Copper-Catalyzed C–H Stereoselective Cyanation of Alkenes by Using an α-Iminonitrile as a Cyanating Reagent

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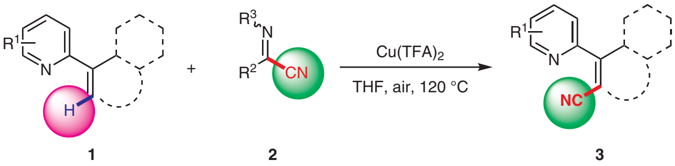

The first Cu-catalyzed alkenes C–H bond cyanation
Cu(II)-promoted C–CN bond cleavage

16 Examples; up to 87% yield
High regioselectivity
Operational simplicity

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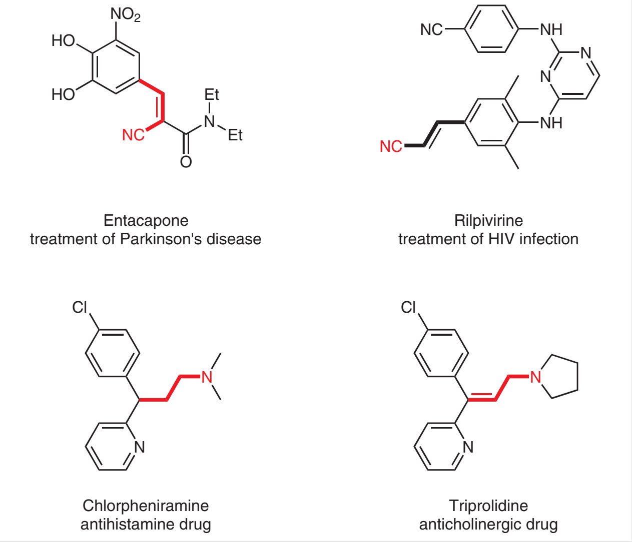
Abstract The first copper-catalyzed cyanation through alkene C–H bond activation by using an α-iminonitrile as a cyanating agent has been realized. The approach efficiently constructs acrylonitriles in good yields with the advantages of high regioselectivity, cost-benefit, and operational simplicity.

Key words copper catalysis, C–H activation, cyanation, iminonitriles, alkenes, acrylonitriles

α,β-Unsaturated nitriles (acrylonitriles) are an important building blocks in organic synthesis, and are often important constituents of pharmaceutically relevant molecules.[1] Some examples of such products that are currently used in the pharmaceutical industries are shown in Figure 1.



