

## Cu-Catalyzed C–H Alkenylation with Vinyl Boronates

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Dedicated to the 70th anniversary of Shanghai Institute of Organic Chemistry

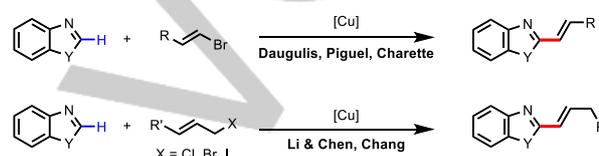
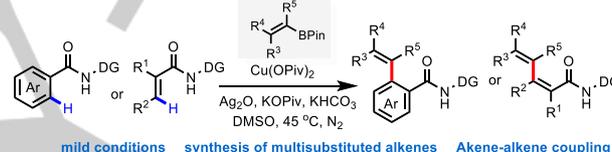
**Abstract:** An efficient Cu-catalyzed C–H alkenylation with acyclic and cyclic vinyl boronates has been realized for the first time using an oxazoline-aniline directing group under mild conditions. The scope of the vinyl boronates and the compatibility with functional groups including heterocycles are significantly superior than Pd-catalyzed C–H coupling with vinyl boronates, providing a reliable access to multisubstituted alkenes and dienes in high efficiency. Subsequent hydrogenation of the product from the internal vinyl boronates will lead to installation of secondary alkyls. Notably, the direct coupling of heterocyclic alkene with heterocyclic vinyl boronates offers a new route for synthesis of substituted piperidine or tetrahydropyran derivatives which are valuable in medicinal chemistry.

Cu-catalyzed or mediated C–H functionalization has attracted great attention due to the abundance, low cost, and low toxicity of copper.<sup>[1–3]</sup> Since the early finding of its capability of functionalizing the aromatic C–H bonds,<sup>[1]</sup> diverse range of C–H activation reactions have been developed,<sup>[2–3]</sup> thus providing a complementary approach to construct carbon-carbon or carbon-heteroatom bond. It is worth noting that Cu(II)-catalyst has been shown to catalyze transformations that are not successful with Pd catalysts. The exceptional tolerance of heterocycle is also a practical advantage of Cu catalysts.<sup>[3a,3c]</sup> However, development in this field is still at an early stage compared to the state of the art Pd-catalyzed C–H functionalizations<sup>[4]</sup>. Here we report a Cu(II)-catalyzed alkenylation of benzoic acid and acrylic acid derivatives with vinyl boronates for the first time. With the aid of an oxazoline-aniline directing group, a series of multisubstituted alkenes and dienes were constructed in high efficiency in the presence of cyclic and acyclic alkenyl boronates. Hydrogenation of the resulted internal alkenes could also provide corresponding secondary alkylated arenes (Scheme 1c).

Substituted alkenes and dienes are ubiquitous motifs in natural products, pharmaceuticals, and organic materials.<sup>[5]</sup> In addition, they are widely used synthons participating in many reduction and oxidation processes.<sup>[6]</sup> C–H coupling with vinyl boronates could provide an attractive route for this class of compounds.<sup>[7]</sup> Attempts to achieve this transformation using Pd

catalysts have been largely unsuccessful due to the decomposition of vinylboronates in the presence of Pd(II) catalysts<sup>[8]</sup>. Our early finding of Cu-catalyzed C–H coupling with aryl-boronate<sup>[3d]</sup> prompted us to investigate the feasibility of using Cu catalysts to effect this transformation.

## A. Known Cu-catalyzed C–H alkenylation with vinyl halides or allylic halides

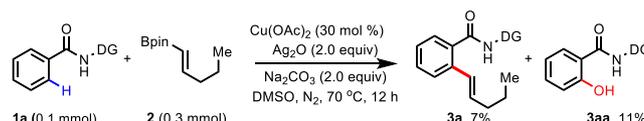
B. This Work: Cu-catalyzed C(sp<sup>2</sup>) H alkenylation with vinyl boronates

## C. Access to secondary alkylated products via hydrogenation



Scheme 1. Synopsis for Cu-Catalyzed C–H Alkenylation with Vinyl Boronates

Recently, Daugulis<sup>[9d]</sup>, Piguél<sup>[9c]</sup>, Charette<sup>[9b]</sup> and others<sup>[9a]</sup> have demonstrated the direct alkenylation of acidic C–H in the presence of strong base with vinyl halides. Employing allylic halides via an allylation/isomerization sequence, Li, Chen<sup>[10a]</sup>, and Chang<sup>[10b]</sup> have achieved the C–H alkenylation of relatively more acidic aryl C–H bonds (benzoxazoline or fluorinated benzenes). Despite of those progress, Cu-catalyzed alkenylation of inert C–H bond remains a significant challenge. We envisioned Cu-catalyzed C–H coupling with alkenyl boronates could be an attractive approach owing to the availability of vinyl boronates.



