Heterocycles

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N,*N*-Dimethylformamide: A Multipurpose Building Block

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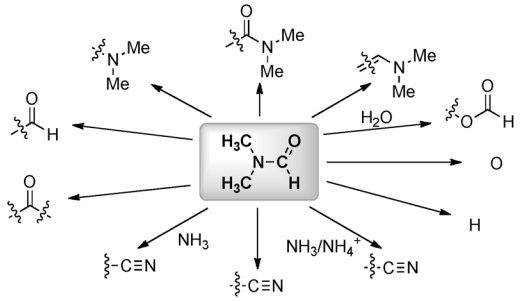
amines · cyanides · heterocycles · nitrogen · synthetic methods

Often used as a common solvent for chemical reations and utilized widely in industry as a reagent, N,N-dimethylformamide (DMF) has played an important role in organic synthesis for a long time. Numerous highly useful articles and reviews discussing its utilizations have been published. With a focus on the performance of DMF as a multipurpose precursor for various units in numerous reactions, this Minireview summarizes recent developments in the employment of DMF in the fields of formylation, aminocarbonylation, amination, amidation, and cyanation, as well as its reaction with arynes.

1. Introduction

The primary use of *N*,*N*-Dimethylformamide (DMF) is as an effective polar solvent for various chemical reactions. Additionally, DMF is a multipurpose reagent widely used in chemistry. For instance, DMF can be utilized as an effective ligand in the preparation of metallic complexes.[1] Furthermore, it can also participate in reactions as a dehydrating agent,[2] as a source for a reducing agents,[3] or even as a catalyst.[4] More importantly, because of its structure, DMF can participate in many reactions by serving as a multipurpose building block for various units, such as O, -CO, -NMe_2, -$CONMe_2$, -Me, -CHO, etc. (Scheme 1). Recently, a well-documented review on the different roles DMF plays in reactions was published by Muzart.[5a] In recent years, chemists have achieved important developments in the field by employing DMF as the reaction precursor; the developements include transition metal catalyzed aminocarbonylation and cyanation reactions, C–H activation processes, etc. This Minireview will focus on the latest developments of reactions using DMF as a precursor for cyanation, aminocarbonylation, amidation, formylation, cycloaddition, and some other reactions especially involving C–H activation processes. Some important functions of DMF, such as serving as an effective ligand, as well as a reducing and dehydrating agent, were documented in reviews by Muzart and others,[5] and are not discussed herein. We hope this review will serve as a handy reference for chemists interested in using DMF in organic synthesis and discovering new roles for DMF.



Scheme 1. Various functional groups that can be derived from DMF.

2. Serving as a Precursor in Formylation Reactions

The formylation of numerous substrates, such as electron-rich aromatic or heteroaromatic compounds,[6] as well as electron-rich alkenes and 1,3-dienes,[7] has been achieved by utilizing Vilsmeier reagents (**2**), which are usually prepared from N,N-disubstituted formamides and acid chlorides (Scheme 2). The relevant works have been well documented in many reviews.[8]

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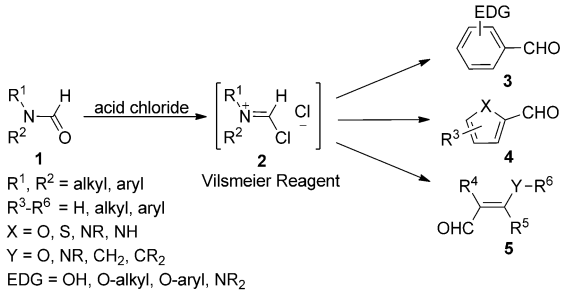


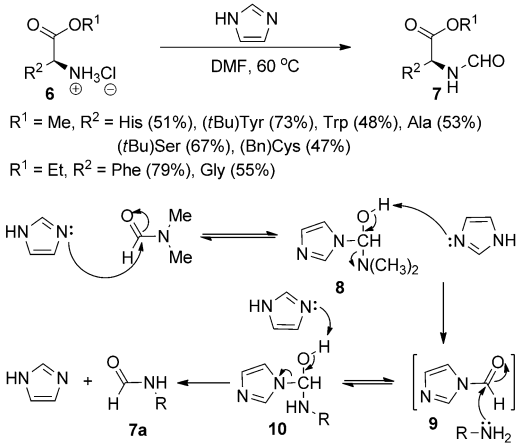
Scheme 2. Vilsmeier–Haack formylation. EDG = electron-donating group.

