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Direct Access to Versatile Electrophiles via Catalytic Oxidative Cyanation of Alkenes

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Abstract

Nucleophilic attack on carbon-based electrophiles is a central reactivity paradigm in chemistry and biology. The steric and electronic properties of the electrophile dictate its reactivity with different nucleophiles of interest, allowing the opportunity to fine-tune electrophiles for use as coupling partners in multi-step organic synthesis or for covalent modification of proteins in drug discovery. Reactions that directly transform inexpensive chemical feedstocks into versatile carbon electrophiles would therefore be highly enabling. Herein, we report the catalytic, regioselective oxidative cyanation of conjugated and non-conjugated alkenes using a homogeneous copper catalyst and a bystanding F^+ oxidant to furnish branched alkenyl nitriles that are difficult to prepare using existing methods. We show that the alkenyl nitrile products serve as electrophilic reaction partners for both organic synthesis and the chemical proteomic discovery of covalent protein ligands.

Graphical abstract

Alkenes are inexpensive, widely available feedstocks that are sourced from petroleum or renewable resources. In addition to being ubiquitous, they possess a unique reactivity profile, and numerous alkene functionalization reactions are utilized to synthesize organic molecules with diverse functions. Although alkenes are now recognized as fundamental building blocks in synthesis,¹ they remain fundamentally challenging to regioselectively

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Supporting Information

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Notes

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modify with strategically important functional groups. In particular, given the utility of alkenyl nitriles in material science, pharmaceutical chemistry, and agrochemistry (Figure 1A),² the direct, regioselective cyanation of alkenes would be a synthetically enabling transformation that would dramatically simplify access to such privileged structures. As this transformation is unknown in literature, the goal of the present study was to develop a robust catalytic method to address this unmet challenge (Figure 1B).

Alkenyl nitriles are bis-electrophiles with the potential for selective reactivity at two sites. The cyano group is a key precursor for functional groups including acids, aldehydes, alcohols, and amines,³ and the β -position of the alkene is polarized for addition of various nucleophiles.⁴ The broad utility of alkenyl nitriles has inspired considerable efforts towards their synthesis with key contributions including Wittig/Horner–Wadsworth–Emmons olefination,⁵ Peterson olefination⁶ and acrylamide/oxime dehydration.⁷ Most of these methods, however, suffer from restricted substrate scope due to the use of strong bases and the limited accessibility of the starting materials. Catalytic methods for the synthesis of alkenyl nitriles from alkenes, alkynes, and other precursors have also been developed, though often again exhibiting poor regioselectivity and limited substrate scope, as well as employing hazardous hydrogen cyanide or cyanogen chloride/bromide as the cyanide source.⁸ A significant advancement was achieved by Nakao and Hiyama, who reported the carbocyanation of alkynes to access acrylonitriles.⁹ Recently, Ritter has developed an elegant catalytic method for anti-Markovnikov hydrocyanation of terminal alkynes.¹⁰ Milstein recently disclosed a manganese-catalyzed α -olefination of nitriles with primary alcohols via dehydrogenative coupling, providing an alternative method to access α -alkenyl nitriles.¹¹

“Branched” β -unsubstituted alkenyl nitriles are more sterically accessible compared to other substitution patterns and hence have enhanced reactivity,^{4,12} which has been capitalized upon in their use in the synthesis of diverse compounds, ranging from β -amino acids to non-steroidal anti-inflammatory drugs.^{12,13} Existing routes to branched alkenyl nitriles possess the limitations alluded to above; for instance, catalytic hydrocyanation of terminal alkynes employs hazardous HCN and exhibits substrate-dependent regioselectivity.^{8b,13} Devising methods for accessing branched alkenyl nitriles of expanded structural diversity and tunable reactivity from readily available alkenes and a convenient cyanide source remains an important unaddressed synthetic challenge.

