A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

## Accepted Article

**Title:** Copper-Catalyzed ortho-Functionalization of Quinoline N-Oxides with Vinyl Arenes

**Authors:** Hui Hu, Xiaoping Hu, and Yuanhong Liu



**To be cited as:** *Angew. Chem. Int. Ed.* 10.1002/anie.202007699

**Link to VoR:** https://doi.org/10.1002/anie.202007699

WILEY-VCH

10.1002/anie.202007699


WILEY-VCH

# Copper-Catalyzed *ortho*-Functionalization of Quinoline *N*-Oxides with Vinyl Arenes

Hui Hu, Xiaoping Hu, Yuanhong Liu*

Dedicated to Professor Tamotsu Takahashi on the occasion of his retirement from Hokkaido University

**Abstract:** An efficient copper-catalyzed regioselective C-H alkenylation and borylative alkylation of quinoline *N*-oxides with vinyl arenes in the presence of pinacol diborane has been developed. The reaction proceeds through the borylcupration of the vinyl arenes followed by nucleophilic attack of the resulting alkyl copper species to the quinoline *N*-oxides. Benzoquinone and KO$^t$Bu were identified as the necessary additives at the second step of the reaction that are crucial for the success of the reaction. A wide range of C2-functionalizaed quinolines were obtained with good functional group tolerance, which may find utilities in pharmaceuticals and synthetic chemistry.

Quinoline derivatives are known to have a wide application in pharmaceutical, agrochemical and industrial chemistry, which also serve as useful building blocks in synthetic organic chemistry.[1] Especially, C2-substituted quinoline derivatives have been found to exhibit various biological activities, such as CysLT$_1$ antagonist,[2a] antileishmanial activity,[2b] antimalarial activity[2c] and P-selectin inhibitors for the treatment of atherosclerosis and deep vein thrombosis[2d] etc. (Figure 1).[2] Consequently, much efforts have been made to develop the efficient methodologies for the synthesis of C2-substituted quinolines.[3]

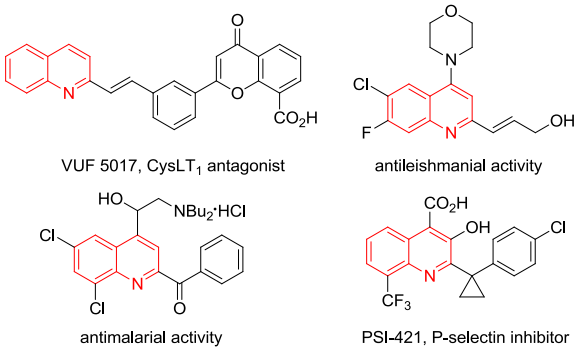
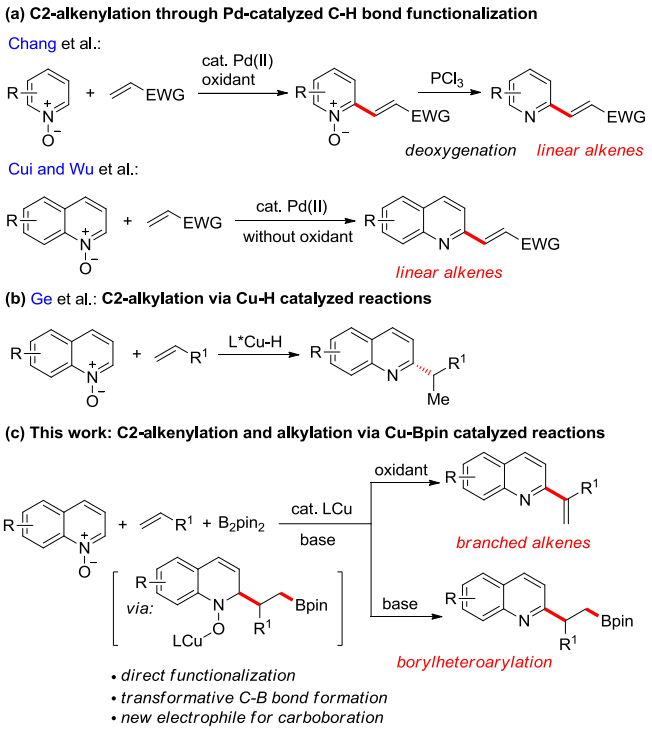



