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Copper-promoted/catalyzed C–N and C–O bond cross-coupling with vinylboronic acid and its utilities

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Abstract—The mildest method of N-vinylation has been discovered. The synthetic utilities of the N- and O-vinylated products include protecting group, cyclopropanation and Grubbs' ring closure metathesis reactions.

Copper-promoted carbon–nitrogen (C–N) and carbon–oxygen (C–O) oxidative-coupling reactions of NH/OH-containing substrates with arylboronic acids have emerged as a powerful synthetic methodology since the initial reports.[1] This novel methodology is characterized by the mild reaction conditions (room temperature, weak base, in air) and is useful for the synthesis of nitrogen- and oxygen-containing compounds found in pharmaceuticals, crop-protection chemicals and material sciences. Many extensions and applications of this new methodology have been reported.[2–6]

N-Vinylation has previously been carried out by a variety of methods including mercuric acetate/sulfuric acid-catalyzed vinylation of benzimidazoles with vinyl acetate,[7] alkylation of benzimidazoles with dibromoethane followed by elimination,[8a] palladium(II)-catalyzed vinylation of amides with electron-deficient acrylates and analogs,[9a] palladium(0)-catalyzed vinylation with vinyl bromides[9b] and triflates,[9c] copper(I) thiophenecarboxylate-catalyzed vinylation of amides with vinyl iodides[10] and cesium hydroxide-catalyzed addition of alcohols and amine derivatives to alkynes and styrenes.[11]

The drawbacks of these methods are elevated temperatures and a lack of generality and/or substrate scope. In an effort to expand our copper(II) acetate oxidative-coupling chemistry, we have discovered that a novel stereospecific N/O-vinylation can be accomplished with vinylboronic acid under mild reaction conditions.[12] These N-vinylated products are not easily accessible via the classical enamine condensation route. The resulting vinylamines or ethers are also useful synthetic intermediates.

A variety of NH/OH-substrates were reacted with *trans*-1-hexenylboronic acid in the presence of pyridine/triethylamine and copper(II) acetate (stoichiometric or 10 mol% copper) under five different conditions, as shown in Table 1: (A) stoichiometric $Cu(OAc)_2$ in air; (B) catalytic $Cu(OAc)_2/O_2$; (C) catalytic $Cu(OAc)_2$/TEMPO in air; (D) catalytic $Cu(OAc)_2$/pyridine N-oxide in air; (E) catalytic $[Cu(OH)\cdot TMEDA]_2Cl_2/O_2$ (Collman conditions[3c]). All NH-containing substrates (entries 1–5) afford very good yields under stoichiometric conditions with retention of the *trans*-configuration.[13] These substrates are also capable of undergoing oxidative-coupling under catalytic conditions. For benzimidazolinone **2** (entry 1), catalytic $Cu(OAc)_2/O_2$ (61%) is the best system. Similarly for 2-pyridinone **4** (entry 2) $Cu(OAc)_2/O_2$ (96%) works best. For benzimidazole **6** (entry 3) and indazole **8** (entry 4), $Cu(OAc)_2$/pyridine N-oxide (90 and 88%, respectively) is the superior system. For phthalimide **10** (entry 5) we found that the Collman[3c] system, $[Cu(OH)\cdot TMEDA]_2Cl_2/O_2$, gave the best yield. Although $Cu(OAc)_2$/TEMPO is one of the best catalytic systems for aryl boronic acid cross-coupling, it surprisingly gave poor results for the vinylboronic acid cross-coupling. The *O*-vinylation of 3,5-di-*t*-butyl phenol **10** (entry 6) required a stoichiometric amount of copper(II) acetate to afford a 52% yield of the corresponding *trans* vinyl ether.

We hypothesize that the mechanism (Scheme 1) of the reaction involves a rapid coordination and dissolution of copper(II) acetate by the NH substrate to form the amine-copper(II) complex **A**. Transmetallation of the

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vinylboronic acid with **A** gives the amine-vinyl-copper(II) complex **B** which may very slowly reductively eliminate to afford **C**. Alternatively, and most probably, **B** undergoes air oxidation to yield the corresponding higher oxidation-state copper(III) complex **D**[14] which can undergo more efficient reductive elimination to give **C**.

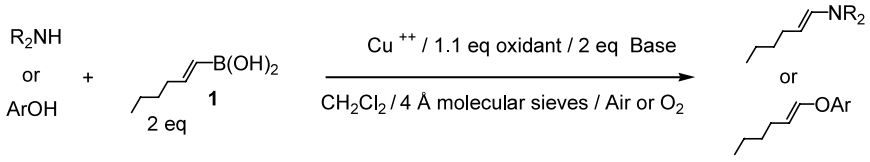
With the success of the facile generation of vinylamines and ether, we decided to explore the synthetic utilities of these products. The vinyl group is useful as a protecting group[7b,8] (Table 2). The cleavage of the vinyl group is simply achieved by mild acid treatment for **3** (entry 1), **13** (entry 2) and **9a** (entry 3). However, for **11** (entry 4) and **7** (entry 5) acidic treatment at 70°C did not result in deprotection. These vinyl groups can be removed by ozonolysis.

