

# Cu-Catalyzed Oxidative Allylic C–H Arylation of Inexpensive Alkenes with (Hetero)Aryl Boronic Acids

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alkenes, thus offering an alternative method to allylic arylation reactions that employ more traditional coupling partners with preinstalled leaving groups (LGs) at the allylic position.

T he need to innovate and discover new C–C bondforming reactions is central in organic chemistry.<sup>1</sup> In contrast to the well-explored  $C(sp^2)-C(sp^2)$  bond-forming reaction,<sup>2</sup> the transition-metal-catalyzed construction of C- $(sp^2)-C(sp^3)$  has been less-described.<sup>2</sup> Among those coupling reactions of particular interest, allylic arylation is a powerful and important transformation in organic synthesis to generate an arylated stereogenic sp<sup>3</sup>-hybridized center while preserving the olefin moiety.<sup>2b,c</sup>

and nontoxic Cu<sub>2</sub>O without the need to use prefunctionalized

For a decade, considerable attention has been devoted to the construction of the allylarene moiety.<sup>3-10</sup> One of the efficient ways of constructing arylated allyl compounds is the transitionmetal- (TM) catalyzed cross-coupling reaction with organometallic reagents, which proceed either through a  $\pi$ -allyl intermediate or by a formal SN<sub>2</sub>'-type allylation.<sup>8a</sup> Arylboronic acid derivatives as milder nucleophiles have emerged as advantageous partners for the aryl-allyl coupling reaction due to their availability, stability, excellent functional-group compatibility, and ease of handling (Scheme 1, eq 1). However, these methods suffer from the use of electrophilic substrates with preinstalled leaving groups (LGs) at the allylic position, narrowing the scope of this transformation. To overcome this issue, an alternative and more eco-friendly approach is to directly convert the allylic C-H bond of alkene feedstocks.9 Inspired by Nakamura's fundamental work on iron-catalyzed allylic arylation with aryl Grignard reagents,<sup>9a</sup> Glorius and co-workers have reported the unique example of a transition-metal-catalyzed allylic C-H arylation using aryl boron reagents with unfunctionalized olefins by bimetallic [Rh<sup>III</sup>]/[Ag<sup>I</sup>]-catalyzed allylic C(sp<sup>3</sup>)-H activation (Scheme 1, eq 2).<sup>9b</sup>

Along with the development of oxidative cross-couplings via the generation of  $\pi$ -allyl metal intermediates,<sup>11</sup> Cu-catalyzed allylic C–H functionalization by hydrogen atom abstraction (HAA), a Kharasch–Sosnosvky-type reaction,<sup>12</sup> has emerged as a promising approach for allylic C(sp<sup>3</sup>)–H bond Scheme 1. Transition Metal-Catalyzed Allylic Arylation with Aryl Boron Reagents

1) Allylic Arylation by Suzuki-Miyaura coupling

LG = OAc, OPh, Cl, etc..

$$R \xrightarrow{LG} + Ar - BR_2 \xrightarrow{[TM]} R^{(TM)}$$

2) Rh-catalyzed Allylic Arylation by C-H activation



3) This work: Cu-catalyzed Allylic C-H arylation with arylboronic acids



heterofunctionalization.<sup>13–15</sup> This C–H allylic radical functionalization process has been found to be highly atom- and step-economical and has the further advantage of using cheap,

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∕**∧**Ar

abundant, and nontoxic copper salts. However, no example so far for the formation of allylarene units by allylic C–H arylation has been reported via the interception of the allylic radical formed during the HAA process from alkenes by an ArCu<sup>II</sup> intermediate, which itself is generated by transmetalation from an arylboronic acid with the Cu<sup>II</sup>–OR species (Scheme 1, eq 3).<sup>16</sup> Herein, we will present our recent research and developments on regioselective Cu-catalyzed oxidative allylic C–H arylation by radical relay in the presence of a vast number of commercially available arylboronic acids within the petrochemical feedstock of terminal and internal olefins.

