

Switchable Synthetic Strategy toward Trisubstituted and **Tetrasubstituted Exocyclic Alkenes**

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Supporting Information

ABSTRACT: An efficient and facile method for the construction of tri- or tetrasubstituted exocyclic alkenes is achieved via a Cu(I)-catalytic system. This protocol exhibits mild conditions, low-cost catalyst, good functional group tolerance, and good yields. The selectivity toward tri- or tetrasubstituted alkenes can be delicately controlled by adjustment of base and solvent. A preliminary mechanism study manifested that the reaction undergoes a radical process, where B₂pin₂ plays an indispensable role.



xocyclic multisubstituted alkenes are frequently encoun-E tered motifs in diverse organic materials, pharmaceuticals, and agrochemicals.¹ Additionally, further derivatization of exocyclic alkenes renders these compounds versatile precursors for the construction of more complex molecules.²

Retrosynthetic analysis reveals that cyclization from a functionalized alkyne precursor should provide the most straightforward approach to this type of compound. During past several years, chemists have made great efforts in the construction of exocyclic multisubstituted alkenes.^{3,4} For example, Kambe et al. reported a silver-catalyzed carbomagnesiation of alkynes with alkyl halides and a stoichiometric amount of Grignard reagents in 2011 (Scheme 1a).⁵ In 2013, Cook et al. developed a palladium-catalyzed alkyne insertion/reduction reaction of unactivated alkyl iodides (Scheme 1b).6 In 2017, Martin et al. described a visible-light-promoted atom transfer radical cyclization of unactivated alkyl iodides (Scheme 1c).7 Although great progress has been made in this field, more practical protocols involving cheap catalysts still need to be developed. During the past decade, copper catalysts have been extensively exploited due to their low cost, stability, and easy operability. In recent years, our and other groups have developed a series of efficient copper-catalyzed conversions for the construction of various important organic synthetic motifs.^{8,9} Although the mechanisms for copper-catalyzed reactions remain elucidated, copper salts proved to be effective and promising catalysts in various chemical transformations. Herein, we present an efficient, practical, and most important of all, switchable synthetic approach toward trisubstituted and tetrasubstituted exocyclic alkenes through a copper-catalyzed intramolecular cyclization in the presence of B_2pin_2 (Scheme 1d).

We proposed the copper-catalyzed intramolecular carboboration for the construction of multisubstituted exocyclic alkenes based on our previous report on copper-catalyzed carboboration of alkynes.¹⁰ Notably, most of the reaction involved activated

Scheme 1. Previous Methods for the Synthesis of Exocyclic **Multisubstituted Alkenes**



alkyl halides instead of unactivated alkyl halide as electrophiles. Actually, when we operated this reaction with acetylenic iodides based on our previous studies, this transformation did not proceed.

Therefore, we need to develop a new reaction system for the intramolecular carboboration of alkynes so that the exocyclic alkenes can be conveniently established.

Our study was initiated by examining the intramolecular annulation of acetylenic iodides with (6-iodohex-1-yn-1-yl)

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benzene (1a) being the benchmark substrate under a copper catalytic system. As mentioned earlier, under our previously optimized condition for intermolecular alkyne carboboration, which involves a Cu(I)/n-Bu₃P catalytic system, no desired product was detected (Table 1, entry 1). However, when this

