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Stereoselective Direct Copper-Catalyzed Alkenylation of Oxazoles with Bromoalkenes

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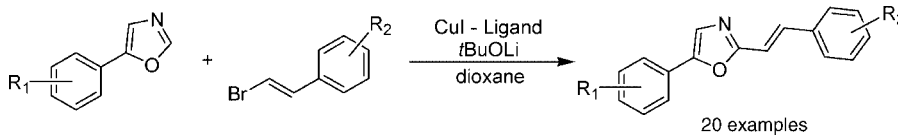
ABSTRACT



A copper-catalyzed direct alkenylation of oxazoles with bromoalkenes has been developed. The method is both regio- and stereoselective and tolerates a variety of functional groups. A wide range of 2-*E*-vinyl-substituted oxazoles were obtained in high yields including the highly fluorescent alkaloid annuloline.

An oxazole motif is an ubiquitous feature in both natural products and synthetic compounds finding, among others, applications as fluorescent dyes, pharmaceuticals, and polymers. Increasing interest in polyfunctionalized oxazoles has driven the development of rapid, high-yielding, and cost-effective methods for their elaboration.[1] For instance, Cossy et al. have very recently reported a novel and elegant approach to 2- and 4-vinyl-functionalized oxazoles involving a ruthenium-catalyzed olefin cross-methathesis reaction of vinyl oxazoles.[2] In the pursuit of an ongoing medicinal chemistry program, we were interested in generating a variety of C-2 vinyl-substituted oxazoles based on the direct alkenylation of a readily available oxazole scaffold. In recent years, transition-metal-catalyzed direct functionalization of oxazoles and related heterocycles has gained significant attention. In particular, the direct arylation with aryl halides[3,4] and to a lesser extent alkenylation with alkenes/alkynes[5,6] and alkynylation[7] have been developed. A wide range of metal catalysts including palladium, rhodium, or ruthenium

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(4) For selected examples of direct arylation of oxazoles, see: (a) Lewis, J. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1589. (b) Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 1970. (c) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404, and references cited therein. (d) Ferrer Flegeau, E.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2008**, *10*, 2717, and references cited therein. (e) Besselièvre, F.; Mahuteau-Betzer, F.; Grierson, D.; Piguel, S. *J. Org. Chem.* **2008**, *73*, 3278. (f) For a mechanistic discussion, see: Sanchez, R. S.; Zhuravlev, A. *J. Am. Chem. Soc.* **2007**, *129*, 5824.

(5) For examples of alkenylation on heteroaromatics with alkynes, see: (a) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. *J. Am. Chem. Soc.* **2008**, *130*, 2448. (b) Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8872. (c) Nakao, Y.; Kanyiva, K. S.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 8146. (d) Murakami, M.; Hori, S. *J. Am. Chem. Soc.* **2003**, *125*, 4720.

(6) For examples of alkenylation on heteroaromatics with alkenes, see: (a) Matsuura, Y.; Tamura, M.; Kochi, T.; Sato, M.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 9858. (b) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528.

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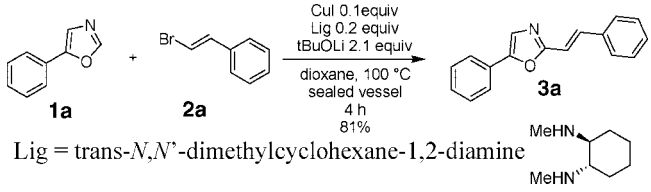
have been exploited for these processes. However, the use of copper catalysts remains quite rare[4c,8] despite the clear advantage in cost-effectiveness. An attractive, yet unexplored, approach would be the direct alkenylation of oxazoles and related electron-rich heterocycles with vinyl halides. At the outset of our studies, there was limited literature precedent for the direct alkenylation of (hetero)aromatics with bromoalkenes, and in particular copper-catalyzed direct alkenylation was unknown. Oi and Inoue have reported the ortho-selective direct alkenylation of 2-aryloxazolines with various alkenyl bromides by ruthenium complexes.[9] Daugulis et al. described the coupling of 3-haloacrylates with anilides.[10] During the preparation of our manuscript, two notes on direct alkenylation with bromoalkenes were published. Daugulis et al. have shown copper-catalyzed direct alkenylation of pentafluorobenzene with β-bromostyrene in high yield.[8b] Doucet et al. described the use of alkenyl bromides for a palladium-catalyzed C−H bond activation of benzoxazole and benzothiazole with moderate to good yields.[11]

Herein, we report a novel method for the direct copper-catalyzed alkenylation of 5-phenyloxazoles and related compounds with various styryl halides. This approach provides straightforward and efficient access to a wide variety of 2-*E*-alkenyloxazoles in a stereoselective manner and is illustrated by an expedient three-step synthesis of the alkaloid annuloline.