We first established the reaction conditions to promote the arylation of cyclohexene (2) with 4-methoxyphenylboronic acid (1a) as the arylation agent (Table 1).<sup>17</sup> To our delight,

MeO	$a \qquad b(OH)_2 + $	[Cu] (10 Ligand (10 oxidant (2 DMSO, 130 R <sup>1</sup> L1: R <sup>1</sup> = Tol L2: R <sup>1</sup> = 4-P	mol%) ) mol%) e equiv) MeO. °C, 24 h MeOC <sub>6</sub> H <sub>4</sub>	3 a MEt <sub>2</sub>
entry	[Cu]	ligand	oxidant	3a (%)
1	[Cu(NCMe) <sub>4</sub> ]PF <sub>4</sub>	L1	DTBP	53 (47) <sup>b</sup>
2	CuTc	L1	DTBP	72 (60) <sup>b</sup>
3	Cu <sub>2</sub> O	L1	DTBP	80 (72) <sup>b</sup>
4	Cu <sub>2</sub> O	L1	DCP	24
5	Cu <sub>2</sub> O	L1	TBHP	n.r.
6	Cu <sub>2</sub> O	L1	NFSI	n.r.
7	Cu <sub>2</sub> O	L2	DTBP	75 (64) <sup>b</sup>
8	Cu <sub>2</sub> O	L3	DTBP	32
9	Cu <sub>2</sub> O	Phen	DTBP	7
10	Cu <sub>2</sub> O	dppf	DTBP	40
11 <sup>c</sup>	Cu <sub>2</sub> O	L1	DTBP	52
12 <sup>d</sup>	Cu <sub>2</sub> O	L1	DTBP	92 (83) <sup>b</sup>

 Table 1. Optimization of the Reaction Conditions<sup>a</sup>



when the previous  $DTBP/L1/[Cu(CH_3CN)_4]PF_4$  catalytic system was employed in pure DMSO,<sup>16f</sup> the expected 3arylated cyclohexene 3a was formed in a 47% isolated yield after 24 h at 130 °C (Table 1, entry 1). Following this encouraging preliminary result, other copper salts were examined. A number of Cu<sup>I</sup> sources, such as CuBr, CuI, CuOAc, CuBr·DMS, and CuOTf, were effective, but none of them gave better results.<sup>17,18</sup> In parallel, we were pleased to find that CuTc and Cu<sub>2</sub>O provided better yields of 60% and 72%, respectively (Table 1, entries 2 and 3, respectively). Both the oxidant DTBP and the solvent DMSO were crucial to achieve the high yield. When other oxidants (Table 1, entries 4-6) and solvents (e.g., DMAc, DMF, CH<sub>3</sub>CN, and chlorobenzene) were used,<sup>17</sup> **3A** was produced in a low yield. To circumvent the formation of the homocoupling biphenyl byproduct and therefore further improve the yield, we turned our attention to other ligands.<sup>17,19</sup> In contrast to bidentate phosphines, nitrogen-containing ligands (bipyridine or phenanthroline-type), and N-heterocyclic carbenes,<sup>17</sup> it

turned out that the use of tertpyridines L1 and L2 as tridentate ligands was crucial for the reaction efficiency (Table 1, entries 7–10). Indeed, it is well-known that their strong  $\sigma$ -donor and  $\pi$ -acceptor properties play an essential role in the stabilization of copper(II) and copper(III) intermediates.<sup>20</sup> Furthermore, another important feature of the tertpyridine ligand is its ability to assist single-electron processes, allowing copper-promoted radical processes in catalytic processes.<sup>20</sup> We reasoned that the addition of extraneous base as well as the use of boronic ester might be helpful.<sup>21</sup> Unfortunately, these two hypotheses led to lower yields of the desired product 3A.<sup>17</sup> Decreasing the catalytic Cu<sub>2</sub>O loading from 10 to 5 mol % and the ratio of cyclohexene from 10 to 5 equiv lead to a drastic yield decrease. The best reaction performance was attained by stretching the reaction time from 24 to 48 h and decreasing the temperature of the reaction from 130 to 80 °C (Table 1, entries 11 and 12, respectively). Under these optimized reaction conditions, the 3-arylated cyclohexene 3a was produced in an 83% isolated yield. Interestingly, the optimized protocol was also easily scaled up from 0.5 to 5.0 mmol without a significant decrease of the yield (80%).

With the optimized conditions in hand, we set out to probe the scope of this Cu-catalyzed allylic C-H arylation with different arylboronic acids 1. As shown in the Scheme 2, the



"Reaction conditions are as follows: 1a-q (0.5 mmol), 2 (10 equiv),  $Cu_2O$  (10 mol %), L1 (10 mol %), DTBP (2 equiv), and DMSO (1.5 mL) under N<sub>2</sub> at 80 °C for 48 h.

reaction appears to be relatively insensitive to the electronic properties of the boronic acid. Indeed, *para*-substituted boronic acids bearing both electron-rich (3b and 3c) and electron-deficient (3d) arenes underwent effective coupling in good yields. Meanwhile, 2-napthalene boronic acid 1e also proved to be a suitable coupling partner, furnishing the arylated product 3e in a 74% yield. Ortho- and meta-

substituted phenyl boronic acids also exhibited good reactivities to give the desired products (3f-3i) in moderate to good yields. Di- and trisubstituted boronic acids on the aryl ring were also compatible as coupling partners. It should be emphasized that a high functional-group tolerance was observed, including methyl ester (3j), ketone (3k), cyano (3l), and halides (Br, Cl, and F; 3m-3o, respectively), which subsequently could provide potential points for further chemical modulation. Nevertheless, a low yield (36%) was obtained when the electron-withdrawing substituent p-NO<sub>2</sub> was flanked on the aromatic moiety (3p). Interestingly, boronic acid bearing the heterocycle 1q was well tolerated and converted to the corresponding product 3q in a 52% yield.