To this end, we envisioned a copper-catalyzed oxidative cyanation, according to the catalytic cycle depicted in Figure 1C. A suitable N–F (F^+) oxidant (e.g., Selectfluor)¹⁴ would oxidize Cu(I) species **I** to Cu(III)–F intermediate **II**.¹⁵ Transmetalation with TMS-CN would generate Cu(III)–CN species **III**, which would then coordinate to the alkene and transfer the cyanide group to give highly reactive cyanoalkylcopper(III) species **IV/IV'**. Subsequent formal β -H elimination¹⁶ would afford the desired alkenyl nitrile product and a reduced copper species (represented in Figure 1 as Cu(III)–H intermediate (**V**), which then undergoes HX reductive elimination) to close cycle. Alternative mechanistic pathways involving single-electron transfer (SET) events to arrive at the same products could also be envisioned. Conceptually, this approach takes inspiration from recent progress in copper-catalyzed C(benzylic)–H cyanation¹⁷ and cyanofunctionalization of conjugated alkenes

(e.g., styrenes),¹⁸ as well as classical palladium(II)-catalyzed Wacker oxidation of alkenes with OH and NH nucleophiles^{1d,e} and palladium(0)-catalyzed Heck-type coupling of alkenes and aryl halides.^{1a}

We initiated our study of oxidative cyanation with phthalimide-derived terminal alkene **1a**, a β -amino acid precursor,¹³ as the model substrate (Table 1). To our delight, cyanation of **1a** proceeded to give the desired product **4a** in 43% yield when using CuBr as catalyst, pyrox (**L1**) as the ligand, and Selectfluor as the bystander F⁺ oxidant.¹⁵ Notably, only the branched product corresponding to cyanide insertion at the internal alkene carbon was observed, potentially due to favorable positive charge buildup at this position during the cyanide transfer step. During initial experiments, a noticeable exotherm was observed upon addition of TMSCN into the reaction system, accompanied by complete consumption of **1a** within 30 min. We investigated a variety of different copper salts in an effort to suppress decomposition, ultimately leading to the identification of (CuOTf)₂•toluene as the optimal precatalyst (entries 1–4). Additional tuning of substituents on the pyrox core (**L2** and **L3**, entries 5 and 6) or replacement with other *N,N*-bidentate ligands (**L4–L7**, entries 7–10) led to diminished yields. Control experiments in the absence of copper or ligand led to partial consumption of the alkene *via* uncharacterized decomposition pathways and no detectable product formation.

The scope of non-conjugated terminal alkenes was next explored (Table 2). Phthalimide-containing alkenes bearing different alkyl chain lengths were compatible with the reaction conditions (**4a–c**). A variety of functional groups in varying proximity to the alkene, including amides, esters, halides, arenes, and triphenylsilane, were also tolerated (**4d–l**). Notably, bromo, chloro, and triphenylsilyl groups offer the opportunity for further downstream diversification. The reaction could be performed on a larger scale (4 mmol) without erosion of yield (see **4j**). We were especially intrigued to find that alkene hydrocarbons, dodec-1-ene and undec-1-ene, as well as unsaturated fatty ester, methyl undec-10-enoate, were competent substrates (**4m–o**). These are challenging substrates because there are no polarizing or chelating substituents in the vicinity of the alkene.

We next investigated styrenes (**4p–z**). Due to the high inherent reactivity of these substrates, lower temperature (0 or –10 °C) was found to be optimal in these cases. Substrates bearing electron-donating (**4p**, **4q**, and **4v**) or -withdrawing groups (**4w–y**) reacted to produce the desired products in synthetically useful yields (35–75%). Compound **4q**, a key intermediate in the production of ibuprofen,¹⁹ was prepared in 52% yield on 6.5 mmol scale. Halide substituents on the different positions of the arene were well tolerated (**4r–u**).

In order to test the compatibility of the reaction in more structurally intricate contexts, several alkenes embedded in biologically relevant molecules and active pharmaceutical agents were demonstrated, including those derived from terpenes (**4aa** and **4ab**), (*S*)-(+)-ketopinonic acid (**4ac** and **4ad**), a diketopiperazine (**4ae**), non-natural amino acids (**4af** and **4ag**), and various steroids (**4ah–aj**). These examples exemplify the synthetic utility of the oxidative cyanation reaction and its compatibility with complex molecules.

