

Catalytic Diverse Radical-Mediated 1,2-Cyanofunctionalization of Unactivated Alkenes via Synergistic Remote Cyano Migration and Protected Strategies

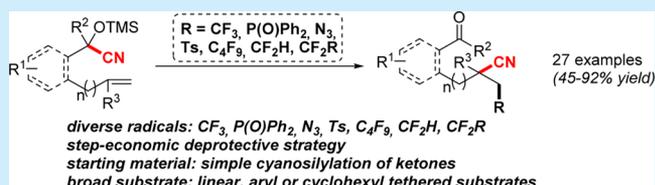
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S Supporting Information

ABSTRACT: A catalytic radical protocol for 1,2-cyanofunctionalization of unactivated alkenes involving remote cyano migration triggered by addition of diverse carbon- and heteroatom-centered radicals to alkenes has been developed. This powerful strategy provides a diverse platform for the collection of a variety of synthetically important β -functionalized alkyl nitriles bearing densely functionalized carbonyl, cyano, and other various functional groups within the same molecules. The substrates TMS (trimethylsilyl)-protected alkenyl cyanohydrins are straightforwardly accessible via simple cyanosilylation of the corresponding ketones.

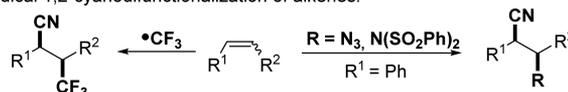


The straightforward transformation of unactivated alkenes into various complex molecules provides an efficient platform in organic synthesis in the past several decades.¹ Among intensive research in this area, the recently explored 1,2-difunctionalization of unactivated alkenes triggered by addition of in situ generated radicals to alkenes to realize the halo-, oxy-, thio-, amino-, and carbo-functionalization has become a hot topic, providing the most attractive strategy for the simultaneous incorporation of two functional groups into alkenes.² Given alkyl nitriles as one of the most important building blocks owing to their participation in the straightforward synthesis of aldehydes, carboxylic acids, and amines, the catalytic cyanofunctionalization of unactivated alkenes to simultaneously incorporate the cyano group and diversely functional groups should be of great significance in organic synthesis. Although significant progress has been made in cyanofunctionalization of alkenes,³ there are still limitations in these methodologies. Due to the unavailability of systematic study in this area, most of them are inherently restricted to copper-catalyzed cyanotrifluoromethylation of alkenes^{3b-d} or the substrate scope is only limited to activated alkenes for azidocyanation and aminocyanation,^{3a,e} thus hindering their widespread adoption in the collection of diversely β -functionalized nitriles (Scheme 1a). Therefore, the development of a general and efficient method to realize the 1,2-cyanofunctionalization of unactivated alkenes for the concomitant incorporation of a cyano group and multiple functional groups into organic molecules is highly desirable.

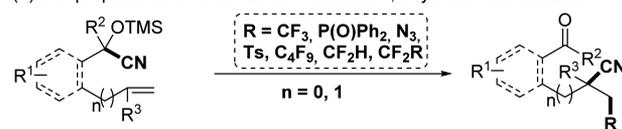
In our continuous efforts in radical-initiated remote hydrogen migration chemistry,⁴ we envisioned the possibility of developing a novel cyanofunctionalization of unactivated alkenes through remote cyano migration triggered by addition of the diverse

Scheme 1. 1,2-Cyanofunctionalization of Alkenes

(a) Radical 1,2-cyanodifunctionalization of alkenes:



(b) Our proposal for diverse radical-mediated 1,2-cyanofunctionalization:



1, straightforward access from cyanosilylation of ketones

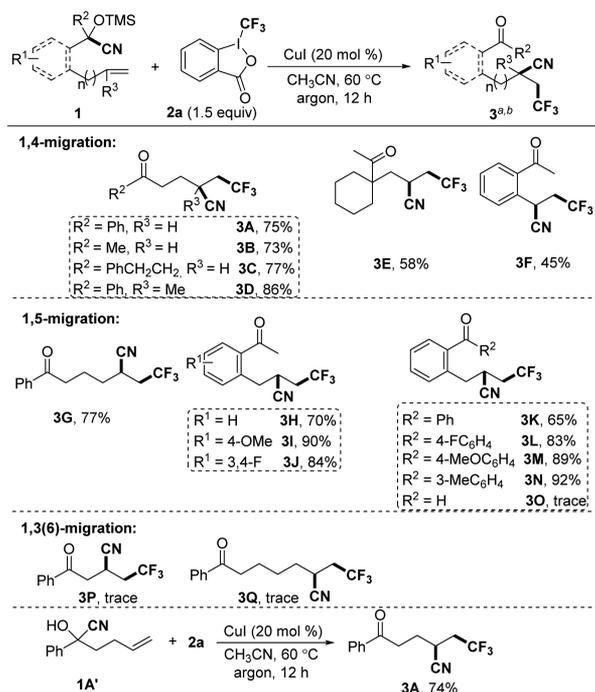
carbon- and heteroatom-centered radicals to alkenes. A unique feature of the aforementioned hydrogen migration process resides in the preference for the generation of a lower-energy radical,⁵ thus providing a driving force for remote hydrogen atom abstraction by an inherently high-energy sp^3 carbon-centered radical generated from the addition of a radical to an alkene. On the other hand, protecting groups are always unavoidable in natural product synthesis because of the functional group reactivity and tolerance toward the harsh conditions. To further modify the functional group, a deprotection step is inevitable.⁶ Thus, the efficient combination of a deprotection step and modification of the obtained functional group represents a step-economical strategy and will shorten the synthetic route. Based on the above assumption and from the point of step economy, we rationally design the TMS (trimethylsilyl)-protected alkenyl