Table 1. Optimization of Reaction Conditions ^a					
	Cu cat. (10 mol %), B ₂ pin ₂ (1.5 equiv) base (2 equiv), solvent, Ar			Bpin	
Ph I		11, 4 11		' 🚺 T	
1a				2a	3a
				yield ^b (%)	
entry	catalyst	base	solvent	2a	3a
1 ^c	CuCl	NaO ^t Bu	THF	n.d.	n.d.
2	CuCl	NaO ^t Bu	THF	16	52
3	CuCl	K_2CO_3	THF	0	0
4	CuCl	DBU	THF	<5	0
5	CuCl	NaOH	THF	12	37
6	CuCl	NaOCH ₃	THF	33	31
7	CuCl	LiO ^t Bu	THF	53	22
8	CuBr	LiO ^t Bu	THF	48	28
9	CuI	LiO ^t Bu	THF	51	30
10	CuBr ₂	LiO ^t Bu	THF	47	32
11	CuCl	LiO ^t Bu	dioxane	26	34
12	CuCl	LiO ^t Bu	MeCN	33	20
13	CuCl	LiO ^t Bu	DMF	71(64)	13
14	CuCl	LiO ^t Bu	DMSO	<5	14
15	CuCl	_	DMF	n.d.	n.d.
16	-	LiO ^t Bu	DMF	n.d.	n.d.
17 ^d	CuCl	NaO ^t Bu	THF	0	34
18 ^d	CuCl	NaOH	THF	0	25
19 ^{<i>d</i>,<i>e</i>}	CuCl	NaOH	THF	0	84(80)
20 ^{<i>d</i>,<i>e</i>}	CuCl	NaOH	DMSO	23	39
$21^{d,e}$	CuCl	NaOH	MeCN	0	52
22 ^{<i>d</i>,<i>e</i>}	CuCl	NaOH	dioxane	<5	29
23 ^{<i>d</i>,<i>e</i>}	CuCl	NaOH	toluene	0	12

^{*a*}Reaction conditions: **1a** (0.5 mmol, 1 equiv), [Cu] (0.05 mmol, 10 mol %), B_2pin_2 (0.75 mmol, 1.5 equiv), base (1 mmol, 2 equiv). ^{*b*}Yields determined by GC. The value in parentheses is the isolated yield. ^{*cn*}-Bu₃P (24 mol %). ^{*d*}Ph₂SiH₂ (0.75 mmol, 1.5 equiv), B_2pin_2 (0.25 mmol, 0.5 equiv), rt, 4 h. ^{*e*}NaOH (2 mmol, 4 equiv). n.d. = not detected. For details of the optimization, see the Supporting Information.

reaction was conducted without ligand, exocyclic tri- and tetrasubstituted alkenes were isolated separately (Table 1, entry 2). In view of the resulting tri- or tetrasubstituted alkenylboron derivatives being utilized as highly versatile intermediates to access diverse tri/tetrasubstituted alkenes via manifold methods, such as Suzuki–Miyaura coupling,¹¹ Petasis reaction,¹² transition metal-catalyzed conjugate addition,¹³ etc., we are devoted to optimizing the transformation process to afford both trisubstituted and tetrasubstituted alkenylboron derivatives selectively. At the beginning, we screened a variety of bases (Table 1, entries 3-7). When using K₂CO₃ as base, no desired product tetrasubstituted 2a was obtained. When stronger base NaOH was used, product 2a was isolated with 12% yield (entry 5). Subsequently, several other strong bases have been tested, and LiO^tBu was confirmed as the optimal base to afford 2a with 53% yield (entry 7), although trisubstituted olefin 3a was formed in 22% yield. Next, various copper catalysts were screened, and no better yield was afforded compared to CuCl (entries 8-10).

Then, various dry solvents were screened, and eventually, the results identified *N*,*N*-dimethylformamide (DMF) as the optimal solvent, giving the desired product **2a** with 71% yield (entries 11-14). However, there is still 13% of trisubstituted olefin **3a** formed along with **2a** (entry 13). It is noteworthy that in the absence of B₂pin₂ or CuCl, no expected **2a** or **3a** was observed (entries 15-16).

