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Direct Approaches to Nitriles via Highly Efficient Nitrogenation Strategy through C−H or C−C Bond Cleavage

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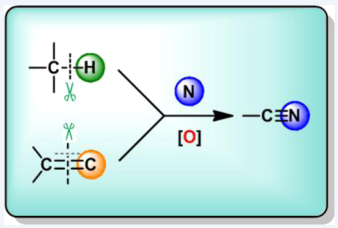
CONSPECTUS: Because of the importance of nitrogen-containing compounds in chemistry and biology, organic chemists have long focused on the development of novel methodologies for their synthesis. For example, nitrogen-containing compounds show up within functional materials, as top-selling drugs, and as bioactive molecules. To synthesize these compounds in a green and sustainable way, researchers have focused on the direct functionalization of hydrocarbons via C−H or C−C bond cleavage. Although researchers have made significant progress in the direct functionalization of simple hydrocarbons, direct C−N bond formation via C−H or C−C bond cleavage remains challenging, in part because of the unstable character of some N-nucleophiles under oxidative conditions.



The nitriles are versatile building blocks and precursors in organic synthesis. Recently, chemists have achieved the direct C−H cyanation with toxic cyanide salts in the presence of stoichiometric metal oxidants. In this Account, we describe recent progress made by our group in nitrile synthesis. C−H or C−C bond cleavage is a key process in our strategy, and azides or DMF serve as the nitrogen source. In these reactions, we successfully realized direct nitrile synthesis using a variety of hydrocarbon groups as nitrile precursors, including methyl, alkenyl, and alkynyl groups. We could carry out C_{sp^3}−H functionalization on benzylic, allylic, and propargylic C−H bonds to produce diverse valuable synthetic nitriles. Mild oxidation of C═C double-bonds and C≡C triple-bonds also produced nitriles.

The incorporation of nitrogen within the carbon skeleton typically involved the participation of azide reagents. Although some mechanistic details remain unclear, studies of these nitrogenation reactions implicate the involvement of a cation or radical intermediate, and an oxidative rearrangement of azide intermediate produced the nitrile. We also explored environmentally friendly oxidants, such as molecular oxygen, to make our synthetic strategy more attractive. Our direct nitrile synthesis methodologies have potential applications in the synthesis of biologically active molecules and drug candidates.

INTRODUCTION

Nitrogen-containing compounds occupy a significant position in living matter, dyes, and medicines.[1] Therefore, the preparation of N-containing compounds has always been an important topic in organic synthesis. In general, the methods for C−N bond formation include substitution reactions (both nucleophilic and electrophilic amination), cross coupling, cycloaddition, condensation, and rearrangement reactions.[2] Among them, the development of catalytic cross coupling reactions provides efficient approaches to N-containing compounds. In the past decade, some direct C−H aminations and amidations have been significantly developed.[3] Despite the significance, improvement is still needed in the C−N bond formation through C−H or C−C bond cleavage. For example, the functionalization of a specific C−H bond in simple substrates requires highly regioselective catalytic systems.[3] Meanwhile, C−N bond formation through simple C═C double bond and C≡C triple bond cleavage is still rarely reported.[4]

Nitriles are versatile building blocks and precursors in organic synthesis.[5] The cyano group itself is ubiquitous in useful medicines and functional materials. Traditional methodologies for the preparation of nitrile compounds include Sandmeyer and transition-metal mediated cyanation reactions,[6] transformations from amines, alcohols,[7] amides, or oximes,[8] and direct cyanations through C−H bonds.[9] However, cyanide salts and stoichiometric metal oxidants are usually employed, some of which cause unpleasant conditions and operations.

To build nitriles in high efficiency, we had tried to develop the direct approach from some readily available hydrocarbons through C−H/C−C bond cleavage by using nonmetal oxidants and simple nitrogen sources. Recently, on the basis of our copper catalyzed direct transformation of methyl arenes to aryl nitriles under mild conditions, we have developed some novel approaches to aromatic, alkenyl, and propargylic nitriles, via C_{sp^3}−H functionalization. Furthermore, unactivated olefins and alkynes are successfully converted into nitriles through C−C bond cleavage. In addition, we found that DMF can be employed as a cyano source for direct C−H cyanation reactions.

DIRECT TRANSFORMATION OF METHYL ARENES TO ARYL NITRILES

We were inspired by the reported direct ammoxidation of methyl arenes,[10a] although it required very harsh conditions and had low selectivity and limited substrate scope. We hypothesized that the direct C−H functionalization may execute under mild conditions employing a radical process due to the high activity of a radical

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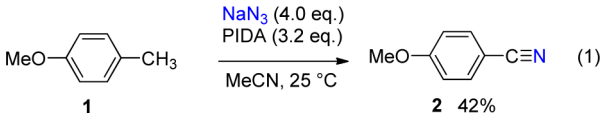
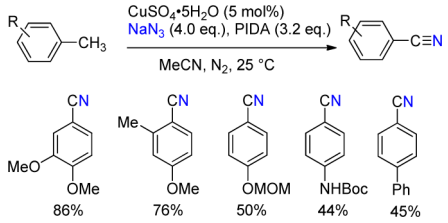
intermediate. This project was initially investigated by using the electron-rich *para*-methylanisole (**1**) as the substrate in the presence of sodium azide as the nitrogenation reagent (eq 1).[10b]



Many oxidants were screened to oxidize sodium azide for the initial generation of an azide radical to trigger the designed nitrogenation transformation. To our delight, when phenyliodonium diacetate (PIDA) was employed as an oxidant, three benzylic C−H bonds were broken to give aryl nitriles in moderate yield even at room temperature. The efficiency of this transformation can be promoted by catalytic amounts of copper salts such as $CuSO_4{\cdot}5H_2O$.

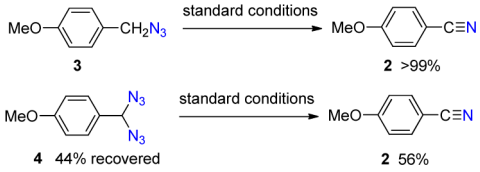
Various *para*-heteroatom-substituted toluenes with electron-donating groups were well tolerated (Scheme 1). The requirement of a heteroatom substituent at the *para*-position provides a possibility for the regioselectivity control. For example, the *meta* methyl group is untouched in the reaction of 4-methoxy-1,2-dimethylbenzene (76%, Scheme 1). Some hydroxyl protecting groups are easily removable, providing the possibility of further functional group transformations. There are still some drawbacks in the above-mentioned method: (1) the substrate scope is limited; *p*-heteroatom-substituent on the aromatic ring of methyl arenes is required; (2) excess amounts of azides and oxidants were loaded in this transformation.