In addition to these formylation processes, the formylation of amines to afford amides is another important method in organic sythesis. The utilization of DMF as a formylation reagent has been well developed, as has been summarized in Muzart's review.[5]

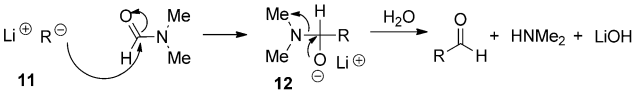
Very recently, Hudson et al. developed a simple, convenient protocol for the N formylation of amino acid esters and primary amines utilizing only imidazole in warm DMF.[9] A wide scope of amino acid esters were formylated by this transformation. Importantly, no racemization was observed during the reactions, and the authors have proposed a plausible mechanism for this reaction as depicted in Scheme 3. Nucleophilic attack of imidazole on DMF leads to the formation of the tetrahedral intermediate **8**. Decompostion of **8** results in the formation of the reactive N-formyl imidazole **9**, which has been postulated to act as an acyltransfer reagent.[10] The authors have tried to isolate or detect the presence of **9** in the reaction mixture containing no external nucleophile, but failed presumably because of its thermal instability. Nucleophilic attack of the amino acid esters or amines on the intermediate **9** gives the tetrahedral intermediate **10**, which collapses with the formation of the N-formylated products **7a**.

The formylation of organolithium compounds by DMF is another widely employed approach for the introduction of formyl groups, and has been illustrated in detail in Muzart's review.[11] Corresponding aldehydes are usually formed in the process of the addition of organolithium compounds to DMF, with subsequent hydrolysis of the alcoholate (Scheme 4).

The groups of Baumgarten and Taydakov realized an alternative method for formylation in which Grignard re-



Scheme 3. N formylation of amino acid esters.

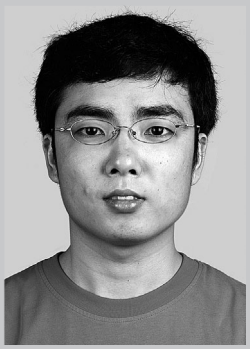


Scheme 4. Formylation of organolithium compounds.

agents and DMF were employed.[12] Using organomagnesium bromide as a key intermediate indicates that this formylation may proceed in a similar way as that depicted in Scheme 4.

3. Serving as a Precursor in Aminocarbonylation Reactions

In 2001, the group of Indolese observed the formation of dimethylamide in the reductive carbonylation of 3-bromobenzotrifluoride (**13**) in DMF [Eq. (1) in Scheme 5].[13] With the employment of imidazole, which is known as a powerful Lewis base and acylating catalyst, and the adjustment of the Pd/P ratio, an 89 % yield of the amide **14** was obtained . Since this reaction was conducted under CO (5 bar), DMF was considered to be the amine source. On the basis of this discovery, they developed a method for the preparation of primary amides (**15**–**18**) by carbonylation of aryl halides using formamides as the amine source (Scheme 5). According to the proposed mechanism, the amide is formed by the



Shengtao Ding was born in Henan, China. He received his B.Sc. in 2009 from Peking University. He completed his M.Sc. in medicinal chemistry in July 2011 under the supervision of Prof. Ning Jiao. He is now pursuing his Ph.D. studies at the Hong Kong University of Science and Technology. His research interests include new synthetic methods involving transition-metal catalysis.

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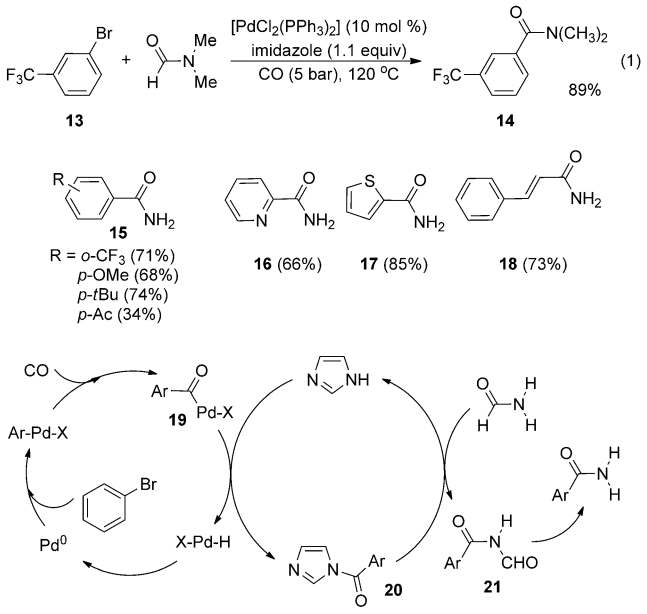