**Figure 1.** Bioactive C2-substituted quinoline derivatives

Recently, pyridine or quinoline *N*-oxides, which serve as *N*-activated pyridines, have emerged as ideal and versatile synthetic intermediates for the introduction of functional groups at the C2-position of *N*-heterocycles.[4] A wide variety of chemical transformations including deoxgenative or non-deoxgenative reactions has been developed employing pyridine or quinoline *N*-oxides as the substrates, such as arylation,[5] alkylation,[6] radical reaction,[7] 1,3-dipolar cycloaddition,[8] transition-metal-catalyzed C-H bond functionalization[9] etc.[10] Although much progress has been achieved, the regioselective C-C bond formation reactions of *N*-Oxides with unsaturated π-systems such as alkenes have less been developed. For instance, Chang et al. reported a Pd-catalyzed C-H functionalization of pyridine *N*-oxides with electron deficient olefins, in which the *N*-oxide activator was removed in a subsequent reaction with $PCl_3$.[11a] Cui and Wu developed a C2-vinylation of quinoline *N*-Oxides under external-oxidant-free conditions.[11b] However, only linear alkenes can be obtained through these methods (Scheme 1a).[11-12] Recently, Ge reported a copper-catalyzed enantioselective alkylation of *N*-Oxides via a chiral Cu-H species[13] (Scheme 1b). On the other hand, copper-catalyzed 1,2-difunctionalization of alkenes through trapping of the Csp$^3$-Cu intermediate with C, N or O-electrophiles has received significant attention, since these methods could install both the boronate and other functional groups, and the resulting alkylboranes can be elaborated further.[14-15] However, the catalytic borylcuprations using heteroaryl *N*-oxides as electrophiles have not yet been reported. This might be due to



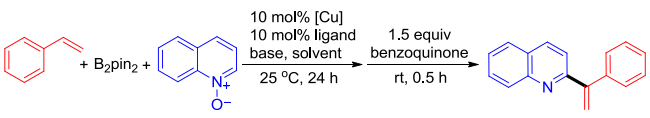

**Scheme 1.** Regioselective functionalization of pyridine or quinoline *N*-oxides with alkenes

[*] H. Hu, Xiaoping Hu, Prof. Y.-H. Liu
State Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032 (P. R. China)
E-mail: yhliu@sioc.ac.cn
[**] We thank the National Key R&D Program of China (2016YFA0202900), the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB20000000), Science and Technology Commission of Shanghai Municipality (18XD1405000) for financial support.
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

the following challenges: 1) the direct trapping of the alkyl-copper intermediate with carbon-based electrophiles is more difficult due to the instability of the $Csp^3$-Cu bond, currently, most studies focused on the use of alkyl- or acyl halides, or pseudohalides as the electrophiles.[15] 2) The resulting deoxgenated heterocycles may coordinate with the metal to induce catalyst deactivation. 3) Side reactions such as dimerization of quinoline *N*-oxides under the basic conditions[16] or N-O bond reduction by diborane reagent[17] might compete with the main reaction pathway. In this paper, we describe the first example of copper-catalyzed C2-functionalization of quinoline *N*-oxides with alkenes in the presence of diborane and a base. Notably, the additives used in the additional step in this one-pot operation play important roles for obtaining the desired products, thus, either a 1,1'-disubstituted alkene or a borylated product could be obtained selectively (Scheme 1c).

Initially, in order to understand the possible background reactions, several control reactions were examined. Indeed, the N-O bond of the quinoline *N*-oxide could be reduced by bis(pinacolato)diboron ($B_2pin_2$) (30% yield of quinoline was formed after 24 h in THF at room temperature). Stirring a mixture of quinoline *N*-oxide and a base such as KO$^t$Bu in THF led to the deoxygenated dimmer 2,2'-biquinoline in 39% yield. When addition of $B_2pin_2$, KO$^t$Bu and quinoline *N*-oxide in THF simultaneously, quinoline was observed as a major byproduct, and the dimerization product could be minimized.[18] Nevertheless, we reasoned that a proper choice of the reaction conditions might solve the problem associated with the reactivity and chemo-selectivity. We then optimized the reaction conditions using styrene (**1a**), $B_2pin_2$ and quinoline *N*-oxide (**2a**) as the model substrates. However, although a thorough screening of the copper-catalysts, ligands, bases, diboron reagents and additives was performed, no desired borylated product was formed. Interestingly, in some cases, trace of alkenylated product 2-(1-phenylvinyl)quinoline (**3a**) was detected. Occasionally, it was found that when the reaction mixture was exposed to the air for 12 h at room temperature after the reaction was complete, the yield of **3a** could be improved. We speculated that the oxygen might serve as an oxidant to facilitate the formation of **3a**. To our delight, when 1,4-benzoquinone was added after the reaction was complete, **3a** could be formed rapidly and cleanly within 0.5 h. With this in mind, we screened again the reaction conditions by adding benzoquinone at the end of the reaction (Table 1). In the presence of 10 mol% CuCl and $PCy_3$, 1.5 equiv of KO$^t$Bu and $B_2pin_2$, the desired alkene **3a** could be formed as the major product in 45% yield (Table 1, entry 1). To overcome this side reaction, the effect of ligands was investigated. Bidentate phosphine ligands of dppb and dppf showed low reactivity (entries 2-3). Gratifyingly, with the bulky ligands Cyxantphos and Xantphos, the yields of **3a** could be improved remarkably to 56% and 71%, respectively (entries 4-5). The strongly electron-donating ligand of *N*-heterocyclic carbene (NHC) complex such as IPr was not effective in this reaction (entry 7). Possibly, the reaction is not only governed by the electronic effects of the alkyl-copper species, but also relys on its stability. The yields were diminished when KO$^t$Bu was replaced by NaO$^t$Bu and LiO$^t$Bu, whereas the weaker bases such as $K_3PO_4$ and $NaHCO_3$ failed to give the desired product (entries 8-11). The amounts of the base and $B_2Pin_2$ were also crucial to the reaction efficiency. Increasing or decreasing their amounts led to the lower yields (entries 12-13).[18] Other copper catalysts such as CuTc or $Cu(OAc)_2$ could also be used for this reaction (entries 14-15). Control experiments demonstrated that copper catalyst and ligand were essential for the reaction (entries 17-18).