Scheme 1. Direct Transformation of Methyl Arenes to Aryl Nitriles

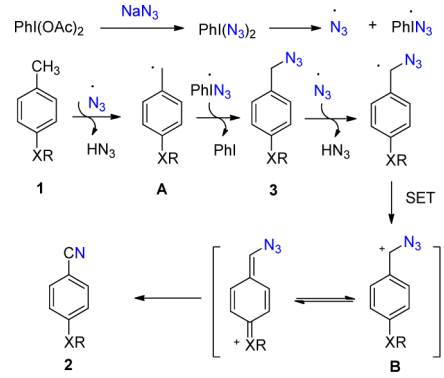


To get in-depth mechanistic insight in this reaction, control experiments with possible intermediates were investigated (Scheme 2).[10b] Since 4-methoxybenzonitrile (**2**) cannot be obtained in the absence of PIDA or NaN_3, the azide radical was involved in this transformation. Benzylic azide (**3**) was converted into **2** quantitatively, whereas **4** gave the product in 56% yield with 44% recovered starting material. These results indicate that **3** was more likely the key intermediate involved. When **1** was reacted under molecular oxygen, 4-methoxybenzaldehyde was obtained in 16% yield, indicating that the formation of aryl nitriles may proceed through a benzylic radical, **A**, which can be trapped by molecular oxygen.[11] The radical is oxidized to give the benzylic cation through single electron transfer (SET). Finally, the cation **B** undergoes a Schmidt type rearrangement to afford the product.[12] The cation could be stabilized by the α-N_3 group and *para*-substituent on the aromatic ring (Scheme 3). Most recently, Wang and co-workers reported a direct transformation of methyl arenes into aromatic nitriles using *tert*-butyl nitrite as the nitrogen source and oxidant.[13]

Scheme 2. Control Experiments



Scheme 3. Proposed Mechanism



This direct transformation of methyl arenes to aryl nitriles provides potential applications in organic synthesis. For instance, disoxaril tetrazole analogue **7** has broad spectrum antipicornavirus activity and was reported to be prepared from an expensive starting material, 4-hydroxy-3,5-dimethylbenzonitrile.[14] Regarding methyl group as a precursor of nitrile, the aryl nitrile intermediate **6** was prepared from the functionalized methyl arene **5** in high regioselectivity controlled by the heteroatom substituent at the *para*-position of the methyl group. By using this method as the key step, **7** was obtained in a 10% overall yield for six steps from inexpensive starting materials (Scheme 4).

DIRECT TRANSFORMATION OF METHYL IMINES TO α-IMINONITRILES

α-Iminonitriles are versatile precursors for many compounds such as α-ketoacids, amides, *N*-alkylketene-imines, cyanoenamides, and amidines.[15] According to the reported cases, there are still inadequacies in substrate scope, manipulation, and reagents in the preparation procedures. Inspired by our previous work, methyl imines were intended to build these kinds of nitriles through the direct C_{sp^3}−H functionalizaion strategy. Therefore, the reaction of readily available imines **8** was investigated under similar conditions by using PIDA as the oxidant.[16] This proposed nitrogenation was successfully achieved by using $TMSN_3$ as the nitrogen source (Scheme 5). The reaction showed good tolerance of different substituent groups under the optimized conditions as shown in Scheme 5. Notably, although the specific role of sodium bromide is not clear yet, it is effective to improve the yields of the desired α-iminonitriles **9**.

This transition-metal-free reaction was carried out under air at room temperature. The direct transformation of methyl imines in a one-pot fashion shows potential application value in organic synthesis (eq 2). Notably, N-heterocyclic compound **10** also performed well to give **11**, which is difficult to obtain in traditional manners (eq 3).

EFFICIENT TRANSFORMATION FROM BENZYL OR ALLYL HALIDES OR ESTERS TO ARYL OR ALKENYL NITRILES

As previously mentioned, benzylic azide has been proven to be the key intermediate to afford aryl nitrile. We therefore

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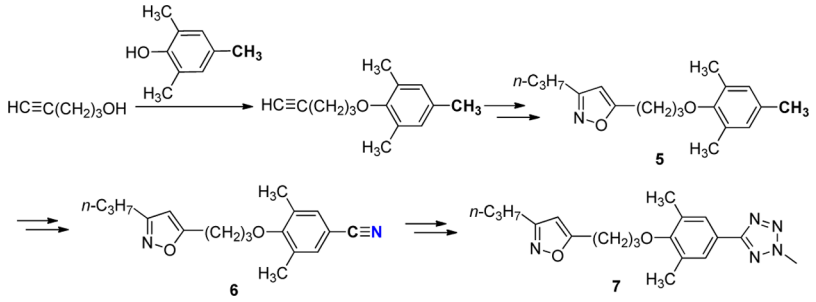
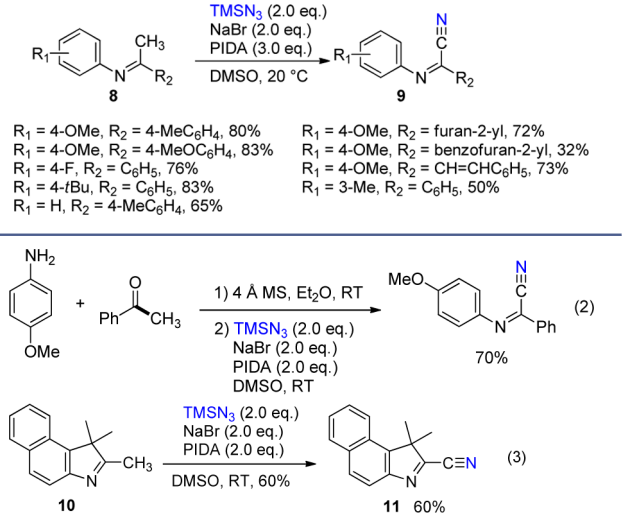
Scheme 4. Synthesis of a Tetrazole Analogue Related to Disoxaril



Scheme 5. Transformation of Methyl Imines to α-Iminonitriles



envisioned that a tandem substitution reaction of allyl and benzyl halides (**12** and **14**) to generate allyl and benzyl azides *in situ* and the subsequent oxidative rearrangement process should be possible to prepare the corresponding aryl and alkenyl nitriles (**13** and **15**).[17,18]

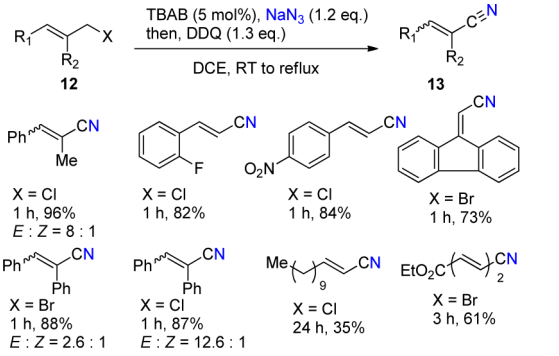
The reactions proceeded well with a wide range of allyl chlorides and bromides to give the corresponding alkenyl nitriles in moderate to excellent yields (Scheme 6). Even alkyl-substituted allyl chlorides can give the product but in a little lower yield. In the runs of trisubstituted alkenyl substrates, *E*-isomers were isolated as major products. The reactions of benzyl halides were also highly functional group tolerant. In addition, a methylthio group is also compatible in the reaction without further oxidation (Scheme 7).

Furthermore, allyl acetates **16** have been employed for the synthesis of alkenyl nitriles. A tandem Pd-catalyzed Tsuji–Trost reaction for the formation of *allyl azides in situ* and the subsequent oxidative process are involved in this transformation.[19] After the Tsuji–Trost reaction step, a catalytic amount of sulfur was employed to poison the Pd-catalyst. Then the generated allyl azides are further oxidized by DDQ to form the nitrile products **17** (Scheme 8).

