C–H Activation

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

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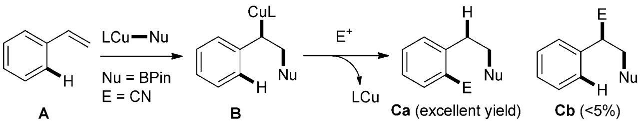
Dedicated to the MPI für Kohlenforschung on the occasion of its centenary

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.*

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,c,h] and carbonyls,[1a,e,f,g] 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 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 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]

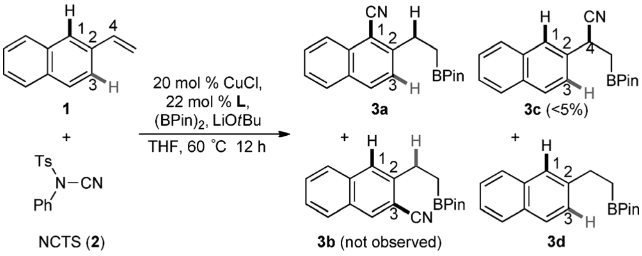


- excellent site selectivity for **Ca**
- *ortho*-selective C–H functionalization of arenes
- *anti*-Markovnikov hydrofunctionalization of olefins

Scheme 1. Copper-catalyzed borylation/*ortho* C–H cyanation of styrenes. Pin = pinacol.

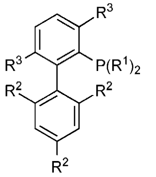
As a part of our work to develop catalytic methods for the enantioselective difunctionalization of olefins,[7,8] we sought

Table 1: Optimization of reaction conditions.[a]

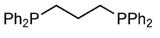


Entry	L	Yield [%] 3 a	3 b
1	**L1**	84	< 5
2[b]	**L1**	90	0
3	**L2**	55	10
4	**L3**	70	6
5	**L4**	25	7
6	**L5**	59	11
7	**L6**	63	9
8	**L7**	0	0
9	**L8**	95	0
10[c]	**L8**	88	< 5
11[d]	**L8**	0	0
12[e]	–	0	0

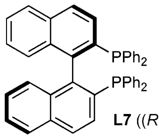
[a] Reaction conditions: 1 (0.20 mmol), 2 (0.30 mmol), CuCl (0.040 mmol), **L** (0.044 mmol), LiO*t*Bu (0.31 mmol), THF (0.50 mL), 60 °C, 12 h. Yields of **3 a–d** were determined by ^{1}H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard. [b] 1,4-Dioxane (0.70 mL), 80 °C, 12 h. [c] CuCl (5 mol %), **L8** (6 mol %), 1.0 mmol scale. [d] TsCN was used instead of **2**. [e] In the absence of CuCl and ligand. THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.



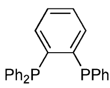
R^1 = Cy, R^2 = R^3 = H, **L1** (CyJohnPhos)
R^1 = *t*Bu, R^2 = R^3 = H, **L2** (JohnPhos)
R^1 = Ph, R^2 = R^3 = H, **L3** (PhJohnPhos)
R^1 = Cy, R^2 = *i*Pr, R^3 = H, **L4** (XPhos)
R^1 = Cy, R^2 = *i*Pr, R^3 = OMe, **L5** (BrettPhos)



L6 (dppp)



L7 ((*R*)-BINAP)



L8 (DPPBz)