We next moved on to investigate internal 1,2-disubstituted alkenes (Table 3), which are significantly more challenging substrates in catalytic alkene functionalization due to the instability of the secondary alkyl-metal species involved. Indeed, initial experiments with a broad range of internal alkenes revealed that this class of substrates typically leads to intractable product mixtures (see SI), indicating that our catalytic system is not *generally* applicable for internal alkenes at this stage in development. Nevertheless, several encouraging preliminary results merit discussion. Several alcohol- and amine-derived *E/Z*-internal alkenes were converted to the corresponding products **4ak–ap** in 38–71% yield with high regioselectivity. Furthermore, the products were obtained as single *E/Z*-stereoisomers, with the stereochemical outcomes consistent with a *syn*-cyanocupration/C–C bond rotation/*syn*-β-H elimination pathway. For acyclic substrates, the yield and regioselectivity were found to be sensitive to subtle structural changes, with the combination of a heteroatom at the bishomoallylic position and a terminal methyl group on the other end of the alkene giving the best results. Several cyclic internal alkenes were also reactive. For example, cyclic allylic alcohol derivatives (**1aq** and **1ar**) and 1-tosyl-1,2,3,6-tetrahydropyridine (**1as**) were competent substrates, although the regioselectivity was lower than in comparable linear cases. Indene also proved to be well tolerated in this reaction, affording the desired product in 43% yield (**4at**). The fact that conjugated products are obtained with cyclic alkenes suggests that a different mechanism may be operative in these cases compared to acyclic alkenes, and the details of this phenomenon are currently under investigation.

To demonstrate the synthetic versatility of the alkenyl nitrile products, several diversifications of **4j** were performed (Figure 2A). First, 2-benzylacrylonitrile was converted to 2-benzylacrylic acid (**5a**), a key intermediate towards the pharmaceutical agent acetophan.²⁰ Next, selective reduction of the nitrile (DIBAL-H) and alkene (Pd/C) provided the corresponding aldehyde (**5b**) and alkyl nitrile (**5c**), respectively. Hydration to the amide (**5d**) and ethanolysis to the ethyl ester (**5e**)—an established β-amino acid precursor²¹—could similarly be performed under standard conditions. We also found that the polarized nature of the alkene makes it an efficient dienophile in Diels–Alder cycloaddition with anthracene (56% yield, **5f**). Lastly, **4j** was a competent Michael acceptor in Baran’s modified Ni-catalyzed Giese reaction,²² effecting net 1,2-carbocyanation over the two steps. These applications, among many others that could be envisioned, demonstrate that oxidative cyanation unveils a rich breadth of organic reactivity that is inaccessible to the parent alkene.

The Mayr electrophilicity scale of Michael acceptors designates acrylonitrile as being slightly more reactive than *N,N*-dimethylacrylamide,^{4b} suggesting that alkenyl nitriles may constitute attractive reactive groups for the development of covalent protein ligands. We accordingly synthesized and compared the proteomic reactivity of bis(trifluoromethyl)phenyl alkenyl nitrile **4y** with the corresponding acrylamide analogue **6**, as well as with chloroacetamide **7**, which we had previously found to exhibit broad engagement of cysteine residues in the human proteome (Figure 2B).²³ Using a chemical proteomic platform that broadly assesses and quantifies cysteine-small molecule interactions in native biological systems,²⁴ we found that the alkenyl nitrile **4y** displayed an overall proteomic reactivity that was similar to acrylamide **6**, but much lower than chloroacetamide

7 (Figure 2C). A number of cysteines were found to be engaged, or “liganded”, by all three of the tested electrophilic compounds, but other sites showed favored interactions with only one of these probes (Figure 2D). Of particular note was the discovery of proteins that strongly and preferentially reacted with alkenyl nitrile **4y** (e.g., PEF1; Figure 2E). These data indicate that alkenyl nitriles may serve as a valuable class of Michael acceptors for developing chemical probes that target proteins not yet addressed by more commonly used electrophilic groups (chloroacetamides and acrylamides). The oxidative cyanation of alkenes should provide straightforward access to libraries of alkenyl nitriles with tunable steric and electronic properties for future covalent inhibitor development. For example, with styrenes the electrophilicity can be tuned by modifying the substituents on the arene.

