ORGANIC CHEMISTRY

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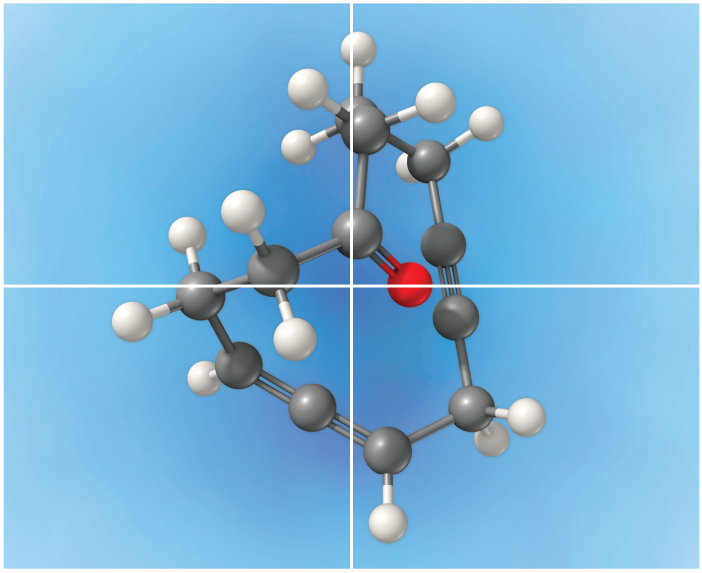

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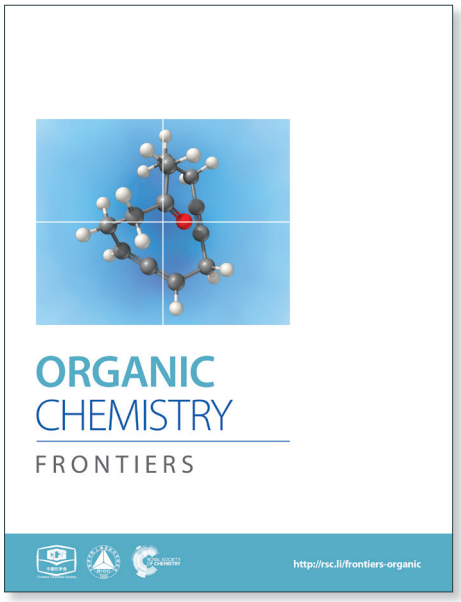

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Cu-, or Fe-Catalyzed C-H/C-C Bond Nitrogenation Reactions for the Direct Synthesis of N-Containing Compounds

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CONSPECTUS: Nitrogen-containing compounds are widely present in both natural products and synthetic compounds, for example, they show up within functional materials, top-selling drugs, as well as bioactive molecules. Thus, organic chemists have paid considerable attention in developing novel methodologies for their preparation. To synthesize these compounds in a green and sustainable way, researchers have focused on the direct functionalization of hydrocarbons via C–H and/or C–C bond cleavage. Although significant progress have made in the direct functionalization of simple hydrocarbons, direct incorporation of N-atoms into the simple substrates via C–H and/or C–C bond cleavage remains challenging due to the inert chemical bonds and the unstable character of some N-sources under oxidative conditions.

The azide reagents are frequently used as nitrogen source in incorporating nitrogen into carbon skeleton. Although exact reaction pathway remains unclear, the detailed mechanistic studies revealed that the carbon cation containing azido group may exist as the key intermediate which would undergo Schmidt-type rearrangement to afford nitriles, tetrazoles, arylamines, or other kinds of nitrogen-containing compounds. In consideration of high cost and toxicity of heavy metal, copper and iron, as inexpensive, readily accessible metals, have already shown their unique utilities. This account attempts to focus on C-H/C-C bond nitrogenation reactions *via* Cu, Fe catalysis, as well as their applications in synthetic chemistry.

INTRODUCTION

Nitrogen-containing compounds are of great importance in medicinal chemistry because they exhibit interesting and diverse biological activities.[1] For examples (Fig.1), the COX-2 inhibitor and colecoxib derivative, exhibits valuable biological activities,[1f] Valsartan acts as blockade of

angiotensin-II receptors,[1g] Atorvastatin, one of the top selling drugs worldwide since 2003, blocks the production of cholesterol,[1h] and Rizatriptan is a triptan drug used for the treatment of migraine headaches.[1i] Moreover, in material sciences, the presence of nitrogen in the structures of polymers can have a profound effect on their electronic, physical, or surface properties.[1] The construction of the C–N bond is significant as it offers the chance to incorporate nitrogen atoms into organic molecules. In general, the methods for C–N bond formation include substitution reactions (both electrophilic and nucleophilic amination), condensation, cycloaddition, rearrangement and cross coupling reactions.[2] Among them, The advent of catalytic cross coupling reactions provides efficient approaches to *N*-containing compounds. In the past decades, some direct C-H aminations have been significantly developed.[3] Despite significant advancements in this area, the direct construction of the C–N bond via C-H and/or C-C bond cleavage is still a challenging task, because it requires: 1) to find suitable conditions for the generation of highly active catalytic species; 2) to control the regio- and chemo-selective of C-H and/or C-C bond cleavage; 3) to form the stable N-partners under oxidative conditions.

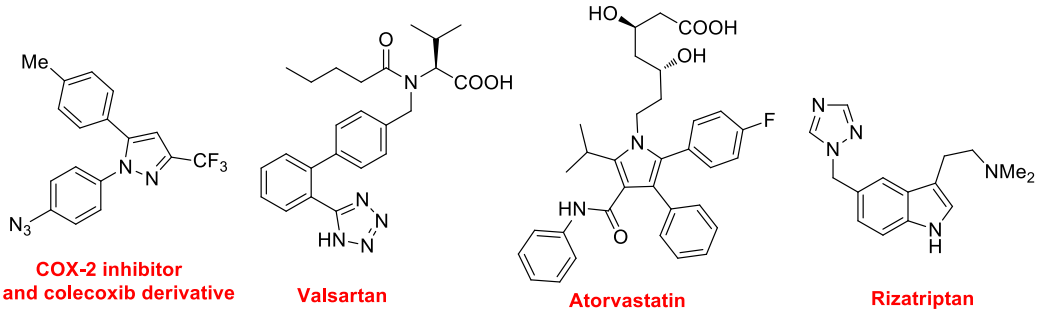


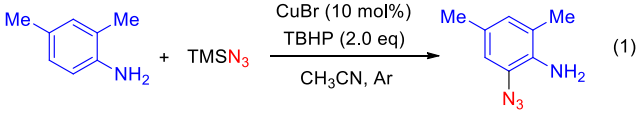
Fig.1 Typical N-containing molecules in pharmaceuticals

The C-H bond and the C-C bond are the most widespread and fundamental bonds existing in organic compounds. The transformation of these bonds plays an important role in modern scientific research. Recently, we have developed some novel approaches to *ortho*-azido aniline, nitriles, amides, arylamines, and tetrazoles derivatives *via* C-H and/or C-C bond cleavage from some readily available substrates by using simple nitrogen sources under mild conditions.

Copper-catalyzed C−H azidation of anilines

Organic azides are widely used in organic synthesis as valuable intermediates and building blocks, particularly in the synthesis of nitrogen-containing heterocycles, in peptide chemistry, material science, polymer chemistry and drug discovery.[4] Moreover, aryl azide has found its biological and industrial use as photoaffinity labeling agents.[4] Thus, the direct synthesis method of aryl azide is highly desirable.