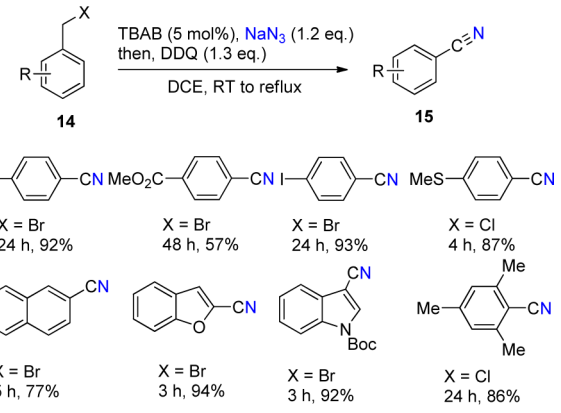
DIRECT OXIDATIVE TRANSFORMATION OF ALLYLARENES OR ALKENES TO ALKENYL NITRILES

Alkenyl nitriles are building blocks widely used in the synthesis of pharmaceuticals, agrochemicals, and natural products.[20] Although fascinating examples of allylic amination by palladium catalysis have been disclosed,[21] the direct transformation of allyl

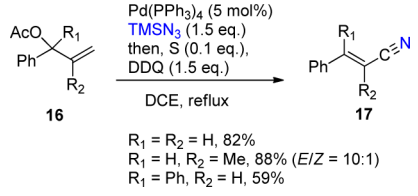
Scheme 6. Transformation from Allyl Halides to Alkenyl Nitriles



Scheme 7. Transformation from Benzyl Halides to Aryl Nitriles



Scheme 8. Efficient Approach to Alkenyl Nitriles from Allyl Esters



arenes via C_{sp^3}–H activation remains attractive.[22] The designed tandem C–H azidation and oxidative arrangement of allyl arenes was therefore investigated. When DDQ was employed as the oxidant, 1-allylbenzene **18** gave the desired product (*E*)-3-phenyl-2-propenenitrile **19** in 19% yield (eq 4).[23] In recent years, iron salts have emerged as efficient catalysts in C–heteroatom bond formation through C_{sp^3}–H functionalization.[24] It was exciting

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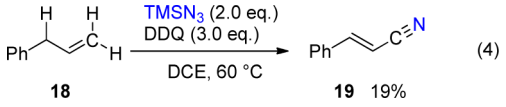
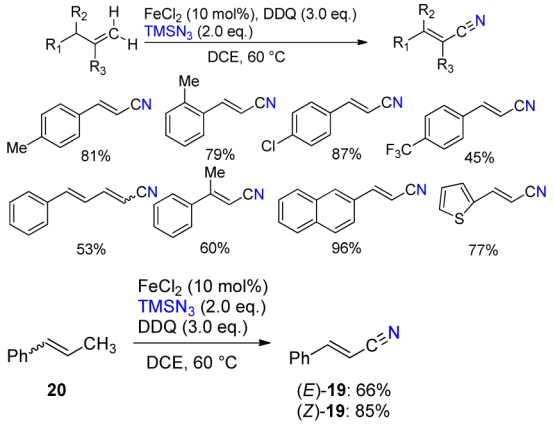


(4)

that the desired product was isolated in 95% yield using $FeCl_2$ as the catalyst.

Various allyl substrates were investigated under the iron catalytic oxidative conditions (Scheme 9). The allylarenes

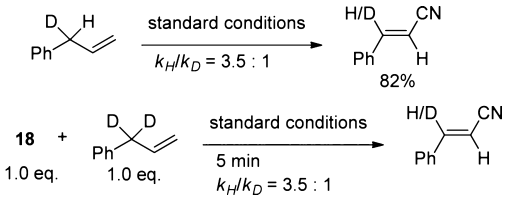
Scheme 9. Transformation of Allylarenes or Alkenes to Alkenyl Nitriles



bearing different substituents were compatible in this transformation. Notably, 3,3- and 2,3-disubstituted propenes gave the corresponding trisubstituted alkenyl nitriles in moderate yields with high stereoselectivity. The reactions of 3-allylarenes made our protocol noteworthy. Both (*E*)- and (*Z*)-propenylbenzene **20** can provide **19** in high stereoselectivity, indicating that a π-allyl species may be involved in the reaction. Unfortunately, when the simple aliphatic (*E*)-deca-1,4,9-triene was employed as the substrate, no desired nitrile product was obtained.

The mechanism studies indicate that the activation of the allyl C_{sp^3}–H bond should be the rate-determining step (Scheme 10).

Scheme 10. Mechanism Studies

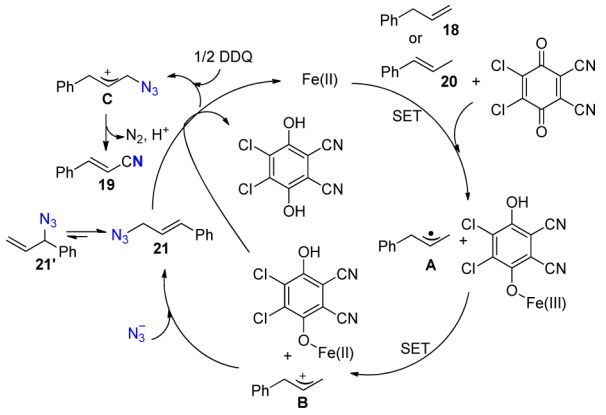


Both intra- and intermolecular kinetic isotopic effects were evident (k_H/k_D = 3.5 and 4.6, respectively). In addition, no azide substitution product was observed by reducing the amount of DDQ.

A SET oxidation mechanism is proposed for this reaction (Scheme 11). Initially, allyl arene **18** or **20** undergoes successive iron-assisted single-electron oxidation to produce the corresponding allyl cation **B**. Subsequently, **B** experienced nucleophilic attack to give allyl azides **21** and **21′**, which would exist as an equilibrating mixture by [3,3]-sigmatropic rearrangement.[25] Azide **21** is further oxidized to generate allyl azide cation **C**, which undergoes Schmidt-type rearrangement to afford the desired nitrile **19**.

The allyl cation intermediate is also involved in other nitrogenation reactions developed by us (Scheme 12).[26] The cation

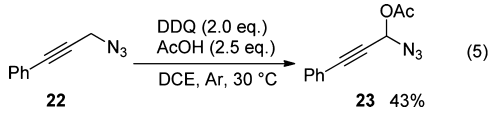
Scheme 11. Proposed Mechanism



would be attacked by azide to form allylic azide cation **A** under oxidative conditions. Then the aryl migration to the proximal nitrogen with the extrusion of nitrogen gas could generate intermediate **B**.[12] It is demonstrated that **B** is an active species to be trapped by diverse nucleophiles. For instance, tetrazoles would be formed by the nucleophilic addition and cyclization of excess azides, while acrylamides were produced in the presence of water.

OXIDATIVE TRANSFORMATION OF ARYL PROPARGYLIC AZIDES TO ARYL PROPIOLONITRILES

After achieving the goal by direct allylic C_{sp^3}–H functionalization, we began to concentrate on propargylic C_{sp^3}–H activation. Although aryl propiolonitriles are useful building blocks to many chemical and biological active molecules,[27] limited cases were reported to synthesize them from simple starting materials under mild conditions.[28] We envisioned that propargylic azide **22** may be the proper substrate for the transformation. However, an unexpected C–O coupling product **23** was observed when acetic acid was employed as an additive (eq 5).[29]



(5)

During the optimization, no desired aryl propiolonitrile **24** was detected in most cases except in the presence of DDQ. However, the product may be consumed due to the potential [2 + 2] cycloadditions with DDQ.[30] Finally, $(CuOTf)_2$·PhMe is found to be essential to the desired reaction when tert-butyl hydroperoxide (TBHP),[31] which has been widely used in metal catalyzed dehydrogenative couplings, is employed as the oxidant (Scheme 13).[32] Various aryl propargylic azides can produce **24** in moderate to good yields, whereas aliphatic substrates did not work under these conditions.