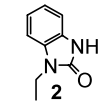
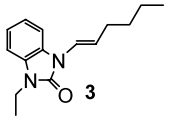
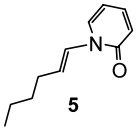
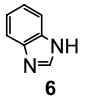
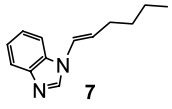
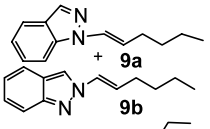
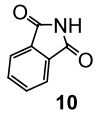
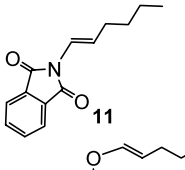
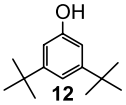
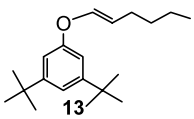
The Simmons–Smith reaction[15] is an efficient method for synthesizing cyclopropylamine or ether from the products of the N/O-vinylation. This reaction gave good yield for **3** (66%, entry 1), **11** (79%, entry 2) and **13** (75%, entry 3). In general, these products are difficult to obtain by simple alkylation with cyclopropyl iodide (Table 3).

The N/O-vinylated products are also useful intermediates for Grubbs' ring closure metathesis reaction[16] (RCM) to generate novel heterocycles (Scheme 2). Heterocycles **22** and **24**[17] can be obtained in 45[18] and 44% yield, respectively. To the best of our knowledge, **22** is the first demonstration of RCM with electron-rich N-vinyl substrate.

In conclusion, N/O-vinylation has been achieved in good yields through the oxidative-coupling of vinylboronic acid with NH/OH-containing substrates in presence of stoichiometric or catalytic copper(II) acetate. This efficient and extremely mild method gives N-vinylated products which are not easily accessible via the classical enamine condensation route. We continue to explore the mechanism and scope of this powerful

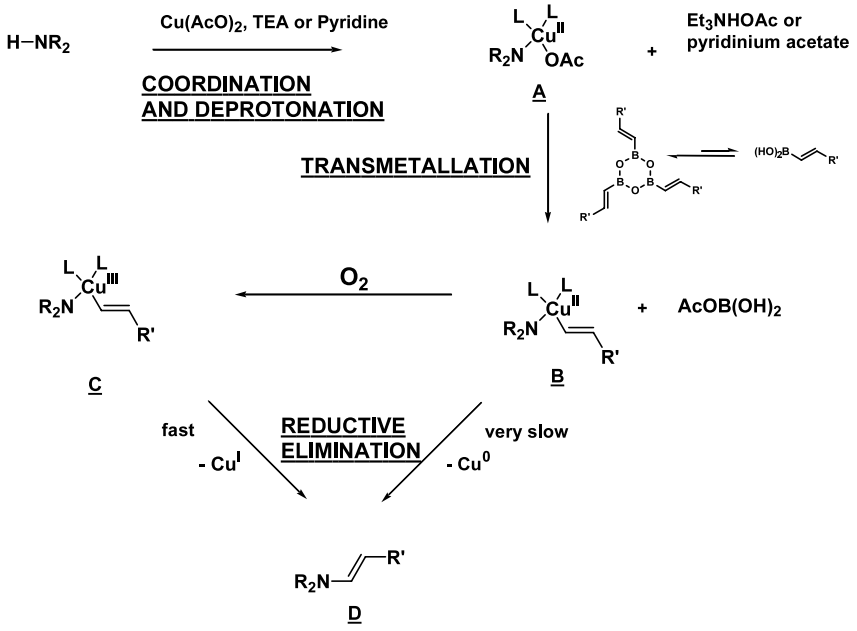
Table 1. C–N and C–O bond cross-coupling of vinyl boronic acid and NH- or OH-containing substrates