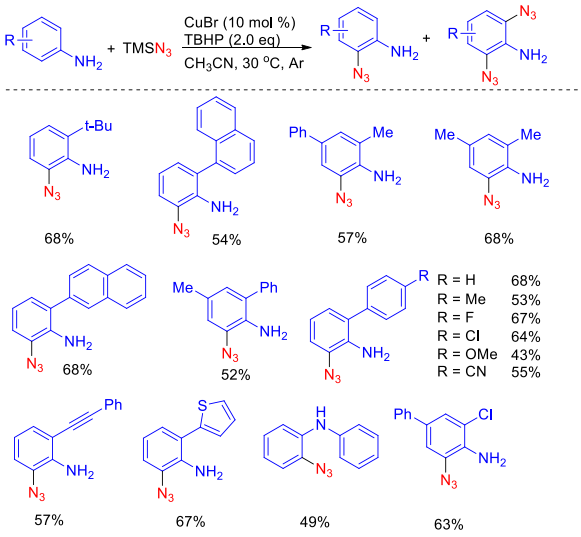
Recently, Yu and coworkers reported a Cu-catalyzed of aerobic oxidative aryl C−H bond functionalizations *via* a single electron transfer (SET) process.[5] The amine group of aniline substrates assisted vinyl C-H bond activation and alkenylation were individually disclosed by the groups of You[6a,b] and Zhang.[6c] We found that the *ortho*-azidation of aniline derivatives directed by amino group could be achieved by Cu-catalysis under mild conditions (Eq 1).[7a] It is noteworthy that Wang and coworkers developed a $Cu(ClO_4)_2$-catalyzed aerobic oxidative direct adization of arenes[7b] using sodium azide as azide source and air as terminal oxidant under mild conditions through a significantly proved Cu(III) involved mechanism.[7c-d] Recently, Fan et al. reported a successful $Cu(OAc)_2$-catalyzed azidation of anilines using azidobenziodoxolone as an azidating agent.[7e]



(1)

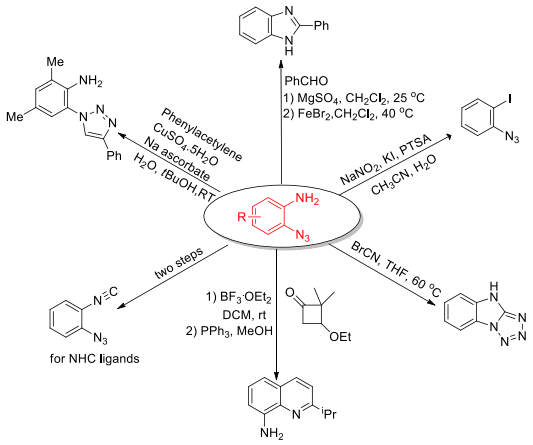
The reaction was performed in the presence of $TMSN_3$ and TBHP using CuBr as the catalyst at 30 ^oC in CH_3CN by using 2,4-dimethyl aniline as model substrate, the desired 2-azido-4,6-dimethylaniline was obtained in 68% yield. The catalytic system displayed outstanding chemoselectivity, which was illustrated by a remarkable functional-group tolerance. Moreover, both primary as well as secondary amines proved to be suitable substrates. However, there are still some limitations of the above mentioned method: 1) when *ortho*-unsubstituted anilines were employed as the substrates, both mono- and di-azidated products were obtained; 2) when secondary amine was employed, a large amount of starting material remained, thus leading to relatively low yields; 3) The reaction of arylamines with a tertiary amino group did not work under the standard conditions, indicating that a free N-H bond is required for this transformation (Scheme 1).

Scheme 1. Cu(I)-catalyzed direct azidation of anilines



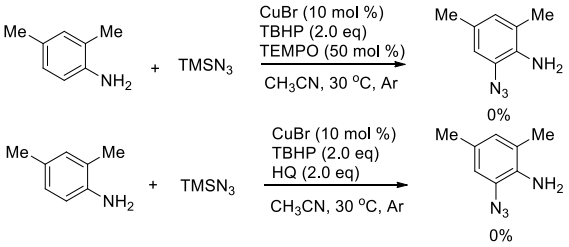
The power of the amino-directed C-H bond azidation approach was elegantly illustrated by the subsequent diversification of the thus obtained *ortho*-azido anilines (Scheme 2).[7a]

Scheme 2. Diversification of *ortho*-azido anilines



To further understand the mechanism, radical inhibitors 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) or hydroquinone (HQ) were added in the reaction, the formation of **2a** was completely inhibited, thus indicating that a radical process may be involved (Scheme 3).

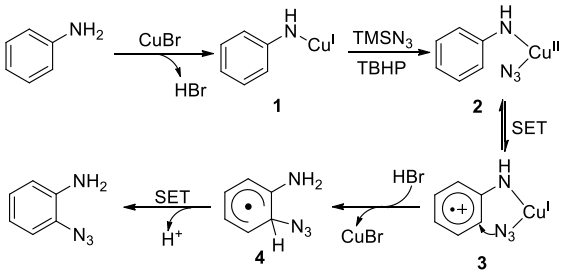
Scheme 3. Mechanism studies



Although the mechanism of this transformation is not completely clear yet, on the basis of the mechanistic studies, we proposed that intermediate **1** is initially generated by the coordination of copper to the substrate.[8] Subsequently, intermediate **1** combines with an azide radical generated

in situ from $TMSN_3$ and TBHP to form intermediate **2**. A single electron transfer (SET) from the aryl ring to the metal center (from **2** to **3**) may involve in this process.[5] Then, azido group transfer into the aryl ring with release of CuBr forms intermediate **4**, which undergoes deprotonation *via* SET process leads to the product (Scheme 4).

Scheme 4. Proposed mechanism of cu(I)-catalyzed direct azidation of anilines

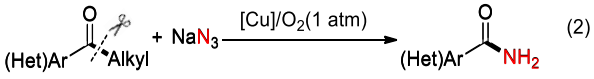


The present chemistry demonstratesthe first example of copper catalyzed direct *ortho* C-H azidation of arenes. This reaction uses inexpensive copper catalyst under remarkably mild conditions to enable siteselectively direct C-N bond formations on readily available aniline derivatives with broad substrate scope. Moreover, the removable amino group could be converted into H ,Cl, Br, I, CN, and OH by Sandmeyer reaction.

Cu-Catalyzed aerobic oxidative C−C bond cleavage for C−N bond formation

Carbon−carbon (C−C) bonds are ubiquitous in organic compounds. Compared with highly developed C−C bond forming reactions, chemoselective cleavage of C−C bond is always on the cutting edge in organic chemistry, biodegradation and industry applications. Among them, the cleavage of C−C single bond is the most challenging issue and draws great attentions due to their thermodynamic stability and uncontrollable selectivity.[9] Recently, some elegant examples of C−C bond cleavage of ketones substrates with the carbonyls functional fragment as the leaving group have been reported.[10,11] By using 1,3-dione substrates, we developed the Cu-catalyzed aerobic oxidative esterification reaction for the synthesis of α-ketoesters combing C-C(CO) σ-bond cleavage, dioxygen activation and oxidative C-H bond functionalization processes.[11a] The group of Bi and Liu[11b] reported a copper-catalyzed C(CO)−C(methyl) bond cleavage under oxygen atmosphere, which terminates at the aldehydes stage without being overoxidized. In our continuing interest in the construction of C−N bond, we designed a novel copper-catalyzed aerobic oxidative C−C bond cleavage to directly convert aryl alkyl ketones to benzamides (eq

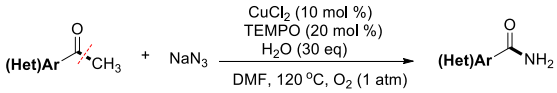
2).[12]