Scheme 2. Initial Attempt Under Previous Cu-Catalyzed Arylation Conditions

In our initial screening using a readily removable oxazoline-aniline directing group<sup>[3d]</sup>, we found that cross-coupling of substrate **1a** with (*E*)-1-pentenylboronic acid pinacol ester (**2**) proceeded in 7% yield of mono-alkenylated product along with

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11% yield of a hydroxylation byproduct under previous arylation conditions (66% yield for arylation, Scheme 2).<sup>ref</sup> After systematically tuning the reaction parameters, the yield of alkenylation products is improved to 86% as measured by NMR (77% isolated yield) with a mono/di selectivity of 2.1/1.0. The optimized conditions consist of copper(II) benzoate (30 mol %), KOPIv (2.0 equiv), KHCO<sub>3</sub> (2.0 equiv), DMSO (2.0 mL). The reaction is run under N<sub>2</sub> atmosphere at 45 °C. Control experiments demonstrated that the reaction cannot proceed in the absence of copper(II) benzoate and bases, while only trace amount of the desired alkenylation products were observed without the use of Ag<sub>2</sub>O (entry 6). Both KOPIv and KHCO<sub>3</sub> are crucial for maintaining the high efficiency (entries 3-4), in which KOPIv played a major role providing **3a** in 66% yield alone. It is noteworthy that the reaction can also be carried out under air, albeit with lower yield and 6% of hydroxylated byproduct (entry 7). Cu(OAc)<sub>2</sub> and Cu(OPiv)<sub>2</sub> could also promote this C–H alkenylation reaction with a slightly lower yields in comparison with (PhCO<sub>2</sub>)<sub>2</sub>Cu (entries 9-10). Notably, the reaction temperature is pivotal for suppressing the formation of the hydroxylation byproduct (entries 11-13). Higher temperature normally led to lower yield of desired alkenylation product and higher yield of hydroxylation byproduct (see SI for more information). Replacement of DMSO by other solvents, like MeOH, dioxane, MeCN, toluene, and dichloromethane, shut down the reaction, while DMF provided the desired products in 54% yield (entries 14-16). In addition, reducing the loading of (PhCO<sub>2</sub>)<sub>2</sub>Cu, tuning the concentration, all led to inferior results.

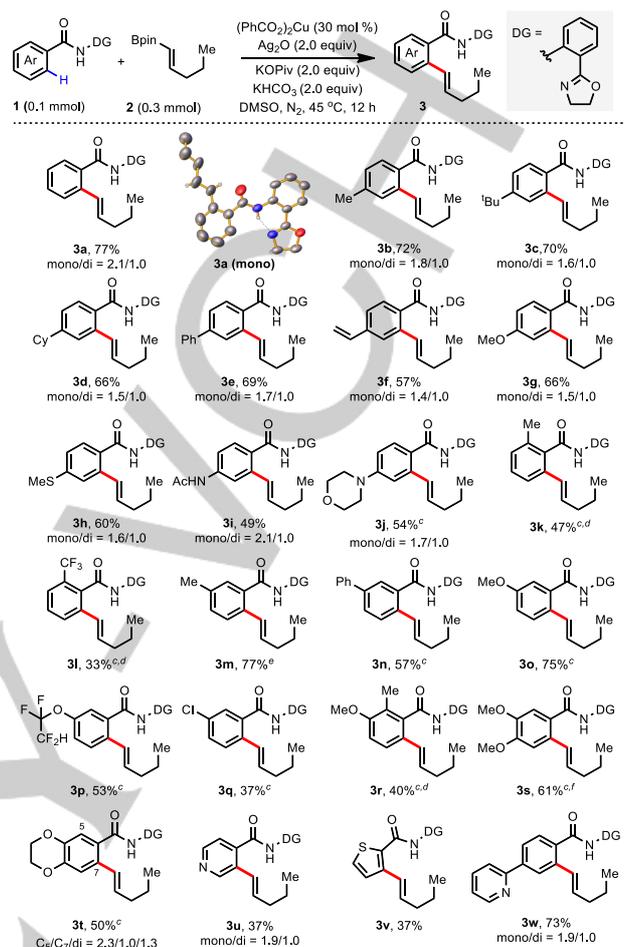
**Table 1.** Effects of Reaction Parameters.<sup>[a]</sup>