Entacapone
treatment of Parkinson's disease

Rilpivirine
treatment of HIV infection

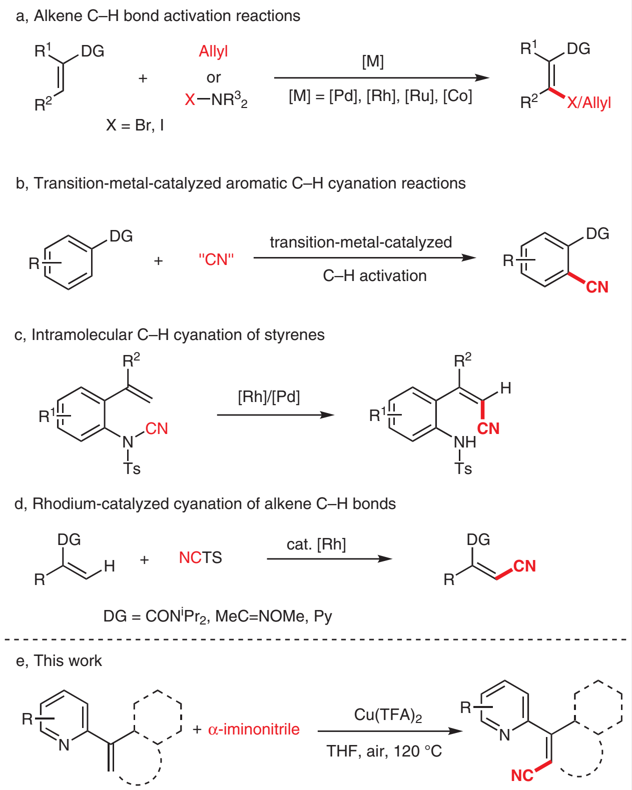
Chlorpheniramine
antihistamine drug

Triprolidine
anticholinergic drug

Figure 1 Examples of pharmaceutically important acrylonitriles

Moreover, acrylonitriles can be easily converted into other important functionalized compounds. Consequently, many methods for synthesizing acrylonitrile derivatives have been developed, including the Peterson olefination,[2] the Wittig/Horner–Wadsworth–Emmons reaction,[3] acrylamide dehydration,[4] carbocyanation of alkynes,[5] cross-metathesis,[6] and oxime dehydration.[7] However, these methods suffer from various drawbacks, such as a limited substrate scope or poor stereoselectivity. To circumvent such problems, alternative methods have been developed, including the transition-metal-catalyzed cyanation of alkenyl halides[8] or alkenyl metal reagents.[9] However, this also has some disadvantages, in that it requires prior functionalization of the starting materials, which often leads to poor compatibility with some functional groups.

In the last decade, direct C–H activation has emerged as a straightforward and useful tool for organic synthesis.[10] The majority of the currently developed C–H activation reactions, especially, in the field of alkene C–H bonds activation, employ precious second-row transition-metals such as rhodium,[11] palladium,[12] ruthenium,[11a,13] or other metals[14] as catalysts (Scheme 1, a). For instance, Loh and coworkers developed palladium-catalyzed[12a] and rhodium(III)-catalyzed[11a] direct C–H activations of alkenes. Subsequently, Zhang, Zhong, and co-workers[13a] developed a ruthenium-catalyzed direct C–H activation reaction of electron-deficient alkenes. In addition, transition-metal-catalyzed aromatic C–H cyanation reactions have been extensively studied (Scheme 1, b),[15] whereas there are few reports of the direct cyanation of nonactivated alkene C–H bonds. In 2013, Wang and Falk reported the first example of an intramolecular C–H cyanation of a styrene through a rhodium(I)/palladium-catalyzed N–CN bond-cleavage reaction (Scheme 1, c).[16] Later, Chaitanya and Anbarasan[11b] accomplished a selective, rhodium-catalyzed, chelation-assisted cyanation of the C–H bonds of alkenes, and in 2015, Fu and co-co-workers reported a Rh(III)-catalyzed direct vinylic C–H cyanation reaction for the synthesis of alkenyl nitriles (Scheme 1, d).[11d]

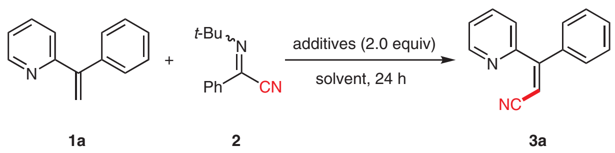


Scheme 1 Transition-metal-catalyzed alkene C–H bond-activation and cyanation reactions

Noble metals are used as catalysts in almost all the above cases, which adds to the cost of the reactions and is not conducive to industrial manufacture. With the advantages of greater abundance, lower price, ready availability, and lower toxicity, a number of first-row transition metals have recently been used increasingly as catalysts for C–H activation reactions.[17] Inspired by these pioneering works, and as a continuation of our interest in developing simpler and more-efficient methods for cyanation,[4,18] we describe a C–H cyanation reaction of alkenes in which copper is used as a catalyst (Scheme 1, e).

Initially, we found the cyanation of aromatic C–H bonds with an α-iminonitrile as a nitrile source proceeded in good yield in the absence of palladium.[18b] Encouraged by this result, we attempted to using copper to catalyze the cyanation of alkene C–H bonds. We started our investigations by using 2-(1-phenylvinyl)pyridine as a model substrate with 1.5 equivalents of (2*E*)-(*tert*-butylimino)(phenyl)acetonitrile (**2**) and 2.0 equivalents of $Cu(TFA)_2{\cdot}xH_2O$ in tetrahydrofuran (THF) under air at 100 °C for 24 hours.[19] To our surprise, the acrylonitrile **3a** was obtained in 71% yield (Table 1, entry 1). Subsequently, various solvents were screened (entries 2–5); however, none of these was superior to THF. Raising the temperature increased the yield of product (entries 6 and 7). Catalyst screening showed that $Cu(TFA)_2{\cdot}xH_2O$ appeared to be the most effective (entries 8–13). We also tried reducing the amount of Cu(II) in the catalyst system (entries 15 and 16), but obtained a lower yield, suggesting that the copper serves not only as a catalyst, but also as an oxidant.