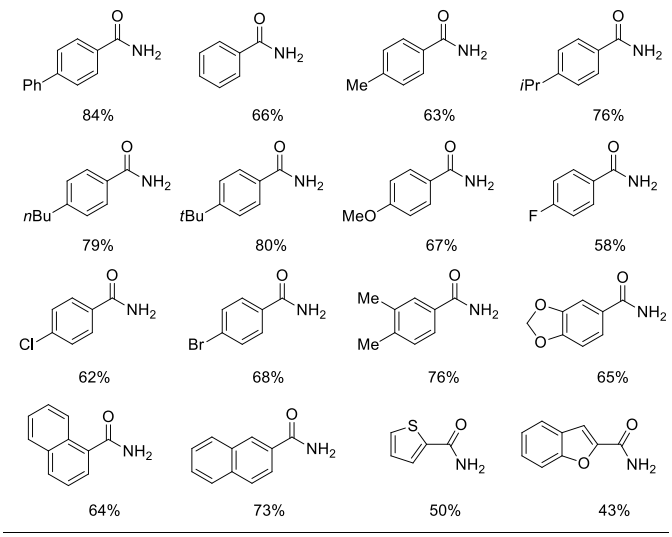


(2)

The conditions optimization indicated that the nitrigenation of 4'-phenylacetophenone with sodium azide afforded 4-phenylbenzamide in 84% yield when the reaction was catalyzed $CuCl_2$ in DMF at 120 ^oC in the presence of TEMPO and O_2 (1 atm). Under the standard condition, various substituted acetophenones can be smoothly converted to benzamides. Aryl ketones with electron-donating as well as electron-withdrawing substituents at the aryl ring can be tolerated well**.** Besides, the aryl methyl ketones could be expanded to heteroaryl ketones (Scheme 5).

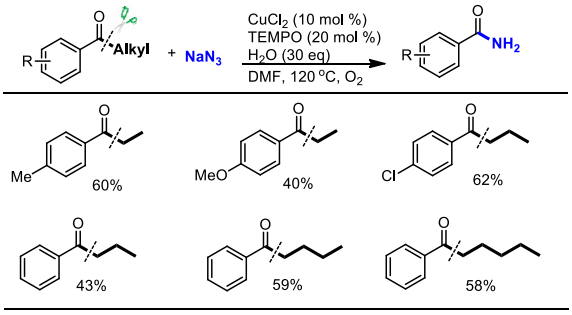
Scheme 5.Transformation of aryl methyl ketones to benzamides





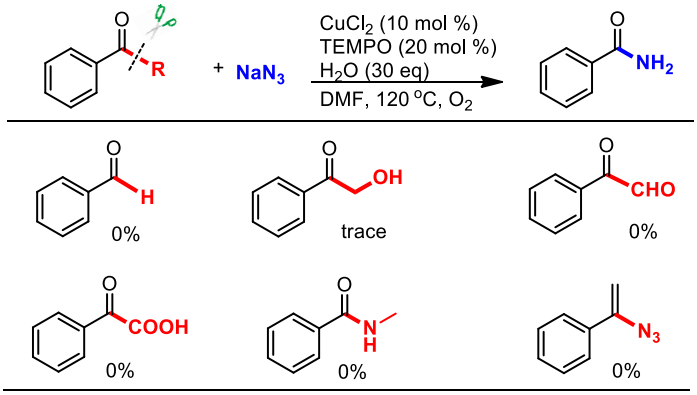
It is noteworthy that relatively inactive aryl ketones substrates with long-chain alkyl group which were not tolerated in both of the reported α-ketoesters,[11a] and aldehydes[11b] formation reactions vis C(CO)−C bond cleavage, can be successfully convert to corresponding benzamides by our developed protocol (Scheme 6).

Scheme 6 Transformation of aryl ketones substrates with long-chain alkyl group



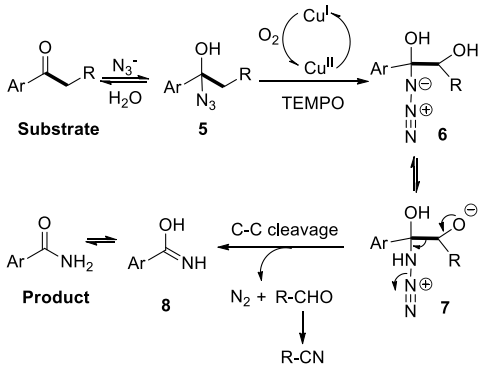
To elucidate the reaction pathway, some potential intermediates such as the corresponding aledhyde, α-hydroxy ketone, α-ketoaldehyde, α-keto carboxy acid, and amide species were prepared and tested under the standard conditions (Scheme 7). Howevre, none of them afforded the desired product (Scheme 7). These results indicated that the ketone substrate may prefertially reacts with azide nucleophile, then undergoes oxidation processes under Cu/O_2 system. Furthermore, *N*-methylbenzamide showed no efficiency under standard conditions which ruled out Schmidt type reaction of acetophenone and sodium azide in this system. In addition, (1-azidovinyl)benzene was completely unreactive under standard conditions.

Scheme 7. Mechanistic studies



Based on the above results, a plausible mechanism was proposed. The substrate initially underwent a reversible equilibrium with intermediate **5**. The subsequent aerobic oxidation of intermediate **5** occurs to generate α-hydroxylated intermediate **6** in the Cu/O_2 oxidative system.[11,13] The subsequent rearrangement of intermediate **6** via its resonance structure **7** produces intermediate **8** through C−C bond cleavage with releasing molecular nitrogen and aldehyde as byproduct. Finally, tautomerization of **8** affords the desired amide product (Scheme 8).

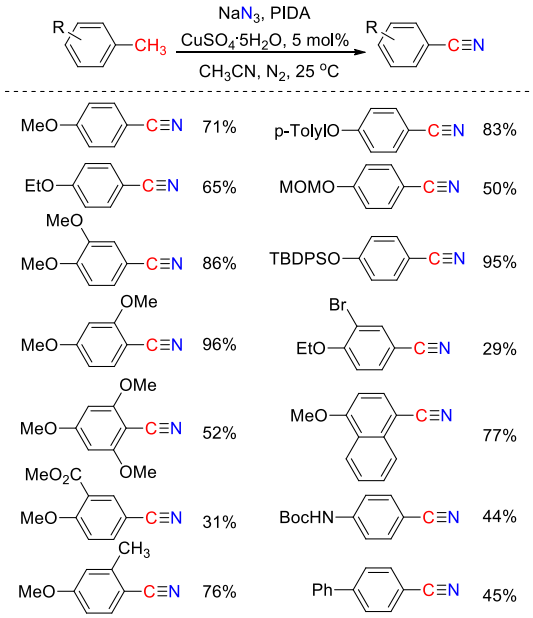
Scheme 8. Proposed mechanism



Cu- or Fe-promoted direct synthesis of aryl nitriles and alkenyl nitriles *via* Csp3-H nitrogenation

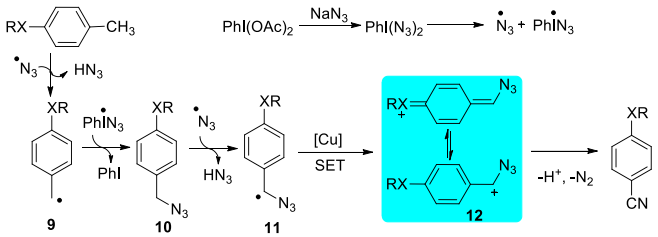
Nitriles are building blocks widely used in the synthesis of pharmaceuticals, agrochemicals, and natural products.[14] Recently, we reported a direct transformation of methyl arenes to aryl nitriles *via* three benzylic C–H bonds cleavage employing phenyliodonium diacetate (PIDA) as oxidant and sodium azide (NaN_3) as the nitrogenation source. The efficiency of this transformation could be significantly improved by the addition of catalytic amount of $CuSO_4$ $5H_2O$ salt. As a limitation, a hetero-atom or aryl substituent at the *para*-position of the methyl group of the toluene substrates is required for this direct transformation (Scheme 9).[15]. Significantly, Wang and co-workers developed a Pd-catalyzed direct transformation of methyl arenes into aromatic nitriles using *tert*-butyl nitrite (TBN) as the nitrogen source and oxidant,[16] in which the substrate scope is much broader.