Entry	Deviation from optimal conditions	Yield (%) (mono/di)	Entry	Deviation from optimal conditions	Yield (%) (mono/di)
1	none	86 (2.1/1.0)	9	Cu(OAc) <sub>2</sub> was used	78 (2.4/1.0)
2	No (PhCO <sub>2</sub> ) <sub>2</sub> Cu	N.D.	10	Cu(OPiv) <sub>2</sub> was used	83 (2.1/1.0)
3	No KOPIv	6 (6.0/0)	11	30 °C	68 (4.2/1.4)
4	No KHCO <sub>3</sub>	66 (2.3/1.0)	12	50 °C	70 (2.0/1.0)
5	No bases	N.D.	13	60 °C	51 (1.0/1.0)
6	No Ag <sub>2</sub> O	trace	14	DMF instead of DMSO	54 (5.8/1.0)
7	air instead of N <sub>2</sub>	70 (2.6/1.0)	15	Dioxane instead of DMSO	N.D.
8	(PhCO <sub>2</sub> ) <sub>2</sub> Cu (20 mol%) was used	70 (4.4/1.0)	16	CH <sub>3</sub> CN instead of DMSO	N.D.

[a] The yield was determined by <sup>1</sup>H NMR using dibromomethane as an internal standard. [b] Isolated yield.

Under the optimal conditions, we next evaluated the scope of the benzoic acids using (*E*)-1-pentenylboronic acid pinacol ester (**2**) as alkenylating reagent. Normally, the *ortho*-substituted substrates gave lower yields in comparison with *meta*- and *para*-substituted benzoic acids (**3k-l**). Both electron-rich and electron-deficient group substituted benzoic acid are well tolerated, giving the corresponding alkenylated arenes in moderate to good yields. The *para*-substituted substrates (**3b-j**, **3w**) provided a mono- and di-products mixture in high efficiency, while the mono-alkenylation happened with *meta*-substituted substrates

**Table 2.** Evaluation of Benzoic Acids.<sup>a,b]</sup>



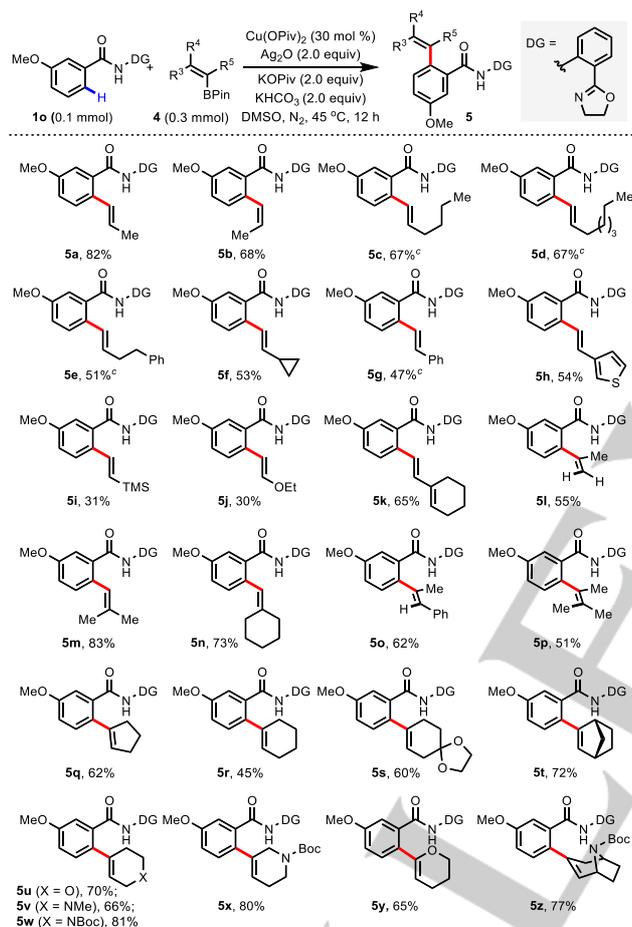
[a] Reaction conditions: **1** (0.1 mmol), **2** (0.3 mmol), Cu(PhCO<sub>2</sub>)<sub>2</sub> (0.03 mmol), Ag<sub>2</sub>O (0.2 mmol), KOPIv (0.2 mmol), KHCO<sub>3</sub> (0.2 mmol), DMSO (2.0 mL), N<sub>2</sub>, 45 °C, 12 h. [b] Isolated yield. [c] Cu(OPiv)<sub>2</sub> (0.03 mmol). [d] 60 °C. [e] Cu(PhCO<sub>2</sub>)<sub>2</sub> (0.035 mmol), 50 °C. [f] 9 h.