A single electron transfer (SET) mechanism is proposed in this transformation (Scheme 14). Two types of possible intermediates are likely generated through this Cu/TBHP catalytic system, both of which can be converted into propargylic azide cations. Finally, a Schmidt-type rearrangement gives the desired products.

DIRECT TRANSFORMATION OF OLEFINS TO OXO-NITRILES VIA C=C DOUBLE-BOND CLEAVAGE

The C=C double bond is among the valuable bonds broadly existing in pharmaceuticals, functional materials, and natural

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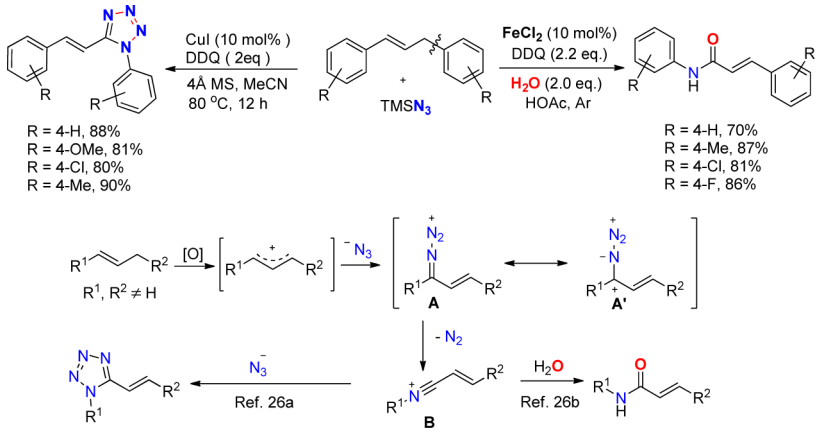
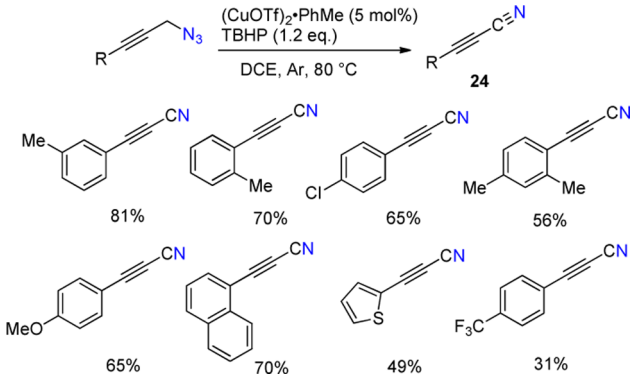
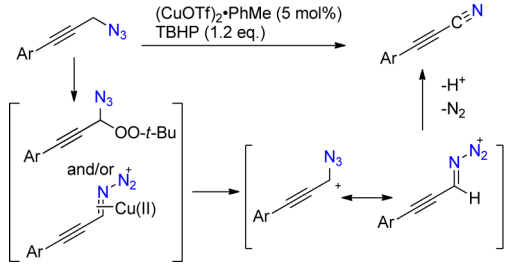
Scheme 12. Direct Approaches to Tetrazoles and Acrylamides via Allyl Cations



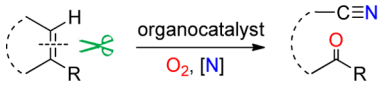
Scheme 13. Transformation of Aryl Propargylic Azides to Aryl Propiolonitriles



Scheme 14. Proposed Mechanism



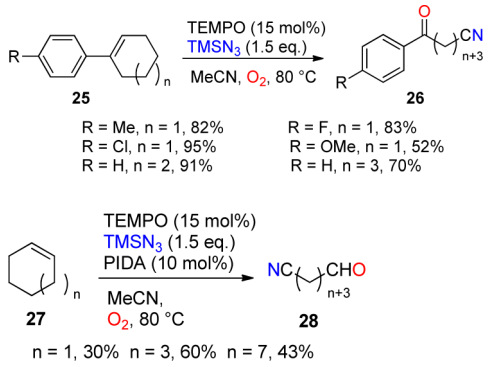
products. The functionalization of the C═C double bond is intriguing in synthetic methodology.[33] After developing some approaches to N-containing compounds through an oxidative nitrogenation strategy, we envisioned that C═C double bond nitrogenation could be realized by an azide mediated radical process (eq 6). Although transition-metal catalyzed C═C



double-bond functionalization has been highly developed in recent decades,[34] we proposed organocatalysis as an alternative solution by its own merits.[35] Molecular oxygen has been considered as an ideal terminal oxidant,[36] as well as the potential O source. Inspired by the *N*-hydroxyphthalimide (NHPI) catalyzed oxygenation reaction of olefins,[37a] many catalysts such as NHPI, azodiisobutyronitrile (AIBN), and benzoyl peroxide (BPO) have been screened to realize the C═C double bond nitrogenation. Interestingly, when $TMSN_3$ was employed as the nitrogen source, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) was identified as an efficient catalyst to the internal alkenes for the synthesis of oxo-nitriles through C═C double bond cleavage.[37b]

Various terminal and disubstituted alkenes were subsequently investigated (Scheme 15). The reaction proceeds well with

Scheme 15. Direct Transformation of Olefins to Oxo-nitriles



benzylic alkenes **25**. To enhance the efficiency of the reaction with aliphatic olefins **27**, a series of additives were investigated. The oxo-nitrile products could be obtained in moderate yield in the presence of PIDA, although its role was not clear yet.[38]

The synthesis of many multipurpose oxo-nitriles underscores the utility of this direct transformation of olefins. For example, (*S*)-ketamine **29**, an anesthetic and analgesic medicine, was prepared from oxo-nitrile **30** in many steps.[39] Our strategy gave a concise route to this compound in 86% yield (Scheme 16).

Preliminary mechanistic studies have been investigated (Scheme 17). TEMPO is the essential catalyst in this transformation (Scheme 17). The result of an ^{18}O labeling experiment shows molecular oxygen as the oxygen source of the product (Scheme 17). Furthermore, α-azido ketone was reacted in the control experiments, but no oxo-nitrile was obtained. In addition, β-hydroxy azides did not work under the standard conditions (Scheme 17).[40] These results indicate that both α-azido ketone and β-hydroxy azides are not involved in this transformation.