Scheme 9. Direct transformation of methyl arenes to aryl nitriles



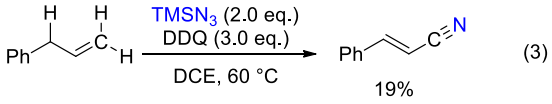
The benzylic azide was proposed to be the key intermediate to afford aryl nitrile. Azide radical can be produced by the combine of PIDA and NaN_3. The hydrogen abstraction of methyl arenes affords benzylic radical **9**, followed by the formation of benzylic azide **10,** which is further abstracted a hydrogen to form the radical **11**. The radical species **11** is then further oxidized to benzylic cation **12** through single electron transfer (SET). Eventually, the benzylic cation **12** undergoes a Schmidt type rearrangement[17] to afford the desired aryl nitriles. The cation can be stabilized by the *para*-substituent on the aromatic ring (Scheme 10). Similar strategy was also applied in synthesis of α-iminonitriles.[18] Besides, by employing this oxidative strategy, the transformation of some organo azides to corresponding nitriles have been developed.[19]

Scheme 10. Proposed mechanism of the direct transformation of methyl arenes to aryl nitriles



Inspired by this work, we envisioned that the tandem Csp3-H azidation and oxidative rearrangement of allyl arenes would afford the corresponding alkenyl nitriles. Although fascinating examples of allylic amination by palladium catalysis have been disclosed,[20] the direct transformation of allyl arenes *via* Csp^3–H activation remains challenging.[21] Therefore, the designed tandem C-H azidation and oxidative rearrangement of allyl arenes was then investigated. When DDQ was employed as the oxidant, 1-allylbenzene gave the desired product

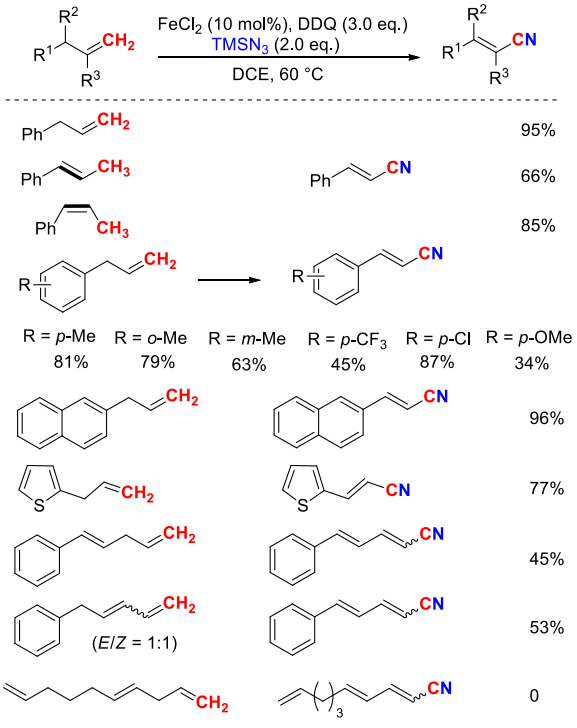
(*E*)-3-phenyl-2-propenenitrile in 19% yield under the reaction condition (eq 3).[22] To our delight, yield of the desired product was promoted to 95% when using 10 mol% $FeCl_2$ as the catalyst.



(3)

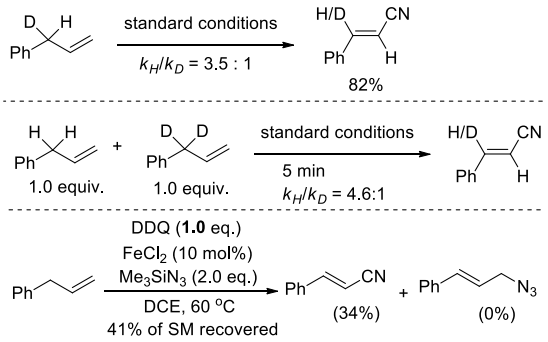
Various allyl substrates were investigated under the iron catalytic oxidative conditions. The allylarenes bearing different substituents were compatible in this transformation. Substitutes at different positions of the aryl ring (*para*-, *meta*-, and *ortho*-position) do not affect the efficiencies. Notably, a heteroaryl substituted propene, such as 1-allyl-2-thiophene provided corresponding nitrile in 77% yield. A simple aliphatic (*E*)-deca-1,4,9-triene was tested too, but no desired product was detected. Both (*E*)- and (*Z*)-propenylbenzene can provide in high stereoselectivity, indicating that a π-allyl species may be involved in the reaction (Scheme 11).

Scheme 11. Transformation of allylarenes or alkenes to alkenyl nitriles



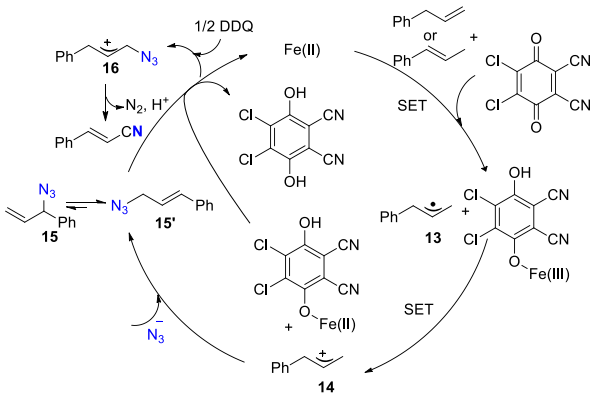
The allyl Csp^3–H bond activation was proposed to be the rate-determining step. Both intra- and intermolecular kinetic isotopic effects were evident (k_H/k_D = 3.5 and 4.6, respectively). Besides, no azide substitution product was observed by reducing the amount of DDQ (Scheme 12).

Scheme 12. Mechanism studies



An SET oxidation mechanism is proposed for this reaction. Initially, allyl arene undergoes successive iron-assisted single-electron oxidation to produce the corresponding allyl cation **14**. Subsequently, **14** experienced nucleophilic attack to give allyl azide **15** and **15**', which would exist as an equilibrating mixture by [3,3]-sigmatropic rearrangement. Allyl azide **15** is further oxidized to generate allyl azide cation **16**, which undergoes Schmidt-type rearrangement to afford the desired nitrile (Scheme 13).