**Table 1. Optimization studies for the formation of 3a**[a]




**1a** 1.5 equiv **2a** (1.5 equiv) **3a**

| entry | [Cu] | ligand | base (equiv) | solvent | yield(%)[b] |
|---|---|---|---|---|---|
| 1 | CuCl | $PCy_3$ | KO$^t$Bu (1.5) | THF | 45 |
| 2 | CuCl | dppb | KO$^t$Bu (1.5) | THF | 20 |
| 3 | CuCl | dppf | KO$^t$Bu (1.5) | THF | 21 |
| 4 | CuCl | Cyxantphos | KO$^t$Bu (1.5) | THF | 56 |
| **5** | **CuCl** | **Xantphos** | **KO$^t$Bu** (1.5) | **THF** | **71** |
| 6 | CuCl | bipy | KO$^t$Bu (1.5) | THF | 14 |
| 7 | CuCl | IPr | KO$^t$Bu (1.5) | THF | 15 |
| 8 | CuCl | Xantphos | NaO$^t$Bu (1.5) | THF | 57 |
| 9 | CuCl | Xantphos | LiO$^t$Bu (1.5) | THF | 37 |
| 10 | CuCl | Xantphos | $K_3PO_4$ (1.5) | THF | 0 |
| 11 | CuCl | Xantphos | $NaHCO_3$ (1.5) | THF | 0 |
| 12 | CuCl | Xantphos | KO$^t$Bu (1.0) | THF | 30 |
| 13 | CuCl | Xantphos | KO$^t$Bu (2.0) | THF | 29 |
| 14 | CuTc | Xantphos | KO$^t$Bu (1.5) | THF | 65 |
| 15 | $Cu(OAc)_2$ | Xantphos | KO$^t$Bu (1.5) | THF | 64 |
| 16 | CuCl | Xantphos | KO$^t$Bu (1.5) | 1,4-dioxane | 51 |
| 17 | - | Xantphos | KO$^t$Bu (1.5) | THF | 0 |
| 18 | CuCl | - | KO$^t$Bu (1.5) | THF | 18 |

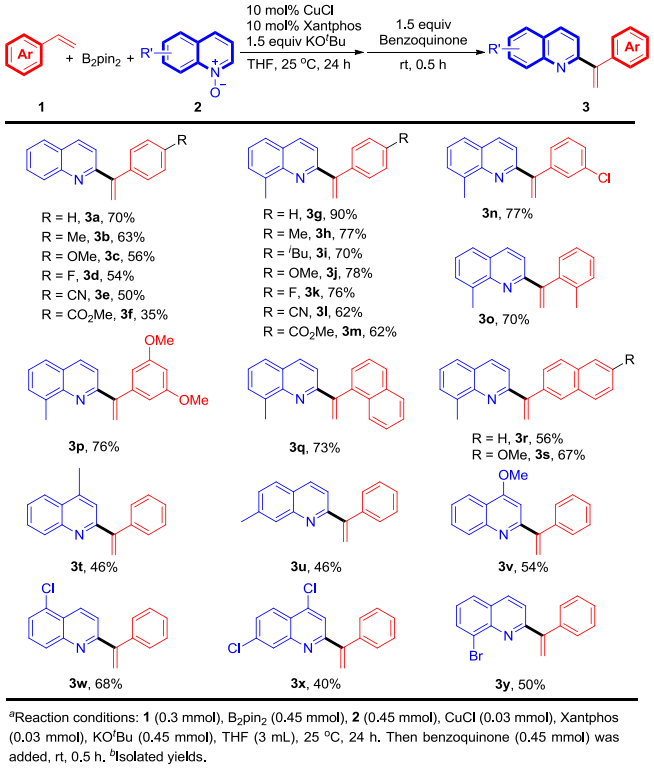
[a]Reaction conditions: **1a** (0.2 mmol), $B_2pin_2$ (0.3 mmol), **2a** (0.3 mmol), [Cu] (0.02 mmol), ligand (0.02 mmol), base (0.3 mmol), solvent (2 mL), 25 °C, 24 h. Then benzoquinone (0.3 mmol) was added, rt, 0.5 h. [b]NMR yields using 1,3,5-trimethylbenzene as an internal standard.