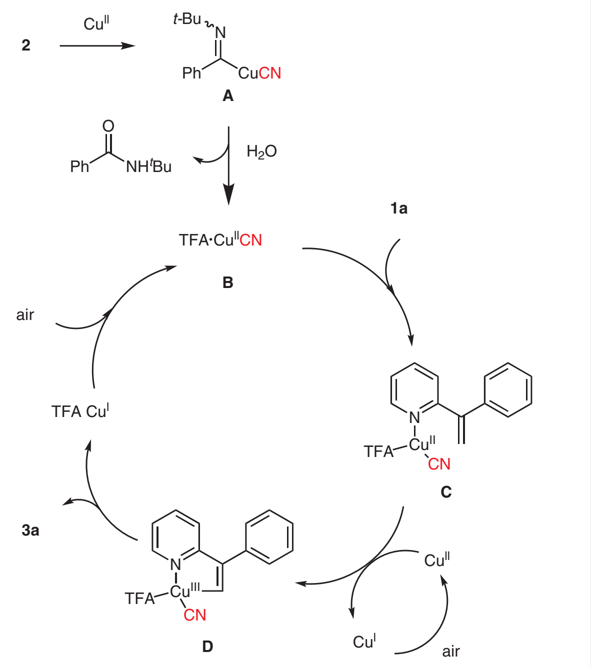
Table 1 Optimization of the Reaction Conditions[a]



Entry	Additive	Solvent	Temp (°C)	Yield[b] (%)
1	$Cu(TFA)_2{\cdot}xH_2O$	THF	100	71
2	$Cu(TFA)_2{\cdot}xH_2O$	toluene	100	33
3	$Cu(TFA)_2{\cdot}xH_2O$	1,4-dioxane	100	65
4	$Cu(TFA)_2{\cdot}xH_2O$	DCE	100	40
5	$Cu(TFA)_2{\cdot}xH_2O$	DMF	100	37
6	$Cu(TFA)_2{\cdot}xH_2O$	THF	80	55
7	$Cu(TFA)_2{\cdot}xH_2O$	THF	120	73
8	$CuCl_2$	THF	120	<10
9	$CuBr_2$	THF	120	trace
10	$Cu(OAc)_2$	THF	120	<10
11	$Cu(OTf)_2$	THF	120	0
12	$CuSO_4$	THF	120	trace
13	CuI	THF	120	0
14	$Cu(TFA)_2{\cdot}xH_2O$	THF	120	58[c]
15	$Cu(TFA)_2{\cdot}xH_2O$	THF	120	40[d]
16	$Cu(TFA)_2{\cdot}xH_2O$	THF	120	66[e]
17	–	THF	120	0
18	$Cu(TFA)_2{\cdot}xH_2O$	THF	120	70[f]

[a] Reaction conditions: **1a** (0.5 mmol), **2** (1.5 equiv), additive (2.0 equiv), solvent (2 mL), 24 h, under air in a sealed tube.
[b] Isolated yield.
[c] 12 h.
[d] Additive (1.2 equiv).
[e] Additive (1.5 equiv).
[f] H_2O (10.0 equiv).