Scheme 13. Proposed mechanism for this alkenyl nitriles synthesis method

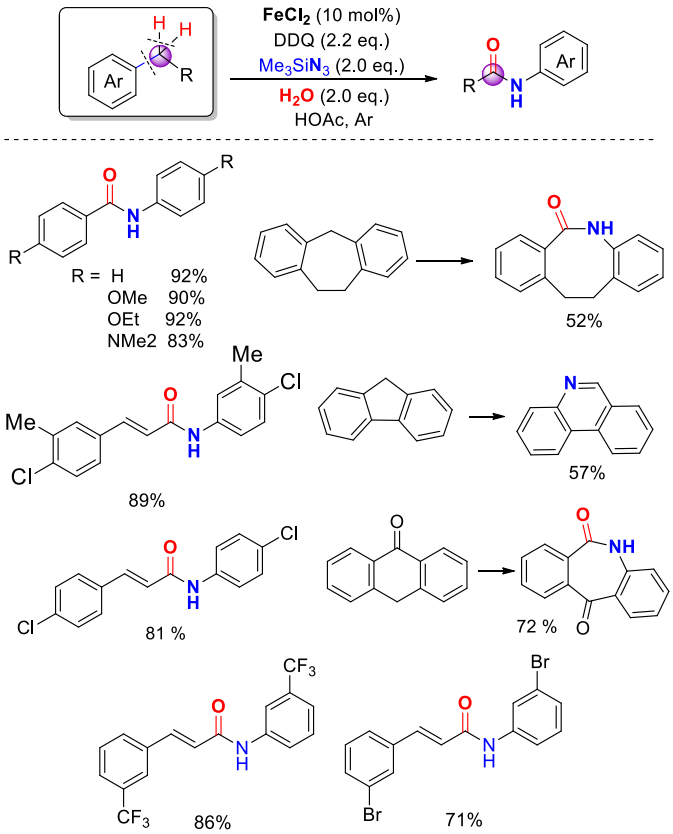


Iron-catalyzed nitrogenation of simple hydrocarbons through C-H and C-C bonds cleavage for the synthesis amides

The development of more atom-efficient, novel catalytic method for the preparation of amides at mild conditions has been one of the hot topics in organic synthesis, due to their important moieties in organic chemistry, biology and pharmaceutical molecules.[25] Although the functionalized compounds prepared by direct C-H or C-C bond activation has been the focus of significant recent interest, the amide bond formation through C-H and/or C-C bond cleavage remains challenging.[26] Inspired by our previous direct aryl and alkenyl nitriles synthesis methods and to further enhance the utility of azide in synthezing nitrogen-containing molecules, we demonstrated a novel iron-catalyzed transformation of benzyl hydrocarbons to corresponding

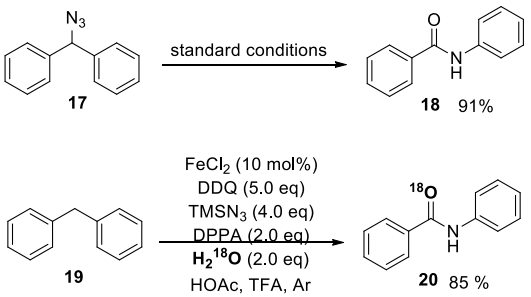
amides through C-H and C-C bonds cleavage under mild conditions. The substrates scope is broad and the ring expansion can be significantly achieved by this present strategy to generate lactams. In addition, under the optimized reaction conditions, (E)-1,3-diphenypropenes can be converted into the corresponding acrylamides in good to excellent yields, the high chemoselectivity indicate that the aryl groups have a better migration ability to the nitrogen atom than alkenyl groups in the rearrangement process (Scheme 14).[27]

Scheme 14. Direct transformation of benzyl hydrocarbons and 1,3-diphenypropenes to amides



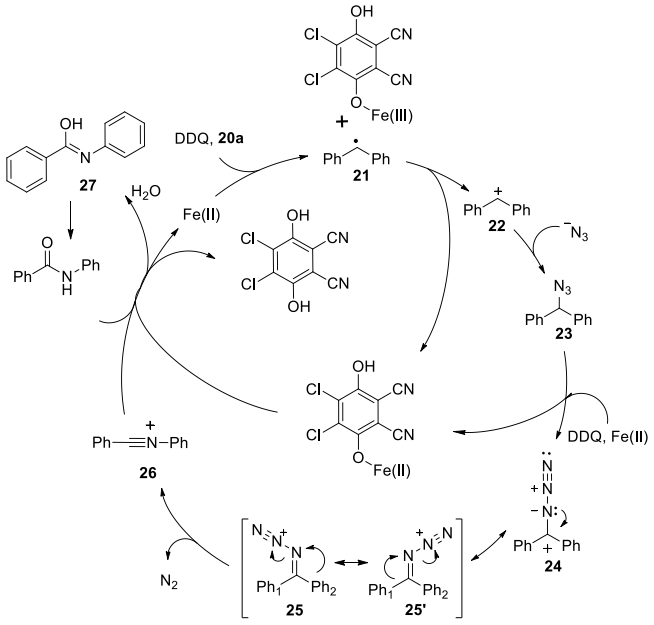
To better understand the mechanism, several possible intermediates have been investigated. All of these results suggest that the reaction does not undergo the process of oxidation of diphenylmethane to benzophenone followed by the Schmidt reaction. The possible intermidate (azidomethylene)dibenzene **17** was synthesized and subjected to the standard conditions, afforded the amide product **18** in 91% yield. The reaction conducted in the presence of $H_2{}^{18}O$, afforded the desired isotope labeled product **20** expectedly (Scheme 15).[27]

Scheme 15. Mechanism studies



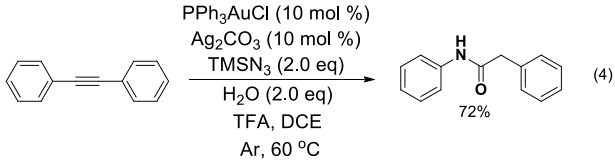
A SET oxidation mechanism is proposed for the reaction. Initially, substrate undergoes the iron-assisted SET oxidation with DDQ[22] to produce the corresponding diphenylmethyl radical **21**, which could be further oxidized to the diphenylmethyl cation **22**. Then diphenylmethyl cation **22** is attacked by azide anion to afford **23**, which would be oxidized to diphenylmethyl azide cation **24** by the iron assisted DDQ oxidative system. Subsequent isomerization of diphenylmethyl azide cation **24** leads to intermediates **25** and **25'**. For the unsymmetrical substrate, two isomeric iminodiazonium ions (**25** and **25'**) would be produced in this step. As in the Beckmann rearrangement, the *trans* group migrates from carbon to nitrogen to generate intermediate **26**. Subsequent nucleophilic attack by H_2O leads to the desired amide product *via* isomerization of the intermediate **27** (Scheme16).

Scheme 16. Proposed mechanism



The mechanistic insights into this novel transformation motivateus to discover other new types of reactions *via* C-C bond cleavage by using other nucleophiles instead of H_2O to trap

intermediate **26**. Moreover, we also successfully developed a direct amide synthesis method *via* the Csp^2-Csp bond cleavage of aryl substituted alkynes, which offers a novel application of alkynes in amide synthesis (eq 4).[28]



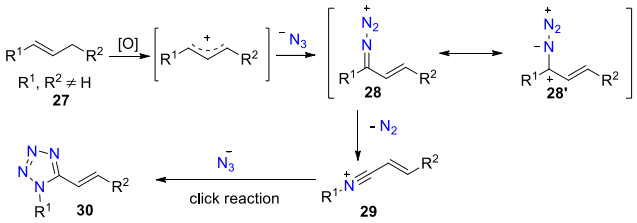
(4)

Cu-catalyzed nitrogenation of simple hydrocarbons through C-H and C-C bonds cleavage for the synthesis tetrazoles

Tetrazoles are of the high utility in chemistry and biology, in particular 1,5-disubstituted tetrazoles. Thus, many methods have been developed for their synthesis.[23] However, these approaches have some limitations, such as the use of protic acid catalysts, preactivated starting materials, andtedious workups, hence a direct synthesis method for their access remains attractive.

