Heterocycles

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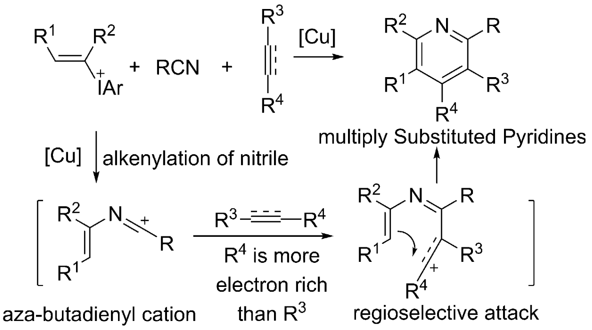
Copper-Catalyzed [2+2+2] Modular Synthesis of Multisubstituted Pyridines: Alkenylation of Nitriles with Vinyliodonium Salts

Jinyu Sheng[+], *Yong Wang*[+], *Xiang Su, Ru He, and Chao Chen**

Dedicated to Professor Gerhard Erker on the occasion of his 70th birthday

Abstract: *A [2+2+2] modular synthesis of multisubstituted pyridines, with excellent regioselectivity, has been realized by copper catalysisand involves three distinct components: vinyliodonium salts, nitriles, and alkynes. The reactions proceeded with the facile formation of an aza-butadienylium intermediate by alkenylation of the nitrile with a vinyliodonium salt. Moreover, the alkynes in the reaction were extended to alkenes, which are an advantage of expense and relative scarceness of alkynes.*

As one of the most prevalent heterocyclic backbones, pyridines are present in biosystems, natural products, pharmaceuticals, reagents for organocatalysis, ligands of metal catalysis, as well as functional materials.[1] Most substituted pyridines have to be produced synthetically because of the lack of natural sources.[2] Thus, classic methodologies for the construction of functionalized pyridine rings have been developed from substrates bearing functional groups, and involve either carbonyl condensation or cycloaddition reactions.[2,3] Moreover, modern metal-mediated cross-coupling chemistry is widely appreciated as it directly installs substituents on heterocycles and provides chemists with vast synthetic options.[4] However, the ever-growing demand for rapid access of heavily substituted pyridines calls for even more efficient synthetic methods, and in response to this demand is the recent construction of pyridines by multicomponent reactions (MCRs).[5] Among these MCRs, transition-metal catalyzed [2+2+2] cycloadditions for pyridine synthesis are attractive because of the simplicity, flexibility, and availability of starting materials.[6] It is known that most of the catalytic [2+2+2] cycloaddition reactions have to employ noble metals, including Ru, Rh, Co, Au etc., and some suffer additionally from low regioselectivity because of the different orientations of the alkyne. Nevertheless, both problems have been alleviated with recent advances by using more specific substrates or stoichiometric amounts of metal promoters.[2b,7] Additionally, there are only a few methods to synthesize pyridines by copper catalysis, and they employ limited substrates.[8] Hence the attraction to the development of new approaches to pyridines from common building blocks bearing more diversified substituents. To this end, we would like to report a novel modular method leading to heavily substituted pyridines from three simple components. The method is of wide scope, requires an inexpensive copper catalyst, and demonstrates excellent regioselectivity (Scheme 1). The new modular synthesis starts with vinyliodonium salts, nitriles, and alkynes of different electronic properties, and proceeds through the facile formation of an aza-butadienylium intermediate by the selective alkenylation of nitriles with vinyliodonium salts,[9] and it rapidly yields pyridines with excellent regioselectivity.



Scheme 1. A[2+2+2] three-component process for pyridine synthesis.

