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Copper-Catalyzed Regioselective *ortho* C–H Cyanation of Vinylarenes**

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Abstract

A copper-based catalytic technique for the regioselective ortho C–H cyanation of vinylarenes has been developed. This method provides an effective means for the selective functionalization of vinylarene derivatives. A copper-catalyzed cyanative dearomatization mechanism is proposed to account for the regiochemical course of this reaction.

Keywords

C–H activation; copper; cyanation; difunctionalization; dearomatization

Transition-metal-catalyzed direct C–H functionalization is an attractive strategy to streamline chemical synthesis.[1,2] During the past decade, chelation-assisted C–H activation has been employed to devise a range of synthetically useful functionalization reactions of aromatic compounds.[1] In these processes, relatively strong σ-directing groups, such as pyridines[1b,1c,1h] and carbonyls,[1a,1e,1f,1g] are usually required to coordinate to the transition metal center, thereby enhancing reactivity as well as controlling site selectivity. In contrast, weakly coordinating π-directing groups, such as C=C double bonds, have rarely been utilized, and in particular, the *ortho* selective C–H functionalization of styrenes remains a challenge.[3,4]

Herein we report a combined copper-catalyzed borylation/*ortho* C–H cyanation reaction of vinylarenes. In this process, the C=C double bond is used as both a reaction site and a 'directing group' for the C–H functionalization event (Scheme 1). Overall, this method introduces a synthetically versatile cyano group,[5] while simultaneously performing a catalytic anti-Markovnikov hydrofunctionalization of the olefin.[6]

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As a part of our work to develop catalytic methods for the enantioselective difunctionalization of olefins,[7,8] we sought to use the benzylcopper intermediate (**II**) generated from hydrocupration[7] or borocupration[9] of styrenes (**I**) in a subsequent electrophilic functionalization process. In an attempt to develop a cyanoborylation reaction, we unexpectedly found that the *ortho* C–H functionalized product (**3a**) was generated in 90% yield upon treatment of 2-vinylnaphthalene (**1**) with the electrophilic cyanating agent NCTS (**2**)[10] in the presence of a copper catalyst derived from CyJohnPhos[11] (**L1**) (Table 1, entries 1–2). Notably, cyanation at the less sterically congested C3 position (**3b**) was not observed and benzylic cyanation product (**3c**) was obtained in <5% yield as indicated by ^{1}H NMR spectroscopy. Further experimentation revealed that replacement of the phosphine bound cyclohexyl groups with phenyl (**L2**) or *tert*-butyl (**L3**) resulted in catalysts that were less effective. Increasing the steric bulk of the ligand's biaryl backbone did not lead to further improvement (entries 5–6). Employing bidentate phosphine ligands such as dppp (**L6**) also furnished the C1 cyanation product, albeit in lower yields, while the use of BINAP (**L7**) provided <5% product under otherwise identical reaction conditions. Among various bidentate phosphine ligands examined, DPPBz (**L8**) gave the best results, providing **3a** in 95% yield along with <5% of **3c**.[12] Other commonly used electrophilic cyanating agents such as TsCN were ineffective for the current transformation (entry 11).

We next explored the substrate scope with respect to the vinylarene component (Scheme 2). A variety of 2-vinylnaphthalenes bearing electron-donating or electron-withdrawing functional groups were converted to the C1 cyanated product in good yields (**4b**–**4h**). C3 cyanation was not observed for any of the cases examined. Sterically hindered substrates could be successfully transformed with this method (**4i** and **4j**), and 1-vinylnaphthalenes also represented excellent substrates (**4k** and **4l**). Further, a heterocyclic vinylarene (**4m**) as well as those bearing pendent heterocyclic motifs (**4n**–**4p**) were compatible. Using the **L8**-based catalyst, α- and β-branched vinylnaphthalenes (**4q** and **4r**) also reacted to provide the cyanation products, although in lower yields (see the SI). Finally, styrene can also be cyanated in a similar fashion (73%), although other simple aromatic substrates such as 4-methoxystyrene afforded lower yields of the desired product (30–40%).