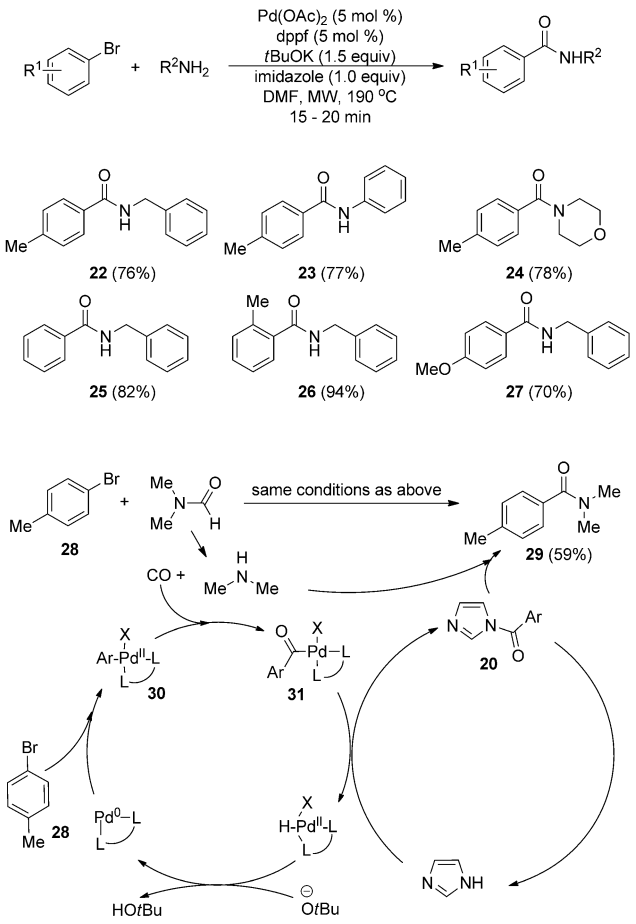
Scheme 5. Aminocarbonylation products arising from the reaction of aryl halides with formamide as an ammonia source.

decomposition of formylimide **21**, which is formed in the reaction of the formamide with the imidazolide **20** (Scheme 5). However, a pathway with the initial decomposition of the formamide to generate the amine, and subsequent addition of imidazolide could not be ruled out.

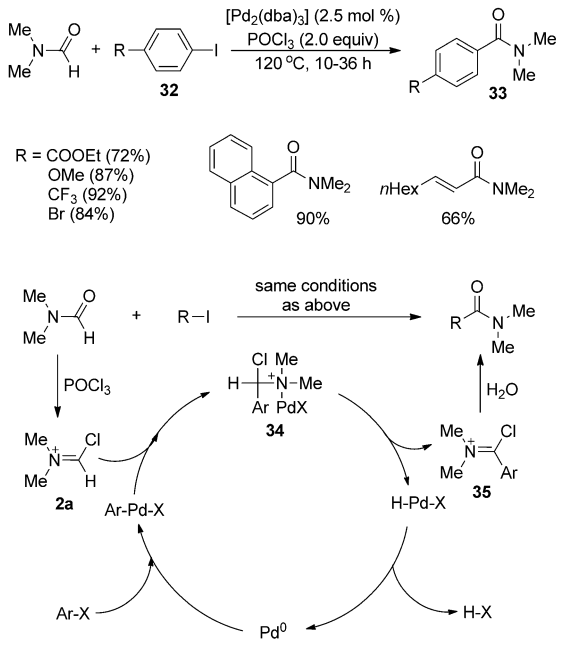
Hallberg and co-workers reported a palladium-catalyzed aminocarbonylation of aryl bromides under microwave irradiation.[14] Though listed as the source of the Me_2NCO unit in Muzart's review, DMF served as a source of CO while this transformation was carried out in the presence of excess of amines, such as benzylamine and aniline (Scheme 6). In the absence of these amines, the dimethylamine, generated from the decomposition of DMF, reacted with the imidazolide intermediate **20** to afford the N,N-dimethylarylcarboxamide product (e.g., **29**).

