2CH_3$,	***(Z)*-3ao,** 41[b]
= 4-NO_2,	***(Z)*-3aj,** NP[c]	= 4-OCH_3,	***(Z)*-3ap,** trace



***(Z)*-3aq,** 38% ***(E)*-3aq',** 19% | ***(Z)*-3ar/*(E)*-3ar',** 54% (75:25)[d] | ***(Z)*-3as/*(E)*-3as',** trace

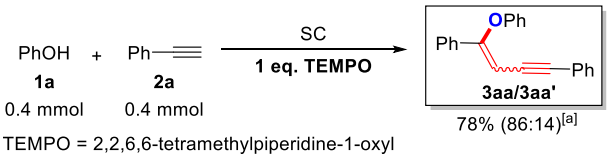
[a] Reaction conditions: **1a** (0.4 mmol), **2** (0.4 mmol), CuI (0.02 mmol), TBAI (0.02 mmol), $PhI(OAc)_2$ (1 equiv), Cs_2CO_3 (2 equiv), DMSO (1 mL) in a sealed tube under air at 110 °C for 22 h with isolated yields.

[b] Because the *E*-isomer is too little to separate and purify, only *Z*-isomer was isolated and analysed.

[c] NP = no desired product.

[d] The *Z*/*E* ratio was determined by ^1H NMR analysis.

To elucidate the reaction mechanism, a series of control experiments has been conducted (Schemes 2-4 and Table 4). Radical trapping experiment was carried out at first by adding 1 equivalent of TEMPO (2,2,6,6-tetramethyl-piperidine-1-oxyl) under the standard conditions and the result indicated that this transformation was not involved in free radicals (Scheme 2).



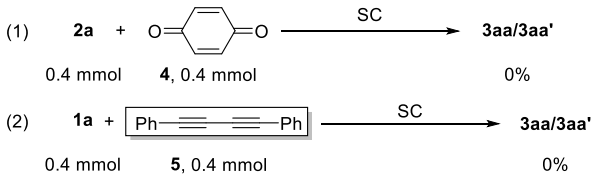
TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl

SC: Standard Conditions (10 mol% CuI, 10 mol% TBAI, 1 eq. $PhI(OAc)_2$, 2 eq. Cs_2CO_3, DMSO, 110 °C, air, 22 h)

[a] The *Z*/*E* ratio was determined by flash silica column chromatography and was calculated by the *Z* and *E* isomer's isolated yields.

Scheme 2. Radical trapping experiment.

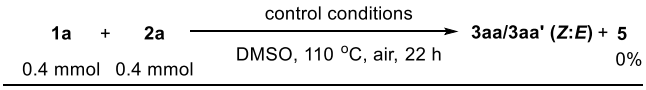
Then experimental results of benzoquinone **4** and 1,4-diphenylbuta-1,3-diyne **5** instead of **1a** and **2a**, respectively, excluded **4** or **5** as the reaction intermediate, and therefore demonstrated that this work differed from Yamamoto's[2a] and Yao's work[14] via palladium catalysis (Scheme 3). Probably due to the high reaction temperature and the lack of extra nitrogen-containing ligand, our reaction did not involve the Glaser−Hay dimerizations via the homocoupling process of the alkynyl-copper complex in the presence of terminal alkynes and copper catalyst.[15]



Scheme 3. Experimental results of **4** and **5**.

The role of each relevant chemical reagent (such as CuI, TBAI, $PhI(OAc)_2$ and Cs_2CO_3) in this reaction was next investigated (Table 4). Although the base was necessary, the influence of Cs_2CO_3 only existed when it combined with the other three partners (Table 4, entry 1) and any two or three factors of them would lead to a poor performance (Table 4, entries 2-9), which might indicate a synergistic effect among them.

