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Copper Catalysis

Copper-Catalyzed Direct Alkenylation of *N*-Iminopyridinium Ylides**

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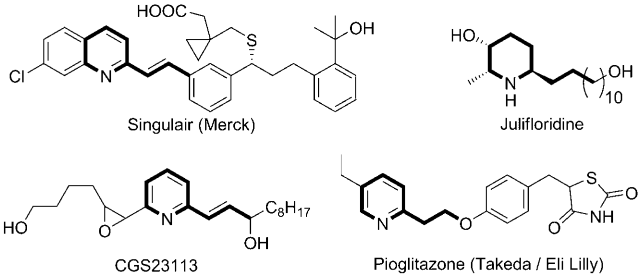
In memory of Keith Fagnou

The pyridine moiety is a privileged structure that is ubiquitous in nature and is often a key component of pharmaceutically active compounds.[1] As such, there has been much interest in the synthesis of substituted pyridine derivatives. 2-Alkenyl pyridine derivatives are of biological interest (Scheme 1) and are important metal ligands. Furthermore, alkenyl pyridine derivatives can be valuable precursors to alkyl pyridines and piperidines, themselves of significant biological importance.[2]



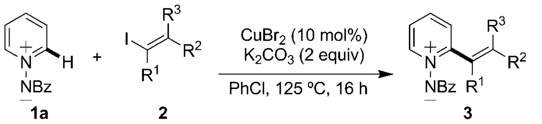
Scheme 1. Biologically important 2-alkenyl or 2-alkyl pyridine derivatives.

Direct arylations have become increasingly important and greener alternatives to traditional cross-coupling reactions.[3] Recent work has shown that such reactions are applicable to activated pyridinium species.[4] In contrast, comparatively little has been published on direct alkenylation reactions; in particular, there are few examples of direct vinylations on activated pyridines. In these cases, symmetrical alkynes with little functionality or relatively simple Heck acceptors were required as the coupling partners.[5] Cognizant of these deficiencies, we believed that *N*-iminopyridinium ylides could provide access to functionalized 2-alkenyl pyridines by a direct alkenylation reaction with functionalized vinyl iodides.

Direct reactions often employ expensive metal catalysts (Pd or Rh). Less costly Fe and Cu catalytic systems are seldom reported. Indeed, although electron-deficient arenes have been reported, applications of these inexpensive metals to the direct functionalization of heterocycles more often employ electron-rich substrates.[6] Herein, we report the first Cu-catalyzed direct alkenylation of *N*-iminopyridinium ylides with inexpensive Cu salts.

Given our success with the direct arylation of *N*-iminopyridinium ylides, we first applied our optimal Pd-catalyzed arylation conditions to alkenylation with (*E*)-β-styryl iodide (**2a**).[7] These conditions gave the vinylated pyridinium **3a** in 36% yield calculated by ^{1}H NMR spectroscopy (Table S1, entry 1; see the Supporting Information) and initial optimization did not lead to a significant increase in yield. It was reasoned that the addition of a Lewis acid could increase the reactivity of the pyridinium by coordination to the *N*-benzoyl moiety. Indeed, the addition of CuBr to the Pd-catalyzed reaction increased the yield of **3a** to 63% (Table S1, entry 2). In light of this result, we postulated that Cu alone might promote the transformation. Gratifyingly, CuBr displayed superior reactivity to $Pd(OAc)_2$ (Table S1, entry 3). Decreasing the ligand loading gave a higher yield (Table S1, entries 4 and 5), and the reaction was successful in the absence of an external ligand (Table S1, entry 6), presumably because the Lewis basic *N*-benzoyl moiety acts as an intramolecular stabilizing group.