Under the optimized conditions (Table 1, entry 5), the substrate scope was investigated (Scheme 2). The method was applicable to a wide range of substituted vinyl arenes. Alkenes bearing electron-donating groups (-Me, -OMe) or electron withdrawing groups (-F, -CN, $-CO_2Me$) at the *para*-position of the aryl rings are well compatible, furnishing the corresponding products in 35-63% yields (**3b-3f**). Generally, electron-rich alkenes gave better product yields than electron-deficient alkenes. It might be due to the formation of more nucleophilic alkyl-Cu intermediates derived from electron-rich alkenes. To our delight, the product yields could be dramatically improved when 8-methylquinoline *N*-oxide **2b** was used as the electrophile, likely due to the reduced side reactions such as deoxygenation etc. For example, electrically neutral styrene provided **3g** in 90% yield. Alkenes bearing various functional groups on the aryl rings such as *p*-$^i$Bu, *p*-F, *p*-CN and *p*-$CO_2Me$ etc. turned out to be efficient substrates, leading to **3h-3m** in 62-78% yields. We observed again that electron-rich alkenes generally exhibit better reactivity than electron-deficient alkenes. The Cl substituent on the aryl ring was well tolerated (**3n**). Sterically encumbered 2-Me-styrene proceeded smoothly (**3o**). Reactions with 1-, 2- or 6-naphthyl substituted alkenes also worked well, leading to **3q-3s** in 56-73% yields. The reactivity of a variety of quinoline *N*-oxides was also examined. *N*-oxides possessing methyl or OMe groups at the C-4 or C-7 position converted to the desired products in moderate yields (**3t-3v**). 5-Chloro-, 4,7-dichloro- or 8-bromo-substituted quinoline *N*-oxides provided the target products in 40-68% yields (**3w-3y**). Unfortunately, the use of substituted styrene and alkyl alkene such as (*E*)-1-methoxy-4-(prop-1-en-1-yl)benzene or but-3-en-1-ylbenzene as the substrates failed to give the desired products. Pyridine *N*-oxide or 2-phenyl pyridine *N*-oxide were also not suitable for this reaction.

10.1002/anie.202007699

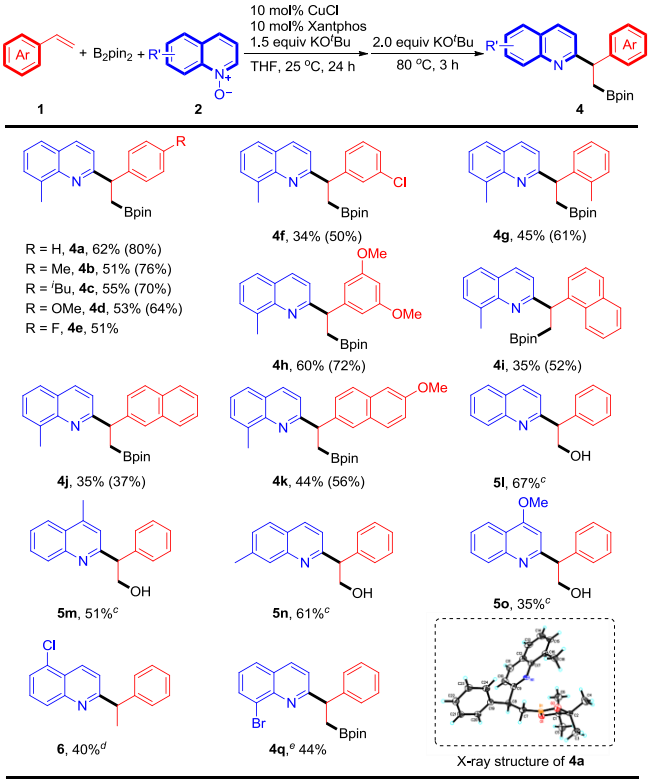







[a]Reaction conditions: **1** (0.3 mmol), $B_2pin_2$ (0.45 mmol), **2** (0.45 mmol), CuCl (0.03 mmol), Xantphos (0.03 mmol), KO$^t$Bu (0.45 mmol), THF (3 mL), 25 °C, 24 h. Then benzoquinone (0.45 mmol) was added, rt, 0.5 h. [b]Isolated yields.