Table 4. The role of each relevant chemical reagent.



entry	control conditions	yield [%] (Z:E)
1	[Cu][a], [I^-][b], $PhI(OAc)_2$[c], Cs_2CO_3[d]	83 (86:14)[e]
2	[I^-], $PhI(OAc)_2$, Cs_2CO_3	12 (91:9)[f]
3	[Cu], $PhI(OAc)_2$, Cs_2CO_3	34 (82:18)[f]
4	[Cu], [I^-], Cs_2CO_3	23 (90:10)[f]
5	[Cu], [I^-], $PhI(OAc)_2$	0
6	Cs_2CO_3	0
7	[Cu], Cs_2CO_3	0
8	[I^-], Cs_2CO_3	0
9	$PhI(OAc)_2$, Cs_2CO_3	0

[a] [Cu] = 10 mol% CuI.

[b] [I^-] = 10 mol% TBAI.

[c] 1 eq. $PhI(OAc)_2$.

[d] 2 eq. Cs_2CO_3.

[e] The Z/E ratio was calculated by the Z and E isomer's isolated yields.

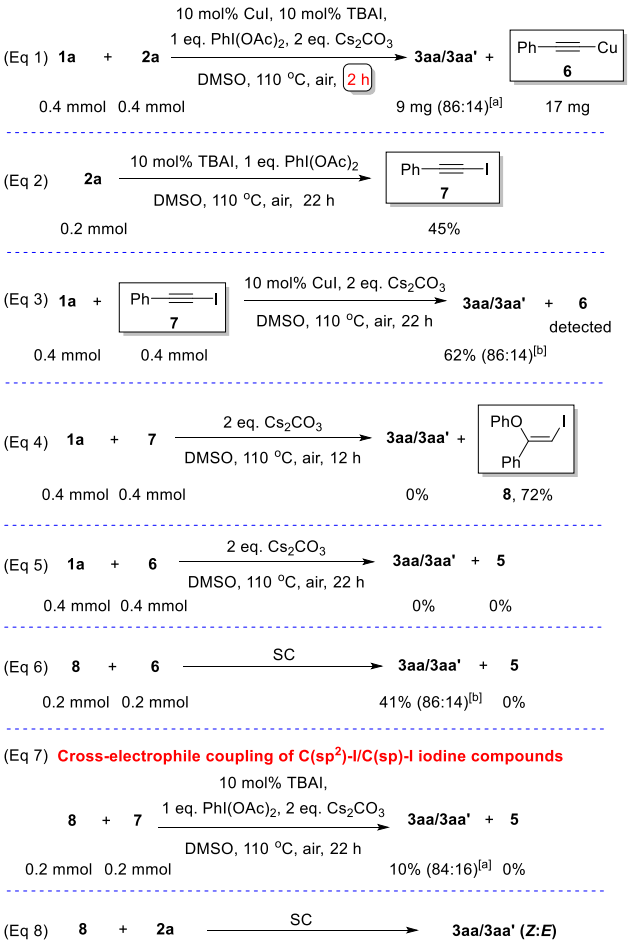
[f] The Z/E ratios were determined by 1H NMR analysis.

The reactivities of intermediates **6**, **7** and **8** were further investigated (Scheme 4). When the model reaction was conducted for 2 h, phenylethynyl copper intermediate **6** was obtained (Scheme 4, Eq 1), which proved that **6** was an important reaction intermediate in our reaction system. What's more interesting was that the treatment of **2a** with TBAI and $PhI(OAc)_2$ in DMSO at 110 °C for 22 h successfully gave (iodoethynyl)benzene **7** in 45% isolated yield (Scheme 4, Eq 2). **7** reacting with **1a** in the presence of CuI and Cs_2CO_3 also afforded ***(Z)*-3aa/*(E)*-3aa'** in