Recently, we demonstrated that arylation of nitriles with diaryliodonium salts produced N-aryl nitrilium intermediates, and some special N-aryl nitrilium salts could be used to prepare a series of heterocycles.[10] Inspired by these findings, we further envisioned the alkenylation of nitriles with vinyliodoniym salts to generate aza-butadienylium intermediates, which should be trapped readily in situ by alkynes to produce pyridines. For this purpose, in preliminary experiments, three different kinds of vinyliodonium salts[11] [$PhCH{=}CHI^{+}ArOTf^{-}$ (**1**$_{\mathbf{Ar}}$) where Ar = Ph, *o*-tol, and mesityl] were reacted with benzonitrile (**2a**) and 1-phenyl-1-butyne (**3a**) using previously developed reaction conditions.[10] To our delight, all vinyliodonium salts gave the desired pyridine **4aaa** in moderate to good yields (Scheme 2). However, the reaction of **1**$_{\mathbf{Ph}}$ also yielded a significant amount of the quinoline **5a**, thus indicating poor chemoselectivity of the vinyl-phenyl iodonium salt (Scheme 2a). The chemoselectivity could not be improved with an increased amount of **1**$_{\mathbf{Ph}}$. Consequently, **1**$_{\boldsymbol{o}\text{-}\mathbf{tol}}$ (**1a**) was examined with **2a** and **3a**, and excitingly, **4aaa** was obtained in 85% yield and the quinoline **5b** was present in only 1% yield (Scheme 2b). The yield of **4aaa** was further

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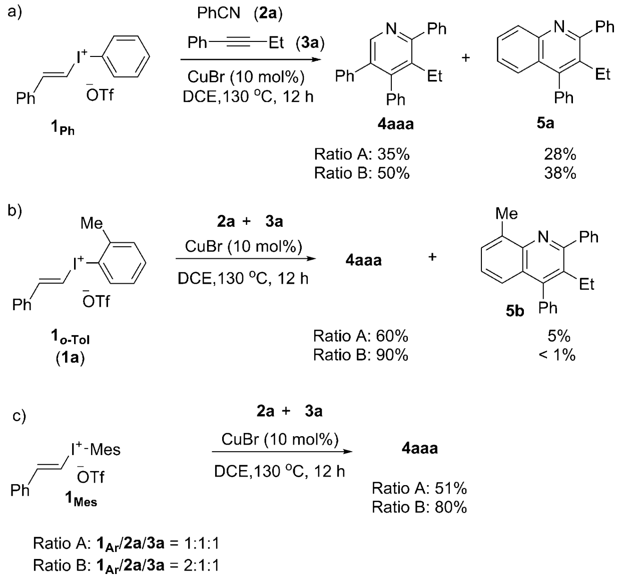
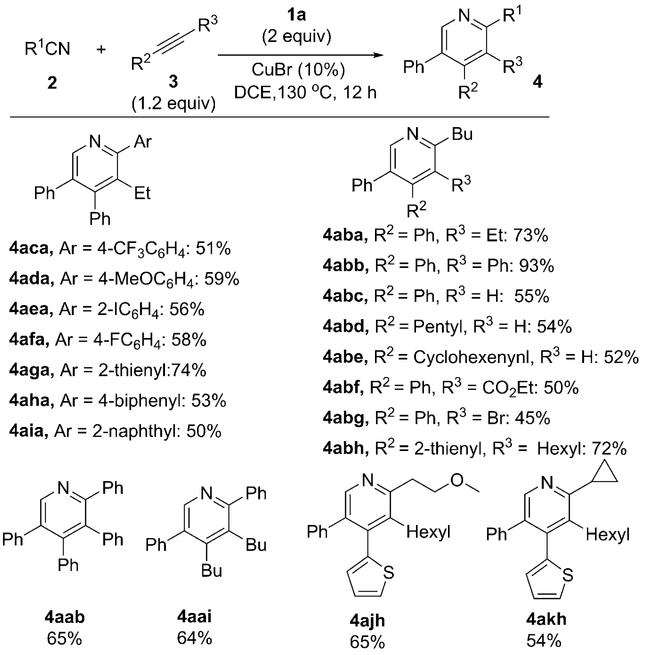


Scheme 2. Screening the aryl group of PhCH=CHI$^+$ArOTf$^-$ ($\mathbf{1_{Ar}}$) for the selective transformation of vinyl, versus aryl groups, into the pyridine product **4aaa**. DCE = 1,2-dichloroethane, Tf = trifluoromethanesulfonyl.