**Scheme 2.** Copper-catalyzed synthesis of 2-alkenylquinolines[a,b]

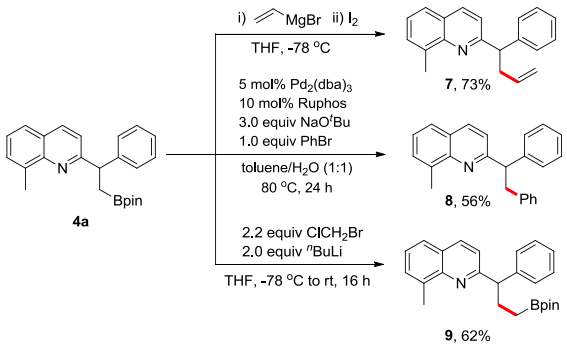



[a]Reaction condition: **1** (0.3 mmol), $B_2pin_2$ (0.45 mmol), **2** (0.45 mmol), CuCl (0.03 mmol), Xantphos (0.03 mmol), KO$^t$Bu (0.45 mmol), THF (3 mL), 25 °C, 24 h. Then KO$^t$Bu (0.6 mmol) was added, 80 °C, 3 h. [b]Isolated yields. The NMR yields are shown in parentheses. [c]Isolated as the corresponding alcohol after oxidation with $NaBO_3 \cdot 4H_2O$. [d]Containing 10% of alkene **3w**. [e]A protodeboronated product **4q'** was also isolated in 29% yield.

**Scheme 3.** Copper-catalyzed synthesis of 2-alkylquinolines[a,b]

Inspired by above results, we envisioned that the desired borylated product might be formed in a deoxygenative manner through variation of different additives used at the second step. Subsequent screening of the base instead of benzoquinone derivatives such as $NaHCO_3$, $Na_2CO_3$, $K_3PO_4$, KO$^t$Bu et al. revealed that KO$^t$Bu served as the most effective base. With styrene **1a** and 8-methylquinoline *N*-oxide **2b** as the substrates, after addition of KO$^t$Bu at the second step and stirred at 80 °C for 3 h, the expected borane **4a** could be formed in 80% NMR yield (60% isolated yield, Scheme 3). Since some borane-containing products might be unstable upon column separation, thus NMR yields were provided for most of the products **4**. Electron donating groups on the aryl rings such as -Me, -$^t$Bu and -OMe were well suitable to afford the expect products in moderate to good yields (**4b**-**4d**). Halogens such as -F and -Cl were also compatible (**4e**, **4f**). 2-Methyl styrene provided **4g** in 61% yield. The use of 3,5-di(MeO)-substituted styrene provided **4h** in good yield. When vinylnaphthalenes were employed, the corresponding products were obtained with synthetically acceptable yields (**4i**-**4k**). In the cases of quinoline *N*-oxides bearing no substituent or with a substituent at other positions such as C4 or C-7, the borane products were not stable during the purification by silica gel column chromatography, then the products were isolated as the alcohol after oxidation with $NaBO_3 \cdot 4H_2O$ (**5l**-**5o**). It was noted that when 5-Cl-quinoline *N*-oxide was used, a protodeboronated product **6** was isolated in 40% yield.[19] The instability of these products might be caused by coordination of the corresponding quinoline nitrogen with the Bpin group resulting in the enhanced reactivity of the C-Bpin bond. 8-bromoquinoline *N*-oxide reacted well with styrene to afford **4q** in 44% yield, along with the formation of a deboronated product **4q'**. The structure of **4a** was confirmed by the X-ray crystallographic analysis.

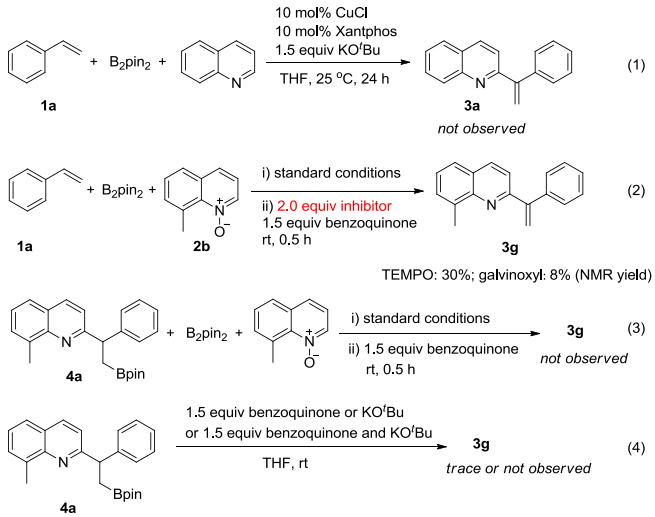
Organoboranes are valuable synthetic intermediates that are widely used in organic and pharmaceutical chemistry. To demonstrate the utility of the borane products, the primary alkylborane **4a** was employed as a building block for the synthesis of various valuable products. Vinylation of **4a** with vinyl Grignard reagent led to **7** in 73% yield. Cross-coupling with aryl bromide catalyzed by Pd provided arylated product **8**. Reaction with $ClCH_2Br$ in the presence of n-BuLi afforded the borane product **9**.[20]




