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Iron-Catalyzed Dehydrogenative sp^3–sp^2 Coupling via Direct Oxidative C–H Activation of Acetonitrile

Huimin Su,[†,∥] Luyao Wang,[†,∥] Honghua Rao,[*,†,‡] and Hao Xu[*,§]

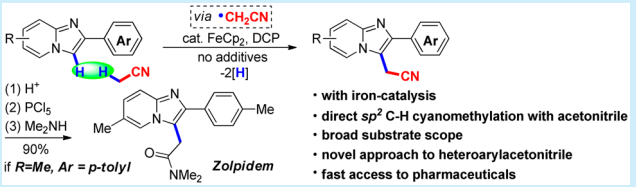
[†]Department of Chemistry, Capital Normal University, Beijing 100048, P. R. China

[‡]Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P. R. China

[§]College of Chemistry and Chemical Engineering, Henan University, Kaifeng 475004, P. R. China

Supporting Information

ABSTRACT: An iron-catalyzed dehydrogenative sp^3–sp^2 coupling of acetonitrile and 2-arylimidazo[1,2-*a*]pyridine has been realized, which can serve as a novel approach toward heteroarylacetonitriles. The merit of this strategy is illustrated by the breadth of functional groups tolerated in the transformation and the fast access to pharmaceuticals (such as zolpidem) directly from the heteroarylacetonitriles.



During the past decades, targeting inert C–H bonds (especially sp^2 C–H bonds) to forge C–C bonds has been routinely employed to effect streamlined approaches toward synthetically valuable synthons[1] and advanced structural features present in natural products and pharmaceuticals,[2] which have revolutionized the art and practice of synthesis.[3] However, activation of intrinsically less reactive sp^3 C–H bonds in aliphatic molecules remains rather rudimentary because previous strategies predominantly rely on the precoordination of a noble transition-metal catalyst with functional groups in substrates (e.g., carboxylic acids,[3,4] amides,[5] imines,[6] heteroarenes,[7] and hydroxyl functionalities[8]) to enable C(sp^3)–C bond-forming reactions with functionalized reactants.[4−8] In light of the aforementioned protocols, the requisition of noble transition-metal catalysts[9] and pre-established functional groups[10] in both coupling partners sometimes causes problems that restrict wider application. Therefore, a distinct and complementary approach, which is the dehydrogenative C–H cross-coupling via oxidative activation of sp^3 C–H bonds, has been recently implemented for C(sp^3)–C bond formations.[11] However, its success hinges on the direct oxidative activation of sp^3 C–H bonds in cycloalkanes,[11h,i,k,l] 1,3-dicarbonyl dervatives,[11d,g] or adjacent to the *N*-[11a−c,j] or *O*-atom,[11e,f,12] and only a few examples are available on dehydrogenative sp^3–sp^2 coupling with the requisition of Pd[12a] or Ru catalysis.[11i,l] In this context, more aliphatic feed stocks and catalytic systems should be exploited to showcase the generality and practicality of the dehydrogenative sp^3–sp^2 coupling through oxidative sp^3 C–H bond activation.

Aryl- or heteroarylacetonitriles are valuable synthons for the versatile reactivity in functional group transformations[13] and the outstanding capacity for heterocycle constructions.[14] Most importantly, the (hetero)arylacetonitrile unit has appeared in several pharmaceutically active molecules, such as levocabastine, verapamil, isoaminile, anastrozole, diphenoxylate, and cilomilast.[15] Therefore, various methods for (hetero)arylacetonitrile motif installations have been developed, including the nucleophilic substitution of benzyl halides with cyanide (Figure 1a),[16] the dehydrations of primary amides or aldoximes (Figure 1b),[17] the nucleophilic substitution of aromatic fluorides followed by decarboxylation (Figure 1c),[18] and the palladium-catalyzed cross-coupling of aryl halides with functionalized acetonitriles such as bromoacetonitrile,[19] TMS-acetonitrile,[20] Bu_3Sn-acetonitrile,[21] and cyanoacetate salts (Figure 1d).[22] These strategies are effective for assembling (hetero)arylacetonitriles, though they sometimes suffer from poor reaction atom-economy and the requisition of toxic transition metal catalysts or harsh conditions.

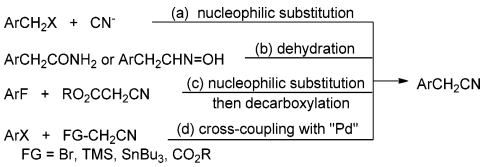


Figure 1. Previous strategies for (hetero)arylacetonitrile construction.