To further expand the scope of our methodology, the Cucatalyzed allylic C–H arylation of other cyclic and acyclic alkene derivatives was investigated, as illustrated in Scheme  $3.^{22}$  By varying the size of rings of the cyclic alkenes during our



<sup>*a*</sup>Reaction conditions are as follows: 1a-q (0.5 mmol), 4-10 (10 equiv),  $Cu_2O$  (10 mol %), L1 (10 mol %), DTBP (2 equiv), and DMSO (1.5 mL) under  $N_2$  at 80 °C for 48 h.

studies, slightly lower yields with both electron-rich and electron-deficient boronic acids were observed in the presence of cyclooctene **4** and cycloheptene **5** compared to those obtained with cyclohexene. Products **12** and **13** were produced in 45% to 77% yields. In contrast, a drop in the yield was observed with cyclopentene **6**, since the efficiency of the arylation is dependent on the electronic properties of the boronic acids. Indeed, while electron-rich boronic acids **1a** and **1c** led to the desired products **14a** and **14c** in 40% and 20% yields, respectively, allylic C–H arylation reactions with electron-deficient boronic acids **1k**, **1n**, and **1i** were unsuccessful. It is noteworthy that a substrate featuring an exocyclic double bond at the cyclohexyl ring could also be arylated from electron-rich **1a** and electron-deficient **1j** boronic acids, giving the corresponding arylated cyclohexene derivatives 15a and 15j in 60% and 53% yields, respectively.

Allylbenzene derivatives 8 and 9 proved to be effective substrates for the allylic C-H arylation reaction with both electron-rich and electron-poor boronic acids, producing the corresponding linear products (E)-16 and (E)-17 with (E)stereochemistry in moderate yields (Scheme 3). It is noteworthy that the reaction with a noncyclic internal olefin, such as 2-methyl-1-phenylpropene 10, worked well to give the corresponding products (E)-18 and (Z)-18 in a 78% yield with a ratio of 10:3, respectively. Finally, when 1-methylcyclohexene 11 was reacted with 4-methoxyphenylboronic acid, a mixture of three products 19-21 was isolated; however, the mixture was inseparable by flash chromatography. Among those, the major coupling compound 19 was obtained via the reaction of the less sterically hindered allylic C-H bond. It appears that the regioselectivity of this allylic C-H arylation is under steric control, thus explaining the formation of the minor arylated exocyclic product 21 while the abstraction of this primary allylic hydrogen is unfavored.

To obtain insight into the mechanism of allylic C–H arylation, a stoichiometric amount of 2,2,6,6-tetramethyl-1piperidine (TEMPO) was used as a radical scavenger. The arylation was completely inhibited, and the methylated TEMPO adduct was observed.<sup>17</sup> This result suggests that the allylic C–H arylation proceed by a radical pathway involving the presence of methyl radicals. Based on previous mechanism studies of Karasch–Sosnovsky-type reactions, three mechanism pathways can be considered for this transformation, as depicted in Scheme 4. Our first mechanistic hypothesis,

Scheme 4. Proposed Mechanisms



pathway A, begins with the decomposition of DTBP initiated by LCu<sup>I</sup> via a single-electron transfer (SET) reaction to produce a *tert*-butoxy radical and the oxidized copper(II) complex I, LCu<sup>II</sup>-OtBu.<sup>23</sup> The formed *tert*-butoxy radical can either decompose by  $\beta$ -scission into acetone and a methyl radical, which can be trapped by TEMPO,<sup>24</sup> or be involved in hydrogen atom abstraction (HAA) step from an alkene to form an allyl radical.<sup>25</sup> In parallel, the copper(II) complex II is generated by the transmetelation reaction of aryl boronic acid with LCu<sup>II</sup>-OtBu (I).<sup>21</sup> Taking into account the known propensity of Cu<sup>II</sup> complexes to react with an organic radical,<sup>21,23,26</sup> we postulated that LCu<sup>(II)</sup>-Ar (II) could then be oxidized by an allyl radical intermediate to yield the Cu<sup>III</sup> species III, which delivers the final product through reductive elimination.<sup>27,28</sup> An alternative pathway B can also be considered that does not involve a transmetalation step but instead has a direct radical coupling of the allyl radical with the aryl group, which is  $\sigma$ -bonded to Cu<sup>II</sup> (II).<sup>29</sup> Finally, another possible pathway C involving an initial transmetalation reaction of aryl boronic acid with  $LCu^{I}$  to give  $LCu^{I}Ar$  (IV) is also conceivable.<sup>30</sup> This latter would then be oxidized by DTBP to yield LCu<sup>II</sup>Ar (II) and release either a methyl radical or a *tert*-butoxy radical.<sup>30</sup> However, we think that pathway C is less likely than pathway A or B. Indeed, as demonstrated by Stahl in regard to the rates of the transmetalation of an aryl group from arylboronic acids to Cu<sup>II,31</sup> our reaction with cyclopentene 4 seems relatively sensitive to the electronic properties of boronic acids.