**Scheme 4.** Transformation of compound **4a**

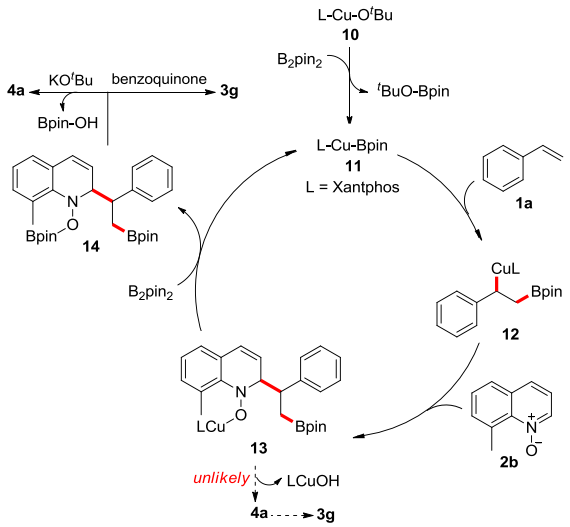
To clarify the reaction mechanism, various control experiments were performed. Reaction with quinoline instead of quinoline *N*-oxide under the standard reaction conditions for the first step did not afford **3a**, indicating that quinoline *N*-oxide was required in this reaction (Scheme 5, eq 1). Addition of a radical scavenger TEMPO or galvinoxyl to the reaction mixture after the

first step of the reaction either gave a lower yield of **3g** or inhibited the reaction efficiently (Scheme 5, eq 2). Thus, a radical pathway is possibly involved for the second step. Isolated borane **4a** could not convert to **3g** under the standard conditions or through the reaction with benzoquinone or KO$^t$Bu (Scheme 5, eq 3 and 4). The results indicated that borane **4** is not the intermediate for alkene **3**. In addition, since the outcome of the reaction strongly depends on the additives at the second step, thus a common intermediate should be involved for their formation.




**Scheme 5.** Control experiments

On the basis of the above results and literatures,[13] a proposed catalytic cycle is shown in Scheme 6. Initially, the copper alkoxide complex **10** reacts with $B_2pin_2$ to give a LCu-Bpin intermediate **11**. Regioselective addition of **11** to the alkene **1a** gives alkylcopper intermediate **12**. Nucleophilic attack of **12** to the iminium ion moiety in quinoline *N*-oxide **2b** provides intermediate **13**, which reacts with $B_2pin_2$ to deliver intermediate **14** and regenerates the LCu-Bpin species **11**. Intermediate **14** aromatizes to give **4a** through elimination of BpinOH upon treatment with KO$^t$Bu. In the presence of benzoquinone, **3g** is furnished. The detailed mechanism for **14** to **3g** is not clear yet. The reaction pathway involving elimination of CuOH in **13** to give the borylated product **4a** is unlikely. Since it can not explain how **3g** is formed. We suggest that a comment intermediate **14** is generated, which accounts for the formation of **3** and **4**.




**Scheme 6.** Proposed catalytic cycle

In conclusion, we have developed a copper-catalyzed regioselective C-H alkenylation and borylative alkylation of quinoline *N*-oxides. Benzoquinone and KO$^t$Bu were identified as the necessary additives at the second step of the reaction that are crucial for the success of the reaction. A wide range of C2-functionalized quinolines were obtained with good functional group tolerance, which may find utilities in pharmaceuticals and synthetic chemistry. We have also shown that for the first time, the catalytically formed alkylcopper intermediate generated via borylcupration of vinyl arenes can be captured by heterocyclic *N*-oxides. Further mechanistic studies and the development of new reactions with *N*-oxides as electrophiles are currently ongoing in our laboratory.

**Keywords:** copper catalysis • quinoline *N*-oxides • borylcupration • alkenylation • borylative alkylation

[1] a) S. Kumar, S. Bawa, H. Gupta, *Mini Rev. Med. Chem*. **2009**, *9*, 1648; b) S. Vandekerckhove and M. D'hooghe, *Bioorg. Med. Chem.* **2015**, *23*, 5098.