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/adsc.201900626

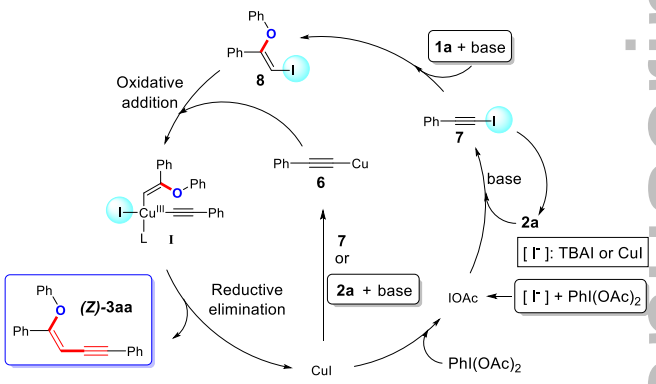


entry	changes from the optimal condition	yield [%] (*Z*:*E*)
1	none	75 (81:19)[a]
2	without CuI	trace
3	without TBAI	28 (80:20)[a]
4	without $PhI(OAc)_2$	12 (81:19)[a]
5	without Cs_2CO_3	0

[a] *Z*/*E* ratios were determined by ^{1}H NMR analysis.
[b] *Z*/*E* ratios were determined by flash silica column chromatography and were calculated by the *Z* and *E* isomers' isolated yields.

Scheme 4. The reactivities of intermediates **6**, **7** and **8**.

62% isolated yield along with a certain amount of compound **6**, which probably meant that **7** was another intermediate in our reaction involving umpolung of **7** (Scheme 4, Eq 3)[16]. On the contrary, we found that compound **8**[17] was obtained as a main product[2f] in the absence of CuI and no desired products **3aa/3aa'** were obtained (Scheme 4, Eq 4), which illustrated the important role of copper catalyst in the reaction. Subsequently, **1a** reacted with **6** instead of **7** under similar conditions and the result showed that desired products **3aa/3aa'** and **5** were not produced (Scheme 4, Eq 5). Further exploration of **8** demonstrated that our reaction probably involved a high-valent copper intermediate[18], but regrettably, owing to the fast reductive elimination of a four-coordinated Cu^{III} intermediate, we cannot obtain the corresponding high-valent copper complex (Scheme 4, Eq 6). Recently, cross-electrophile coupling has been an increasingly popular approach via the combination of metal catalysis and external reductants, which has enabled the advancement of sorts of new cross-coupling processes[19]. Unexpectedly, we obtained an exciting finding on the cross-electrophile coupling of different $C(sp^2)$–I/C(sp)–I iodine intermediates without homocoupling product **5** in the absence of metal catalyst and reductant in the transformation (Scheme 4, Eq 7), which opened an entry to the cross-electrophile coupling enabled by iodine reagents. Screening experiments of **8** and **2a** under a series of control conditions testified that our transformation did undergo a copper/iodide tandem catalytic procedure in this reaction (Scheme 4, Eq 8).



Scheme 5. Plausible mechanism.

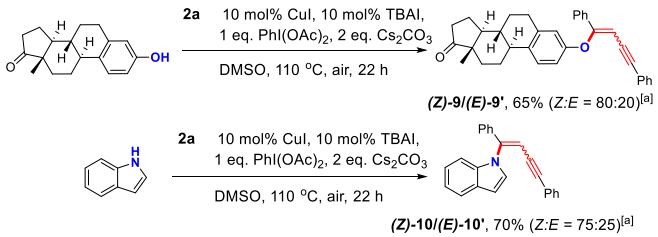
Based on the control experimental results and the previous publications[8,18,19], we tentatively propose a plausible mechanism in Scheme 5. First, the transformation is initiated by the reaction of an iodide source (TBAI or CuI) and $PhI(OAc)_2$ to generate IOAc[20], which works as a strong electrophile against alkyne **2a** to give (iodoethynyl)benzene **7** in the company of a hydrogen/iodine exchange equilibrium process[21]. Then intermolecular nucleophilic addition of phenol **1a** to **7** assisted by base delivers **8** with excellent regio- and stereoselectivity[2f]. Subsequently, **8** rapidly reacts with **6** which is mainly produced by the reaction of **7** and CuI[16] to form a Cu^{III} intermediate **I** via oxidative addition, and then intermediate **I** undergoes reductive elimination to give ***(Z)*-3aa** and release CuI[7d,7e], which can regenerate IOAc assisted by $PhI(OAc)_2$. Since the alkene isomerization in intermediate **I** may occur before the reductive elimination process, a trace amount of ***(E)*-3aa'** is obtained.