To demonstrate the synthetic versatility of the products derived from this method, several derivatization reactions were performed (Scheme 3). Oxidation of the boronate afforded alcohol **5a**,[13] while the BCl_3 mediated amination with benzyl azide provided amine **5b**.[14] Suzuki–Miyaura coupling using our RuPhos-based palladacycle precatalyst[15] delivered the unsymmetrical 1,2-diarylethane bearing a heterocyclic core (**5c**). Furthermore, alcohol **5a** was converted to lactone **5d**, amide **5e**[16] and tetrazole **5f**[17] in excellent yields.

A great deal of effort has been devoted to the selective functionalization of the biaryl backbone of BINOL in an attempt to access new catalysts for enantioselective transformations. However, the regioselective C–H functionalization of BINOL derivatives at the C4 or C5 position remains underdeveloped (Scheme 4).[18] To further demonstrate the utility of our method, we converted **6a** and **6b** into the corresponding cyanated products **7a** and **7b**, respectively. In both examples, a single C–H cyanated isomer was generated.

Additionally, the fully substituted and differentiated benzene ring of **7b** is generated with acceptable yield.[19]

We were also able to effect the formal *ortho* C–H cyanation of 2-vinylnaphthalenes by treating **5a** with DBU in the presence of MsCl at room temperature to furnish **8** in 85% yield (Scheme 5). By regenerating the olefin, the C1 selectivity that we observe complements that of other directed C–H activation processes, where the functionalization of less sterically hindered C3 carbon is usually favored.[20]

In order to gain insight into the reaction mechanism of this process, we prepared 1-deutero-2-vinylnaphthalene (**9**) and subjected it to the standard reaction conditions (Scheme 6). It was found that 88% of the deuterium of **9** was incorporated into **10** at the benzylic position, indicating that a formal 1,3-hydrogen transposition has taken place. In addition, we were able to demonstrate that this hydrogen migration is likely an intramolecular process with respect to the vinylnaphthalene substrate by performing a crossover experiment using **9** and **11**. After confirming that **9** and **11** react at similar rates, we found that converting **11** to **4h** in the presence of **9** did not result in deuterium incorporation, while the amount of deuterium incorporated in **10** was unaffected. Furthermore, a competition experiment between **9** and **1** showed a kinetic isotope effect (KIE) of 0.98±0.02, which is suggestive that the rate-determining step precedes hydrogen migration.

Based on these results, we propose that the current reaction proceeds through a cyanative dearomatization mechanism (Scheme 7). Transmetalation of the phosphine-ligated copper catalyst **12** with the diboron reagent provides **13**, which undergoes subsequent borocupration to afford benzylcopper **14a**.[9a,h] Electrophilic cyanation of **14a** with NCTS (**2**) proceeds in an S_E2' fashion, delivering the dearomatized intermediate **16**, which then undergoes a rapid hydrogen transfer to generate the C1 cyanated product.[21–24] Cyanation at the C3 position (**17**) would disrupt the aromaticity of both benzene rings and is therefore disfavored. At this point the exact reason for the favorable C1 cyanation over benzylic cyanation remains unclear; we are performing computational studies to gain an accurate understanding into this regiochemical outcome.

In conclusion, we have developed a copper-catalyzed *ortho* C–H cyanation of vinylarenes. This protocol provides an effective means to access an array of synthetically versatile building blocks that can be easily transformed into a variety of complex molecules. This C–H functionalization process features unique site selectivity, which originates from a copper-catalyzed electrophilic cyanative dearomatization mechanism. Designing new catalysts to broaden the substrate scope, developing enantioselective variants of the current transformation and engaging other electrophiles of significant synthetic utility in this process are topics of ongoing investigations in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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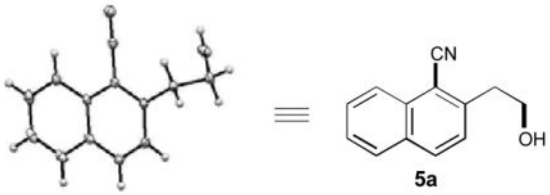
13. The structure of **15a** was confirmed by X-ray diffraction analysis. CCDC 986749 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