Initially, the coupling of 5-phenyloxazole **1a** with *E*-β-bromostyrene **2a** was investigated (Scheme 1).

Scheme 1. Optimized Coupling Conditions



Compound **1a** was readily prepared in one step in 85% yield by the van Leusen reaction of benzaldehyde with *p*-toluenesulfonylmethylisocyanide (TosMIC) and K_2CO_3 in refluxing MeOH.[12] Screening of the conditions for the coupling reaction involved varying the solvent, ligand, metal source, and base. The best results were obtained using copper(I) iodide, trans-*N*,*N*′-dimethylcyclohexane-1,2-diamine as ligand, and lithium *tert*-butoxide in dioxane at 100 °C for 4 h. Product **3a** was isolated in 81% yield as the pure *E* stereoisomer. Crucially, formation of **3a** was not observed if CuI was omitted from the reaction mixture. Also, the use of 2.1 equiv of *t*-BuOLi was found to be optimal since reactions with K_3PO_4, Cs_2CO_3, Ag_2CO_3, LiH, and *t*-BuOK were much slower or did not proceed. Commercial grade dioxane proved to be the better solvent, as reaction in toluene resulted in significantly reduced product yields (39% in 2 h, 58% overnight). Further, the use of the less expensive *N*,*N*′-dimethylethylene-1,2-diamine ligand resulted in lower conversion to product (76%). As a byproduct of the reaction, the dimer of 5-phenyloxazole was obtained in up to 11% yield resulting from the oxidative homocoupling of the organocopper oxazole intermediate. The reactivity of dimethoxystyrene iodide and the corresponding chloride[13] was also studied in the direct alkenylation. Reaction of iodostyrene (entry 5, Table 1) with 5-phenyloxazole **1a** gave *E*-2-alkenyl-5-aryloxazole **3f** in comparable yield (80%), whereas no product was formed when using the chlorostyrene derivative (entry 7).

This optimized protocol was subsequently used to investigate the scope of the direct alkenylation of 5-phenyloxazole **1a** with various readily accessible *E*-β-bromostyrenes (Table 1).[14] Both electron-rich (entries 1−6) and electron-deficient (entries 8−11) β-bromostyrenes reacted regioselectively at the C-2 position of 5-phenyloxazole in very good yields. Substitutions at the ortho-, meta-, or para-positions of the styrene were tolerated. Moreover, these conditions are compatible with a range of functional groups including nitro, cyano, and halides which may be used for further transformations. In addition, the reactivity of isocrotyl bromide was evaluated in the direct alkenylation with **1a** (entry 13) giving compound **3l** in good yield (76%). This result shows the potential scope of the method beyond the bromostyrenes.

The *E*-isomers **3** were obtained exclusively. However, in the ^{1}H NMR of the crude product mixture from the reaction of **1a** with *E*-β-paramethylbromostyrene (Table 1, entry 1), the *Z*-isomer could be detected and was isolated in 4% yield. There is strong evidence to suggest that the *Z*-isomer comes from the coupling of *E*-β-bromostyrene and not from traces of *Z*-β-bromostyrene contained in the starting material. First, when the reaction was run with pure *Z*-β-bromostyrene, no coupling product **3b** was observed. Furthermore, the starting material was fully recovered in stereoisomerically pure form when compound **3b** was subjected to the reaction conditions for several hours (overnight).

These new conditions were also successfully applied to substituted 5-phenyloxazoles and related azoles (Table 2). Both electron-rich (entries 1−2) and electron-poor (entry 3)

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(8) (a) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (b) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (c) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (d) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842. (e) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968.