(**3m-r**) due to the steric hindrance. This protocol features good functional group tolerance with alkyl, aryl, vinyl, amino, chloro, methoxyl, methylthio group, and trifluoromethyl group, in which the compatibility with vinyl group highlights the impressive mild conditions. Heterocyclic substrates (**3u-w**) are also suitable substrates for this alkenylation, albeit lower yields were obtained. Not surprisingly, the C–H alkenylation proceeded at the *ortho*-position to oxazoline-aniline directing group rather than the strong coordinating heterocycle site (**3w**).

Next, the generality of alkenyl boronates were evaluated using **1o** as model substrate. As depicted in Table 3, both *cis* and *trans*-vinyl boronates are compatible with this protocol, giving corresponding *cis* or *trans*-alkenes in high yields (**5a-b**). Alkyl vinyl boronates reacted with **1o** providing the desired products in 51-82% yields (**5a-f**). Notably, the compatibility with cyclopropanyl group indicated this C–H vinylation reaction through a cyclopropanation intermediate rather than a radical process. Styrene and hetero-styrene derived coupling partners

are also tolerated under the mild conditions albeit with moderate yields (**5g-h**). The mild reaction conditions also allowed the coupling with base or acid sensitive alkenylating reagents, like TMS-vinyl, vinyl ether, and diene etc (**5i-k**). Isopropenylboronic acid pinacol ester gave the desired product in 55% yield (**5l**). In addition, disubstituted (**4m-o**), trisubstituted (**4p**), and cyclic vinyl boronates (**4q-t**) are all suitable coupling partners for this reaction. It is worth noting that a broad range of heterocyclic alkenyl boronates are compatible with this reaction, providing a diverse range of novel heteroalkenylated arenes (**5u-z**).

**Table 3.** Scope of Vinyl Boronates.<sup>[a,b]</sup>

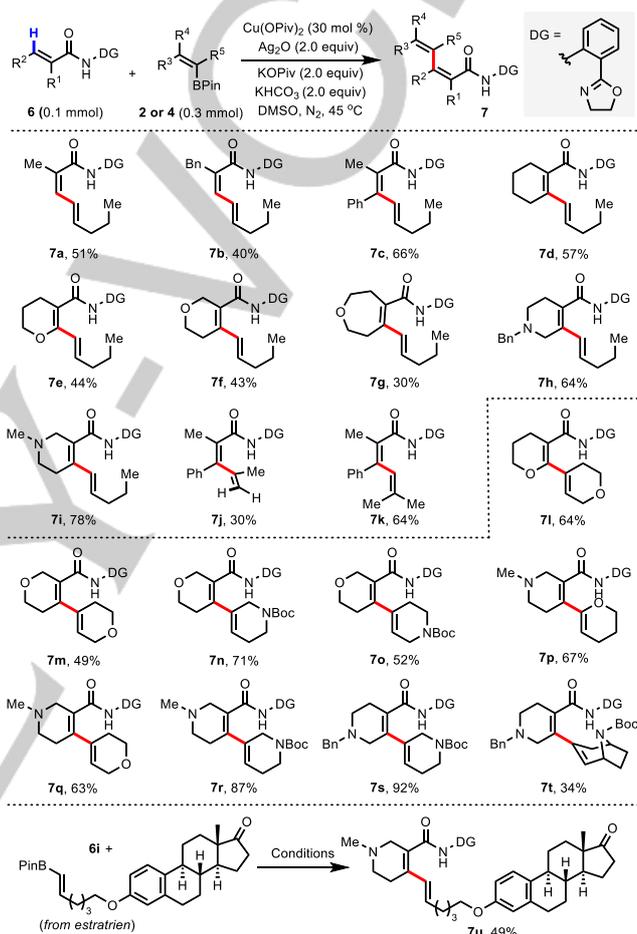


[a] Reaction conditions: **1o** (0.1 mmol), **4** (0.3 mmol), Cu(OPiv)<sub>2</sub> (0.03 mmol), Ag<sub>2</sub>O (0.2 mmol), KOPIv (0.2 mmol), KHCO<sub>3</sub> (0.2 mmol), DMSO (2.0 mL), N<sub>2</sub>, 45 °C, 12 h. [b] Isolated yield. [c] 50 °C.