5a

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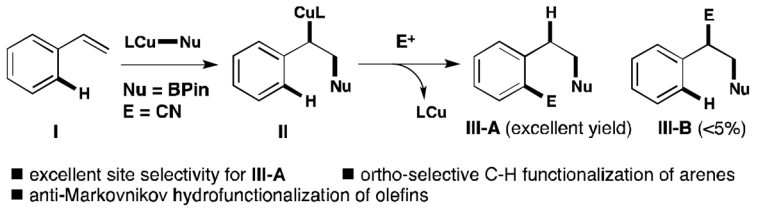
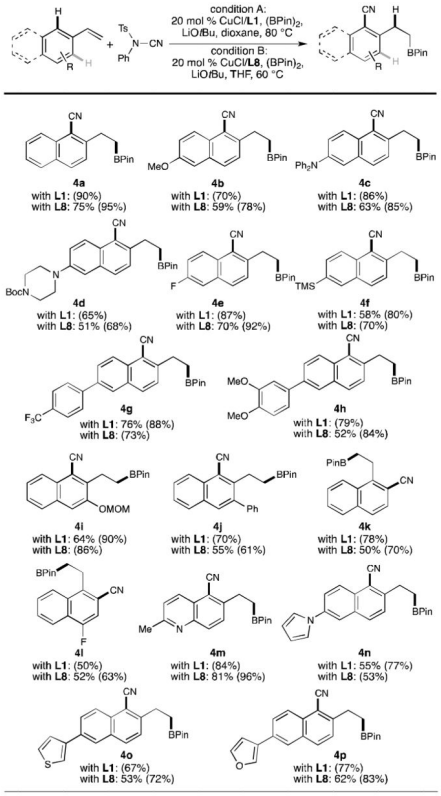


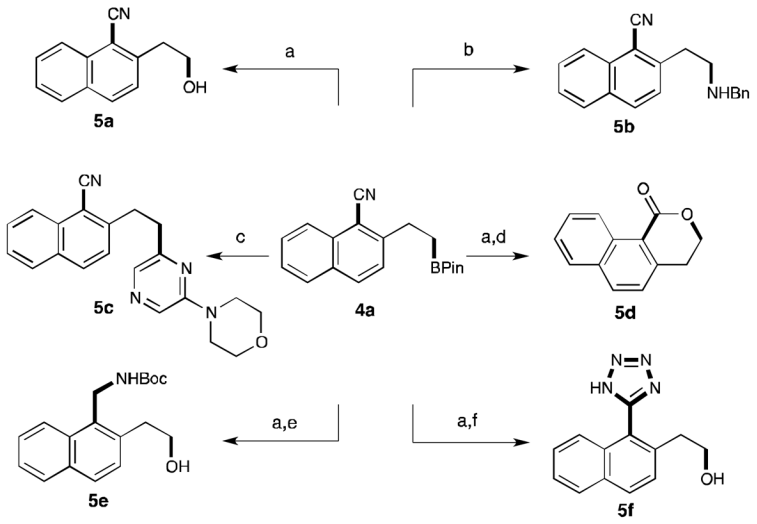
Scheme 1.

Copper-Catalyzed Borylation/*ortho* C–H Cyanation of Styrenes.



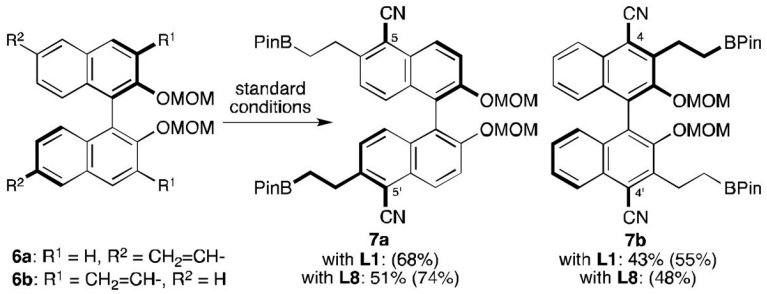
Scheme 2.

Substrate Scope of Vinylarenes. [a]Reaction conditions: vinylarene (0.20–1.0 mmol), **2** (1.2 equiv), B_2Pin_2 (1.1–1.2 equiv), LiO*t*Bu (1.5 equiv), CuCl (20 mol %), **L1** (22 mol %), dioxane (0.30 M), 80 °C or **L8** (22 mol %), THF (0.40 M), 60 °C, 12 h. Yields reported are that of isolated material. Yields in parentheses were determined by ^{1}H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as internal standard. Isolated yields were lower than ^{1}H NMR yields because of product decomposition on silica gel.