Encouraged by these results, we optimized the reaction without any external ligand. The alkenylation was insensitive to the source of Cu; most Cu^{II} and Cu^{I} salts were compatible, as well as Cu^0 dust, and even a penny. In fact, the reaction could be performed in a Cu vessel without any additional metal source to provide a 74% yield calculated by ^{1}H NMR spectroscopy. $CuBr_2$ was chosen because of its low cost and high stability (Table S1, entry 7). The catalyst loading could be decreased to 2.5 mol% and still provide good yields, although 10 mol% were chosen for improved results. Aromatic and ethereal solvents both gave excellent results. Chlorobenzene was chosen because of its lower volatility. The yield of **3a** increased to 85% when 1.5 equiv of the ylide **1** was used, because of statistical suppression of the formation of the 2,6-divinylated by-product (Table S1, entries 9 and 10). Owing to the low cost and high efficiency of K_2CO_3 in the reaction, we elected to continue with this base, and 2 equiv were sufficient to enable the reaction [Eq. (1); Bz = benzoyl].



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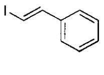
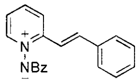
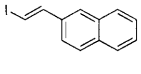
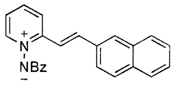
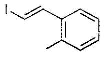
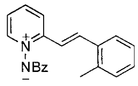
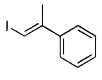
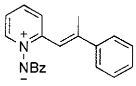
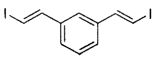
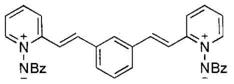
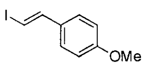
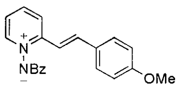
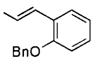
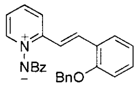
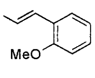
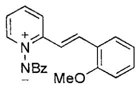
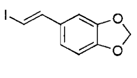
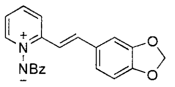
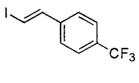
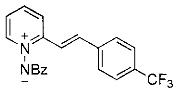
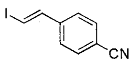
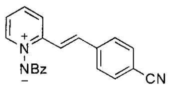
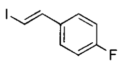
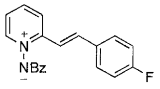
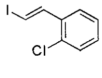
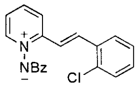
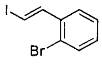
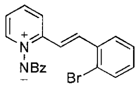
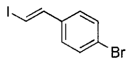
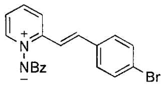
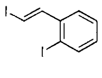
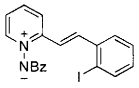
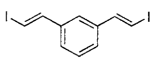
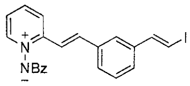
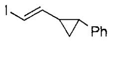
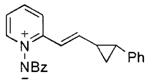
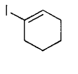
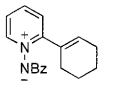
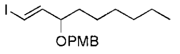
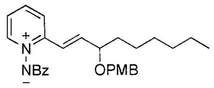
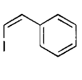
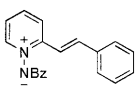
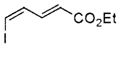
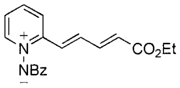
The scope of the Cu-catalyzed reaction was found to be quite general (Table 1).[8] Unsubstituted arenes present on the alkene reacted well (Table 1, entries 1 and 2). The excess ylide employed in the reaction could be recovered to give 93% yield based on recovered starting material (Table 1, entry 1). The alkenylation tolerated substitution on the phenyl functionality with very good yield (Table 1, entry 3) and also on the alkene, where the group is less removed from the reactive site (Table 1, entry 4). Bis(vinyl iodide) **2e** also reacted to give the dipyridinium adduct in synthetically useful yields (Table 1, entry 5). The reaction was successful with both electron-rich (Table 1, entries 6–9) and electron-poor substrates (Table 1, entries 10–12). Perhaps the most striking feature of the reaction is its chemoselectivity. Halogen substituents (Cl, Br, I; Table 1, entries 13–16) were tolerated on the phenyl ring with the reaction occurring selectively on the alkenyl iodide, and no arylated product was detected. These halogenated compounds (**3m**–**3q**) are of particular