Hiyama et al. reported the palladium-catalyzed direct aminocarbonylation of aryl and alkenyl iodides by employing DMF as an amide source (Scheme 7).[15] The addition of phosphoryl chloride ($POCl_3$) is essential for this process. On the basis of the formation of the Vilsmeier reagent from DMF and $POCl_3$, and the oxidative addition of aryl halide to Pd^0, a plausible mechanism involving a Heck-type addition of aryl halides to the imminium species **2a** was proposed as shown in Scheme 7. This transformation could also be achieved with a Pd/C catalytic system as reported by Bhanage and co-workers.[16] However, these two protocols were limited to aryl iodides and DMF only. In 2011, the group of Bhanage developed a $Pd(OAc)_2$/Xantphos catalytic system for this reaction, which is applicable for aryl iodides as well as aryl bromides, and all types of formamide derivatives.[17]

In contrast to the requirement of $POCl_3$ in the above three protocols, Lee et al. developed a nickel/phosphite catalytic system for aminocarbonylations using DMF as an amide source under basic conditions with either NaOMe or KOMe

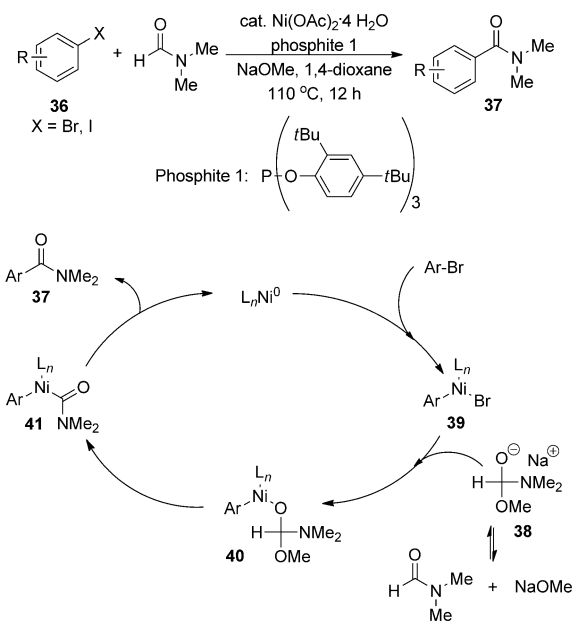


Scheme 6. Aminocarbonylation of aryl bromides using DMF as a CO source. dppf = 1,1′-bis(diphenylphosphino)ferrocene, MW = microwave.



Scheme 7. Aminocarbonylation of aryl and alkenyl iodides using DMF as an amide source. dba = dibenzylideneacetone.

as the base (Scheme 8).[18] Furthermore, they expanded the scope of the substrates and optimized the reaction conditions for the coupling of formamide derivatives.[19] The mechanism

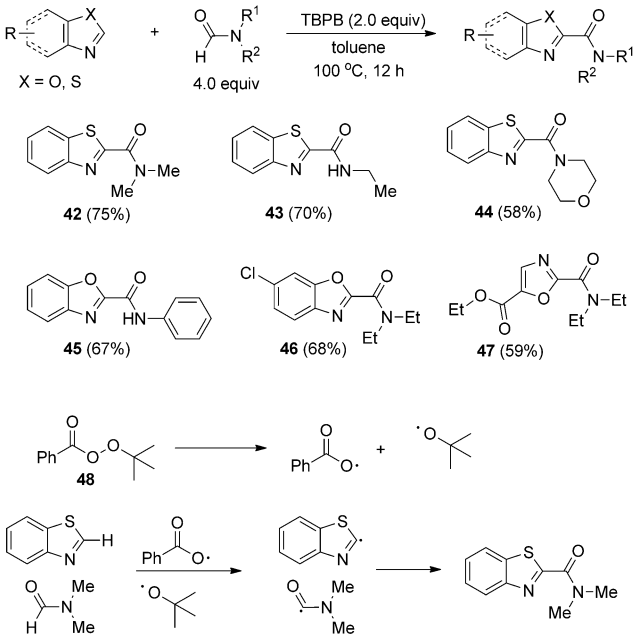


Scheme 8. Aminocarbonylation of aryl halides using a nickel/phosphite catalyst system.