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cyanohydrin **1**, which are easily obtained from simply straightforward cyanosilylation of the corresponding ketones,⁷ as the starting material in our efforts toward the catalytic 1,2-cyanofunctionalization of unactivated alkenes via the 1,4(5)-cyano migration process triggered by addition of diverse carbon- and heteroatom-centered radicals to alkenes (Scheme 2b). To

Scheme 2. Substrate Scope for 1,2-Cyanotrifluoromethylation Reactions



^a0.1 M substrate **1** in 0.2 mmol scale. ^bIsolated yield.

realize this strategy, several challenges should be overcome: (1) The unexpected side reactions, such as the competitive 1,2-oxyfunctionalizations of alkenes, β -hydride elimination, and other transformations, should be overcome.^{2,8} (2) Synergistic TMS deprotection and cyanofunctionalization of alkenes should be well tolerated in the one-pot transformation. (3) The compatibility between unactivated alkenyl TMS-protected cyanohydrin and various carbon- and heteroatom-centered radical precursors with different reactivity properties should be considered. Herein, we report a general and systematic strategy of catalytic 1,2-cyanofunctionalization of unactivated alkenes via the 1,4/5-cyano migration process triggered by trifluoromethylation, phosphonylation, azidation, sulfonylation, perfluoroalkylation, or difluoromethylation of easily accessible TMS-protected alkenyl cyanohydrins to afford diversely β -functionalized alkyl nitriles.⁹

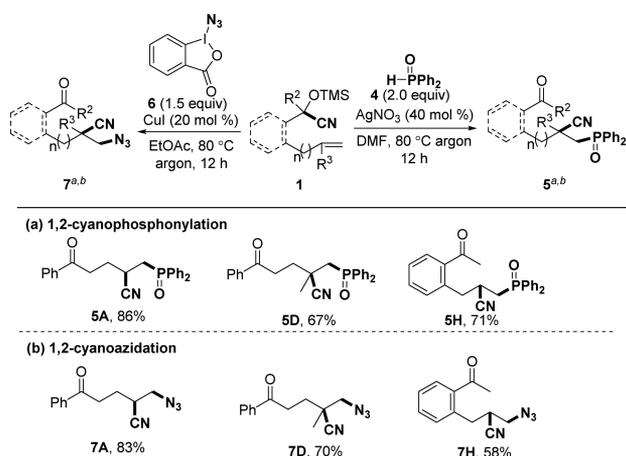
Modular synthetic access to these model substrates **1** would be readily achieved in good yields by straightforward and efficient cyanosilylation from the inexpensive corresponding ketones (see details in the Supporting Information (SI)). Considering the great importance of trifluoromethylated organic molecules in pharmaceuticals and agriculture chemicals,¹⁰ we then initiated our investigations by examining the radical trifluoromethylation reactions of unactivated alkenes. As such, the reaction of substrate TMS-protected alkenyl cyanohydrin **1A** with Togni's reagent **2a**¹¹ was selected for the optimization of reaction conditions. We were delighted to find that the 1,2-cyano-

trifluoromethylation of **1A** proceeded well in the presence of CuBr in EtOAc at 60 °C for 12 h, affording the desired β -trifluoromethylated nitrile **3A** as the sole product via the remote radical 1,4-cyano migration, albeit in 58% yield (Table S1 in SI, entry 1). Fortunately, no oxytrifluoromethylation or β -hydride elimination product was detected, showing the high selectivity of this strategy. Encouraged by this result, after systematically screening the reaction parameters, we finally identified the optimized conditions as the following: the reaction of **1A** and **2a** in 1:1.5 molar ratio, with CuI (20 mol %) as the catalyst, in CH₃CN at 60 °C for 12 h, affording **3A** in 75% isolated yield (Table S1, entry 6). It should be noted that under the standard reaction conditions, the reaction of TMS-removal alkenyl cyanohydrin **1A'** gave a similar result with **1A**, implying the efficiency of the synergistic deprotective cyanotrifluoromethylation strategy was not significantly affected, thus rendering this strategy more synthetically appealing in terms of step-economy values to allow the deprotection step to be omitted (Table S1, entry 13 and Scheme 2).