Table 1: Scope of the alkenyl iodide in the Cu-catalyzed reaction.[a]

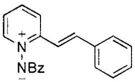
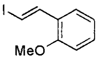
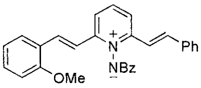
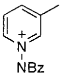
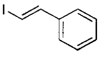
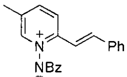
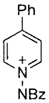
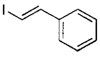
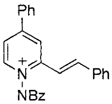
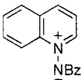
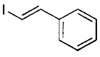
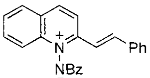
Entry	Alkenyl Iodide	Product	Yield [%][b]
1	 **2a**	 **3a**	81 (93)[c]
2	 **2b**	 **3b**	81
3	 **2c**	 **3c**	78
4	 **2d**	 **3d**	48
5[d]	 **2e**	 **3e**	63
6	 **2f**	 **3f**	87
7	 **2g**	 **3g**	71
8	 **2h**	 **3h**	93
9	 **2i**	 **3i**	75
10	 **2j**	 **3j**	71
11	 **2k**	 **3k**	89
12	 **2l**	 **3l**	83
13	 **2m**	 **3m**	74
14	 **2n**	 **3n**	65
15	 **2o**	 **3o**	74
16	 **2p**	 **3p**	47
17	 **2e**	 **3q**	41
18	 **2q**	 **3r**	53
19	 **2r**	 **3s**	52
20	 **2s**	 **3t**	30
21	 **2t**	 **3a**	71
22	 **2u**	 **3u**	41

[a] Reaction conditions: **1** (1.5 equiv), **2** (1.0 equiv), $CuBr_2$ (10 mol%), K_2CO_3 (2 equiv), PhCl (0.2 M), 125 °C, 16–24 h. Bn = benzyl, PMB = *p*-methoxybenzyl. [b] Yield of isolated product. [c] Yield based on recovered starting material. [d] 3.1 equiv of ylide **1**.

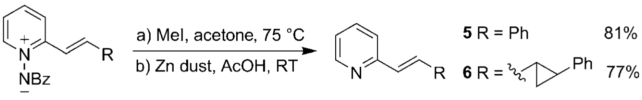
interest, as they contain reactive handles and, as such, could be used as a foundation for the synthesis of more-complex molecules. Substituents on the alkene with sp^3 hybridization gave the corresponding alkenylated pyridinium species in moderate yields (Table 1, entries 18 and 19). Reactants with long alkyl chains displayed poorer reactivity, as iodide **2t** gave compound **3t** in 30% yield (Table 1, entry 20). However, these molecules are still of interest and may be used as scaffolds to build compounds such as CGS23113 (Scheme 1).[9] *Z*-Alkenes are reactive, yielding products with *trans* configuration, possibly as a result of thermal isomerization to the more stable alkene (Table 1, entries 21 and 22).

The scope of the pyridinium ylide was considered next (Table 2). Pyridinium species with substituents at the 2-, 3-, and 4-positions underwent the alkenylation in good yields (Table 2, entries 1–3). In the case of the 3-substituted **1b**, vinylation occurred exclusively at the 6-position. This methodology could also be applied to other *N*-imino ylides; quinolinium species **1d** (Table 2, entry 4) afforded the vinylated product in moderate yield. It is important to note that the N–N bond could be cleaved in the presence of the alkene in very good yields (77–81%) to provide the corresponding 2-alkenylated pyridines (Scheme 2).