From Table 1, we can see that 3a was detected all the time during the optimization process, which might be attributed to the presence of H₂O in the system. However, the addition of exogenous water or *tert*-butanol had little effect on the product distribution (see Supporting Information (SI), Optimization Details and Table B). Nevertheless, we continued to optimize the conditions to afford 3a by selecting a suitable hydride source and reducing the amount of B₂pin₂ (see SI, Optimization Details and Table C). Further screening of different bases was conducted, and Ph₂SiH₂ was chosen as hydride source. However, when we used NaO^tBu as base, the desired product **3a** was obtained with 34% yield along with plenty of terminal elimination product (entry 17). When 2.0 equiv of NaOH were employed, the desired product 3a was obtained with only 25% yield with large amounts of 1a being recovered (entry 18). To our delight, the yield for 3a increased significantly with 4.0 equiv of NaOH as base, giving the desired product 3a with 84% yield. Finally, we obtained the optimization reaction conditions for 2a and 3a, respectively. Using a CuCl/B₂pin₂-catalytic system, LiO^tBu as base, and dry DMF as solvent under room temperature (Condition A), the product 2a can be obtained with optimized yield. When using a CuCl/B₂pin₂-catalytic system, NaOH as base, Ph₂SiH₂ as hydride source, and dry THF as solvent under room temperature (Condition B), product **3a** can be afforded with good yield.

With optimized reaction conditions in hand, we evaluated the substrate scope of acetylenic iodides. Under Condition A (Scheme 2), both electron donating groups, such as methyl and methoxyl, and electron withdrawing groups, such as trifluoromethyl and cyano, can be well tolerated in spite of their positions on the aromatic rings, resulting in the

Scheme 2. Scope of Exocyclic Tetrasubstituted Alkenylborons a,b



^aReaction Condition A: 1 (0.5 mmol, 1 equiv), CuCl (0.05 mmol, 10 mol %), B₂pin₂ (0.75 mmol, 1.5 equiv), LiO^tBu (1 mmol, 2 equiv), DMF (0.1 M), rt, 4 h. ^bIsolated yields.

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tetrasubstituted alkene with 50-70% yields (2a-r). Naphthyl and heteroaryl substrates can also well participate in the reaction (2p, 2q). What is more, when (E)-(8-iodooct-1-en-3-yn-1-yl)benzene was subjected to this condition, 2r was afforded with 70% yield. However, extending the alkyl chain with more than one carbon did not result in the corresponding six-membered exocyclic alkenes (see SI for details).

Meanwhile, various trisubstituted exocyclic alkenes can also be obtained efficiently from the corresponding acetylenic halides with up to 91% yield under Condition B (as depicted in Scheme 3). The electron donating and electron withdrawing groups



^aReaction Condition B: **1** (0.5 mmol, 1.0 equiv), CuCl (0.05 mmol, 10 mol %), B_2pin_2 (0.25 mmol, 0.5 equiv), Ph_2SiH_2 (0.75 mmol, 1.5 equiv), NaOH (2 mmol, 4 equiv), THF (0.1 M), rt, 4 h. ^bIsolated yields.

substituted at the para-position of the aryl group reacted smoothly with high yields from 70 to 91%, including methyl (3b), methoxyl (3d), fluoro (3e), chloro (3f), bromo (3g), trifluoromethyl (3h), cyano (3i), and so on. Various (6iodohex-1-yn-1-yl)benzene bearing substituents at the orthoand meta-positions of the aryl group were also successfully converted into target products with good yields (3j-o). Additionally, heteroaromatic ring-substituted acetylenic halide 1p also can be used for the current reaction, and 3p was obtained in 76% isolated yield. 2-(6-Iodohex-1-yn-1-yl)naphthalene can also be compatible with the transformation affording 3q with 82% yield. These results show that steric hindrance of the substituents on the aromatic ring has little impact on this transformation. When we introduce an oxygen atom to the unactivated alkyl chain, desired product (isomers) 3r was isolated with 86% yield. It is noteworthy that various (7iodohept-1-yn-1-yl)benzenes could also proceed smoothly and provide the corresponding six-membered exocyclic alkenes in moderate yields (3s-u).