Consequently, in view of green and sustainable chemistry, dehydrogenative sp^2 C–H cyanomethylation with acetonitrile should be appealing enough for (hetero)arylacetonitrile constructions. Unfortunately, few protocols have been disclosed to recognize direct coupling between acetonitrile and an sp^2 C–H bond, although Pd-,[23] Ru-,[24] Cu-,[25] Fe-,[26] Mn-catalyzed,[27] and oxidant-mediated[28] oxidative C–H activation of acetonitrile have been extensively studied to accomplish difunctionalizations of activated alkenes. Herein, we introduce an iron-catalyzed sp^3–sp^2 coupling between acetonitrile and 2-arylimidazo[1,2-*a*]-

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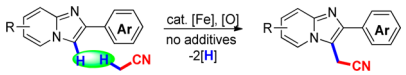
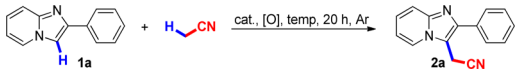
pyridines, forming a novel strategy for heteroarylacetonitrile synthesis through direct oxidative C−H activation of acetonitrile (Scheme 1).

Scheme 1. Dehydrogenative sp^3−sp^2 Coupling via Iron-Catalyzed Oxidative C−H Bond Activation of Acetonitrile



Using **1a** as the model substrate and CHP (2.5 equiv) as the oxidant, we began our investigations into the proposed dehydrogenative coupling of acetonitrile with sp^2 C−H bond. Initially, we posited that copper catalysis, often applied in dehydrogenative C(sp^3)−C bond-forming reactions,[11a−d,f,j] could realize the proposed sp^3−sp^2 coupling reaction, but virtually none of them led to observable product (Table 1, entry 1). By contrast, the catalytic system consisting of iron catalyst (10 mol %) and CHP enabled this reaction, and $FeCp_2$ exhibited higher catalytic activity than other iron catalysts (entries 2−7). Seeking to improve on this result, a series of oxidants, including $(^tBuO)_2$, ^{t}BuOOH, $(BzO)_2$, BzOOBu^t, AcOOBu^t, and DCP, were evaluated in this reaction, among which DCP was much more effective in generating the desired product **2a** in 45% yield (entries 7−13). Additionally, loading 2.0 equiv of DCP displayed a significant increase in reaction efficiency, furnishing product **2a** in 66% yield (entries 14 and 15). However, adjusting the catalyst loading by 5 mol % delivered slightly lower yet serviceable yields (entries 16 and 17), while conducting the reaction at 110 or 90 °C showed a marked dropoff in efficiency (entries 18 and 19). Inspiringly, the largest improvement in reaction efficiency was achieved when the model reaction was run at a lower concentration (0.04 M), affording product **2a** in the highest 80% yield (entry 20). Finally, control experiments run in the absence of oxidant or iron catalyst provided no or only 23% of the product, respectively (entries 21 and 22), thus indicating that the combination of $FeCp_2$ catalyst and DCP oxidant is crucial for this dehydrogenative sp^3−sp^2 C−H coupling reaction.

Table 1. Screening of the Reaction Conditions[a]