A radical pathway is proposed (Scheme 18). Initially, $TMSN_3$ generates azido free radical associated with the formation of intermediate **A**, which is detected by GC-MS. The azido free

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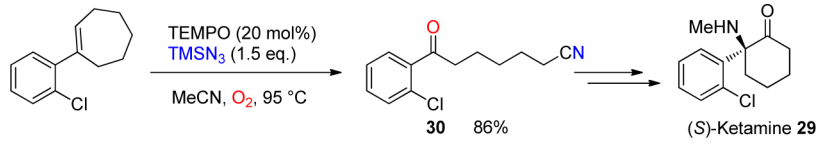
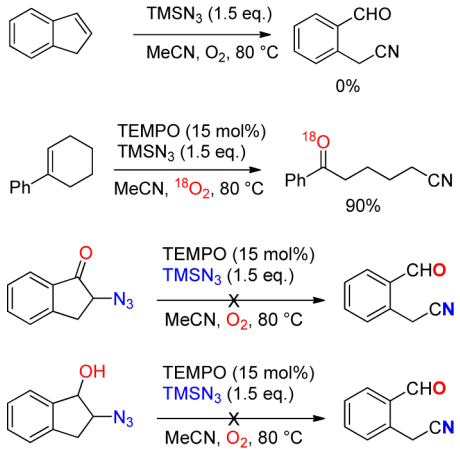
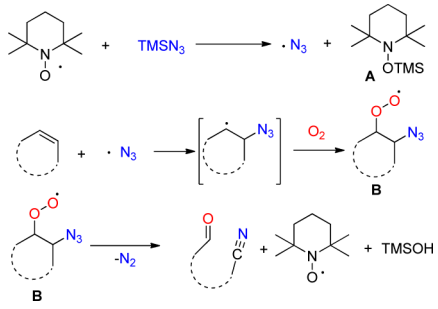
Scheme 16. Synthesis of Key Intermediate of Ketamine



Scheme 17. Mechanistic Studies



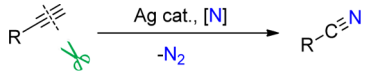
Scheme 18. Proposed Mechanism



radical subsequently attacks the alkene and terminates with molecular oxygen to form peroxide radical **B**. Subsequently, intermediate **B** undergoes a continuous rearrangement with the release of dinitrogen gas, C−C bond cleavage, and heterolysis of the O−O bond to give the product oxo-nitrile. An in-depth study for understanding of the details about the rearrangement is still required.

DIRECT APPROACH TO NITRILES THROUGH C≡C BOND CLEAVAGE

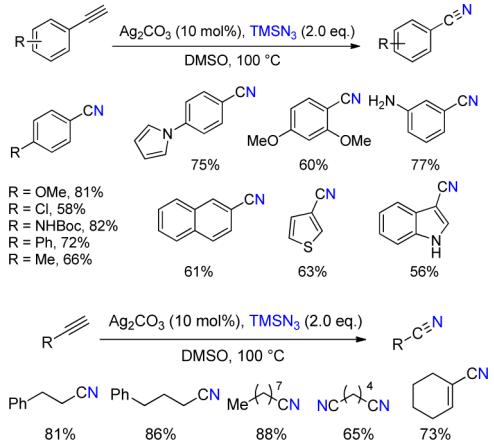
The transition-metal catalyzed cleavage of C≡C bond has been practiced, but the exploration of alkyne transformations still remains to be extended.[41] In this scenario, transition-metal catalytic nitrogenation of acetylenes to nitriles was investigated. A preactivation strategy by a hydroazidation process to introduce an azido group into alkynes was designed. Varying from traditional π-acid catalysis, the silver catalyst is essential to this transformation (eq 7). When $TMSN_3$ was screened to serve as



(7)

nitrogen donor, benzonitrile was obtained in moderate yield.[42] Very recently, an approach to nitriles from internal alkynes was reported by Yanada and co-workers.[43]

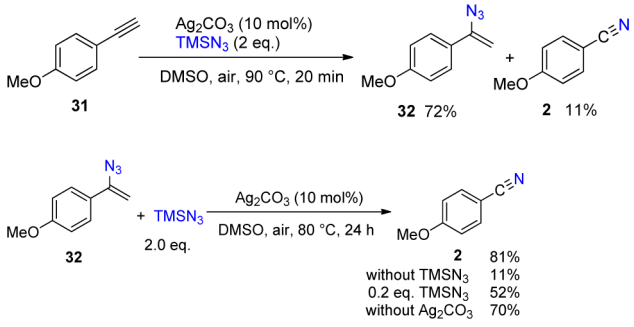
Scheme 19. Direct Approach to Nitriles from Terminal Alkynes



Various phenylacetylene derivatives were well tolerated in this transformation (Scheme 19). Electron-rich substrates gave the corresponding aromatic nitriles in good to excellent yields. Halogen atoms as well as unprotected amide groups on the aromatic rings are compatible to give the corresponding nitrile products. Heterocyclic and aliphatic alkynes also proceeded well in this transformation.

Vinyl azide **32** was identified as the key intermediate (Scheme 20). Notably, additional $TMSN_3$ is required when vinyl azide was

Scheme 20. Mechanistic Studies



employed in the reaction (Scheme 20). The control experiments exclude azirine and tetrazole as the intermediates. Internal alkynes can also generate vinyl azides, but nitriles cannot be obtained under these conditions.[44]

The reaction was monitored by ^1H NMR spectroscopy in DMSO-d_6 (Figure 1). The signal at 4.0 ppm (0−1.5 h) belonged to **31**. The vinyl azide **32**, weak signals of which emerged at 4.93 and 5.53 ppm after 10 min, reached a peak after 1.5 h. The nitrile product **2** was identified to appear after 10 min.

A possible mechanism is proposed (Scheme 21). The silver activated alkyne is initially attacked by azide anion to generate alkenyl metal complex **B**. Vinyl azide **C** may be formed from the protonation of **B** by trace water in the solvent. The subsequent

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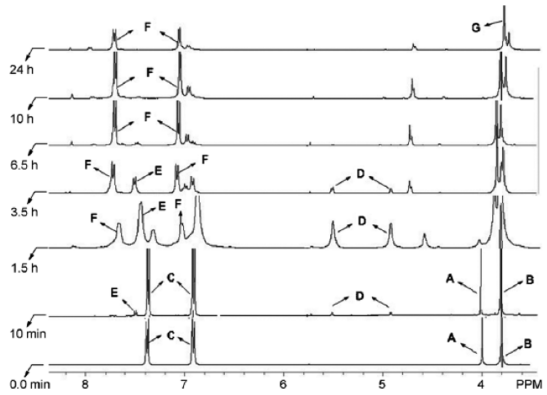
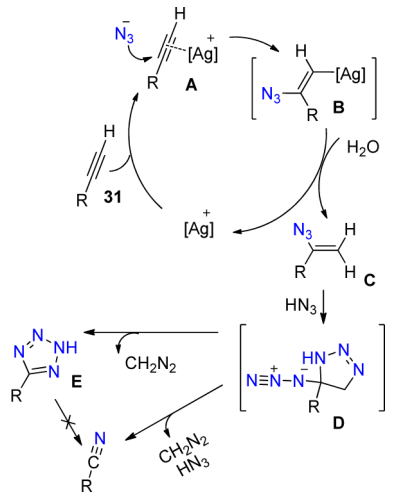


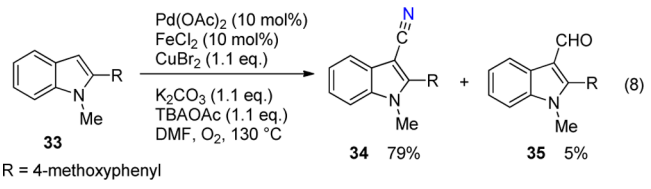
Figure 1. ^{1}H NMR spectroscopy monitoring reaction of **31** (400 MHz, DMSO-d_6). A = **31** alkynyl group, B = **31** methoxy group, C = **31** Ar−H, D = **32** alkenyl group, E = **32** Ar−H, F = **2** Ar−H, and G = **2** methoxy group.

Scheme 21. Proposed Mechanism



cyclization of vinyl azide **C** with azide affords the unstable intermediate **D**.[45] The control experiment excludes **E** as an intermediate under optimized conditions. Alternatively, a continuous rearrangement of **D** is concerned to produce **2** with the extrusion of HN_3 and CH_2N_2, which were detected by GC-MS. The HN_3 may be reused in the cyclization of **C**.