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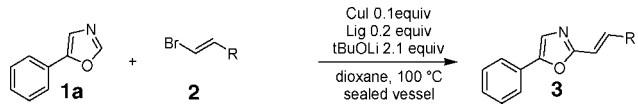
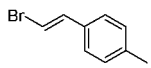
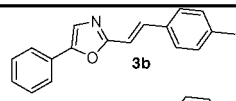
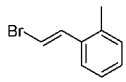
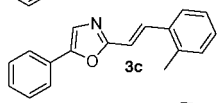
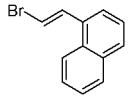
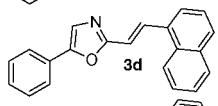
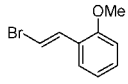
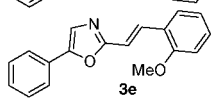
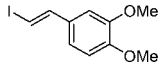
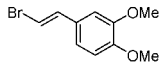
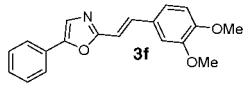
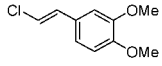
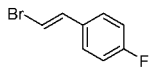
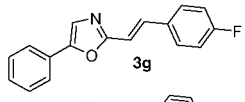
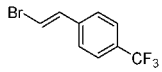
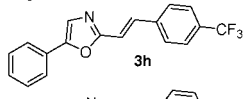
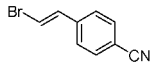
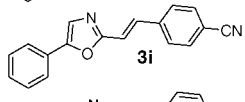
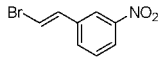
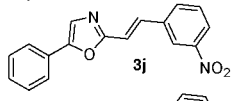
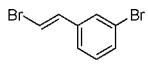
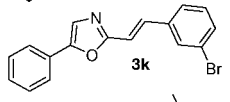
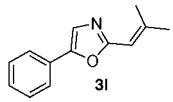
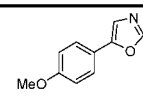
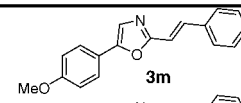
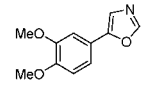
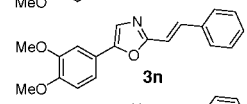
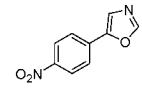
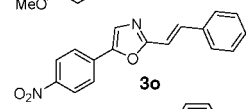
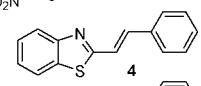
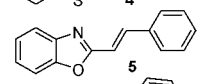
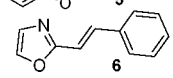
Table 1. Scope of Direct Alkenylation of 5-Phenyloxazole with Bromoalkenes



entry	bromoalkene[a,b]	product	time (h)	yield (%)[c]
1			6	81
2			6	83
3			12	71
4			12	69
5			12	80
6			12	82
7			24	0
8			3	74
9			5	83
10			3	70
11			3	70
12			4	78
13			18	76[d]

[a] Conditions: 5-phenyloxazole **1a** (1 equiv), styryl halides **2** (1.2 equiv). [b] *E*-*β*-Styrenes contain traces of *Z*-isomers. [c] Isolated yields. [d] Run with 2 equiv of isocrotyl bromide.

Table 2. Scope with Respect to the Heterocycles

entry	oxazole	product	time (h)	yield (%)[a]
1			8	76
2			8	73
3			2	65
4			5	77
5			3	33
6			3	58[b]

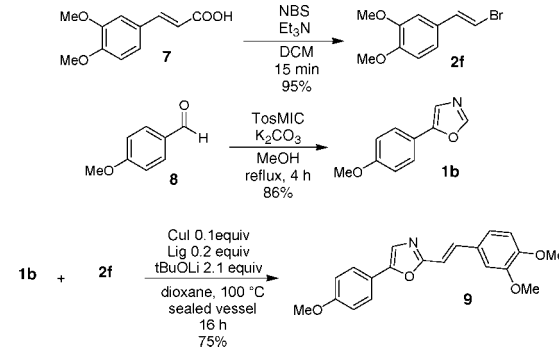
[a] Isolated yields. [b] Reaction run with 1 equiv of *β*-bromostyrene and 1.2 equiv of oxazole.

substrates can be efficiently alkenylated. Benzothiazole (entry 4) and benzoxazole (entry 5) were also reactive, although in the latter case the yield is lower. Remarkably, oxazole, itself, was regioselectively vinylated at the C-2 position in moderate yield (entry 6).