Entry	Substrate	Product	Cu^{++} + oxidant [a]	Base, Temperature	Isolated Yield
1	 **2**	 **3**	**A**	TEA, RT	**92 %**
			B	TEA, RT	**61 %**
			C	TEA, RT	8 %
			D	TEA, RT	24%
			E	None, RT	25%
2	 **4**	 **5**	**A**	Pyridine, RT	**90 %**
			B	Pyridine, RT	**96 %**
			C	Pyridine, RT	5 %
			D	Pyridine, RT	66 %
			E	None, RT	32 %
3	 **6**	 **7**	**A**	Pyridine, RT	**92 %**
			B	Pyridine, RT	69 %
			C	Pyridine, RT	17%
			D	Pyridine, RT	**90 %**
			E	None, RT	77 %
4	 **8**	 **9a** **9b**	**A**	Pyridine, RT	**99 % (7:1)**
			B	Pyridine, 50°C[b]	30 % (9:4)
			C	Pyridine, 50°C[b]	0 %
			D	Pyridine, 50°C[b]	**88 % (8 :3)**
			E	None, 50°C[b]	58 % (9:2)
5	 **10**	 **11**	**A**	TEA, RT	**79 %**
			B	TEA, RT	13 %
			C	TEA, RT	0%
			D	TEA, RT	30%
			E	None, RT	**73%**
6	 **12**	 **13**	**A**	TEA, RT	**52 %**
			B	TEA, 50°C[b]	12 %
			C	TEA, 50°C[b]	12 %
			D	TEA, 50°C[b]	6 %
			E	None, 50°C[b]	0%

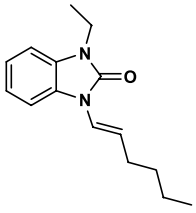
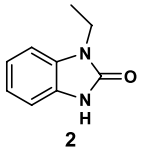
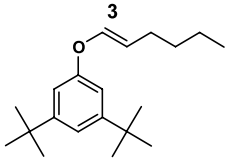
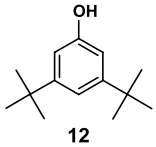
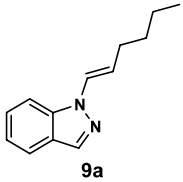
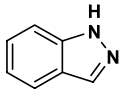
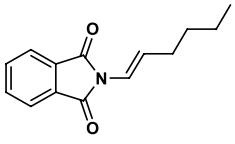
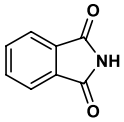
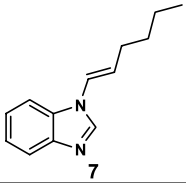
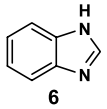
[a] *Conditions*: (A) 1.1 equiv. $Cu(OAc)_2$ in air. (B) 0.1 equiv. $Cu(OAc)_2$ and O_2. (C) 0.1 equiv. $Cu(OAc)_2$, 1.1 equiv. TEMPO in air. (D) 0.1 equiv. $Cu(OAc)_2$, 1.1 equiv. pyridine *N*-oxide in air. (E) 0.1 equiv. $[Cu(OH)TMEDA]_2Cl_2$ and O_2.

[b] DMF as solvent.



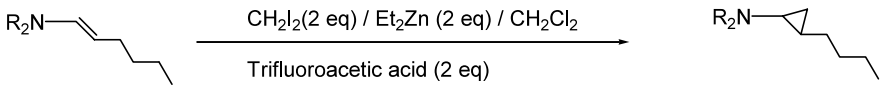
Scheme 1. Possible Mechanism of N-vinylation with *trans*-1-hexenylboronic acid.

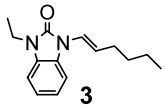
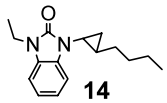
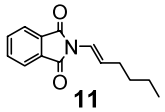
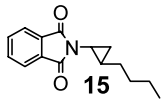
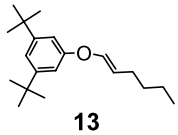
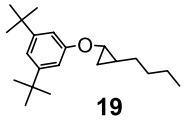
Table 2. Cleavage of the vinyl group (protecting group)

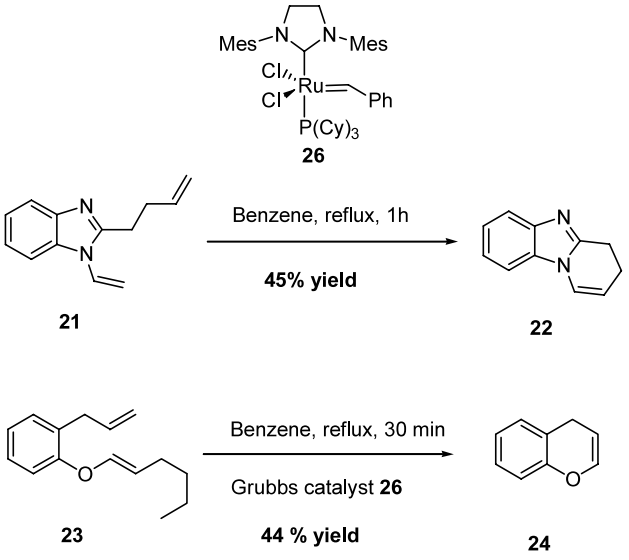
Entry	Substrate	Product	Time	Isolated yield	Conditions
1	 3	 2	18 hours	84 %	A
2	 13	 12	3 hours	100 %	A
3	 9a	 8	48 hours	85 %	A
4	 11	 10	5 min	91 %	B
5	 7	 6	5 min	88 %	B

Conditions: A = HCl 2 M in MeOH:dioxane (1:1); B = (1) O_3/MeOH/−78°C, (2) Me_2S/rt.