With the optimal conditions in hand, we next explored the reaction scope with TMS-protected alkenyl cyanohydrins (Scheme 2). The cyanotrifluoromethylation reaction of alkenes via 1,4-cyano migration was first examined. The linear substrates possessing aryl or aliphatic groups were found to be suitable substrates for the reaction to afford β -trifluoromethylated nitriles **3B** and **3C** in 73% and 77% yields under the standard reaction conditions. The reaction of 1,1-disubstituted alkenes **1D** provided the desired β -trifluoromethylated nitrile **3D** in excellent yield (86%). In addition to simple linear substrates, the cyclic substrate **1E** was also applicable to this transformation, giving the desired product **3E** in 58% yield. Noteworthy is that the aryl tethered substrates **1F**, where the alkene moiety is conjugated with an aryl ring, proceeded as well to generate **3F** in 45% yield. Encouraged by the above success, we next turned our attention to the 1,5-cyano migration process. Gratifyingly, upon treatment with the standard reaction conditions, **1G** furnished **3G** in 77% yield. Further expansion of the substrate scope revealed that the aryl tethered substrates bearing electron-neutral (**1H**), -rich (**1I**), or -deficient (**1J**) aryl groups did not affect the reaction efficiency to deliver **3H–3J** in 70–90% yields. Substrates with an aryl ring α to the alcohol group reacted effectively in this reaction. Furthermore, substituents that are electron-neutral (**1K**), -deficient (**1L**), or -rich (**1M** and **1N**) on the aryl ring were tolerated well to afford the corresponding highly functionalized β -trifluoromethylated nitriles **3K–3N** in 65–92% yields. Unfortunately, the reaction of **1O–1Q** afforded almost no desired product **3O–3Q** under the standard reaction conditions. It is encouraging to note that the diverse substrates containing both linear and tethered backbones are all tolerated under the current catalytic system, showing a broader substrate scope than that for the just reported method.⁹

The successful synthesis of β -trifluoromethylated nitriles from unactivated alkenes prompted us to screen other radicals for straightforward access to more types of β -functionalized nitriles. Gratifyingly, the reaction of **1** with diphenylphosphine oxide **4** (2.0 equiv) in the presence of AgNO₃ (40 mol %) in DMF at 80 °C provided the sole 1,2-cyanophosphonylation product **5** with high selectivity (Scheme 3a). Further expansion of the substrate scope showed that β -phosphonyl nitriles **5A**, **5D**, and **5H** were obtained efficiently under similar conditions in 67–86% yields via a 1,4(5)-cyano migration process. Furthermore, the successful catalytic installation of an azide radical to substrate **1** delivered the desired β -azido nitriles **7A**, **7D**, and **7H** in 58–83%

Scheme 3. Radical-Initiated 1,2-Cyanophosphonylation and Cyanoazidation

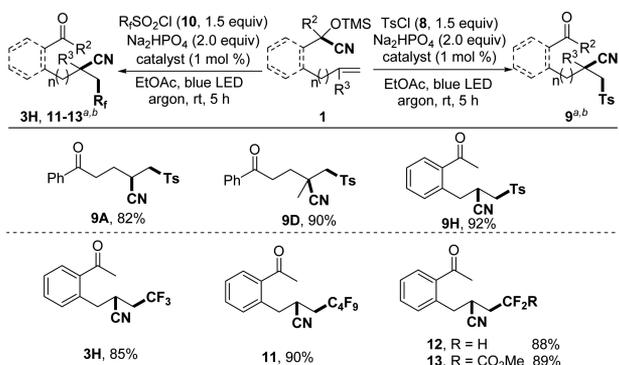


^a0.1 M substrate **1** in 0.2 mmol scale. ^bIsolated yield based on **1**. DMF = *N,N*-dimethylformamide.

yields with iodine(III) reagent azidoidine (**6**)¹² with 20 mol % CuI as the catalyst, demonstrating the excellent compatibility of the protocol with the azide radical (Scheme 3b).