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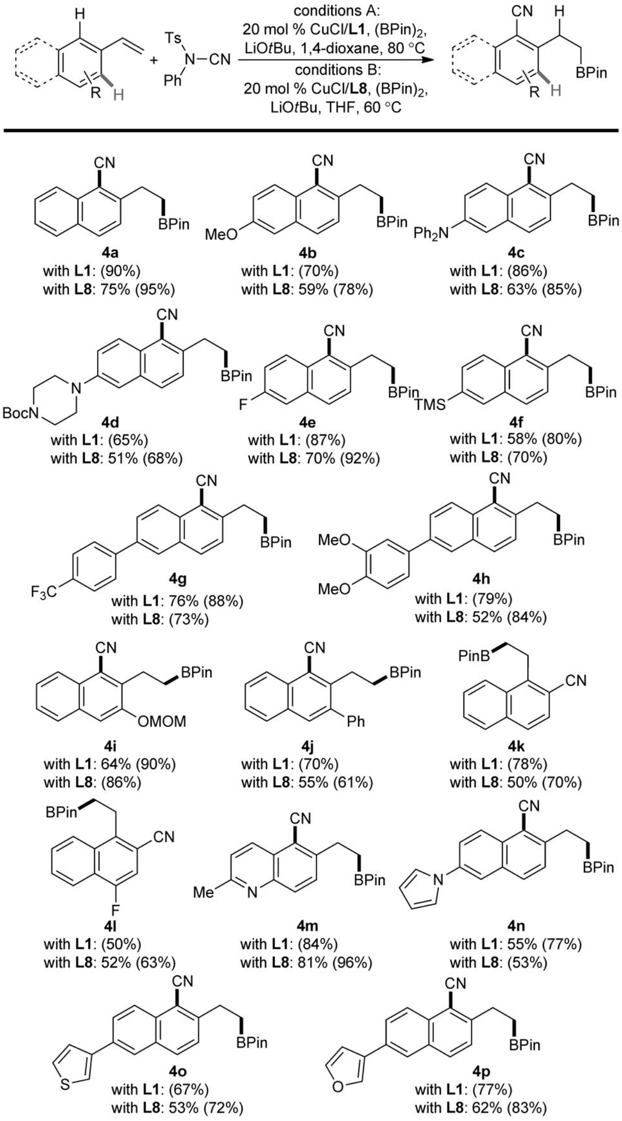
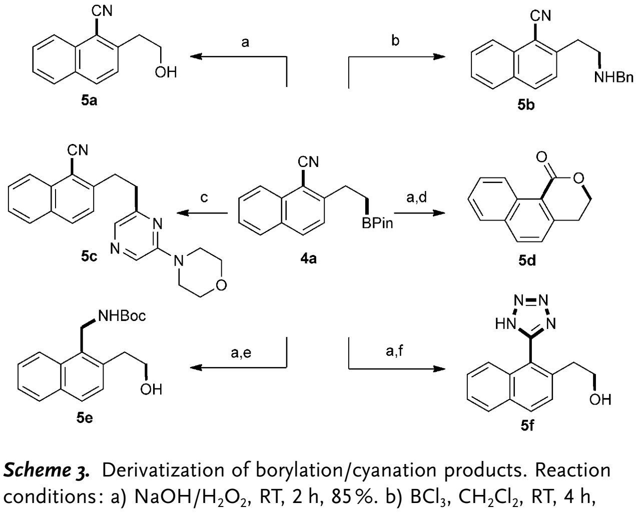


Scheme 2. Substrate scope of vinylarenes. Reaction conditions: vinylarene (0.20–1.0 mmol), **2** (1.2 equiv), B_2Pin_2 (1.1–1.2 equiv), LiO*t*Bu (1.5 equiv), CuCl (20 mol%), **L1** (22 mol%), 1,4-dioxane (0.30 M), 80 °C or **L8** (22 mol%), THF (0.40 M), 60 °C, 12 h. Yields reported are that of the isolated material. Yields within parentheses were determined by ^{1}H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard. Yield of isolated product were lower than yields determined by ^{1}H NMR spectroscopy because of product decomposition on silica gel. Boc = *tert*-butoxycarbonyl, MOM = methoxymethyl, TMS = trimethylsilyl.

to use the benzylcopper intermediate **B**, generated from hydrocupration[7] or borocupration[9] of the styrenes **A**, 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 and 2). Notably, cyanation at the less sterically congested C3-position (**3b**) was not observed and the benzylic cyanation product **3c** was obtained in less than 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 which were less effective. Increasing the steric bulk of the ligand's biaryl backbone did not lead to further improvement (entries 5 and 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 less than 5% product under otherwise identical reaction conditions. Among various bidentate phosphine ligands examined, DPPBz (**L8**) gave the best results, thus providing **3a** in 95% yield along with less than 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 into the C1-cyanated product in good yields (**4b–h**). 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–p**) were compatible. By using the **L8**-based catalyst, 2-(prop-1-en-2-yl)naphthalene and 2-(prop-1-en-1-yl)naphthalene also reacted to provide the cyanation products, albeit in lower yields (see the Supporting Information). Finally, styrene can also be cyanated in a similar fashion (73%) using the **L8**-based catalyst, although other simple aromatic substrates such as 4-methoxystyrene afforded lower yields of the desired product (30–40%).

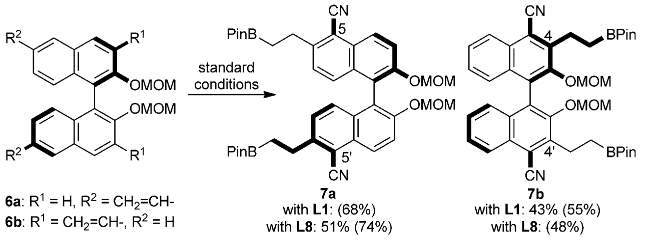
To demonstrate the synthetic versatility of the products derived from this method, several derivatization reactions were performed (Scheme 3). Oxidation of the boronate afforded the alcohol **5a**,[13] while the BCl_3-mediated amina-



Scheme 3. Derivatization of borylation/cyanation products. Reaction 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%.