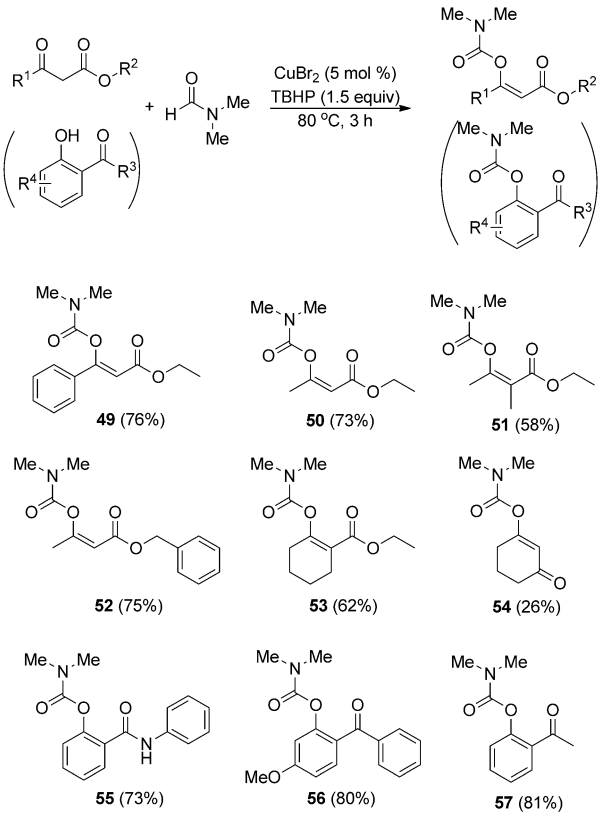
was proposed as depicted in Scheme 8. The base is thought to attack the carbonyl carbon atom in DMF to form the alkoxide/DMF adduct **38**, which then coordinates to the nickel complex **39**. The nickel-coordinated alkoxide/DMF adduct **40** is converted into the nickel amido intermediate **41**, which gives the amide product through reductive elimination.

In 2011, the group of Wang reported the direct aminocarbonyaltion of azoles with DMF through metal-free C–H activation in the presence of *tert*-butyl perbenzoate (TBPB; Scheme 9).[20] Formamides containing different substituents on N do react with azoles and produce the corresponding products in good yields. As reported, the reaction was suppressed by a radical scavenger, such as TEMPO in a dose-dependent manner. A free-radical process was proposed by the author and presumably is initiated by the homolytic cleavage of TBPB, thus generating a carboxyl radical and an alkoxyl radical. Subsequently, the radical species abstract hydrogen atoms from benzothiazole and DMF, thus leading to the corresponding free radicals, which react with each other to generate the cross-coupling product (Scheme 9).

Very recently, Reddy et al. reported a copper-catalyzed aminocarbonylation of β-ketoesters and *ortho*-substituted phenolic compounds.[21] In this oxidative C–O coupling, the $(CH_3)_2NCO$ unit was afforded by the direct C–H bond activation of DMF. Various enol and phenol carbamates were synthesized by this process (Scheme 10). As described in this report, a key factor for the formation of products might be the coordinating ability of the substrates with the metal. No product was detected when the reaction was tested in the



Scheme 9. Direct aminocarbonyaltion of azoles with DMF through metal-free C–H activation in the presence of *tert*-butyl perbenzoate.



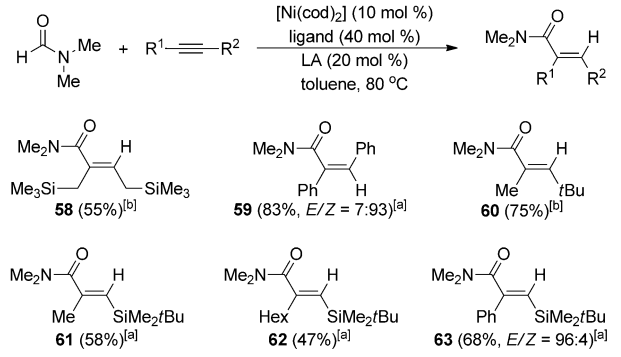
Scheme 10. Copper-catalyzed synthesis of enol carbamates and 2-carbonyl-substituted phenol carbamates by direct C–H bond activation of DMF. TBHP = *tert*-butyl hydroperoxide.

presence of TEMPO, thus indicating the possibility of a radical pathway.