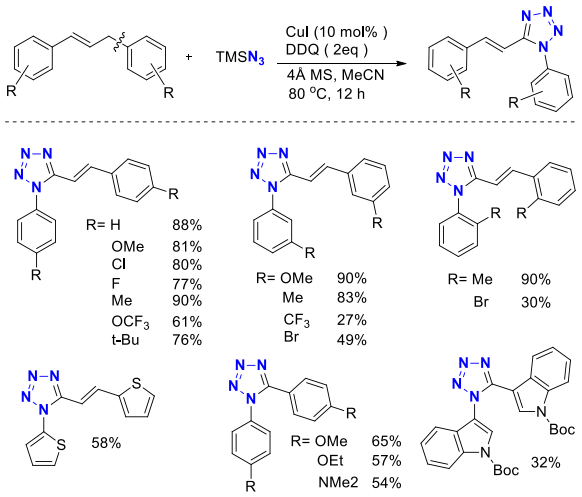
Inspired by the above amide construction, this work, we envisioned that the allylic azide cation would undergo aryl migration to the proximal nitrogen with the extrusion of nitrogen gas to generate intermediate **29**. We tried to trap this intermediate **29** by using the excess azide as the nucleophile to produce tetrazole product **30** (Scheme 17).[24]

Scheme 17. Envisioned pathway in forming tetrazoles



To test this hypothesis, we employed (E)-1,3-diphenylprop-1-ene as the substrate in the preliminary investigation. After extensively condition screening, we found that the reaction of (*E*)-1,3-diphenylprop-1-ene with 5.5 equivalents of $TMSN_3$ as nitrogen source catalyzed by CuI in the presence of DDQ oxidant in MeCN at 80 °C worked well to afford the desired (*E*)-1-phenyl-5-styryl-1H-tetrazole in 88% yield. Under the standard condition, various substituted 1,3-diarylprop-1-enes could easily be converted into the corresponding tetrazoles in good yields. Notably, bisheteroaryl methanes could be successfully converted into the corresponding 1,5-diheteroaryl tetrazoles too, albeit in moderate yields (Scheme 18).

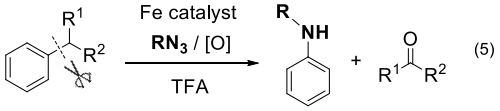
Scheme 18. Direct synthesis of tetrazoles



This protocol demonstrates a novel and efficient Cu-promoted implanting of nitrogen into simple hydrocarbon molecules to construct 1, 5-disubstituted tetrazoles through C-H and C-C bonds cleavage under mild and neutral reaction conditions, it not only extends the application of azides in organic transformations, but also offers an alternative method to prepare 1,5-disubstituted tetrazoles, which are ubiquitous structural units in numerous biologically active compounds.

$FeCl_2$-promoted arylamines synthesis from alkylarenes through C-C bond nitrogenation

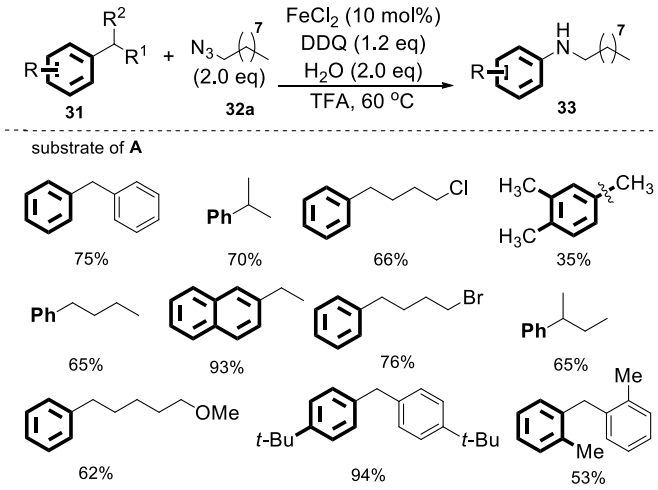
Arylamines are common and fundamental industrial feedstocks. For instance, *N*-alkylanilines are widely used in the synthesis of important dyes, polymers, herbicides, insecticides, pharmaceuticals, plant growth agents and antiknock agents for gasoline engines.[29] On the basis of above reactions, after the generation of carbon cation intermediate, we tried to use alkyl azide to trap the cation intermediate and for the subsequent rearrangement *via* C-C bond cleavage (eq 5)[30]



Interestingly, when diphenylmethane was treated with 1-azidononane, the reaction catalyzed by $FeCl_2$ in the presence of DDQ as the oxidant in trifluoroacetic acid (TFA) afforded the desired nitrogenation product *N*-nonylaniline in 75% isolated yield with the generation of 72% GC yield of benzaldehyde. Under the optimized reaction conditions, various diarylmethanes and benzyl alkanes were found to be compatible to this protocol. The nitrogenation process can also be extended to inert benzyl alkanes, furnishing the desired *N*-alkyl aniline in good yields. The iron

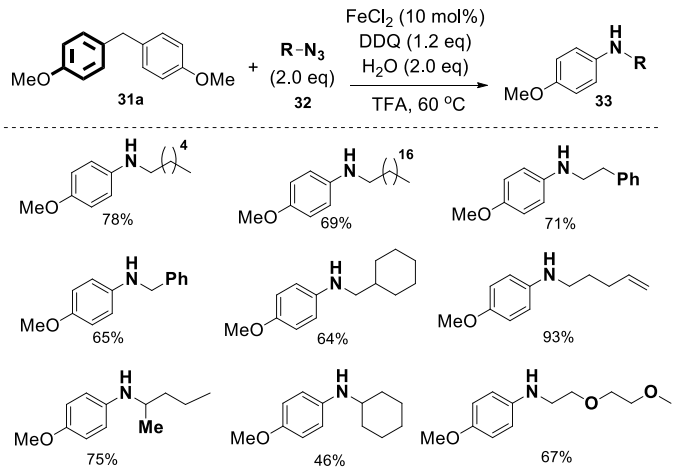
catalyst was found to be essential in other cases employing relative unactivated alkylarenes as the substrates (Scheme 19).

Scheme 19. Direct synthesis of aniline from various benzyl hydrocarbons



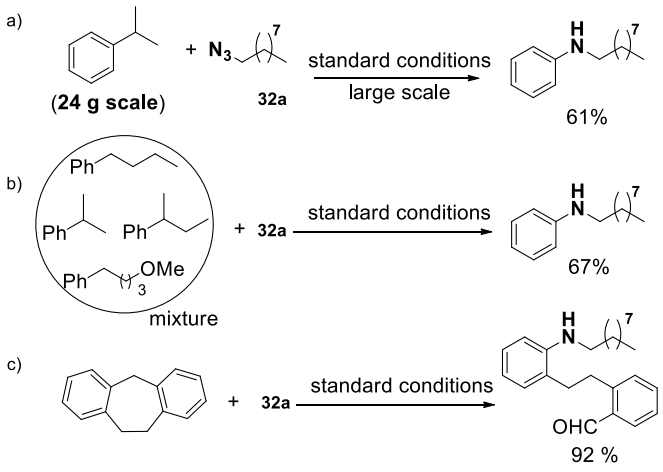
Moreover, different alkyl azides can be applied in the reaction, the length of alkyl chain did not affect the efficiencies, therefore extending the utility of this transformation. Alkyl azides with functional groups at the alkyl chain such as phenyl, alkenyl and ethylene glycol units were also compatible (Scheme 20).