[2] a) M. E. Zwaagstra, S. H. H. F. Schoenmakers, P. H. J. Nederkoorn, E. Gelens, H. Timmerman, M. -Q. Zhang, *J. Med. Chem*. **1998**, *41*, 1439; b) V. S.Gopinath, J. Pinjari, R. T. Dere, A. Verma, P. Vishwakarma, R. Shivahare, M. Moger, P. S. K. Goud, V. Ramanathan, P. Bose, M. V. S. Rao, S. Gupta, S. K. Puri, D. Launay, D. Martin, *Eur. J. Med. Chem.* **2013**, *69*, 527; c) A. J. Saggiomo, S. Kano, T. Kikuchi, K. Okubo, M. Shinbo, *J. Med. Chem*. **1972**, *15*, 989; d) A. Huang, A. Moretto, K. Janz, M. Lowe, P. W. Bedard, S. Tam, L. Di, V. Clerin, N. Sushkova, B. Tchernychev, D. H. H. Tsao, J. C. Keith, G. D. Shaw, R. G. Schaub, Q. Wang, N. Kaila, *J. Med. Chem*. **2010**, *53*, 6003.

[3] a) S. M. Prajapati, K. D. Patel, R. H. Vekariya, S. N. Panchal, H. D. Patel, *RSC Adv*. **2014, *4*,** 24463; b) D. Orozco, V. V. Kouznetsov, A. Bermudez, L. Y. V. Mendez, A. R. M. Salgado, C. M. M. Gomez, *RSC Adv*. **2020, *10*,** 4876.

[4] J. A. Bull, J. J. Mousseau, G. Pelletier, A. B. Charette, *Chem. Review*, **2012**, *112*, 2642.

[5] a) H. Andersson, F. Almqvist, R. Olsson, *Org. Lett.* **2007**, *9*, 1335. b) H. Andersson, T. S. L. Banchelin, S. Das, R. Olsson, F. Almqvist, *Chem. Commun.* **2010**, *46*, 3384. c) X.-P. Chen, X.-L. Cui, F.-F. Yang, Y.-J. Wu, *Org. Lett.* **2015**, *17*, 1445. d) L. Bering, A. P. Antonchick, *Org. Lett.* **2015**, *17*, 3134.

[6] a) F. Zhang, X.-F. Duan, *Org. Lett*. **2011**, *13*, 6102. b) O. V. Larionov, D. Stephens, A. Mfuh, G. Chavez, *Org. Lett*. **2014**, *16*, 864. c) W. Jo, J. Kim, S. Choi, S. H. Cho, *Angew. Chem. Int. Ed*. **2016**, *55*, 9690.

[7] a) A. P. Colleville, R. A. J. Horan, S. Olazabal, N. C. O. Tomkinson, *Org. Process Res. Dev.* **2016**, *20*, 1283. b) W. Zhou, T. Miura, M. Murakami, *Angew. Chem. Int. Ed*. **2018**, *57*, 5139.

[8] R. Loska, K. Szachowicz, D. Szydlik, *Org. Lett.* **2013**, 15, 5706.

[9] a) L.-C. Campeau, S. Rousseaux, K. Fagnou, *J. Am. Chem. Soc*. **2005**, *127*, 18020. b) J.-P. Leclerc, K. Fagnou, *Angew. Chem. Int. Ed*. **2006**, *45*, 7781. c) K. S. Kanyiva, Y. Nakao, T. Hiyama, *Angew. Chem. Int. Ed*. **2007**, *46*, 8872. d) B. Xiao, Z.-J, Liu, L. Liu, Y. Fu, *J. Am. Chem. Soc*. **2013**, *135*, 616.

[10] a) H. Wang, X.-L. Cui, Y. Pei, Q.-Q. Zhang, J. Bai, D.-H. Wei, Y.-J. Wu, *Chem. Commun.* **2014**, *50*, 14409; b) Z.-Y. Wu, H.-Y. Song, X.-L. Cui, C. Pi, W.-W. Du, Y.-J. Wu, *Org. Lett.* **2013**, *15*, 1270; c) C.-W. Zhu, M.-L. Yi, D.-H. Wei, X. Chen, Y.-J. Wu, X.-L. Cui, *Org. Lett.* **2014**, *16*, 1840.

[11] a) S. H. Cho, S. J. Hwang, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 9254; b) J. -L. Wu, X. -L. Cui, L. -M. Chen, G. -J. Jiang, Y. -J. Wu, *J. Am. Chem. Soc.* **2009**, *131*, 13888.