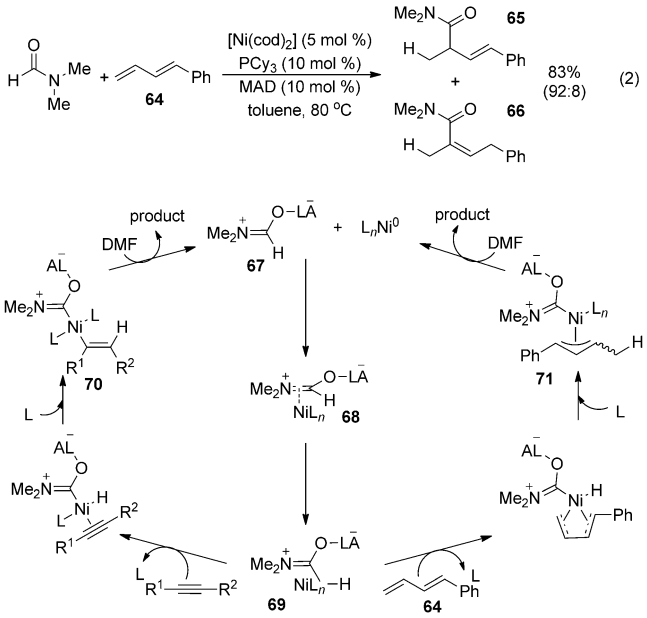
Transition metal catalyzed insertion of unsaturated bonds into the C–H bond in DMF is another alternative to

aminocarbonylation reactions. This process is also termed hydrocarbamoylation.

In 2009, Nakao, Hiyama and co-workers reported a nickel-catalyzed hydrocarbamoylation of alkynes (Scheme 11) and 1,3-dienes [Eq. (2) in Scheme 12; MAD = (2,6-*t*Bu$_2$-4-



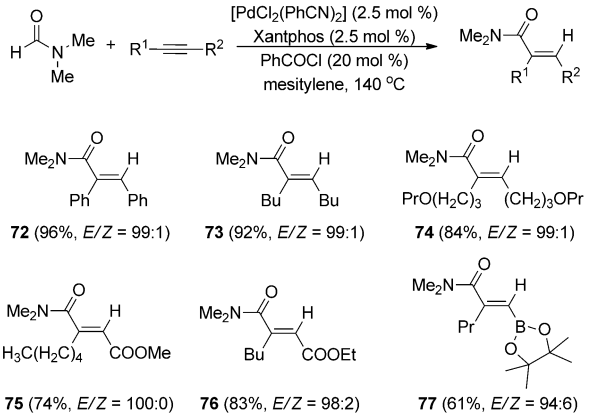
Scheme 11. Hydrocarbamoylation of acetylenes by nickel/Lewis acid catalysis. [a] Used P*t*Bu$_3$ and AlMe$_3$. [b] Used PCy$_3$ and BPh$_3$. cod = 1,5-cyclooctadiene, L.A. = Lewis acid.



Scheme 12. Proposed mechanism for hydrocarbamoylation of multiple bonds by nickel/Lewis acid catalysis.

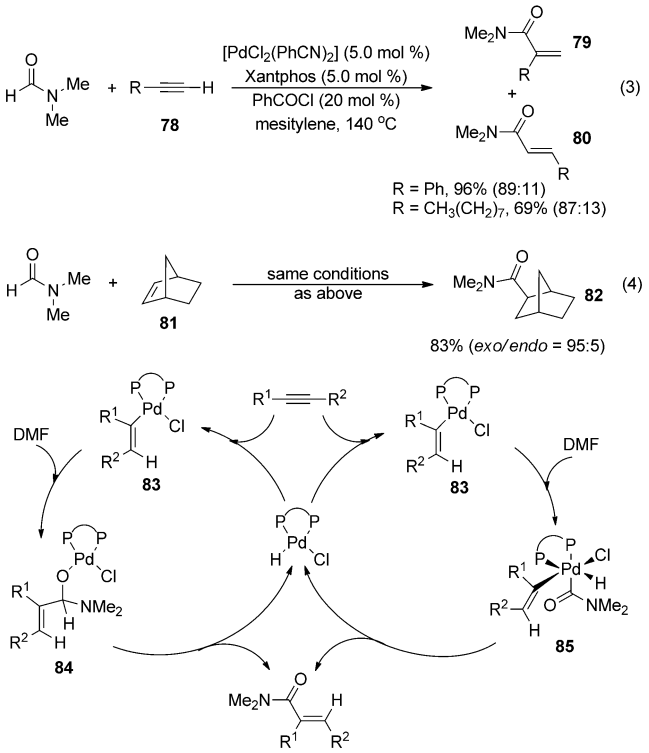
MeC$_6$H$_2$O)$_2$AlMe].[22] Various unsaturated amides were obtained. A Lewis acid was used as a cocatalyst in this intermolecular hydrocarbamoylation, and it significantly increased the stereo- and regioselectivity. The proposed mechanism for this reaction is shown in Scheme 12. The coordination of the Lewis acid to DMF makes the formyl C(sp^2)–H bond reactive enough to undergo oxidative addition to a nickel(0) species. Subsequent hydronickelation of alkynes assisted by the coordination of alkynes to the nickel center gives the alkenylnickel intermediate **70**, which upon reductive elimination affords the product. In the reaction with 1,3-dienes, coordination and subsequent migratory insertion of 1,3-dienes (e.g., **64**) into the H–Ni bond at the terminal double bond generates the π-allyl nickel intermediate **71**, which undergoes reductive elimination to form a C–C bond selectively at the methyl-substituted carbon center of the allyl ligand to give the product. The authors also mentioned that an alternative mechanism through a nickeladihydrofuran intermediate could not be excluded.