Scheme 20. Scope of organic azide in this transformation



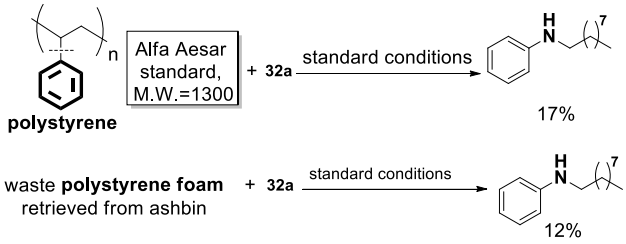
In addition, this protocol can be conducted in 24 g large scale in lab (a, Scheme 21). Even the mixture of alkyl benzenes can also be smoothly converted (b, Scheme 21), which demonstrates the potential for applying this oxidative unactivated C-C bond cleavage strategy to the conversion of a crude mixture of benzyl hydrocarbons from oil and coal industry to a single *N*-alkyl aniline products. Moreover, the present strategy was also applicable to the ring opening reactions (c, Scheme 21).

Scheme 21. Direct transformation of various benzyl hydrocarbons into aniline



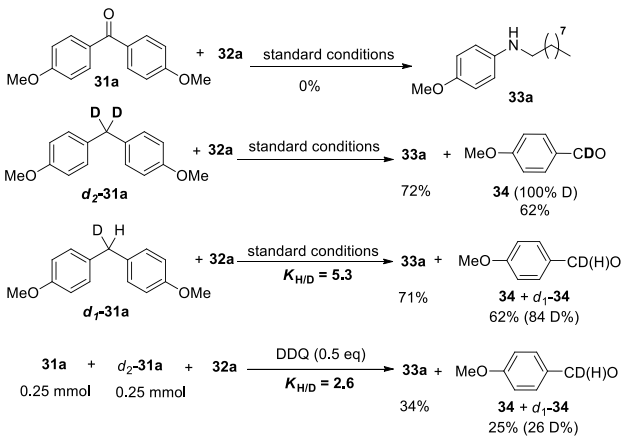
Significantly, the desired *N*-nonylaniline was obtained in 17% yield when polystyrene was used as the substrate. Moreover, the waste polystyrene foam can also be used as reactant to afford *N*-nonylaniline in 12% yield. This may provides a novel concept for the polystyrene degradation and reuse (Scheme 22).

Scheme 22. Direct transformation of polystyrene into aniline



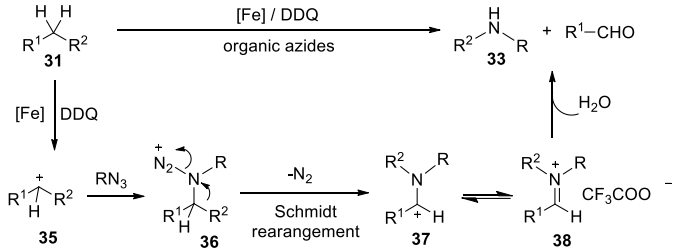
The mechanistic studies rule out the pathway through the oxidation of diphenylmethane to benzophenone. Furthermore, deuterated substrates ***d*$_2$-31a** was subjected to the reaction and produced the deuterated product 4-methoxybenzaldehyde **34** in 62% yield, which may exclude the pathway of the initial oxidation to ketone or the formation of imine intermediate *via* nitrene before the aryl shift step. Furthermore, the intra- and inter-molecular kinetic isotopic effects (k_H/k_D) were 5.3 and 2.6 respectively (Scheme 23).[31]

Scheme 23. Mechanistic studies



Although the exact mechanism is not clear, a possible pathway could initiate from iron-assisted oxidation[32] of substrate to cation **35**, which would be attacked by nucleophilic organic azides[15] to generate intermediate **36**. The following Schmidt-type rearrangement[17] process *via* excursion of nitrogen gas and *trans* migration of aryl group R_2 from carbon to nitrogen atom generating intermediate **37**. Subsequent isomerization of cation **37** leads to iminium cation, which may exist as iminium trifluoroacetic acid salt **38** in the reaction mixture. Finally, *N*-alkyl anilines and benzaldehydes were generated *via* hydrolysis of **38** (Scheme 24).

Scheme 24. Proposed mechanism



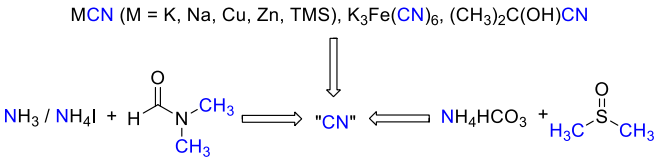
This protocol offers a new route for aryl amides synthesis by employing benzyl hydrocarbons and very stable alkyl azides as substrates, even the unseparated alkylarenes mixture and the polystyrene could be employed too, which offers a new strategy for degradation and reuse of polystyrene. A Schmidt type rearrangement process is proposed for this transformation involving release of nitrogen and migration of the aryl group from the carbon to the nitrogen atom.

Direct transformation of N,N-dimethylformamide (DMF) to –CN

Although azides exhibit powerful function to build N-containing compounds, some features like toxicity and explosibility of these reagents limit their further applications. Traditional CN sources include metal cyanide salts and acetone cyanohydrins, which provide cyanide unit in its entirety in

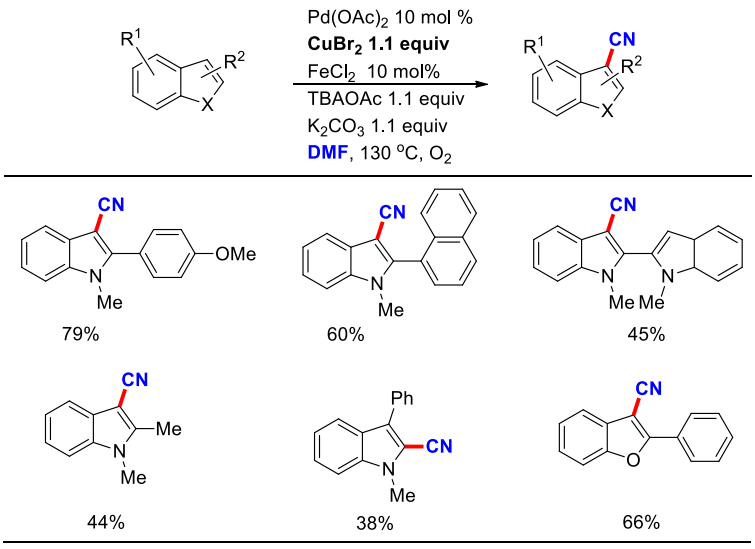
metal catalyzed cyanation of aryl halides. The stoichiometric toxic cyanide salts are inevitably used in the reaction. To solve this problem, many safe and readily available cyanide sources generated *in situ* are developed by diverse groups in recent years.[33] Interestingly, a combined cyanide source from DMF and ammonia or ammonium salts have been reported by Chang for various cyanation reactions, whereas the combination of ammonium salts and DMSO were also used as safe cyanide source for the cyanation of indole C–H bonds. These studies revealed that DMF and DMSO are not only polar solvents, they also have been employed as versatile synthetic precursors to give a number of functional units (Scheme 25).[34]

Scheme 25. Direct transformation of N,N-dimethylformamide (DMF) to –CN



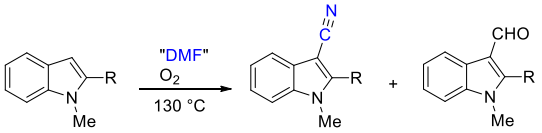
Recently, we developed a direct C-H cyanation of indoles just by using DMF as the CN source (Scheme 26),[35] The control experiments indicated that $CuBr_2$ and $Pd(OAc)_2$ are essential to this direct cyanation reaction. $FeCl_2$, was efficient additive to promote the efficiency of this transformation.