To demonstrate the broad applicability of our method, different coupling partners such as structurally complex bioactive compound endofolliculina and indole were tested for this transformation (unoptimized) as shown in Scheme 6. And the reactions proceeded smoothly under standard conditions, respectively yielding the expected products ***(Z)*-9**/***(E)*-9'** and ***(Z)*-10**/***(E)*-10'** in good yields, albeit in slightly lower stereoselectivity.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/adsc.201900626



[a] *Z*/*E* ratios were determined by ^{1}H NMR analysis.

Scheme 6. Applications of our approach.

In conclusion, we have developed an efficient extra-ligand-free approach to the enynyl-aryl ether scaffold via distinctive copper/iodide tandem catalysis. The reaction features broad functional group tolerance (38 examples including endofolliculina and indole) with good regio- and stereoselectivity (*Z*-isomers major) in moderate to excellent isolated yields. More important, the present findings on copper/iodide tandem catalysis not only open a distinct dimension of Cu catalysis, but also enrich the known catalytic mechanism of cross-electrophile coupling involving iodine compounds without reductant. Currently, further studies of our desired products are still underway and will be reported in due course.

Experimental Section

General Information

Reagents and solvents were purchased from commercial sources (Energy Chemical and J&K) and were used without further purification. All reactions were monitored by TLC with silica gel coated plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 600 spectrometer. The chemical shift was given in dimensionless δ values and was frequency referenced relative to TMS in ^{1}H and ^{13}C NMR spectroscopy. Chemical shifts were reported relative to $CDCl_3$ (δ = 7.26 ppm) for ^{1}H NMR and relative to $CDCl_3$ (δ = 77 ppm) for ^{13}C NMR. Peak multiplicities were recorded as follows: s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, and br = broad singlet or a combination of them, *J*-values were in Hz. And high-resolution mass spectra were obtained from Q-TOF instrument by electrospray ionization (ESI). Melting points were measured on a Gongyi Yuhua Instrument X-5 digital display micro melting point apparatus and were uncorrected.

General Experiments for Synthesis of Compounds *(Z)*-3/*(E)*-3', *(Z)*-9/*(E)*-9' and *(Z)*-10/*(E)*-10'

Phenols **1** or indole (0.4 mmol), phenylacetylenes **2** (0.4 mmol), TBAI (tetrabutylammonium iodide) (8 mg, 0.02 mmol, 10 mol%), CuI (4 mg, 0.02 mmol, 10 mol%), $PhI(OAc)_2$ (64 mg, 0.2 mmol, 1 equiv), Cs_2CO_3 (130 mg, 0.4 mmol, 2 equiv) and DMSO (1 mL) were put into a 10 mL sealed tube under an atmosphere of air at 110 °C for 22 h. And the progress of this reaction was monitored by TLC. After the reaction system was cooled to room temperature, the resultant was extracted with ethyl acetate and water, then dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash silica column chromatography, eluting with PE to afford corresponding compounds ***(Z)*-3/*(E)*-3'**, ***(Z)*-9/*(E)*-9'** and ***(Z)*-10/*(E)*-10'**.

Acknowledgements

We are grateful to the Research Funds for the Central Universities (XDJK2017B015 and XDJK2018C040), the Doctoral Fund of Southwest University (SWU111075 and SWU117056), the Beijing National Laboratory of Molecular Sciences (BNLMS) (20140130) and the National Natural Science Foundation of China (Grants 21672173) for the support of this research.