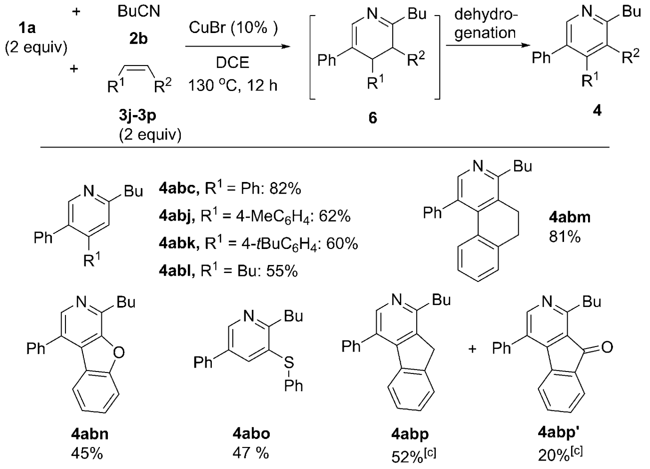
Scheme 3. The scope with respect to the nitriles and alkynes for pyridine synthesis.

raised to 90 % with 2 equivalents of **1a**. As expected, the reaction of $\mathbf{1_{Mes}}$ supplied **4aaa** as the sole product, albeit in lower yield (80 %; Scheme 2c). Hence, **1a** was chosen as the model vinyliodnium component to react with **2a** and **3a**. With further optimization of the copper salts, solvents, and substrates ratios, reaction conditions were discovered to deliver **4aaa** in 92 % yield (for details see Table 1 in the Supporting Information).

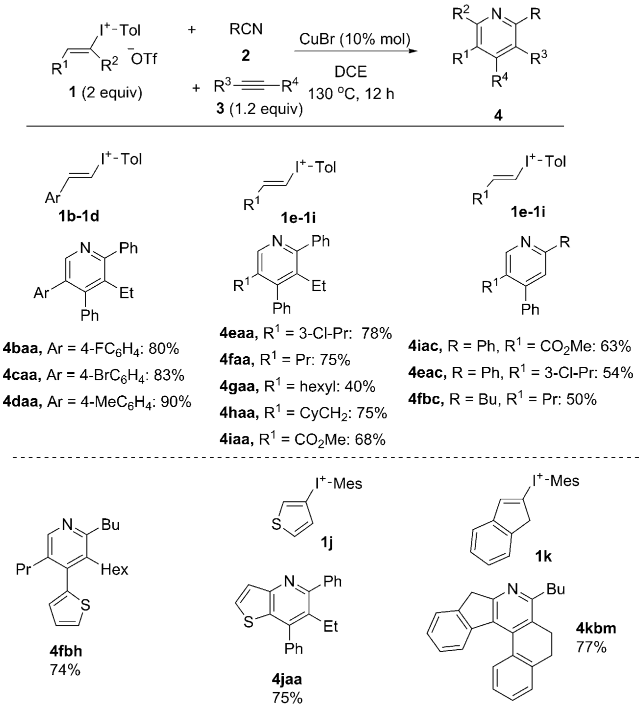
Under the optimized reaction conditions, the scope with respect to the nitrile and alkyne substrates was studied. The results are summarized in Scheme 3. Firstly, a variety of nitriles (**2**) were evaluated in the reaction to synthesize pyridines with a range of substituents at the 2-position, including substituted phenyl, naphthyl, thienyl, and alkyl groups (**4aaa–aia**). 3-Methoxypropanenitrile and cyclopropyl-carbonitrile also worked well to give **4ajh** and **4akh,** respectively, with the sensitive substituents remaining intact. Next, a range of alkynes were examined to modify the substituents at the 3- and 4-positions of the pyridines. As shown in Scheme 3, reactions using either terminal or internal alkynes bearing aryl, alkyl, halogen, and ester groups proceeded smoothly. The use of terminal alkynes, including phenyl acetylene, 1-heptyne, and 1-cyclohexenyl acetylene, afforded the pyridines **4abc–abe** with the substituents allocated to the 4-position. The employment of aryl-alkyl acetylene produced 4-aryl-3-alkyl pyridines in high yields and phenylpropiolate (**3f**) afforded the 3-ester-substituted pyridine **4abf** in 50 % yield. Furthermore, when (bromoethynyl)benzene (**3g**) was used, **4abg** was formed exclusively. Apparently, this synthetic method gave pyridines with great regioselectivity when asymmetric alkynes were used. The high regioselectivity is attributed to the electrophilic process of the annulation reaction.[10]

Aside from acetylenes, alkenes also worked in the reaction with **1a** and nitriles to form the pyridines **4abj–abp** (Scheme 4). In this situation, the reaction presumably gave, at first, dihydropyridines, which underwent dehydrogenation spontaneously.[8,12] An exception was benzothiophene, as the product **4abo** was obtained by a de-arylation process. Starting with indene, **4abp** was formed in 80 % yield as determined by GC, and it was oxidized to give **4abp′** in 20 % yield during isolation. The possibility of incorporating alkenes is highly important because alkenes (**3j–l**) are less expensive than the corresponding alkynes. Additionally, in the case of **3m–p**, the corresponding cyclic alkynes are typically inaccessible.