The exploration of CN sources is an ongoing issue in organic synthesis.[46] We have developed many direct transformations using azides as the nitrogen source. Despite the significance of azides and the traditional metal cyanide salts, many safe and readily available reagents as CN sources generated *in situ* have been developed in recent years.[47] These studies revealed that DMF and DMSO not only are polar solvents but also could be versatile synthetic precursors to give a number of functional units.[48] Recently, we developed direct C−H cyanation of indoles just by using DMF as the CN source (eq 8),[49] although the mechanism is still not completely clear.



CONCLUSION

Through these developed nitrogenation processes of simple hydrocarbons, various common groups, such as methyl, alkenyl, and alkynyl groups, could be considered as the precursors of nitriles. Direct C_{sp^3}−H functionalization, including benzylic, allylic, and propargylic C−H bonds, has been realized to produce diverse synthetically valuable nitriles. The C═C double-bond and C≡C triple-bond also proceeded well under mild oxidative conditions for the synthesis nitriles. The incorporation of nitrogen was usually accomplished by the participation of azide reagents. The mechanistic studies of these transformations revealed that, although some details are still unclear, a cation or radical intermediate is involved in these nitrogenation reactions. In most cases, an oxidative rearrangement of an azide intermediate is involved to give nitriles. To get practical insight into these reactions, environmentally friendly reagents, such as molecular oxygen, were investigated to make our strategy more attractive. Versatile building blocks such as DMF have emerged as "CN" sources in the research. Ultimately, the exploration of efficient, readily available, and safe nitrogenation reagents are always favorable.

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Notes

The authors declare no competing financial interest.

Biographies

Teng Wang was born in 1984 in Beijing, China. He received his Ph.D. degree (2013) from Tianjin University with Prof. Jun-An Ma. Since 2010, he has been an exchange student in Prof. Ning Jiao's group in State Key Laboratory of Natural and Biomimetic Drugs, Peking University. His research interests include developing nitrogenation strategies via inert bond activations.

Ning Jiao received his Ph.D. degree (2004 with Prof. Shengming Ma) at Shanghai Institute of Organic Chemistry, CAS. He spent 2004−2006 as an Alexander von Humboldt postdoctoral fellow with Prof. Manfred T. Reetz at Max Planck Institute für Kohlenforschung. In 2007, he joined the faculty at Peking University as an Associate Professor and was promoted to Full Professor in 2010. His current research efforts are focused on (1) development of green and efficient synthetic methodologies through single electron transfer (SET) process, (2) aerobic oxidation, oxygenation, and nitrogenation reactions, and (3) the activation of inert chemical bonds.

REFERENCES

(1) (a) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances: Synthesis, Patents, Applications*, 4th ed.; Thieme: Stuttgart, Germany, 2001.

(2) (a) Hartwig, J. F. Transition Metal Catalyzed Synthesis of Arylamines and Aryl Ethers from Aryl Halides and Triflates: Scope and Mechanism. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067. (b) Hein, J. E.; Fokin, V. V. Copper-Catalyzed Azide−Alkyne Cycloaddition (CuAAC) and Beyond: New Reactivity of Copper(I) Acetylides. *Chem. Soc. Rev.*

2010, *39*, 1302−1315. (c) Lipkowitz, K. B.; Scarpone, S.; McCullough, D.; Barney, C. The Synthesis of N-Substituted Tetrahydropyridines Using the Hetero-Cope Rearrangement. *Tetrahedron Lett.* **1979**, 2241−2244.

(3) (a) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. Recent Advances in the Transition Metal-Catalyzed Twofold Oxidative C−H Bond Activation Strategy for C−C and C−N Bond Formation. *Chem. Soc. Rev.* **2011**, *40*, 5068−5083. (b) *Handbook of C−H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, Germany, 2005. (c) *C−H Activation*; Yu, J.-Q., Shi, Z., Eds.; Topics in Current Chemistry, Vol. *292*; Springer-Verlag: Berlin, 2010.

(4) (a) Grubbs, R. H.; Chang, S. Recent Advances in Olefin Metathesis and Its Application in Organic Synthesis. *Tetrahedron* **1998**, *54*, 4413−4450. (b) Fürstner, A.; Davies, P. W. Alkyne Metathesis. *Chem. Commun.* **2005**, 2307−2320.

(5) (a) Fatiadi, A. J. In *Preparation and Synthetic Applications of Cyano Compounds*; Patai, S., Rappaport, Z., Ed.; Wiley: New York, 1983. (b) Miller, J. S.; Manson, J. L. Designer Magnets Containing Cyanides and Nitriles. *Acc. Chem. Res.* **2001**, *34*, 563−570. (c) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. Nitrile-Containing Pharmaceuticals: Efficacious Roles of the Nitrile Pharmacophore. *J. Med. Chem.* **2010**, *53*, 7902−7917.

(6) (a) Sandmeyer, T. Ueber die Ersetzung der Amidgruppe durch Chlor in den aromatischen Substanzen. *Eur. J. Inorg. Chem.* **1884**, *17*, 1633−1635. (b) Ellis, G. A.; Romney-Alexander, T. M. Cyanation of Aromatic Halides. *Chem. Rev.* **1987**, *87*, 779−794.

(7) (a) Oishi, T.; Yamaguchi, K.; Mizuno, N. Catalytic Oxidative Synthesis of Nitriles Directly from Primary Alcohols and Ammonia. *Angew. Chem., Int. Ed.* **2009**, *48*, 6286−6288. (b) Chen, F.-E.; Kuang, Y.-Y.; Dai, H.-F.; Lu, L.; Huo, M. A Selective and Mild Oxidation of Primary Amines to Nitriles with Trichloroisocyanuric Acid. *Synthesis* **2003**, *17*, 2629−2631.

(8) (a) Yang, S. H.; Chang, S. Highly Efficient and Catalytic Conversion of Aldoximes to Nitriles. *Org. Lett.* **2001**, *3*, 4201−4211. (b) Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. A General and Convenient Catalytic Synthesis of Nitriles from Amides and Silanes. *Org. Lett.* **2009**, *11*, 2461−2464. (c) Yamaguchi, K.; Fujiwara, H.; Ogasawara, Y.; Kotani, M.; Mizuno, N. A Tungsten−Tin Mixed Hydroxide as an Efficient Heterogeneous Catalyst for Dehydration of Aldoximes to Nitriles. *Angew. Chem., Int. Ed.* **2007**, *46*, 3922−3925.

(9) (a) Mariampillai, B.; Alliot, J.; Li, M.; Lautens, M. A Convergent Synthesis of Polysubstituted Aromatic Nitriles via Palladium-Catalyzed C−H Functionalization. *J. Am. Chem. Soc.* **2007**, *129*, 15372−15379. (b) Yan, G.; Kuang, C.; Zhang, Y.; Wang, J. Palladium-Catalyzed Direct Cyanation of Indoles with $K_4[Fe(CN)_6]$. *Org. Lett.* **2010**, *12*, 1052−1055. (c) Jia, X.; Yang, D.; Zhang, S.; Cheng, J. Chelation-Assisted Palladium-Catalyzed Direct Cyanation of 2-Arylpyridine C−H Bonds. *Org. Lett.* **2009**, *11*, 4716−4719.