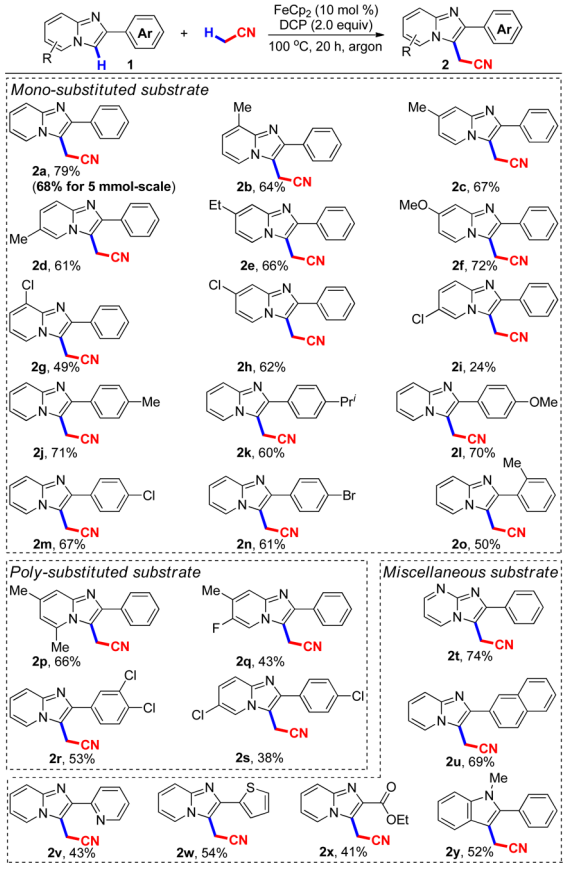


entry	cat. (mol %)	[O] (equiv)	temp (°C)	yield[b] (%)
1[c]	"Cu" (10)	CHP (2.5)	100	
2	$FeCl_3$ (10)	CHP (2.5)	100	20
3	$Fe(NO_3)_3{\cdot}9H_2O$ (10)	CHP (2.5)	100	16
4	$FeCl_2$ (10)	CHP (2.5)	100	21
5[c]	$FeBr_2$ (10)	CHP (2.5)	100	29
6	dppf (10)	CHP (2.5)	100	29
7	$Fe(Cp)_2$ (10)	CHP (2.5)	100	33
8	$Fe(Cp)_2$ (10)	^{t}BuOOH (2.5)	100	trace
9	$Fe(Cp)_2$ (10)	$(^tBuO)_2$ (2.5)	100	13
10	$Fe(Cp)_2$ (10)	$(BzO)_2$ (2.5)	100	-
11	$Fe(Cp)_2$ (10)	BzOOBu^t (2.5)	100	23
12	$Fe(Cp)_2$ (10)	AcOOBu^t (2.5)	100	24
13	$Fe(Cp)_2$ (10)	DCP (2.5)	100	45
14	$Fe(Cp)_2$ (10)	DCP (2.0)	100	66
15	$Fe(Cp)_2$ (10)	DCP (1.5)	100	42
16	$Fe(Cp)_2$ (5)	DCP (2.0)	100	60
17	$Fe(Cp)_2$ (15)	DCP (2.0)	100	59
18	$Fe(Cp)_2$ (10)	DCP (2.0)	110	34
19	$Fe(Cp)_2$ (10)	DCP (2.0)	90	trace
20[d]	**$Fe(Cp)_2$ (10)**	**DCP (2.0)**	**100**	**80**
21[d]	$Fe(Cp)_2$ (10)		100	0
22		DCP (2.0)	100	23

[a]Reaction conditions: **1a** (0.20 mmol), acetonitrile (2.0 mL), cat. (10 mol %), [O] (2.5 equiv), 100 °C, under argon for 20 h. [b]Determined by ^{1}H NMR with mesitylene as the internal standard. [c]Cu(OAc), CuI, CuBr, CuCl, CuBr·SMe_2, $CuCl_2$, $CuBr_2$, $Cu(OAc)_2$, $Cu(OTf)_2$, or CuO was used as the catalyst. [d]Acetonitrile (5 mL) was used. [O] = oxidant, CHP = cumene hydroperoxide, DCP = dicumyl peroxide

With optimal reaction conditions in hand, we first probed the generality of this dehydrogentative sp^3−sp^2 coupling reaction with respect to the monosubstituted substrate. As shown in Scheme 2, unfunctionalized substrate **1a** underwent the titled reaction efficiently (**2a**, 79% yield; 68% for gram-scale synthesis), while functionalized ones exhibited variant reactivities. For example, substrates bearing electron-donating groups (e.g., Me, Et, and OMe) on a pyridyl unit performed smoothly to deliver the desired products in good yields (**2b−f**, 61−72% yield), and no drastic change in efficiency was observed regarding the position of substituents (**2b−d**, 61−67% yield); in contrast, electron-withdrawing groups (e.g., Cl) at different positions gave reduced yields and showed marked differences in efficiency (**2g−i**, 24−62% yield). Surprisingly, substituents on the phenyl unit did not affect the efficiency of this process, furnishing the desired

Scheme 2. Substrate Scope[a]



[a]Reaction conditions: **1** (0.20 mmol), acetonitrile (5 mL), $FeCp_2$ (10 mol %), DCP (2.0 equiv), 20 h, 100 °C, under argon. Isolated yields were given. [b]Reaction time: 30 h.

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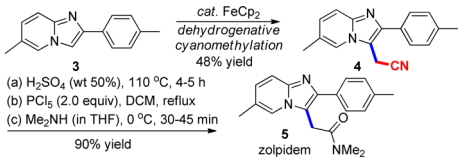
products in good yields in the presence of electron-donating (e.g., Me, ^{i}Pr and OMe; **2j**–**l**, 60–71% yield) or -withdrawing groups (e.g., Cl and Br; 67% for **2m** and 61% for **2n**). The steric limit of substituent was also investigated, and a detrimental effect on the coupling efficiency was observed when 2′-methylated substrate **1o** was used as the coupling partner (cf. **2j** and **2o**).

Subsequently, the polysubstituted reactants were examined under optimal reaction conditions, and it was found that an assortment of electron-donating and -withdrawing groups on the pyridyl or phenyl unit were viable for this transformation (**2p**–**r**, 43–66% yield). In addition, substituents on both units could also undergo the proposed reaction to give product **2s** in 38% yield.

