

Iron-Facilitated Direct Oxidative C–H Transformation of Allylarenes or Alkenes to Alkenyl Nitriles

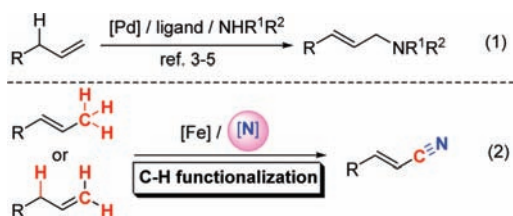
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Abstract: This paper describes the first direct approach to alkenyl nitriles from allylarenes or alkenes facilitated by an inexpensive homogeneous iron catalyst. Three C–H bond cleavages occur under the mild conditions during this process. Mechanistic studies indicate that the cleavage of the allyl C(sp³)–H bond is involved in the rate-determining step. This observation may provide an opportunity to achieve C(sp³)–H functionalization catalyzed by an iron catalyst.

Selective C(sp³)–H functionalization of simple hydrocarbons is one of the most important strategies for developing novel methodologies in organic synthesis.^{1,2} Recently, elegant examples of C–N bond formation through Pd-catalyzed direct linear intermolecular allylic amination of terminal alkenes via C(sp³)–H activation (eq 1) have been significantly disclosed by the groups of White,³ Liu,⁴ and others.⁵ An allylpalladium species was proposed as the key intermediate in these processes. To the best of our knowledge, homogeneously catalytic C≡N bond formation through cleavage of three allylic C(sp³)–H bonds under mild conditions has not been disclosed to date.⁶ Alkenyl nitriles are unique structural units and versatile building blocks in organic synthesis for natural products, pharmaceuticals, agricultural chemicals, and dyes.⁷ Although a plethora of methods have been developed because of their importance in chemistry and biology,^{8,9} the direct transformation from the corresponding allyl derivatives via C(sp³)–H activation (eq 2) is still an extremely attractive but challenging task.



In the past decades, iron catalysis has attracted a lot of attention because of its low price and environmentally benign features.¹⁰ Significantly, iron-catalyzed C(sp³)–H transformations for the formation of C–heteroatom bonds have been recently disclosed, albeit in limited cases.¹¹ We describe herein the first direct oxidative C(sp³)–H transformation of 1- and 3-allylarenes or alkenes to alkenyl nitriles facilitated by an iron catalyst through the cleavage of three C–H bonds (eq 2).

Table 1. Direct Transformation of Allylbenzene (**1a**) to Cinnamonitrile (**2a**)^a

entry	catalyst (mol %)	oxidant	yield of 2a (%) ^b
1	Pd(OAc) ₂ (10)	DDQ	41
2	CuI (10)	DDQ	58
3	CuBr (10)	DDQ	50
4	CuCl (10)	DDQ	58
5	CuBr ₂ (10)	DDQ	54
6	FeCl ₂ (10)	DDQ	98 (95)
7	FeCl ₂ (5)	DDQ	84
8	Fe(OTf) ₂ ·2MeCN (10)	DDQ	83
9	none	DDQ	19
10	FeCl ₂ (10)	O ₂	0
11	FeCl ₂ (10)	TBHP	10
12 ^c	FeCl ₂ (10)	DDQ	0

^a Reaction conditions: **1a** (0.5 mmol) and Me₃SiN₃ (1.0 mmol), catalyst, and oxidant (1.5 mmol) in dry DCE (2 mL) with stirring at 60 °C under air for 2 h. ^b GC yield using *n*-dodecane as an internal standard; the number in the parentheses in entry 6 is the isolated yield. ^c NaN₃ (2.0 equiv) and tetra-*n*-butylammonium bromide (0.05 equiv) were used instead of Me₃SiN₃.

We initially investigated the transformation of 1-allylbenzene (**1a**) under our former radical conditions, wherein methyl aromatics could be successfully converted into aryl nitriles.¹² However, none of the expected product (*E*)-3-phenyl-2-propenenitrile (cinnamonitrile, **2a**) was detected. To our delight, the Pd(OAc)₂-catalyzed reaction of **1a** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidant in 1,2-dichloroethane (DCE) at 60 °C produced **2a** in 41% yield with high stereoselectivity (Table 1, entry 1). Gratifyingly, **2a** was formed in 95% yield when inexpensive FeCl₂ was employed as the catalyst (entry 6). Other metal catalysts, such as Cu salts or Fe(OTf)₂, exhibited low efficiencies (entries 1–5 and 8). Attempts using other oxidants such as O₂, *tert*-butyl hydroperoxide (TBHP), or benzoquinone (BQ) were not successful (entries 10 and 11; also see the Supporting Information).

With the optimized conditions in hand, various allylarenes were investigated with 10 mol % FeCl₂ as the catalyst (Table 2). Substituents at the para, meta, and ortho positions of the arene group did not affect the efficiencies (entries 4–6). It is noteworthy that 3,3- and 2,3-disubstituted propenes (**11–n**) were tolerated in this transformation, leading to the corresponding trisubstituted alkenyl nitriles in moderate yields with high stereoselectivity (40–60%; entries 12–14). Notably, a heteroaryl-substituted propene, 1-allyl-2-thiophene (**1k**), provided **2k** in 77% yield (entry 11). In addition, the alkenyl-substituted