This methodology, combined with the van Leusen reaction to obtain the requisite 5-substituted oxazole starting material, has been applied to the synthesis of annuloline **9**. This alkaloid, isolated from the roots of ryegrass (*Lolium multiflorum*),[15] shows an intense blue fluorescence upon exposure to UV irradiation and was the first oxazole-containing natural product ever isolated.

The four total syntheses of annuloline described to date all require nontrivial preparation of building blocks before a final oxazole ring formation step.[16] Our annuloline synthesis is a convergent three-step sequence (Scheme 2)

Scheme 2. Synthesis of Annuloline



which begins with the preparation of the dimethoxy-*β*-bromostyrene **2f** from the corresponding cinnamic acid by a modified Hunsdiecker reaction in 95% yield[14a] and formation of the oxazole **1b** (86%) by reaction of *p*-anisaldehyde with TosMIC. Then, direct alkenylation under our optimized

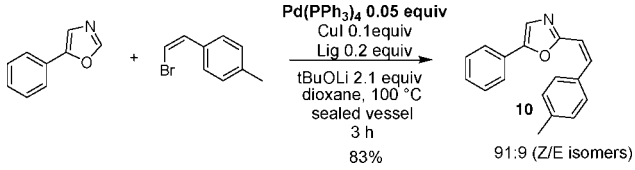
(15) Axelrod, B.; Belzile, J. R. *J. Org. Chem.* **1958**, *23*, 919.

(16) (a) Karimoto, R. S.; Axelrod, B.; Wolinsky, J.; Schall, E. D. *Tetrahedron Lett.* **1962**, *3*, 83. (b) Brossi, A.; Wenis, E. *J. Heterocycl. Chem.* **1965**, *2*, 310. (c) Doyle, M. P.; Buhro, W. E.; Davidson, J. G.; Elliott, R. C.; Hoekstra, J. W.; Oppenhuizen, M. *J. Org. Chem.* **1980**, *45*, 3657. (d) Molina, P.; Fresneda, P. M.; Almendros, P. *Heterocycles* **1993**, *36*, 2255.

conditions afforded 2-alkenyl-5-aryloxazole in 91% yield as an 11.5:1 mixture of *E*- and *Z*-isomers. Crystallization from hot cyclohexane/dichloromethane gave exclusively annuloline *E*-**9** in 75% yield.

Although under our coupling conditions *Z*-β-bromostyrenes, prepared according to Uenishi's method,[17] were not reactive, preliminary experiments indicate that this methodology can be extended to the preparation of *Z*-2-alkenyloxazoles by the addition of 5 mol % of palladium(0) tetrakis to the reaction mixture. In this way, compound **10** was isolated in 83% yield as a 10:1 mixture of *Z*/*E* isomers (Scheme 3).[18]

Scheme 3. Direct Vinylation of 5-Phenyloxazole with *Z*-β-Bromostyrene



In conclusion, we have developed new conditions for C−H bond functionalization which enables a direct and stereoselective copper-catalyzed alkenylation of oxazoles and related heterocycles with styryl iodides or bromides. This reaction tolerates many functional groups and allows the preparation of *E*-2-styryl-5-phenyloxazoles in high yields. Encouragingly, the unreactivity of *Z*-β-bromostyrene has been overcome by simply adding palladium(0) tetrakis to the reaction medium. Efforts are now underway to extend this methodology to other classes of *E*- and *Z*-bromoalkenes. Similarly, mechanistic investigations are currently in progress in our laboratory and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for compounds **3a**−**o**, **4**, **5**, **6**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801512Q

(17) (a) Uenishi, J.; Kawahama, R.; Yonemitsu, O. *J. Org. Chem.* **1998**, *63*, 8965. (b) Other preparation method: Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron Lett.* **2001**, *42*, 3893.

(18) Control experiments showed that the reaction does proceed comparably when copper is omitted. Further investigations are currently underway.