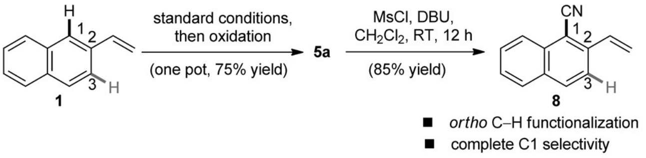
tion with benzyl azide provided the amine **5b**.[14] Suzuki–Miyaura coupling using our RuPhos-based palladacycle precatalyst[15] delivered the unsymmetrical 1,2-diarylethane bearing a heterocyclic core (**5c**). Furthermore, **5a** was converted into the lactone **5d**, amide **5e**,[16] and tetrazole **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]



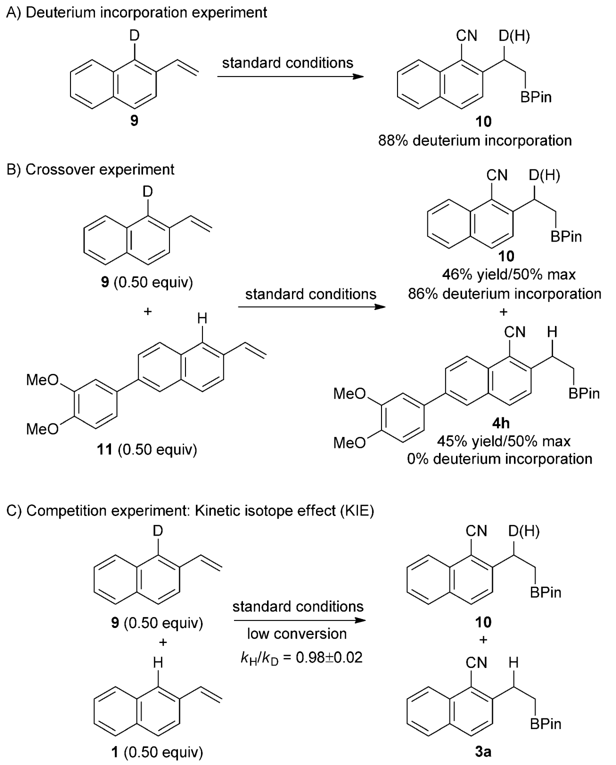
Scheme 4. Regioselective cyanation of binol scaffolds.

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 is usually favored.[20]



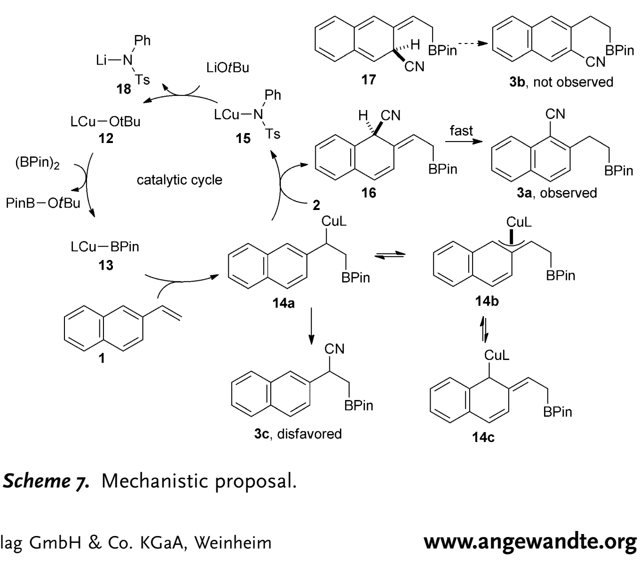
Scheme 5. Unmasking the boronic ester: Formal *ortho* C–H cyanation of vinylarenes. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Ms = methanesulfonyl.

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, thus 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** into **4h** in the presence of **9** did not result in deuterium incorporation, whereas 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.



Scheme 6. Mechanistic studies.

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 the



Scheme 7. Mechanistic proposal.

benzylcopper **14a**.[9a,h] Electrophilic cyanation of **14a** with NCTS (**2**) proceeds in an S_E2' fashion, thus delivering the dearomatized intermediate **16**, which then undergoes a rapid hydrogen transfer to generate the C1-cyanated product.[21–24] Cyanation at C3 (**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 which 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.

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Keywords: C−H activation · copper · dearomatization · ligand design · synthetic methods

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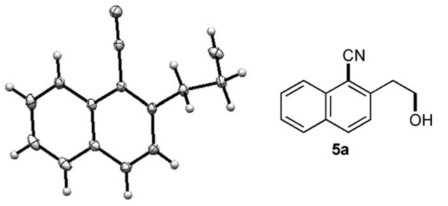

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