Further investigation with respect to the scope of vinyliodonium triflates was conducted (Scheme 5).[11] It was exciting to find that aryl (**1b–d**), alkyl (**1e–h**) and ester (**1i**) substituents on the vinyl motifs all gave the desired products. Styrene was also tested with **1e** and **2a**, and formed the



Scheme 4. The scope with respect to the alkenes for pyridine synthesis.

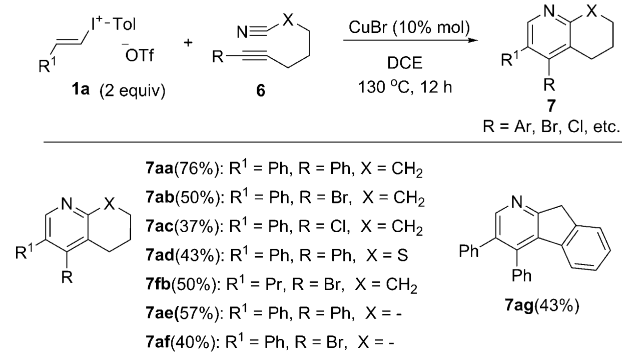


Scheme 5. The scope with respect to the vinyliodonium triflates for pyridine synthesis.

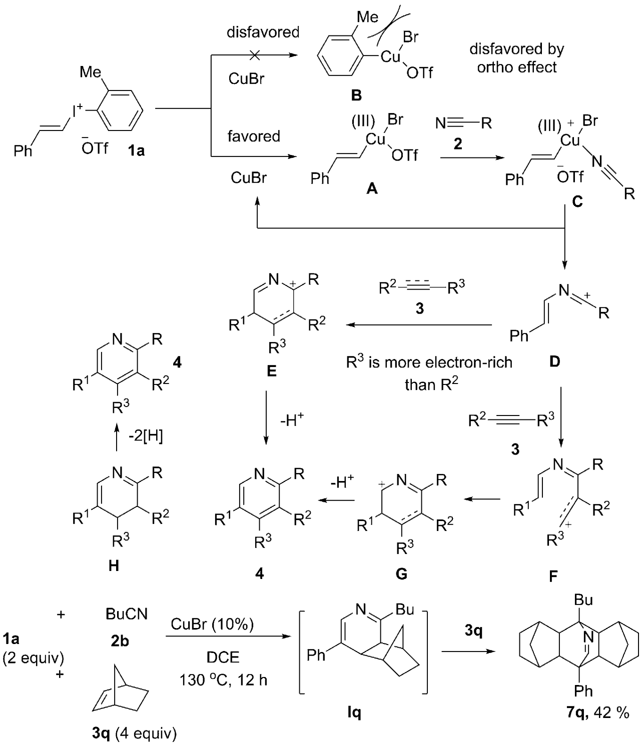
desired product **4eac**. Surprisingly, both thiophene-and indene-substituted motifs opened access to the fused fully substituted pyridines **4jaa** and **4kbm**, respectively.

Pyridines fused with carbocycles and heterocycles are privileged scaffolds in various bioactive natural products (especially in alkaloids) and synthetic therapeutic agents.[13] If alkynes were tethered with nitriles (such as ω-cyano-1-alkynes), polycyclic pyridines would be produced with our reaction.[14] In fact, **1a** reacted with a range of ω-cyano-1-alkynes to give fused pyridines (Scheme 6). The process is capable of direct synthesis of chloro- and bromopyrdines, which are useful building blocks.