In summary, we have developed a direct regioselective Cucatalyzed coupling of allylic C(sp<sup>3</sup>)-H bonds by radical relay using both electron-rich and electron-deficient heteroaryl boronic acids in the presence of inexpensive and readily available unactivated terminal and internal olefins. This methodology provides an unprecedented method for the construction of allylarenes and represents an important extension to the traditional Kharasch-Sosnovsky reaction for the allylic  $C(sp^3)$ -H functionalization. We have demonstrated the excellent functional-group tolerance of this reaction method as well as its good chemo- and regioselectivity with terminal olefins. Additionally, this new  $C(sp^2)-C(sp^3)$  allyl coupling has the advantage of using cheap, abundant, and nontoxic Cu<sub>2</sub>O, and offers a compelling alternative to allylic arylation reactions that employ more traditional coupling partners with preinstalled leaving groups (LGs) at the allylic position.

# ASSOCIATED CONTENT

# **3** Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00812.

Experimental procedures, screening data, compound characterization, and spectra of new compounds (PDF)

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#### Notes

The authors declare no competing financial interest.

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## DEDICATION

In memory of Pr. Victor Snieckus (1937–2020)

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(16) To date, the only examples involving the formation of C-Cbonds through Cu-catalyzed allylic C-H functionalization are allylic C-H cyanation, allylic C-H trifluoromethylation, allylic C-H cyanation, allylic C-alkylation, and allylic C-H alkynylation. For Cu-catalyzed allylic C-H cyanation, see: (a) Li, J.; Zhang, Z.; Wu, L.; Zhang, W.; Chen, P.; Lin, Z.; Liu, G. Site-specific allylic C-H bond functionalization with a copper-bound N-centred radical. Nature 2019, 574, 516-521. For allylic C-H trifluoromethylation, see: (b) Parsons, A. T.; Buchwald, S. L. Copper-Catalyzed Trifluoromethylation of Unactivated Olefins. Angew. Chem., Int. Ed. 2011, 50, 9120-9123. (c) Xu, J.; Fu, Y.; Luo, D.-F.; Jiang, Y.-Y.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Liu, L. Copper-Catalyzed Trifluoromethylation of Terminal Alkenes through Allylic C-H Bond Activation. J. Am. Chem. Soc. 2011, 133, 15300-15303. (d) Wang, X.; Ye, Y.; Zhang, S.; Feng, J.; Xu, Y.; Zhang, Y.; Wang, J. Copper-Catalyzed C(sp<sup>3</sup>)-C(sp<sup>3</sup>) Bond Formation Using a Hypervalent Iodine Reagent: An Efficient Allylic Trifluoromethylation. J. Am. Chem. Soc. 2011, 133, 16410-16413. For allylic C-H alkylation, see: (e) Li, Z.; Li, C.-J. Allylic C-H alkylation: (e) Catalytic Allylic Alkylation via the Cross-Dehydrogenative-Coupling Reaction between Allylic sp<sup>3</sup> C-H and Methylenic sp<sup>3</sup> C-H Bonds. J. Am. Chem. Soc. 2006, 128, 56-57. For allylic C-H alkynylation, see: (f) Almasalma, A. A.; Mejia, E. Coper-catalyzed Allylic C-H Alkynylation by Cross-Dehydrogenative Coupling. Chem. - Eur. J. 2018, 24, 12269-12273.

(17) For details, see the Supporting Information.

(18) In absence of copper salt, the desired product 3a was not produced; see ref 17.

(19) It is important to note that in absence of ligand, the arylated cyclohexene 3A was obtained in a 12% isolated yield; see ref 17.

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(25) This radical abstraction is exergonic and hence thermodynamically favored, see ref 16f.

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