In 2010, Tsuji and co-workers independently reported a palladium-catalyzed intermolecular hydrocarbamoylation of alkynes with DMF (Scheme 13).[23] This development not only provides a regio- and stereoselective approach to *E*-



Scheme 13. Palladium-catalyzed intermolecular addition of DMF to alkynes. Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene.

configured α,β-unsturated amides from internal alkynes, but also allows terminal alkynes to be used as substrates for the first time [Eq. (3) in Scheme 14]. In addition to alkynes, the addition reaction of DMF with norbornene proceeded with this catalyst system [Eq. (4) in Scheme 14]. Benzoyl chloride was employed as a useful additive in this [PdCl$_2$(PhCN)$_2$]/Xantphos catalytic system. According to the report from Skrydstrup and co-workers on the generation of Pd–H species in situ upon the addition of acid chlorides to a palladium catalyst system,[24] a Pd–H species might be a key intermediate. A possible mechanism was proposed as shown in Scheme 14. An alkenylpalladium intermediate **83** may be formed by the hydropalladation of an alkyne with the Pd–H species. It has been proven that DMF reacts directly with the alkyne, and not through the decomposition of DMF into CO and the corresponding amine, in this transformation. Hence, the formed alkenylpalladium intermediate **83** may either afford the alkoxypalladium intermediate **84** by the insertion of the C=O bond of DMF, or afford the palladium(IV) intermediate **85** by oxidative addition of the formyl C–H bond of DMF. Both intermediates **84** and **85** can provide the product through β-hydride elimination and reductive elimination, respectively.

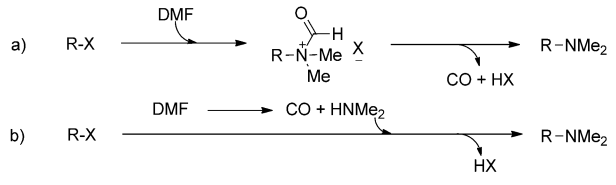


Scheme 14. Proposed mechanism for palladium-catalyzed intermolecular addition of DMF to alkynes.

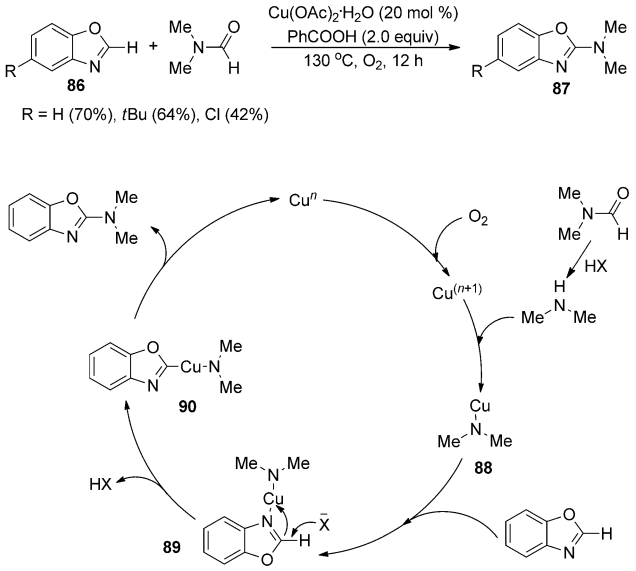
4. Serving as a Source of Dimethylamine in Amination Reactions

DMF has been utilized widely in the amination of aryl halides by serving as an important and convenient source of dimethylamine, which results from facile decomposition of DMF under various reaction conditions.[25–28] As described in by Muzart, there are usually two pathways for the formation of the dimethylamino products: one is the reaction of the substrates with DMF and subsequent elimination of carbon monoxide (Scheme 15a); the other is the reaction with dimethylamine generated in the decomposition of DMF (Scheme 15b).