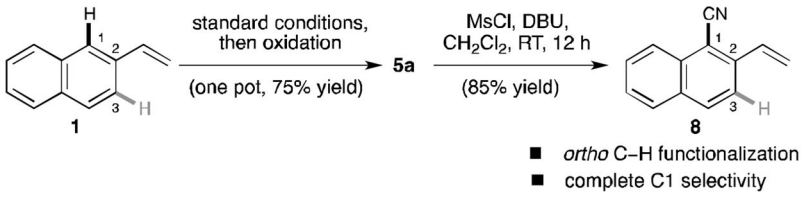
Scheme 3.

Derivatization of Borylation/Cyanation Products. Conditions: a. $NaOH/H_2O_2$, RT, 2 h (85%). b. BCl_3, CH_2Cl_2, RT, 4 h, then BnN_3, 0 °C, 16 h (63%). c. ArCl, 5 mol% RuPhos Precat, 5 mol% RuPhos, K_3PO_4, toluene/H_2O, 80 °C, 12 h (60%). d. conc. HCl/MeOH, 60 °C, 12 h (95%). e. $NiCl_2 \cdot 6H_2O$, $NaBH_4$, Boc_2O, MeOH, 0 °C to RT, 1 h (65%). f. NaN_3, $ZnBr_2$, H_2O/*i*PrOH, 100 °C, 48 h (92%).



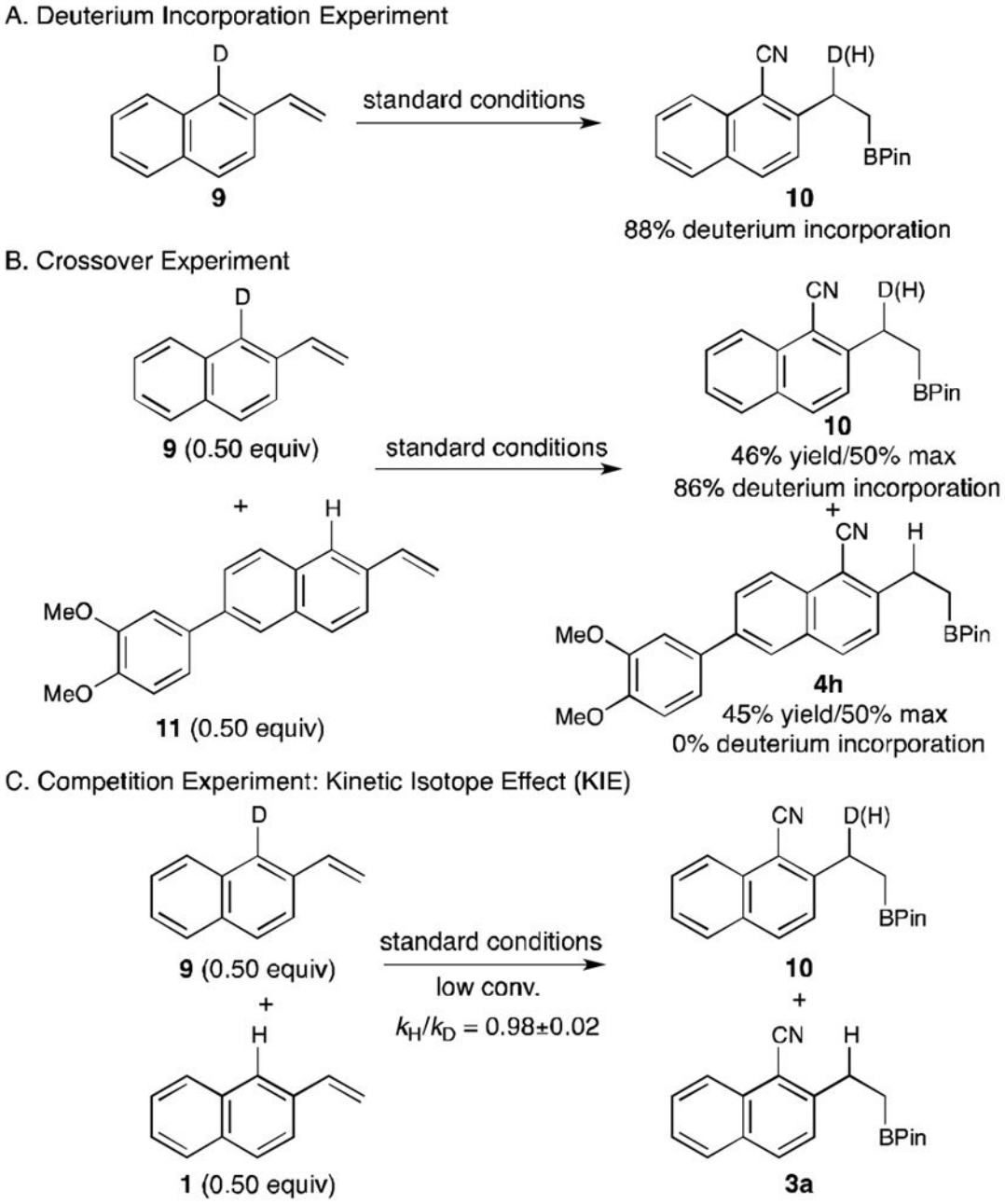
Scheme 4.