[12] For $I_2$ or Brønsted acid promoted C2-alkenylation of quinoline to linear alkenes, see a) Z. -H. Zhang, C. Pi, H. Tong, X. -L. Cui, Y. -J. Wu, *Org. Lett*. **2017**, *19*, 440; b) H. Xia, Y. -H. Liu, P. Zhao, S. -H. Gou, J. Wang, *Org. Lett*. **2016**, *18*, 1796; c) G. E. M. Crisenza, E. M. Dauncey, J. F. Bower, *Org. Biomol. Chem*. **2016**, *14*, 5820.

[13] S. -L. Yu, H. -L. Sang, S. -Z. Ge, *Angew. Chem. Int. Ed*. **2017**, *56*, 15896.

[14] a) N. Matsuda, K. Hirano, T. Satoh, M. Miura, *J. Am. Chem. Soc*. 2013, 135, 4934; b) T. W. Butcher, E. J. McClain, T. G. Hamilton, T. M. Perrone, K. M. Kroner, G. C. Donohoe, N. G. Akhmedov, J. L. Petersen, B. V. Popp, *Org. Lett*. **2016**, *18*, 6428; c) T. Itoh, Y. Kanzaki, Y. Shimizu, M. Kanai, *Angew. Chem. Int. Ed*. **2018**, *57*, 8265; d) J. Lee, S. Radomkit, S. Torker, J. D. Pozo, A. H. Hoveyda, *Nature Chem*., **2018**, *10*, 99.

[15] a) H. Ito, T. Toyoda, M. Sawamura, *J. Am. Chem. Soc*. **2010**, *132*, 5990; b) K. Kubota, E. Yamamoto, H. Ito, *J. Am. Chem. Soc.* **2013**, *135*, 2635; c) H. Yoshida, I. Kageyuki, K. Takaki, *Org. Lett*. **2013**, *15*, 952; d) I. Kageyuki, H. Yoshida, K. Takaki, *Synthesis* **2014**, *46*, 1924; e) K. B. Smith, K. M. Logan, W. You, M. K. Brown, *Chem. Eur. J*. **2014**, *20*, 12032. f) Y. Huang, K. B. Smith, M. K. Brown, *Angew. Chem. Int. Ed*. **2017**, *56*, 13314; g) N.-Y. Wu, X.-H. Xu, F.-L. Qing, *ACS Catal*. **2019**, *9*, 5726.

[16] a) D. E. Stephens, J. Lakey-Beitia, J. E. Burch, H. D. Arman, O. V. Larionov, *Chem. Commun*. **2016**, *52*, 9945; b) H. Wang, Y. Pei, J. Bai, J.-L. Zhang, Y.-J. Wu, X.-L. Cui, *RSC Adv.* **2014**, *4*, 26244.

[17] H. P. Kokatla, P. F. Thomson, S. Bae, V. R. Doddi, M. K. Lakshman, *J. Org. Chem.* **2011**, *76*, 7842.

[18] See supporting information for details.

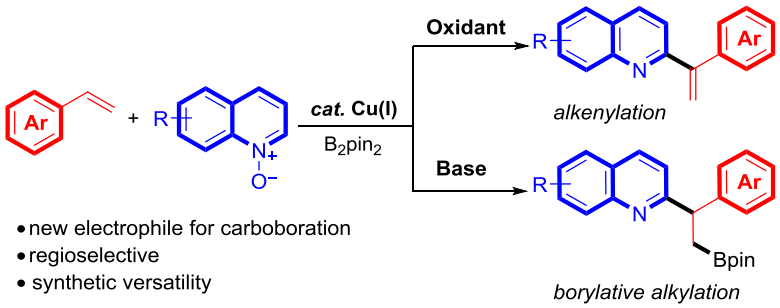
[19] S. Nave, R. P. Sonawane, T. G. Elford, V. K. Aggarwal, *J. Am. Chem. Soc.* **2010**, *132*, 17096.

[20] K. M. Sadhu and D. S. Matteson, *Organometallics*, **1985**, *4*, 1687.

10.1002/anie.202007699


WILEY-VCH

COMMUNICATION




*Hui Hu, Xiaoping Hu, and Yuanhong Liu**

***Page No. – Page No.***

**Copper-Catalyzed *ortho*-Functionalization of Quinoline *N*-Oxides with Vinyl Arenes**

**Borylcupration:** An efficient copper-catalyzed regioselective C-H alkenylation and borylative alkylation of quinoline *N*-oxides with vinyl arenes in the presence of pinacol diborane has been developed. The reaction proceeds through the borylcupration of the vinyl arenes followed by nucleophilic attack of the resulting alkyl copper species to the quinoline *N*-oxides. Benzoquinone and KO$^t$Bu were identified as the necessary additives at the second step of the reaction that are crucial for the success of the reaction.