In summary, we have developed a catalytic method for oxidative cyanation of terminal and select internal alkenes. This transformation enables direct access to branched alkenyl nitriles that are otherwise difficult to prepare. Though a precise reaction mechanism remains unknown at present, a plausible catalytic cycle could involve a high-valent Cu(III) intermediate that is formed *via* oxidation of the Cu(I) catalyst with a bystander F^+ oxidant. The alkenyl nitrile products constitute versatile electrophiles with applications in both organic synthesis and chemical biology. In particular, the attenuated and complementary reactivity displayed by alkenyl nitriles compared to more conventional electrophiles underscores their attractiveness for their future development as covalent small-molecule probes and drug candidates.

Supplementary Material

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Acknowledgments

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Figure 1.

Development of a catalytic oxidative cyanation of alkenes. (A) Representative bioactive molecules and drugs containing alkenyl nitriles or derivatives thereof. (B) Generalized depiction of proposed oxidative cyanation method. (C) Plausible reaction mechanism.

Figure 2.

Synthetic and chemical proteomic applications of alkenyl nitriles. (A) Representative derivatizations of **4j**. (B) Structures (C) and proteomic reactivity of bis(trifluoromethyl)phenyl compounds bearing alkenyl nitrile (**4y**), acrylamide (**6**), and chloroacetamide (**7**) electrophilic groups assessed using the chemical proteomic method isoTOP-ABPP.^{23,24} (C) Waterfall plots representing the top 1,500 cysteine-containing peptides and their corresponding reactivity, or competition ratio ($R_{\text{DMSO/compound}}$), values. High R values correspond to greater reactivities, where cysteines with R values ≥ 4 (dashed line) were considered to be liganded by **4y**, **6** and **7**. (D and E) Representative MS1 spectra showing examples of cysteines that were generally (C18 of REEP5) or preferentially liganded (green color) by **4y**, **6** and **7** (C152 of GAPDH (**7**), C146 of PEF1 (**4y**), and C161 of TIGAR (**6**)).

Table 1Optimization of Reaction Conditions^a

entry	"Cu"	ligand	yield (%) ^b
1	CuBr	L1	43
2	CuF ₂	L1	49
3 ^c	(CuOTf) ₂ •toluene	L1	73
4	Cu(OTf) ₂	L1	62
5 ^{c, d}	(CuOTf) ₂ •toluene	L2	52
6 ^{c, d}	(CuOTf) ₂ •toluene	L3	61
7 ^{c, d}	(CuOTf) ₂ •toluene	L4	49
8 ^{c, d}	(CuOTf) ₂ •toluene	L5	46
9 ^{c, d}	(CuOTf) ₂ •toluene	L6	40
10 ^{c, d}	(CuOTf) ₂ •toluene	L7	22

^a Reaction conditions: **1a** (0.2 mmol), **2** (1.5 equiv), TMS-CN (2 equiv), copper source (5 mol %), and ligand (5.5 mol %) in MeCN (1.0 mL) at room temperature.

^b Isolated yield.

^c The yield was determined by ¹H NMR spectroscopy with CH₂Br₂ as the internal standard.

Table 2

Terminal alkene scope.^a ^aReaction was conducted at room temperature unless noted otherwise.^bSelectfluor (1.8 equiv) and TMSCN (2.4 equiv).

Table 3

Internal alkene scope.^a ^a r.r. = regioselectivity ratio.^b Combined yield of independently isolated major and minor regioisomers. Ratios determined by masses of isolated samples.