Table 3. Cyclopropanation of *N*-vinyl substrates



Entry	Substrate	Product	Isolated yield
1	 **3**	 **14**	66 %
2	 **11**	 **15**	79 %
3	 **13**	 **19**	75 %



Scheme 2. Vinylation of NH/OH-containing substrates: application for Grubbs' ring closure metathesis reaction.

copper-promoted C-heteroatom oxidative-coupling reaction with organometalloids.

Acknowledgements

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12. We have preliminary found that β-styrylboronic acid is a good vinylating agent during our catalytic copper acetate chemistry work.[3a] We have also found that azeotroping a mixture of benzimidazole and *n*-hexanal resulted in no N-vinylation (enamine formation), only decomposition of the aldehyde starting material. We have observed little electronic effect of the vinylboronic acids (4-methoxy-β-styrylboronic acid, 91% yield; β-styrylboronic acid, 79% yield; 4-trifluoromethyl-β-styrylboronic acid, 83% yield) with benzimidazole, similar to arylboronic acids.[1b]
13. **Representative catalytic N-vinylation procedure (condition C) for 1-ethyl-3-hexen-1′-yl-2-benzimidazolinone 3**: To a 20 mL vial equipped with a $CaSO_4$ drying tube was added in sequence 33 mg of 4 Å molecular sieves, *trans*-1-hexen-1-ylboronic acid **1** (85.2 mg, 0.667 mmol, 2.0 equiv.), 3 mL of dry dichloromethane, triethylamine (93 μL, 0.667 mmol, 2.0 equiv.), 1-ethyl-2-benzimidazolinone **2** (54 mg, 0333 mmol, 1.0 equiv.), cupric acetate (6.1 mg, 0.033 mmol, 0.1 equiv.) and TEMPO (57.3 mg, 0.367 mmol, 1.1 equiv.). The reaction was allowed to stir under air at room temperature for 12 h. The reaction was quenched by a solution of 50 μL of NH_3 in MeOH (2 M). The solvent was evaporated under reduced pressure and the residue was dissolved in 3 mL of dichloromethane and purified by silica gel chromatography (eluent: 7% methanol/chloroform) to give 49.5 mg (61% yield, >95% purity) of 1-ethyl-3-hexen-1′-yl-2-benzimidazolinone **3**: ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 1H), 7.11 (m, 2H), 7.00 (m, 1H), 7.11 (d, $J=14.5$ Hz, *trans*, 1H), 6.12 (m, $J=14.5$ Hz, *trans*, 7.3 Hz, 1H), 3.94 (q, $J=7.3$ Hz, 2H), 2.23 (m, 2H), 1.54–1.40 (m, 4H), 1.36 (t, $J=7.4$ Hz, 3H), 0.94 (t, $J=7.3$ Hz, 3H); HRMS calcd for $C_{15}H_{21}N_2O$ $(M+H)^+$ m/e 245.1654 found m/e 245.1646.
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18. **Experimental procedure for RCM to give 3,4-dihydro-benzo[4,5]imidazo[1,2-*a*]pyridine 22**: *N*-vinylbenzimidazole derivative **21** (254 mg, 1.28 mmol) was added to a homogeneous brown solution of Grubbs's catalyst **26** (217 mg, 0.25 mmol) in 10 mL of dry benzene under argon. The resulted mixture was stirred at 80°C for 1 h, at which time TLC showed the reaction to be completed. The reaction mixture was opened to air and stirred for 15 min before it was concentrated. Flash chromatography (silica gel 230–400 mesh, 50% ethyl acetate in hexane) yielded 98 mg of product (45% yield, >95% purity). ^{1}H NMR ($CDCl_3$) δ 7.72–7.69 (m, 1H), 7.37–7.33 (m, 1H), 7.28–7.22 (m, 2H), 7.03 (d, $J=7.7$ Hz, *cis*, 1H), 5.63–5.57 (q, $J=7.7$ Hz, *cis*, 1H), 3.19 (t, $J=8.1$ Hz, 2H), 2.59–2.52 (m, 2H). HRMS calcd for $C_{11}H_{10}N_2$ $(M+H)^+$ m/e 170.0844 found m/e 170.0842.