Finally, several structurally distinct substrates containing pharmaceutically relevant heterocycles were evaluated to fully exemplify the power of this sp^3–sp^2 coupling paradigm. For example, 2-phenylimidazo[1,2-*a*]pyrimidine smoothly reacted to form the desired product in good yield (**2t**, 74% yield). Other substrates with different aromatic rings (e.g., naphthyl, pyridyl, and thienyl) were successfully cross-coupled to generate the desired products in moderate to good yields as well (**2u**–**w**, 43–69% yield). Moreover, the ester group was tolerated to provide an encouraging quantity of product **2x** (41% yield). Notably, 1-methyl-2-phenylindole, structually similar to 2-arylimidazo[1,2-*a*]pyridines, was a competent coupling partner in this protocol (**2y**, 52% yield). However, the use of phenylactonitrile, 3-phenylpropionitrile, propionitrile, butyronitrile, isobutyronitrile, and isovaleronitrile only yielded trace amounts of the target products currently.

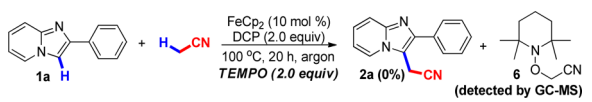
As summarized in Scheme 2, the tolerance of various functionalities highlights the potential for downstream modification of the cyanometylated products via transition-metal-catalyzed cross-coupling reactions or traditional functional group transformations. To further demonstrate the synthetic utility of this protocol, we applied it to the synthesis of the sedative-hypnotic zolpidem: substrate **3** was exposed to the optimized reaction conditions to formally afford product **4** (48% yield), which after acidic hydrolysis, was transformed into the corresponding acid chloride that upon reaction with dimethylamine produced zolpidem **5**[29] in 90% yield over the final three steps (Scheme 3).

Scheme 3. Application of the Dehydrogenative sp^3–sp^2 Coupling Strategy to the Synthesis of Zolpidem



During investigation of the mechanism for this reaction, a single-electron-transfer process is a favorable consideration. Therefore, a radical scavenger, TEMPO, was introduced into the standard reaction conditions: 2.0 equiv of TEMPO results in no conversion of **1a**; however, acetonitrile was transferred into compound **6** (detected by GC–MS) by TEMPO (Scheme 4).

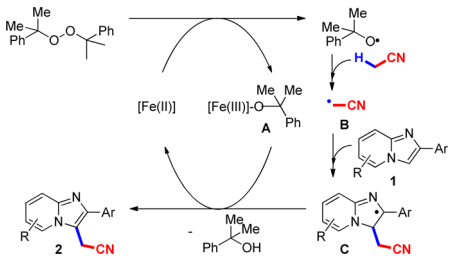
Scheme 4. Investigation into the Reaction Mechanism



The results imply that the cyanomethyl radical might be a key intermediate in this transformation. Furthermore, no desired product **2a** was observed in the absence of DCP (Table 1, entry 21), thus demonstrating that the cyanomethyl radical might be formed upon reaction of acetonitrile with DCP (or cumyloxyl radical from DCP).

On the basis of the above results, a tentative mechanism for this dehydrogenative sp^2 C–H cyanomethylation reaction is proposed in Scheme 5. Initiation occurs by reducing DCP with

Scheme 5. Plausible Mechanism



$FeCp_2$ to generate Fe(III) complex **A** and the cumyloxyl radical, which then abstracts a hydrogen atom from acetonitrile to putatively afford the cyanomethyl radical **B**. The ensuing radical **B** could be well-suited to add to 2-arylimidazo[1,2-*a*]pyridine **1** to give radical **C**, which is believed to undergo direct oxidation by **A** and deprotonation to release the final product **2**. Meanwhile, the Fe(II) complex was regenerated to continue the catalytic cycle.

In summary, we have established a dehydrogenative sp^3–sp^2 coupling between acetonitrile and 2-arylimidazo[1,2-*a*]-pyridines, which serves as a novel approach toward hetero-arylacetonitriles via direct oxidative C–H activation of acetonitrile with Fe catalysis. The power of this sp^3–sp^2 coupling paradigm has been fully exemplified by the breadth of functional groups tolerated in the transformation and the numerous opportunities provided by the cyanomethylation products for further derivatization and fast access to pharmaceuticals. We believe that the aforementioned features associated with this protocol will find broad application among practitioners of synthetic and pharmaceutical chemistry. Further utility of this protocol to realize sequential oxidative C–H activations of acetonitrile fragment to construct fused heterocycles is currently underway 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.7b00678.

Detailed experimental procedures, characterization data and copies of ^{1}H and ^{13}C NMR spectra for the products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: raohonghua@tsinghua.org.cn.
*E-mail: xuhao@henu.edu.cn.

ORCID

Honghua Rao: 0000-0003-1609-5692

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Author Contributions

[‖]H.S. and L.W. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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