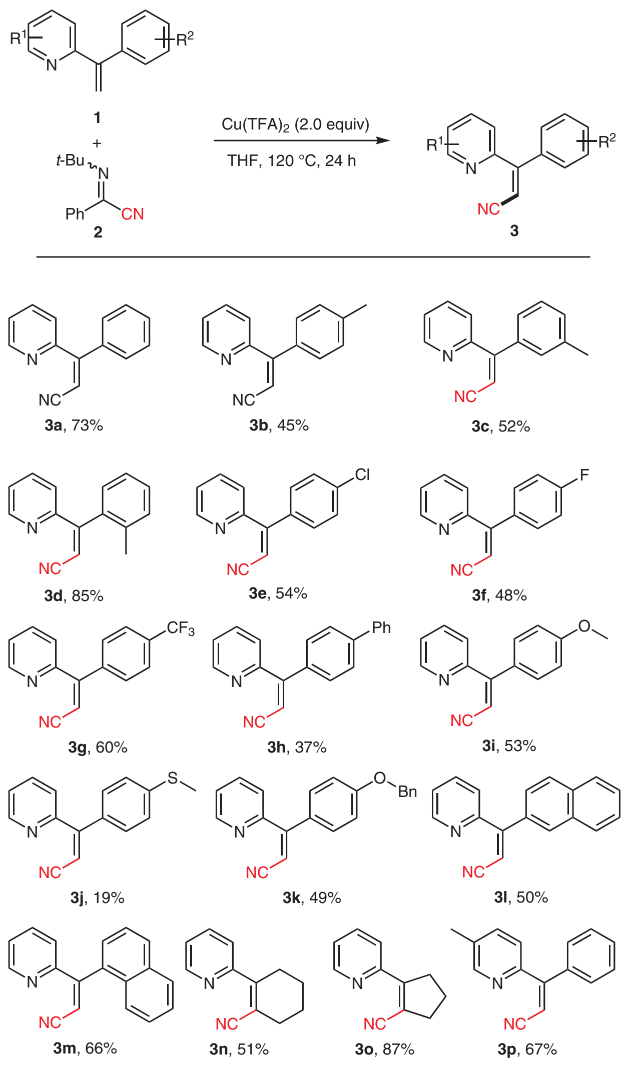
Because the cyanation of **1a** does not take place in the absence of a copper salt (Table 1, entry 17), we consider that the copper(II) cation plays a key role in the process of C–CN bond cleavage to provide cyanide anions. Therefore, a possible catalytic mechanism for the cyanation reaction is depicted in Scheme 2. First, **2** undergoes copper-promoted C–CN bond cleavage to generate intermediate **A**, which is hydrolyzed to form the copper cyanide species **B** and *N*-*tert*-butylbenzamide. Complex **B** then participates in the copper-catalyzed cyanation cycle, which is initiated by oxidative addition of alkene **1a** to form intermediate **C**. Subsequently, intermediate **C** undergoes copper-catalyzed oxidative C–H activation to form intermediate **D**, which undergoes reductive elimination to give product **3a**.



Scheme 2 Proposed mechanism

With the optimized conditions in hand, we then investigated the substrate scope of this reaction by changing the substitution on the arene and the directing group (Scheme 3). Cyanation of 2-(1-phenylvinyl)pyridine derivatives with *para*-, *meta*-, or *ortho*-groups on the phenyl ring proceeded smoothly and showed excellent monoselectivity. Substrates bearing either electron-rich or electron-deficient substituents at the *para*-position of the phenyl ring all worked well. Trisubstituted alkenes were compatible with our conditions, giving the corresponding cyanated products in moderate to good yields. In addition, 5-methyl-2-(1-phenylvinyl)pyridine underwent a smooth reaction to give the desired product **3p** in 67% yield. It is necessary to mention that the electronic effect of the pyridine ring has a marked effect on the reaction, because when compounds containing a fluoro-substituted pyridine, or other directing groups such as quinoline, were tested under our conditions, none of the desired products were obtained.

In conclusion, we have developed the first example of a copper-catalyzed cyanation of nonactivated C–H bonds of alkenes by using an α-iminonitrile as a cyanating reagent. This approach provides an alternative route for the synthesis of acrylonitriles with high regioselectivity and good cost-effectiveness. Further investigations on the synthetic applications of the present method are currently underway in our laboratory.



Scheme 3 Cyanation of alkene substrates. *Reaction conditions*: **1a** (0.5 mmol), 2 (1.5 equiv), Cu(TFA)$_2$ (2.0 equiv), THF (2 mL), 120 °C, 24 h, sealed tube. Isolated yields are reported.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610680.

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(19) **3-Phenyl-3-pyridin-2-ylacrylonitrile; Typical Procedure**
A solution of **1a** (0.50 mmol), α-iminonitrile **2a** (139.5 mg, 0.75 mmol), and Cu(TFA)$_2$ (1.0 mmol) in THF (2.0 mL) was stirred at 120 °C for 24 h, then cooled to r.t. The solvent was then evaporated in vacuo, and the residue was purified by column chromatography [silica gel, PE–EtOAc (9:1)] to give a brown oil; yield: 75 mg (73%).^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.7 (d, J = 3.6 Hz, 1 H), 7.8 (t, J = 7.3 Hz, 1 H), 7.5 (d, J = 7.8 Hz, 1 H), 7.4–7.3 (m, 4 H), 7.3 (d, J = 7.2 Hz, 2 H), 5.8 (s, 1 H). ^{13}C NMR (151 MHz, CDCl$_3$): δ = 161.2 (s), 155.1 (s), 150.0 (s), 137.7 (s), 136.8 (s), 130.5 (s), 128.8 (s), 128.4 (s), 125.0 (s), 124.4 (s), 117.4 (s), 97.3.