To further expand the reaction scope to obtain β -sulfonyl nitriles, we next examine the in situ generated sulfonyl radical to probe whether a similar process could be realized. Unfortunately, our efforts to employ *p*-toluenesulfonic acid or *p*-toluenesulfonyl hydrazide with different oxidants to generate the sulfonyl radicals for the reaction failed (see Table S2 in SI). Notably, the recently developed visible-light-mediated photoredox catalysis has become an environmentally benign tool for the generation of various radical species under extremely mild conditions.¹³ We assumed that the cyanosulfonylation reaction might be realized under the mild photoredox catalysis system. To our delight, the reaction of substrate **1A** with *p*-toluenesulfonyl chloride (**8**) in the presence of photocatalyst [Ir(ppy)₂(dtbbpy)]PF₆ (1 mol %) with 2 equiv of Na₂HPO₄ under visible light initiation provided the desired β -sulfonyl nitrile **9A** in 82% yield in high selectivity (Scheme 4a).¹⁴ Further examination of the substrate scope exemplified that disubstituted alkenes **1D** proceeded smoothly to generate **9D** in 90% yield under standard reaction conditions. Notably, the aryl tethered substrate worked more efficiently to

Scheme 4. Photoredox-Catalyzed 1,2-Cyanosulfonylation and Cyanoperfluoroalkylation



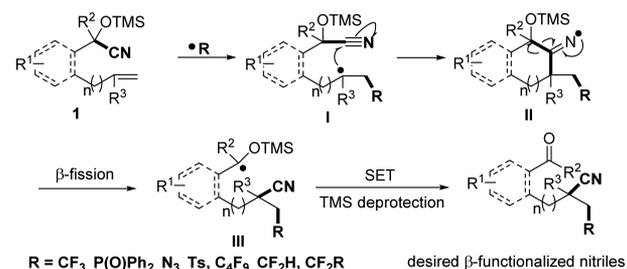
^a0.1 M substrate **1** in 0.2 mmol scale. ^bIsolated yield based on **1**. Catalyst: [Ir(ppy)₂(dtbbpy)]PF₆. TsCl = tosyl chloride.

afford the highly functionalized β -sulfonyl nitrile **9H** in excellent yield (92%). Most importantly, the success of CF₃, C₄F₉, CF₂H, CF₂CO₂Et radical installation to generate **3H**, and **11–13** with sulfonyl chloride (**10a–10d**)¹⁵ via extrusion of sulfur dioxide under photoredox catalysis conditions, demonstrated the generality of the present methodology in simultaneously incorporating the cyano group and various fluoroalkyl radicals into an alkene (Scheme 4).

It should be emphasized that the 1,2-cyanofunctionalization strategy showed high selectivity for diverse radicals, with no 1,2-oxyfunctionalized product or β -hydride elimination product observed. Overall, these features demonstrate that the radical mediated 1,2-cyanofunctionalization of alkenes exhibits broad compatibility for the series of diverse radicals, thus offering a general strategy for simultaneous installation of diversely functional groups and the valuable cyano group into the alkenes.

Based on the above results and previous reports,¹⁶ we proposed a general mechanism for this catalytic protocol (Scheme 5). To initiate the process, the targeted R radicals

Scheme 5. Proposed Reaction Mechanism



were first generated with the corresponding catalyst. Next, the substrate **1** would be attacked by the in situ generated radicals R to give the transient alkyl radical **I**, which would undergo a 5/6-exo radical cyclization reaction to afford the alkyliminyl radical **II**.¹⁶ This high energy radical intermediate would have a driving force to provide the relatively stable TMS-protected ketyl radical **III** via selective β -fission.^{16d} A further SET oxidation and subsequent removal of TMS group provided the desired β -functionalized alkyl nitriles to realize the 1,2-cyanofunctionalization of an unactivated alkene.¹⁷ Further study to disclose the interesting stereoselectivity of the cyano migration is in progress in our lab.¹⁸

In summary, we have developed a general and efficient catalytic radical 1,2-cyanofunctionalization of unactivated alkenes via a remote 1,4(5)-cyano migration process triggered by trifluoromethylation, phosphonylation, azidation, sulfonylation, and perfluoroalkylation of unactivated alkenes in the presence of metal or photoredox catalysis. This protocol exhibits the use of readily available starting materials with high step economy, a broad substrate scope, the compatibility of diverse carbon- and heteroatom-centered radical precursors, and excellent selectivity. This synergistic strategy provides a convenient access to diverse β -functionalized alkyl nitriles bearing densely functionalized valuable carbonyl, cyano, and other various functional groups within the same molecules, which are valuable intermediates and should be of great importance in bulk chemicals. Further mechanistic study is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02960.

Experimental procedures, characterization of all new compounds, Tables S1 and S2 (PDF)

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Notes

The authors declare no competing financial interest.

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(17) Another reaction pathway involving the oxidation of intermediate **I** to carbocation and captured by CN in situ generated from the decomposition of cyanohydrin to ketone can be ruled out since substrates **1P** and **1Q** failed to afford the desired products.

(18) We appreciate one referee suggestion to prepare enantiopure **1A**, whose potential transformation to enantioenriched **3A** would be both synthetically and mechanistically valuable.