Scheme 26. Cyanide sources in organic synthesis



To better understand the distinct role of DMF, a series of labeling reactions were carried out to determine the source of cyanide unit (Scheme 27). The reaction of ^{15}N-labeled DMF can pinpoint that the DMF was the *N*-source of the cyanide group (99% incorporation, entry 1). The labeling experiment indicated that the carbon of CN and CHO hardly originated from the formyl group of DMF (<5% incorporation; entry 2); whereas the dimethylamino group of DMF undertook the carbon source instead. The calculation of isotope abundance of CN and CHO by the inverse gated decoupling ^{13}C NMR revealed that NMe and OMe methyl groups cleaved and exchanged with DMF in the reaction.[36] The ^{18}O labeling experiments showed that the *O*-source of CHO was molecular oxygen.

Scheme 27. Isotope incorporation experiments

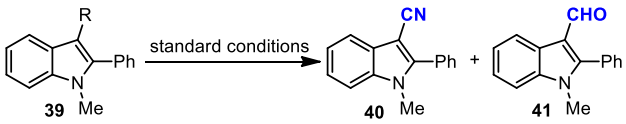


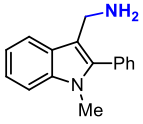
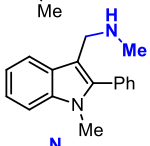
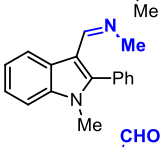
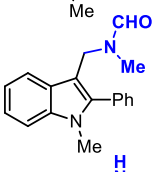
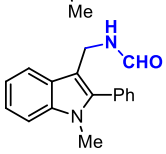
R = 4-methoxyphenyl

Entry	"DMF"	-CN	-CHO
1		-CN 99% ^{15}N incorporation	
2		-CN <5% ^{13}C incorporation	-CHO <5% ^{13}C incorporation
3		-CN 88.7% ^{13}C incorporation	-CHO 93% ^{13}C incorporation

Next, various possible intermediates **39** were synthesized and investigated under optimized conditions. However, none of them can provide the desired nitrile in high yield (Scheme 28). The cyano product was produced in 28% yield in *N*-methylformamide instead of DMF. To investigate the possibility of isonitrile, which can be generated from DMF, as an intermediate, the control experiment were carried out using *tert*-butyl isonitrile or benzyl isonitrile as the solvent. However, no product was observed in these reactions. In addition, if the reaction undergoes oxidative demethylation of DMF, this species may react with copper salts to generate CuCN with losing of "HCO". However, control experiments exclude CuCN involved in this cyanation.

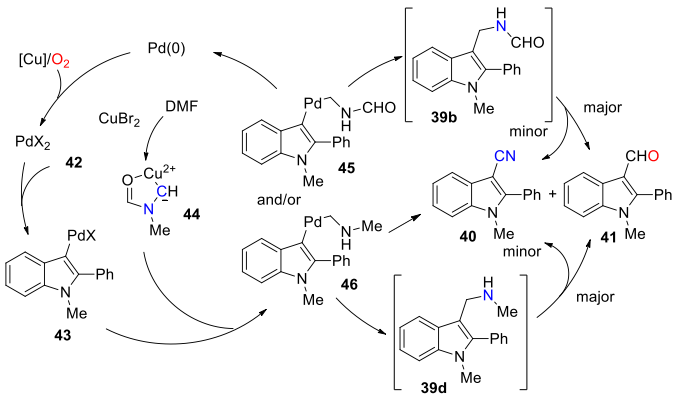
Scheme 28. Reactions of possible intermediates



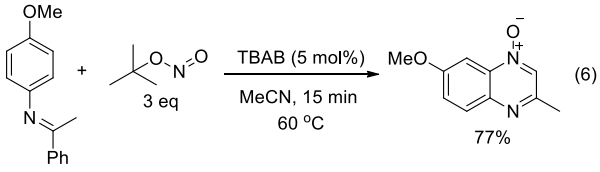
entry	39	yield% of **40**	yield% of **41**
1		12	20
2		18	53
3		trace	76
4		0	0
5		trace	37

The precise mechanism is not clear yet. A proposed pathway is elucidated based on the mechanistic studies (Scheme 29). Regarding complex **44** was documented to form in DMF with copper(II) salts, we consider it would be a possible intermediate in the reaction (as illustration in the mechanism).[37] Initially, the Pd(II) intermediate **43** was given by the electrophilic aromatic palladation. This Pd(II) species react with complex **44** to give **45** and/or **46** *via* C–N cleavages. Subsequently, **39b** and/or **39d** were formed by reductive elimination. The cyanation product could be obtained directly from **46**, whereas a pathway involving **39d** can not be excluded. The aldehyde **41** could be generated from **39b**, although **41** is major product according to the control experiment. Further mechanism studies should be done to explain the influence factors of the **40** : **41** ratio.

Scheme 29. Proposed mechanism



Encouraged by this transformation, we were also interested to develop the nitrogenation reactions with some other N-containing reagents. Recently, we demonstrated an novel synthesis method for quinoxaline N-oxides through the functionalization of C(sp^2)-H and C(sp^3)-H bonds of readily obtainable imines by using simple and commercially available *tert*-butyl nitrite (TBN) as the NO source. This reaction proceeds under mild and transition metal free condition. DFT calculation and EPR measurement suggested that this reaction involved multiple SET processes (Eq. 6).[38]



CONCLUSION

Via Cu or Fe catalyzed C-H and/or C-C bond cleavage from some readily available hydracarbons by using nonmetal oxidants and simple nitrogen sources under mild conditions, novel synthetic approaches to *ortho*-azido aniline, nitriles, amides, arylamines, and tetrazoles have been developed. The azides, DMF, and TBN reagents are used as the potential nitrogen sources in C-N bond formation reaction. Mechanism studies revealed that a cation or radical intermidate is involved in these nitrogenation processes. Despite these contributions and significant progress, many challenges still remain. To meet these, many more mechanistic studies have to be performed to shed more light on the potential intermediates involved during the reactions. The better understanding of mechanism can provide more inspiration on new reaction design. Last but not least, the exploration of safe, efficient and readily available nitrogenation reagents are always

favorable.

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FOOTNOTES

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The authors declare no competing financial interest.

BIOGRAPHICAL INFORMATION

Yujie Liang was born in 1992 in Hainan, China. He received his BS degree at Nankai University in 2014. Then he joined Prof. Ning Jiao's group in State Key Laboratory of Natural and Biomimetic Drugs, Peking University. His research interests include developing highly efficient synthesis method for nitrogen containing compounds *via* inert bond activations.

Yu-Feng Liang was born in 1986 in Jiangxi, China. He received his B.S. and M.S. degrees in 2009 and 2012 with Prof. Hua-Jian Xu at Hefei University of Technology. Then he joined Prof. Ning Jiao's group at Peking University, and is currently a Third-year doctoral candidate. His research interests include developing efficient aerobic oxidation as well as oxygenation reactions with economical and environmentally friendly oxidants.

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) To develop green and efficient synthetic methodologies through Single Electron Transfer (SET) process; 2) Aerobic oxidation, oxygenation and nitrogenation reactions; 3) The activation of inert chemical bonds.

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