Regioselective Cyanation of BINOL Scaffolds.

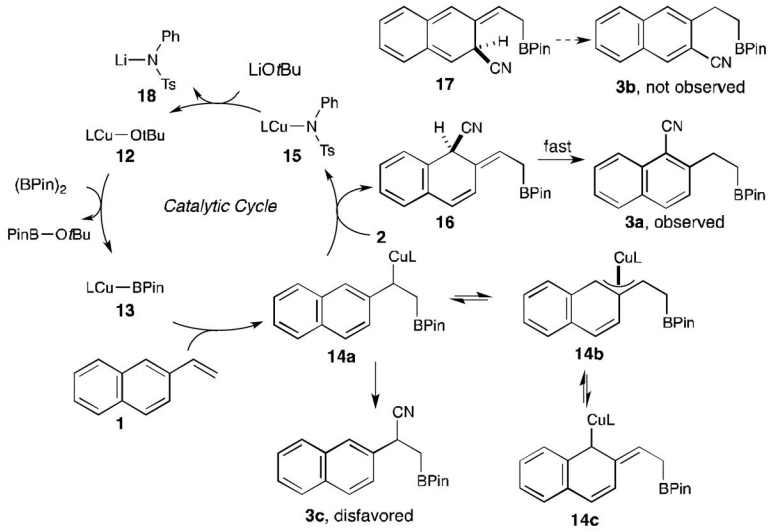


Scheme 5.

"Unmasking" the Boronic Ester: Formal *ortho* C–H Cyanation of Vinylarenes.



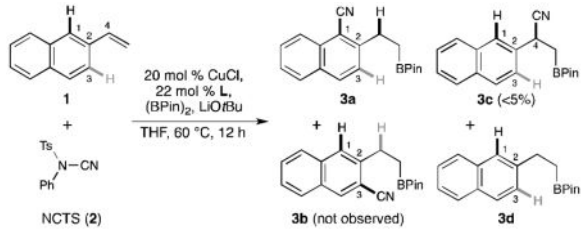
Scheme 6.
Mechanistic Studies.



Scheme 7.
Mechanistic Proposal.

Table 1

Optimization of Reaction Conditions[a].



entry	L	yield of 3a	yield of 3b
1	**L1**	84%	0.5%
2[b]	**L1**	90%	0%
3	**L2**	55%	10%
4	**L3**	70%	6%
5	**L4**	25%	7%
6	**L5**	59%	11%
7	**L6**	63%	9%
8	**L7**	0%	0%
9	**L8**	95%	0%
10[c]	**L8**	88%	2%
11[d]	**L8**	0%	0%
12[e]	-	0%	0%

[a] Reaction conditions: 1 (0.20 mmol), 2 (0.30 mmol), CuCl (0.040 mmol), **L** (0.044 mmol), LiO*t*Bu (0.31 mmol), THF (0.50 mL), 60 °C, 12 h. Yields of **3a**–**3d** were determined by ^{1}H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard.

[b] Dioxane (0.70 mL), 80 °C, 12 h.

[c] CuCl (5 mol %), **L8** (6 mol %), 1.0 mmol scale.

[d] TsCN was used in lieu of **2**.

[e] In the absence of CuCl and ligand.