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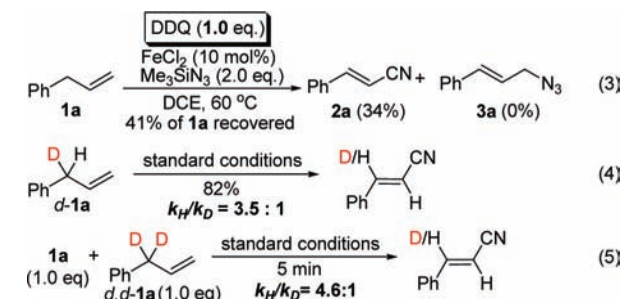
Table 2. Iron-Facilitated Oxidative Transformation of 1- and 3-Allylarenes **1** to Alkenyl Nitriles **2**^a

entry	1	2	yield (%) ^b
1			95
2			66
3			85
4			81
5			79
6			63
7			45
8			87
9			34
10			96
11			77
12			60 ^c
13 ^d			40 ^e
14			51
15			45 ^f
16			53 ^g
17			0 ^h

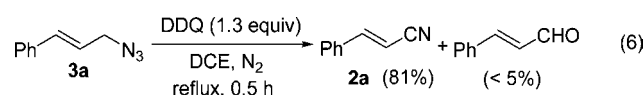
^a Standard conditions: **1** (0.5 mmol) and Me₃SiN₃ (1.0 mmol), FeCl₂ (0.05 mmol), DDQ (1.5 mmol) in dry DCE (2 mL) with stirring at 60 °C under air for 2 h. ^b Isolated yield. ^c No Z isomer was detected. ^d LiOAc (0.5 mmol) was used as an additive in this case. ^e E/Z = 25:1, as determined by ¹H NMR analysis. ^f (2E,4E)-**2o**/(2Z,4E)-**2o** = 5:1, as determined by ¹H NMR analysis; the configurations were specified depending on the calculation of the corresponding coupling constants. ^g The reaction was carried out at 40 °C; (2E,4E)-**2o**/(2Z,4E)-**2o** = 18:1, as determined by ¹H NMR analysis. ^h The reaction was too complicated, and no obvious amount of the desired product was obtained.

propene **1o** survived well, generating **2o** [45%; (2E,4E)-**2o**/(2Z,4E)-**2o** = 5:1] (entry 15). The conjugated alkenes **1p** (E/Z = 1:1) was also successfully converted to **2o** in 53% yield with higher stereoselectivity [(2E,4E)-**2o**/(2Z,4E)-**2o** = 18:1] than in the case of **1o** (entry 16). A simple skipped diene, **1q**, was tested under these optimized conditions, but the reaction was too complicated, and no obvious amount of the desired product **2p** was obtained in this case (entry 17).

Very attractively, 3-allylarenes performed this transformation very well, as both (E)- and (Z)-propenylbenzene were highly stereoselectively converted to **2a** in 66 and 85% yield, respectively (Table 2, entries 2 and 3). These results indicated that π-allyl species are involved in this transformation.



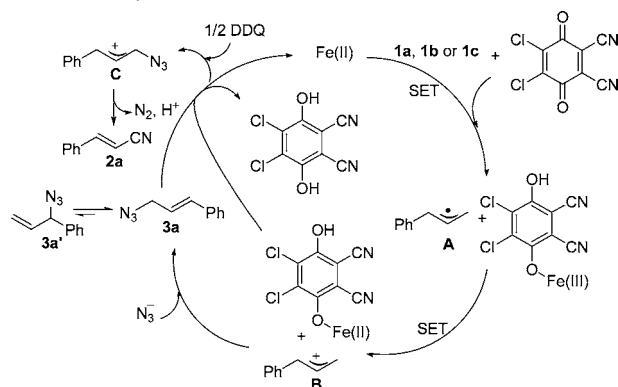
To investigate the mechanism, the reaction of **1a** was carried out using 1.0 equiv of DDQ as the oxidant. Interestingly, cinnamyl azide (**3a**) was not obtained, and 41% **1a** was recovered (eq 3). Furthermore, both intra- and intermolecular kinetic isotopic effects were evident ($k_H/k_D = 3.5$ and 4.6 , respectively) (eqs 4 and 5). All of these results indicated that the cleavage of the allyl C(sp³)-H bond is involved in the rate-determining step.



On the basis of the above results, the mechanism of this transformation shown in Scheme 1 is proposed. Initially, allylarene **1a**, **1b**, or **1c** undergoes iron-assisted single-electron-transfer (SET) oxidation with DDQ¹³ to produce the corresponding allyl radical **A**, which can be further oxidized to the allyl cation **B**. Next, the substitution reaction of allyl cation **B** generates allyl azides **3a** and **3a'**, which would exist as an equilibrating mixture by [3,3]-sigmatropic rearrangement.¹⁴ The fact that the reaction of **3a** with 1.3 equiv of DDQ produces the desired product **2a** (81%) has been proved (eq 6). Allyl azide cation **C** is subsequently formed through subsequent oxidation of **3a** by the iron-assisted DDQ oxidative system. Finally, allyl azide cation **C** undergoes Schmidt-type rearrangement¹⁵ to afford the desired nitrile product **2a**.

In conclusion, we have demonstrated the first homogeneously catalytic transformation of allyl arenes or alkenes to the corresponding alkenyl nitriles under mild conditions facilitated by an inexpensive and nontoxic iron catalyst. During this transformation, three C-H bond cleavages occur. This observation not only provides a new synthetic tool for constructing synthetically and medicinally important alkenyl nitriles but also offers an opportunity to achieve C(sp³)-H functionalization catalyzed by an iron catalyst under mild conditions. Further studies to clearly understand the reaction mechanism and the synthetic applications are ongoing in our group.

Scheme 1. Proposed Mechanism for the Direct Transformation



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Supporting Information Available: Experimental details and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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