References

[1] a) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.***2008**, *41*, 40-49; b) Y. T. He, J. Xu, Z. H. Yu, A. M. Gunawan, L. Wu, L. N. Wang, Z. Y. Zhang, *J. Med. Chem.***2013**, *56*, 832-842; c) Y. T. He, S. J. Liu, A. Menon, S. Stanford, E. Oppong, A. M. Gunawan, L. Wu, D. J. Wu, A. M. Barrios, N. Bottini, A. C. B. Cato, Z. Y. Zhang, *J. Med. Chem.* **2013**, *56*, 4990-5008; d) T. Wang, H. F. Lv, Q. T. Fan, L. Feng, X. J. Wu, J. F. Zhu, *Angew. Chem.* **2017**, *129*, 4840-4844; *Angew. Chem. Int. Ed.* **2017**, *56*, 4762-4766.

[2] a) D. H. Camacho, S. Saito, Y. Yamamoto, *Tetrahedron Lett.* **2002**, *43*, 1085-1088; b) R. Chinchilla, C. Najera, *Chem. Soc. Rev.* **2011**, *40*, 5084-5121; c) L. M. Geary, P. G. Hultin, *J. Org. Chem.* **2010**, *75*, 6354-6371; d) M. H. Babu, V. Dwivedi, R. Kant, M. S. Reddy, *Angew. Chem. Int. Ed.* **2015**, *54*, 3783-3786; e) Z. W. Chen, J. H. Li, H. F. Jiang, S. F. Zhu, Y. B. Li, C. R. Qi, *Org. Lett.* **2010**, *12*, 3262-3265; f) S. H. Wang, P. H. Li, L. Yu, L. Wang, *Org. Lett.* **2011**, *13*, 5968-5971; g) B. Liu, C. H. Lim, G. M. Miyake, *J. Am. Chem. Soc.* **2018**, *140*, 12829-12835; h) P. J. Gonzalez-Liste, J. Francos, S. E. Garcia-Garrido, V. Cadierno, *J. Org. Chem.* **2017**, *82*, 1507-1516; i) S. B. Wagh, R. S. Liu, *Chem. Commun.* **2015**, *51*, 15462-15464.

[3] a) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas, M. C. Kozlowski, *Chem. Rev.* **2013**, *113*, 6234-6458; b) X. Xiao,T. Wang, F. Xu, T. R. Hoye, *Angew. Chem.* **2018**, *130*, 16802-16806; *Angew. Chem. Int. Ed.* **2018**, *57*, 16564-16568; c) Z. Li, W. L. Duan, *Angew. Chem.* **2018**, *130*, 16273-16277; *Angew. Chem. Int. Ed.* **2018**, *57*, 16041-16045.

[4] a) Y. J. Shang, T. Y. S. But, H. Togo, P. H. Toy, *Synlett* **2007**, *1*, 67-70; b) M. M. Hossain, S. G. Shyu, *Tetrahedron* **2014**, *70*, 251-255; c) D. L. Mo, L. X. Dai, X. L. Hou, *Tetrahedron Lett.* **2009**, *50*, 5578-5581.

[5] a) O. Rivada-Wheelaghan, S. Chakraborty, L. J. W. Shimon, Y. Ben-David, D. Milstein, *Angew. Chem.* **2016**, *128*, 7056-7059; *Angew. Chem. Int. Ed.* **2016**, *55*, 6942-6945; b) J. T. D. Lee, Y. Zhao, *Angew. Chem.***2016**, *128*, 14076-14080; *Angew. Chem. Int. Ed.* **2016**, *55*, 13872-13876; c) L. B. Su, J. Y. Dong, L. Liu, M. L. Sun, R. H. Qiu, Y. B. Zhou, S. F. Yin, *J. Am. Chem. Soc.* **2016**, *138*, 12348-12351; d) Q. M. Liang, K. M. Osten, D. T. Song, *Angew. Chem.* **2017**, *129*, 6414-6417; *Angew. Chem. Int. Ed.* **2017**, *56*, 6317-6320; e) A. Haque, R. A. Al-Balushi, I. J. Al-Busaidi, M. S. Khan, P. R. Raithby, *Chem. Rev.* **2018**, *118*, 8474-8597.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