Given the importance of dienes in organic synthesis and their population in bioactive molecules, we turned to investigate the direct coupling of vinyl C–H bond with vinyl boronates. Due to the instability of dienes under oxidative conditions, the direct synthesis of dienes via C–H activation remains challenging. To our delight, various dienes were synthesized under our mild conditions, given a variety types of dienes in 30–78% yields employing Cu(OPiv)<sub>2</sub> as most efficient catalyst (**7a-k**). Moreover, heterocyclic alkene substrates are also compatible providing a

direct method for synthesis of alkenylated heterocycles in high yields (**7e-i**). Notably, the incredible heteroatom tolerance allows the direct coupling of heterocyclic substrates with heterocyclic alkenyl boronates (**7l-t**) in high efficiency. The direct coupling of **6i** with an estratrien-derived vinyl boronate demonstrated the versatility of this process for late-stage functionalization of complex bioactive molecules (**7u**).

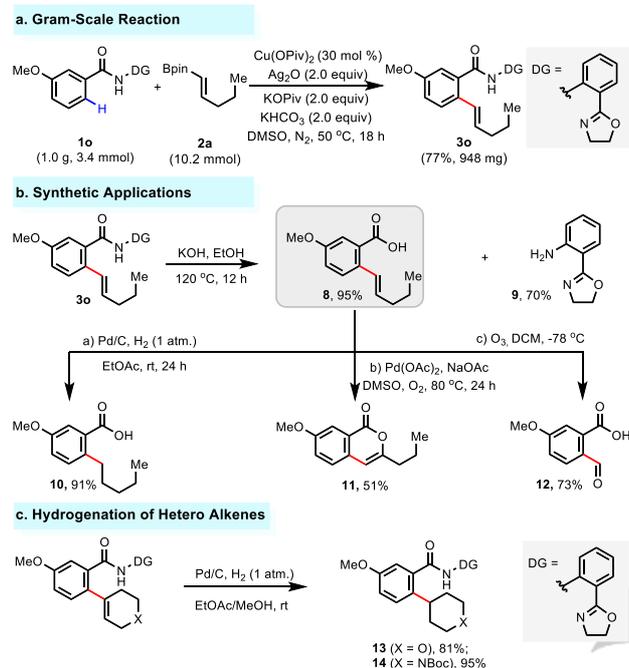
**Table 4.** Alkene-Alkene Coupling.<sup>[a,b]</sup>



[a] Reaction conditions: **6** (0.1 mmol), **2 or 4** (0.3 mmol), Cu(OPiv)<sub>2</sub> (0.03 mmol), Ag<sub>2</sub>O (0.2 mmol), KOPIv (0.2 mmol), KHCO<sub>3</sub> (0.2 mmol), DMSO (2.0 mL), N<sub>2</sub>, 45 °C, and see Supporting Information for detailed reaction time. [b] Isolated yield.

The scalability of this process was examined by the direct coupling of **1o** (1.0 g, 3.4 mmol) with (*E*)-1-pentenylboronic acid pinacol ester (**2**), providing the desired alkenylated product **3o** in 77% yield (Scheme 3a). The directing group (**9**) could be readily removed in the presence of KOH, and was recovered in 70% yield. The resulted alkenylated benzoic acids (**8**) are significant intermediates in organic synthesis, which could be easily transformed to alkylated benzoic acid (**10**), lactam (**11**), and aldehyde (**12**) (Scheme 3b). It is noteworthy that hydrogenation of the heterocyclic alkene derivatives gave alkylated tetrahydropyran (**13**) and piperidine (**14**) in 81% and 95% yield,

respectively (Scheme 3c). Due to the difficulties in installing secondary alkyls via Pd-catalyzed C–H alkylation, this method provides a solution to this persistent problem. In addition, direct synthesis of substituted piperidine or tetrahydropyran derivatives, highly valuable motifs in medicinal chemistry, are noteworthy.



**Scheme 3.** Gram-Scale Reaction and Applications.

In summary, a series of alkenes and dienes were synthesized via Cu-catalyzed C–H alkenylation with cyclic and acyclic vinyl boronates for the first time. The procedure features mild conditions, broad functional group, and heterocycle tolerance, filling a significant gap in directed C–H activation reaction development.

## Acknowledgements

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**Keywords:** copper • C–H alkenylation • vinyl boronates • vinylation

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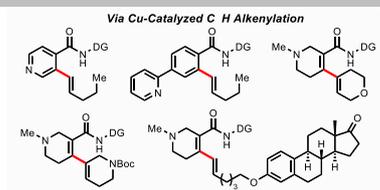
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Layout 1:

## COMMUNICATION

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