As mentioned, the reactions are accomplished with iodonium salts, nitriles, and alkynes, as the three components, with CuBr as the catalyst. It is precedented that diaryliodonium salts can be affected by copper salts to generate electrophilic species, Ar–Cu^{III}.[10,15] Hence, in this reaction, vinyliodonium salts may react with CuBr to afford vinyl-Cu^{III} species (Scheme 7). Presumably, the reaction of **1a** with CuBr generates the vinyl-Cu^{III} **A** rather than tol-Cu^{III} **B** because of the *ortho* effect.[16] Possibly, **A** is easily coordinated by **2** to afford **C**, which undergoes elimination of CuBr to afford the aza-butadienyl cation **D**. The cation **D** is highly electrophilic and is attacked by acetylene in either a concerted cycloaddition step to give intermediate **E**, or through an ionic step to the give intermediates **F** and **G**. Both intermediates could lose a proton to give the pyridine product **4.** This series of cationic procedures ensures the excellent regioselectivity for asymmetric alkynes.



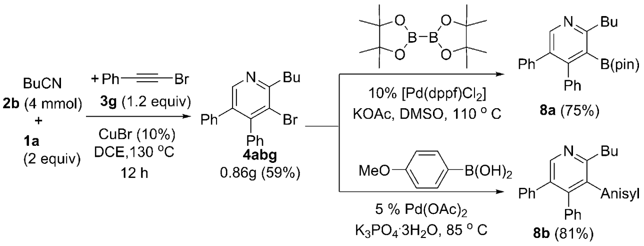
Scheme 6. The use of ω-cyano-1-alkynes in the synthesis of fused pyridines.



Scheme 7. Proposed mechanism of the three-component process for pyridine synthesis.

When acetylene is replaced by an alkene, **D** reacts with the alkene to give the dihydropyridine **H**, which is capable of losing dihydrogen in the reaction (Scheme 7). The dihydropyridine **6** could be trapped in some cases. For instance, when norbornene (**3q**) was reacted with **1a** and **2b**, the product **7q** was isolated in 42% yield, and was formed presumably from the cycloaddition reaction of the dihydropyridine **Iq** with another norbornene.[17]

To demonstrate the value of this new method, the bromopyridine **4abg** was prepared from 4 millimoles of **2b**, and 0.86 grams of the desired product were obtained (59% yield; Scheme 8). Further derivatization of **4abg** was readily realized. For example, upon reaction with bis(pinacolato)diboron, Br was converted into a boronic acid pinacol ester (**8a**), with [Pd(dppf)Cl$_2$] as the catalyst. Moreover, the Suzuki reaction of **4abg** with anisyl boronic acid afforded the



Scheme 8. Scale synthesis and derivatitization of bromopyridine **4abg**.

coupling product **8b** in good yield.[18] These results proved the potential application of this method in organic synthesis.

In summary, an efficient and regioselective approach to multisubstituted pyridines from vinyl-tolyl iodonium salts (**1**), nitriles (**2**), and acetylenes (**3**), through a [2+2+2] reaction, has been realized. The reactions are initiated by the alkenylation of nitriles with vinyliodonium salts and are catalyzed by CuBr. This strategy provides great flexibility in the substitution patterns of pyridines and marks significant progress in the synthesis of multisubstituted pyridines. Moreover, alkenes can be used in the reaction instead of alkynes. We believe that this study paves a new way to access N-heterocycles from iodonium salts.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkynes · copper · heterocycles · multicomponent reactions · synthetic methods

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Communications

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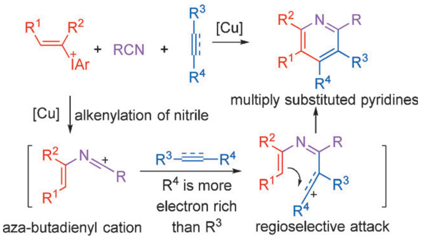
C. Chen* ________________ ■■■■–■■■■

Copper-Catalyzed [2+2+2] Modular Synthesis of Multisubstituted Pyridines: Alkenylation of Nitriles with Vinyliodonium Salts



Three to one! A [2+2+2] modular synthesis of multisubstituted pyridines with excellent regioselectivity has been realized by copper catalysis and involves three distinct components: vinyliodonium salts, nitriles, and alkynes. The reactions proceeded with the facile formation of an aza-butadienylium intermediate by alkenylation of the nitrile with a vinyliodonium salt.