(10) (a) Lücke, B.; Narayana, K. V.; Martin, A.; Jähnisch, K. Oxidation and Ammoxidation of Aromatics. *Adv. Synth. Catal.* **2004**, *346*, 1407−1424. (b) Zhou, W.; Zhang, L.; Jiao, N. Direct Transformation of Methyl Arenes to Aryl Nitriles at Room Temperature. *Angew. Chem., Int. Ed.* **2009**, *48*, 7094−7097.

(11) Mendenhall, G. D.; Steng, X. C.; Wilson, T. Yields of Excited Carbonyl Species from Alkoxyl and from Alkylperoxyl Radical Dismutations. *J. Am. Chem. Soc.* **1991**, *113*, 8976−8977.

(12) (a) Schmidt, K. F. Über den Imin-Rest. *Eur. J. Inorg. Chem.* **1924**, *57*, 704−706. (b) Wolff, H. Schmidt Reaction. *Org. React.* **1946**, 307−336.

(13) Shu, Z.; Ye, Y.; Deng, Y.; Zhang, Y.; Wang, J. Palladium(II)-Catalyzed Direct Conversion of Methyl Arenes into Aromatic Nitriles. *Angew. Chem., Int. Ed.* **2013**, *52*, 10573−10576.

(14) Diana, G. D.; Cutcliffe, D.; Volkots, D. L.; Mallamo, J. P.; Bailey, T. R.; Vescio, N.; Oglesby, R. C.; Nitz, T. J.; Wetzel, J.; Giranda, V.; Pevear, D. C.; Dutko, F. J. Antipicornavirus Activity of Tetrazole Analogs Related to Disoxaril. *J. Med. Chem.* **1993**, *36*, 3240−3250.

(15) Roychowdhury, A.; Kumar, V. V.; Bhaduri, A. P. Diarylimidoylcyanides, an Attractive Class of Intermediate: Novel Synthesis of α-Anilino-β-Nitroenamines, *N*, *N*′-Disubstituted Amidines and Substituted Phenyl Glyoxate. *Synth. Commun.* **2006**, *36*, 715−727.

(16) Chen, F.; Huang, X.; Cui, Y.; Jiao, N. Direct Transformation of Methyl Imines to α-Iminonitriles under Mild and Transition-Metal-Free Conditions. *Chem.—Eur. J.* **2013**, *19*, 11199−11202.

(17) Zhou, W.; Xu, J.; Zhang, L.; Jiao, N. An Efficient Transformation from Benzyl or Allyl Halides to Aryl and Alkenyl Nitriles. *Org. Lett.* **2010**, *12*, 2888−2891.

(18) Nitrile synthesis utilizing primary azide compounds: (a) Lamani, M.; Prabhu, K. R. An Efficient Oxidation of Primary Azides Catalyzed by Copper Iodide: A Convenient Method for the Synthesis of Nitriles. *Angew. Chem., Int. Ed.* **2010**, *49*, 6622−6625. (b) He, J.; Yamaguchi, K.; Mizuno, N. Aerobic Oxidative Transformation of Primary Azides to Nitriles by Ruthenium Hydroxide Catalyst. *J. Org. Chem.* **2011**, *76*, 4606−4610.

(19) Zhou, W.; Xu, J.; Zhang, L.; Jiao, N. An Efficient Approach to Alkenyl Nitriles from Allyl Esters. *Synlett* **2011**, *7*, 887−890.

(20) Fleming, F. F.; Wang, Q. Unsaturated Nitriles: Conjugate Additions of Carbon Nucleophiles to a Recalcitrant Class of Acceptors. *Chem. Rev.* **2003**, *103*, 2035−2078.

(21) (a) Reed, S. A.; White, M. C. Catalytic Intermolecular Linear Allylic C−H Amination via Heterobimetallic Catalysis. *J. Am. Chem. Soc.* **2008**, *130*, 3316−3318. (b) Liu, G.; Yin, G.; Wu, L. Palladium-Catalyzed Intermolecular Aerobic Oxidative Amination of Terminal Alkenes: Efficient Synthesis of Linear Allylamine Derivatives. *Angew. Chem., Int. Ed.* **2008**, *47*, 4733−4736.

(22) (a) Li, Z.; Li, C.-J. Catalytic Allylic Alkylation via the Cross-Dehydrogenative-Coupling Reaction between Allylic sp^3 C−H and Methylenic sp^3 C−H Bonds. *J. Am. Chem. Soc.* **2006**, *128*, 56−57. (b) Lin, S.; Song, C.-X.; Cai, G.-X.; Wang, W.-H.; Shi, Z.-J. Intra/Intermolecular Direct Allylic Alkylation via Pd(II)-Catalyzed Allylic C−H Activation. *J. Am. Chem. Soc.* **2008**, *130*, 12901−12903.

(23) Qin, C.; Jiao, N. Iron-Facilitated Direct Oxidative C−H Transformation of Allylarenes or Alkenes to Alkenyl Nitriles. *J. Am. Chem. Soc.* **2010**, *132*, 15893−15895.

(24) (a) Enthaler, S.; Junge, K.; Beller, M. Sustainable Metal Catalysis with Iron: From Rust to a Rising Star? *Angew. Chem., Int. Ed.* **2008**, *47*, 3317−3321. (b) Sun, C.; Li, B.; Shi, Z.-J. Direct C−H Transformation via Iron Catalysis. *Chem. Rev.* **2011**, *111*, 1293−1314.

(25) Gagneux, A.; Winstein, S.; Young, W. G. Rearrangement of Allylic Azides. *J. Am. Chem. Soc.* **1960**, *82*, 5956−5957.

(26) (a) Chen, F.; Qin, C.; Cui, Y.; Jiao, N. Implanting Nitrogen into Hydrocarbon Molecules through C−H and C−C Bond Cleavages: A Direct Approach to Tetrazoles. *Angew. Chem., Int. Ed.* **2011**, *50*, 11487−11491. (b) Qin, C.; Zhou, W.; Chen, F.; Ou, Y.; Jiao, N. Iron-Catalyzed C−H and C−C Bond Cleavage: A Direct Approach to Amides from Simple Hydrocarbons. *Angew. Chem., Int. Ed.* **2011**, *50*, 12595−12599.

(27) Cheng, Z.-Y.; Li, W.-J.; He, F.; Zhou, J.-M.; Zhu, X.-F. Synthesis and Biological Evaluation of 4-Aryl-5-cyano-2*H*-1,2,3-triazoles as Inhibitor of HER2 Tyrosine Kinase. *Bioorg. Med. Chem.* **2007**, *15*, 1533−1538.

(28) Beccalli, E. M.; Manfredi, A.; Marchesini, A. Alkynes from 5-Aminoisoxazoles. *J. Org. Chem.* **1985**, *50*, 2372−2375.

(29) Wang, T.; Zhou, W.; Yin, H.; Ma, J.-A.; Jiao, N. Iron-Facilitated Oxidative Dehydrogenative C−O Bond Formation by Propargylic Csp^3−H Functionalization. *Angew. Chem., Int. Ed.* **2012**, *51*, 10823−10826.

(30) Kato, S.-I.; Beels, M. T. R.; La Porta, P.; Schweizer, W. B.; Boudon, C.; Gisselbrecht, J.-P.; Biaggio, I.; Diederich, F. Homoconjugated Push−Pull and Spiro Systems: Intramolecular Charge-Transfer Interactions and Third-Order Optical Nonlinearities. *Angew. Chem., Int. Ed.* **2010**, *49*, 6207−6211.