Table 2: Scope of the pyridinium ylide in the Cu-catalyzed reaction.[a]

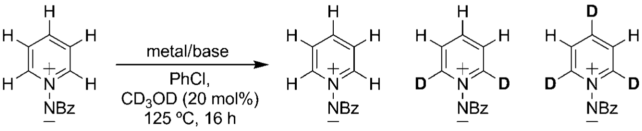
Entry	Pyridinium	Iodide	Product	Yield [%][b]
1	 **3a**	 **2h**	 **4a**	64
2	 **1b**	 **2a**	 **4b**	72
3	 **1c**	 **2a**	 **4c**	76
4[c]	 **1d**	 **2a**	 **4d**	49

[a] Reaction conditions: **1** (1.5 equiv), **2** (1.0 equiv), $CuBr_2$ (10 mol%), K_2CO_3 (2 equiv), PhCl (0.2 M), 125 °C, 16–24 h. [b] Yield of isolated product. [c] CuBr used in place of $CuBr_2$.



Scheme 2. Cleavage of the N–N bond.

Table 3: Deuterium incorporation study.

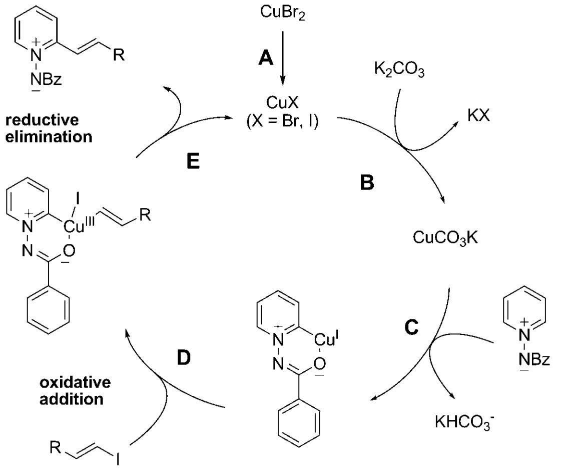


1a **7** **8**

Entry	Metal/base	% D incorporation[a]	LCMS [M+1]	Product
1	none	0	199.2	**1**
2	$CuBr_2$ (10 mol%)	n.a.	201.2	**7**
3[b]	K_2CO_3 (2 equiv)	90	202.2	**8**
4	$CuBr_2$ (10 mol%), K_2CO_3 (2 equiv)	92	201.2	**7**

[a] Incorporation determined by ^1H NMR spectroscopy. [b] Equal D insertion in 2,4,6-positions.

Next, we wished to gain insight into the mechanistic pathway of the reaction. Kinetic isotope effect (KIE) studies yielded a KIE value of 1.45, indicating that the C–H bond breaking event is not rate-limiting. Furthermore D exchange studies (Table 3) clearly demonstrate a directed D incorporation to the 2,6-positions of the pyridinium ring in the presence of Cu (Table 3, entries 2 and 4)[10] compared with indiscriminate D incorporation when no $CuBr_2$ was employed (Table 3, entry 3). This result, coupled with the fact that the direct alkenylation proceeds equally well with a range of Cu salts in different oxidation states, led us to propose the following catalytic cycle (Scheme 3): We believe that Cu^{II} is reduced to Cu^I by the pyridinium ylide (**A**). In cases where Cu^0 is operative, the ylide may add into the copper to generate a Cu^{II} intermediate that yields the reactive Cu^I species through either reduction or disproportionation.[11] Next, there is a carbonate–bromide exchange to generate $CuCO_3$, which is likely to be the reactive species in all cases, regardless of the Cu source (**B**).[11] This species can undergo deprotonation/metalation onto the pyridinium to generate an organocupracycle stabilized by the Lewis basic iminobenzoyl moiety (**C**). Oxidative addition (**D**) into the alkenyl iodide and subsequent reductive elimination (**E**) affords the product.



Scheme 3. Proposed catalytic cycle.

In summary, we have described the first ligand-free Cu-catalyzed direct alkenylation of electron-deficient heteroarenes. The reaction is believed to pass through a Cu^{I}/Cu^{III} catalytic cycle to provide a range of products in good to excellent yields. The reaction is highly chemoselective towards alkenyl iodides, introducing the possibility of preparing a scaffold from which a library of biologically interesting compounds could be constructed. Work is continuing to determine the full extent of these reactions as well as a detailed mechanistic analysis of the process.

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