As the above result shows, multisubstituted aromatic alkenes 2a or 3a can be obtained, respectively, with good yields under optimized Condition A or B. In order to further expand the application of a CuI/B₂pin₂ system, we conducted the reaction with alkyl acetylenic halides. Under Condition A, no product **6** was detected, while under Condition B, tetrasubstituted alkenyl iodide was isolated together with exocyclic trisubstituted alkenes (Scheme 5, eqs 1–2). After optimizing this transformation process (see SI, Optimization Details, Table D), we obtained the reaction conditions for **5** using a Cu(I)/B₂pin₂ system, NaOH (2 equiv) as base, and dry DMSO as solvent under 50 °C (Condition C). Under Condition C, various tetrasubstituted alkenyl iodides can be synthesized efficiently with moderate to good yields (Scheme 4). For example, alkyl iodides possessing *n*-





"Reaction Condition C: 4 (0.5 mmol, 1 equiv), CuI (0.05 mmol, 10 mol %), B₂pin₂ (0.1 mmol, 0.2 equiv), NaOH (1 mmol, 2 equiv), DMSO (0.1 M), 50 °C. ^bIsolated yields.

butyl (5a), cyclopropyl (5b), phenylethyl (5c), *tert*-butyl (5d), and cyclohexenyl (5e) all proceeded well with 45-75% isolated yields. In addition, ester and ether motifs can also be tolerated (Sf-n). Unfortunately, nitro, hydroxyl, amine, and aldehyde groups are not compatible under current conditions.

To gain mechanistic insight into the reaction, several control experiments were carried out (Scheme 5, eqs 3-5). When 2,2,6,6-tetramethyl-1-piperidyloxy (TEMPO), as the radical scavenger, was added into the reaction under standard Conditions A, B, and C (Scheme 5, eqs 3-5), these reactions were remarkably inhibited. In addition, the TEMPO-adduct **8** was obtained in 50% isolated yield (Scheme 5, eq 4). These results indicate that this transformation might involve a radical pathway.

Based on these results, a possible mechanism was proposed as described in Scheme 6, which involved a Cu-catalyzed radical pathway. First, reaction of Cu(I) catalyst with B_2pin_2 affords copper species I through σ -bond metathesis in the presence of base. Then, oxidation of copper(I) species by acetylenic halide reagent through a single electron transfer (SET) process results in a copper(II) species II and alkyl radical intermediate III. Next, more stable radical intermediate IV forms through the cyclization of III. The final fate of intermediate IV depends on its competitive reaction with various coexisting reagents. In the

Scheme 5. Control Experiments



Scheme 6. Proposed Mechanism



presence of excessive B_2pin_2 , the reaction of IV with B_2pin_2 becomes dominant, and compound 2 will be formed preferentially (Path A). In the presence of excessive reductant Ph_2SiH_2 , intermediate IV would be reduced to afford the corresponding trisubstituted alkenyl 3 (Path B). When the B_2pin_2 was decreased to a catalytic amount and no reductant was present, intermediate IV would react with compound 1 to afford corresponding alkenyl iodide 5 together with radical intermediate III (Path C). For Paths A and B, the monovalent copper can be regenerated during the catalytic cycle. However, the copper species in Path C might remain bivalent and passive after initiation of the catalytic cycle.

In conclusion, we have developed an efficient and facile copper-catalyzed intramolecular annulation of acetylenic halides. Five- or six-membered exocyclic alkenes, five-membered exocyclic alkenylboron derivatives, and five-membered exocyclic alkenyl iodides can be efficiently synthesized separately, indicating its potential application. What is more, a broad range of functional groups can be well tolerated under these reaction conditions with good to excellent yields. In addition, the mechanism study suggested that the reaction might undergo a radical pathway via a copper catalytic system. Further studies to elucidate the detailed reaction mechanism and apply this strategy to more complicated molecules are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02801.

Experimental procedures, spectral and analytical data, copies of ¹H and ¹³C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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