(31) (a) Li, C.-J. Cross-Dehydrogenative Coupling (CDC): Exploring C−C Bond Formations beyond Functional Group Transformations. *Acc. Chem. Res.* **2009**, *42*, 335−344. (b) Yang, F.; Li, J.; Xie, J.; Huang, Z.-Z. Copper-Catalyzed Cross Dehydrogenative Coupling Reactions of Tertiary Amines with Ketones or Indoles. *Org. Lett.* **2010**, *12*, 5214−5217. (c) Boess, E.; Schmitz, C.; Klussmann, M. A Comparative Mechanistic Study of Cu-Catalyzed Oxidative Coupling Reactions with

N-Phenyltetrahydroisoquinoline. *J. Am. Chem. Soc.* **2012**, *134*, 5317−5325.
(32) Wang, T.; Yin, H.; Jiao, N. Copper-Catalyzed Oxidative Transformation of Aryl Propargylic Azides to Aryl Propiolonitriles. *Adv. Synth. Catal.* **2013**, *355*, 1207−1210.
(33) For reviews and selected examples: (a) Sharpless, K. B.; Finn, M. G. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1985; Vol. *5*, p 193. (b) Miyamoto, K.; Tada, N.; Ochiai, M. Activated Iodosylbenzene Monomer as an Ozone Equivalent: Oxidative Cleavage of Carbon−Carbon Double Bonds in the Presence of Water. *J. Am. Chem. Soc.* **2007**, *129*, 2772−2773. (c) Travis, B. R.; Narayan, R. S.; Borhan, B. J. Osmium Tetroxide-Promoted Catalytic Oxidative Cleavage of Olefins: An Organometallic Ozonolysis. *J. Am. Chem. Soc.* **2002**, *124*, 3824−3825. (d) Martínez, C.; Muñiz, K. Palladium-Catalyzed Vicinal Difunctionalization of Internal Alkenes: Diastereoselective Synthesis of Diamines. *Angew. Chem., Int. Ed.* **2012**, *51*, 7031−7034.
(34) Jun, C.-H. Transition Metal-Catalyzed Carbon−Carbon Bond Activation. *Chem. Soc. Rev.* **2004**, *33*, 610−618.
(35) Brazier, J. B.; Tomkinson, N. C. O. In *Asymmetric Organocatalysis ()*; List, B., Ed.; Topics in Current Chemistry; Springer-Verlag: Berlin, 2010; Vol. *291*, pp 281−347.
(36) (a) Stahl, S. S. Palladium Oxidase Catalysis: Selective Oxidation of Organic Chemicals by Direct Dioxygen-Coupled Turnover. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400−3420. (b) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. Recent Advances in Transition-metal Catalyzed Reactions Using Molecular Oxygen as the Oxidant. *Chem. Soc. Rev.* **2012**, *41*, 3381−3430.
(37) (a) Lin, R.; Jiao, N. Metal-Free, NHPI Catalyzed Oxidative Cleavage of C-C Double Bond Using Molecular Oxygen as Oxidant. *Org. Lett.* **2012**, *14*, 4158−4161. (b) Wang, T.; Jiao, N. TEMPO-Catalyzed Aerobic Oxygenation and Nitrogenation of Olefins via C═C Double-Bond Cleavage. *J. Am. Chem. Soc.* **2013**, *135*, 11692−11695.
(38) Magnus, P.; Lacour, J.; Evans, P. A.; Roe, M. B.; Hulme, C. Hypervalent Iodine Chemistry: New Oxidation Reactions Using the Iodosylbenzene-Trimethylsilyl Azide Reagent Combination. Direct α- and β-Azido Functionalization of Triisopropylsilyl Enol Ethers. *J. Am. Chem. Soc.* **1996**, *118*, 3406−3418.
(39) Yokoyama, R.; Matsumoto, S.; Nomura, S.; Higaki, T.; Yokoyama, T.; Kiyooka, S. Enantioselective Construction of Nitrogen-Substituted Quaternary Carbon Centers Adjacent to the Carbonyl Group in the Cyclohexane Ring: First Asymmetric Synthesis of Anesthetic (*S*)-Ketamine with High Selectivity. *Tetrahedron* **2009**, *65*, 5181−5191.
(40) Hernández, R.; León, E. I.; Moreno, P.; Suárez, E. Radical Fragmentation of β-Hydroxy Azides. Synthesis of Chiral Nitriles. *J. Org. Chem.* **1997**, *62*, 8974−8975.
(41) (a) Takaya, H.; Noyori, R. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991. (b) Haines, A. H. *Methods for the Oxidation of Organic Compounds. Alkanes, Alkenes, Alkynes, and Arenes*; Academic Press: New York, 1985.
(42) Shen, T.; Wang, T.; Qin, C.; Jiao, N. Silver-Catalyzed Nitrogenation of Alkynes: A Direct Approach to Nitriles through C≡C Bond Cleavage. *Angew. Chem., Int. Ed.* **2013**, *52*, 6677−6680.
(43) Okamoto, N.; Ishikura, M.; Yanada, R. Cleavage of Carbon−Carbon Triple Bond: Direct Transformation of Alkynes to Nitriles. *Org. Lett.* **2013**, *15*, 2571−2573.
(44) Qin, C.; Feng, P.; Ou, Y.; Shen, T.; Wang, T.; Jiao, N. Selective Csp^2−Csp Bond Cleavage: The Nitrogenation of Alkynes to Amides. *Angew. Chem., Int. Ed.* **2013**, *52*, 7850−7854.
(45) Kadaba, P. K. Triazolines XX. Vinyl Azides as Dipolarophiles in 1,3-Dipolar Cycloadditions: Intermolecular Cycloaddition of Hydrazoic Acid and α-Styryl Azide to Give a Tetrazole. *Synlett* **1990**, 349−351.
(46) (a) Grushin, V. V.; Alper, H. Transformations of Chloroarenes, Catalyzed by Transition-Metal Complexes. *Chem. Rev.* **1994**, *94*, 1047−1062. (b) Kim, J.; Kim, H. J.; Chang, S. Synthesis of Aromatic Nitriles Using Nonmetallic Cyano-Group Sources. *Angew. Chem., Int. Ed.* **2012**, *51*, 11948−11959.
(47) (a) Kim, J.; Chang, S. A New Combined Source of "CN" from *N*,*N*-Dimethylformamide and Ammonia in the Palladium-Catalyzed Cyanation of Aryl C−H Bonds. *J. Am. Chem. Soc.* **2010**, *132*, 10272−10274. (b) Ren, X.; Chen, J.; Chen, F.; Cheng, J. The Palladium-Catalyzed Cyanation of Indole C−H Bonds with the Combination of NH_4HCO_3 and DMSO as a Safe Cyanide Source. *Chem. Commun.* **2011**, *47*, 6725−6727. (c) Kim, S.; Choi, J.; Shin, K.; Chang, S. Copper-Mediated Sequential Cyanation of Aryl C−B and Arene C−H Bonds Using Ammonium Iodide and DMF. *J. Am. Chem. Soc.* **2012**, *134*, 2528−2531.
(48) Ding, S.; Jiao, N. *N*,*N*-Dimethylformamide: A Multipurpose Building Block. *Angew. Chem., Int. Ed.* **2012**, *51*, 9226−9237.
(49) Ding, S.; Jiao, N. Direct Transformation of *N*,*N*-Dimethylformamide to −CN: Pd-Catalyzed Cyanation of Heteroarenes via C−H Functionalization. *J. Am. Chem. Soc.* **2011**, *133*, 12374−12377.