[6] a) G. Evano, N. Blanchard in *Copper Mediated Cross Coupling Reactions*, Wiley, Hobokn, New Jersey, **2013**; b) D. W. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450-1460; c) Y. Y. Liu, J. P. Wan, *Chem. Asian J.* **2012**, *7*, 1488-1501; d) S. D. McCann, S. S. Stahl, *Acc. Chem. Res.* **2015**, *48*, 1756-1766; e) X. X. Guo, D. W. Gu, Z. X. Wu, W. B. Zhang, *Chem. Rev.* **2015**, *115*, 1622-1651; f) W. Y. Hao, Y. Y. Liu, *Beilstein J. Org. Chem.* **2015**, *11*, 2132-2144; g) J. P. Wan, Y. F. Jing, *Beilstein J. Org. Chem.* **2015**, *11*, 2209-2222; h) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz, L. Ackermann, *Chem. Rev.* **2019**, *119*, 2192-2452.

[7] a) F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6954-6971; b) L. X. Dai, *Prog. Chem.* **2018**, *30*, 1257-1297; c) S. H. Xia, L. Gan, K. L. Wang, Z. Li, D. W. Ma, *J. Am. Chem. Soc.* **2016**, *138*, 13493-13496; d) F. Monnier, F. Turtaut, L. Duroure, M. Taillefer, *Org. Lett.* **2008**, *10*, 3203-3206; e) K. Jouvin, J. Heimburger, G. Evano, *Chem. Sci.* **2012**, *3*, 756-760.

[8] a) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299-5358; b) A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328-3435; c) T. Wirth in *Hypervalent Iodine Chemistry, in Topics in Current Chemistry*, Springer Press, Switzerland, **2016**; d) J. Berges, B. Garcia, K. Muniz, *Angew. Chem.* **2018**, *130*, 16118-16122; *Angew. Chem. Int. Ed.* **2018**, *57*, 15891-15895; e) J. P. Wan, Z. Tu, Y. Y. Wang, *Chem. Eur. J.* **2019**, *25*, 6907-6910.

[9] Y. B. Wu, D. Xie, Z. L. Zang, C. H. Zhou, G. X. Cai, *Chem. Commun.* **2018**, *54*, 4437-4440.

[10] X. M. Zeng, *Chem. Rev.* **2013**, *113*, 6864-6900.

[11] a) T. T. Lai, D. Xie, C. H. Zhou, G. X. Cai, *J. Org. Chem.* **2016**, *81*, 8806-8815; b) F. Wu, S. Stewart, J. P. Ariyarathna, W. Li, *ACS Catal.* **2018**, *8*, 1921-1925.

[12] a) D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev.* **2004**, *248*, 2365-2379; b) J. C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001-1020; c) T. L. Lohr, T. J. Marks, *Nat. Chem.* **2015**, *7*, 477-482; d) G. K. Zielinski, K. Grela, *Chem. Eur. J.* **2016**, *22*, 9440-9454.

[13] CCDC 1873440 contains the supplementary crystallographic data for ***(Z)*-3wa**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/ data_request/cif.

[14] S. S. Ichake, A. Konala, V. Kavala, C. W. Kuo, C. F. Yao, *Org. Lett.* **2017**, *19*, 54-57.

[15] a) P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem. Int. Ed.* **2000**, *39*, 2632-2657; b) H. A. Stefani, A. S. Guarezemini, R. Cella, *Tetrahedron* **2010**, *66*, 7871-7918; c) D. H. Bai, C. J. Li, J. Li, X. S. Jia, *Chin. J. Org. Chem.* **2012**, *32*, 994-1009.

[16] W. W. Chen, J. L. Zhang, B. Wang, Z. X. Zhao, X. Y. Wang, Y. F. Hu, *J. Org. Chem.* **2015**, *80*, 2413-2417.

[17] L. Wang, J. M. Lear, S. M. Rafferty, S. C. Fosu, D. A. Nagib, *Science* **2018**, *362*, 225-229.

[18] a) A. J. Hickman, M. S. Sanford, *Nature* **2012**, *484*, 177-185; b) A. E. King, T. C. Brunold, S. S. Stahl, *J. Am. Chem. Soc.* **2009**, *131*, 5044-5045; c) H. Zhang, B. Yao, L. Zhao, D. X. Wang, B. Q. Xu, M. X. Wang, *J. Am. Chem. Soc.* **2014**, *136*, 6326-6332; d) L. Liu, M. M. Zhu, H. T. Yu, W. X. Zhang, Z. F. Xi, *J. Am. Chem. Soc.* **2017**, *139*, 13688-13691; e) C. Le, T. Q. Chen, T. Liang, P. Zhang, D. W. C. MacMillan, *Science* **2018**, *360*, 1010-1014; f) R. Giri, A. Brusoe, K. Troshin, J. Y. Wang, M. Font, J. F. Hartwig, *J. Am. Chem. Soc.* **2018**, *140*, 793-806; g) H. Kim, J. Heo, J. Kim, M. H. Baik, S. Chang, *J. Am. Chem. Soc.* **2018**, *140*, 14350-14356.

[19] a) D. J. Weix, *Acc. Chem. Res.* **2015**, *48*, 1767-1775; b) P. Zhang, C. Le, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2016**, *138*, 8084-8087; c) A. M. Olivares, D. J. Weix, *J. Am. Chem. Soc.* **2018**, *140*, 2446-2449; d) K. W. Shimkin, J. Montgomery, *J. Am. Chem. Soc.* **2018**, *140*, 7074-7078; e) T. Z. Lin, J. J. Mi, L. C. Song, J. M. Gan, P. Luo, J. Y. Mao, P. J. Walsh, *Org. Lett.* **2018**, *20*, 1191-1194.

[20] a) R. H. Fan,Y. Sun, Y. Ye, *Org. Lett.* **2009**, *11*, 5174-5177; b) S. C. Lu, P. R. Zheng, G. Liu, *J. Org. Chem.* **2012**, *77*, 7711-7717; c) X. F. Xia, Z. Gu, W. T. Liu, N. N. Wang, H. J. Wang, Y. M. Xia, H. Y. Gao, X. Liu, *Org. Biomol. Chem.* **2014**, *12*, 9909-9913; d) W. W. Chen, J. L. Zhang, B. Wang, Z. X. Zhao, X. Y. Wang, Y. F. Hu, *J. Org. Chem.* **2015**, *80*, 2413-2417; e) D. S. Rao, T. R. Reddya, S. Kashyap, *Org. Biomol. Chem.* **2018**, *16*, 1508-1518.

[21] R. Chung, A. Vo, J. E. Hein, *ACS Catal.* **2017**, *7*, 2505-2510.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

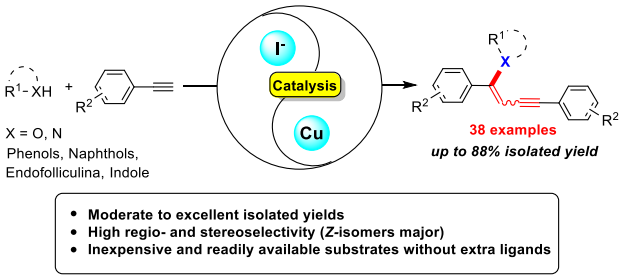
10.1002/adsc.201900626

COMMUNICATION

Regio- and Stereoselective Synthesis of Enynyl-Aryl Ethers Enabled by Copper/Iodide Tandem Catalysis

*Adv. Synth. Catal.***Year**, *Volume*, Page – Page

Yun-Bin Wu,[a] Lin Xiao,[a] Chun-Li Mao,[a] Zhong-Lin Zang,[a] Cheng-He Zhou*,[a] and Gui-Xin Cai*,[a,b]



Accepted Manuscript

This article is protected by copyright. All rights reserved.