In 2011, a copper-catalyzed direct oxidative C–H amination of benzoxazoles with DMF as the dimethylamine source was reported by Li and co-workers (Scheme 16).[29] This catalytic system can be utilized in the synthesis of a variety of substituted benzoxazol-2-amines. The related mechanistic studies indicate that the acid plays an important role in the release of dimethylamine from DMF. Both the copper catalyst and dioxygen oxidant were essential for this reaction.



Scheme 15. Two pathways for the synthesis of dimethylamines.



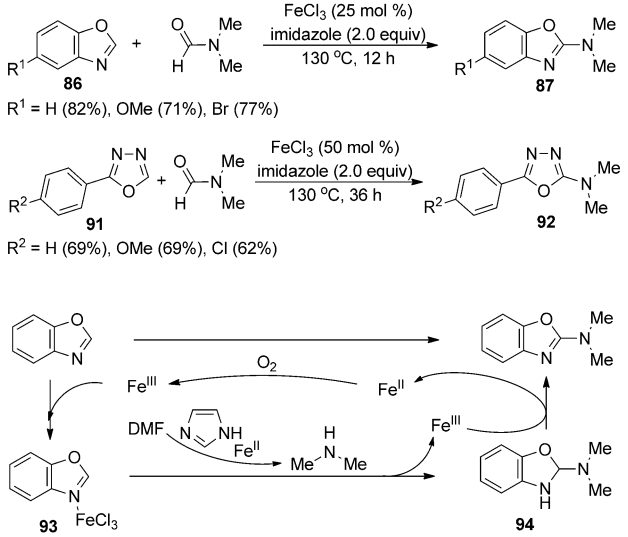
Scheme 16. Copper-catalyzed direct oxidative C–H amination of benzoxazoles with DMF.

For the proposed mechanism, the copper intermediate **88** is initially generated by coordination with the secondary amine and the subsequent elimination of water is assisted by CH_3CO_2H. The intermediate **89** is involved in the proposed process by the coordination of **88** to azole. The subsequent deprotonation/rearrangement of **89** generates **90**, which undergoes reductive elimination to form the product with the regeneration of the copper catalyst to complete the catalytic cycle.

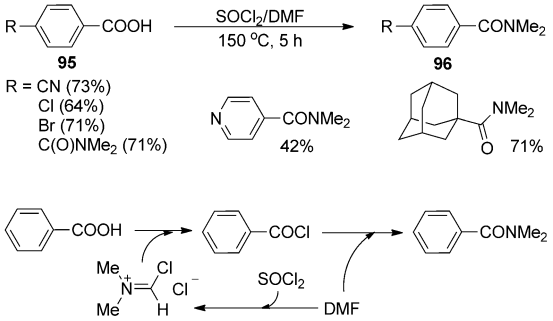
Simultaneously, Yu et al. reported an iron-catalyzed direct amination of azoles using DMF as a dimethylamine source (Scheme 17).[30] Imidazole was used as an additive in this catalytic system and oxygen in air was employed during the transformation process. A plausible mechanism was proposed and is presented in Scheme 17. An iron(III) species plays two roles in this catalytic cycle. Firstly, it could act as the Lewis acid, which activates the C2 position of the benzoxazole. It could also be an oxidant to complete the final rearomatization. As an important parameter in this catalytic system, O_2 was proposed to serve mainly as a co-oxidant for oxidizing iron(II) to iron(III).

5. Serving as a Source of Dimethylamine in Amidation Reactions

There have been some reports on the synthesis of amides just by heating DMF solutions of acyl chlorides, esters, or anhydrides.[31] Recently, Kumagai et al. reported an effective synthesis of *N*,*N*-dimethylamides from carboxylic acids and DMF in the presence of thionyl chloride (Scheme 18).[32] Different from previous work, the Vilsmeier complex from DMF and thionyl chloride was generated in situ, and subsequent chlorination and amidation reactions occurred in a one-pot sequence.



Scheme 17. Iron-catalyzed direct amination of azoles.

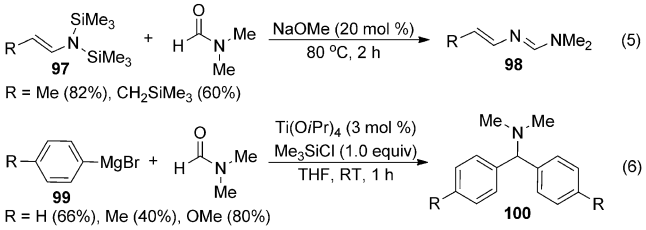


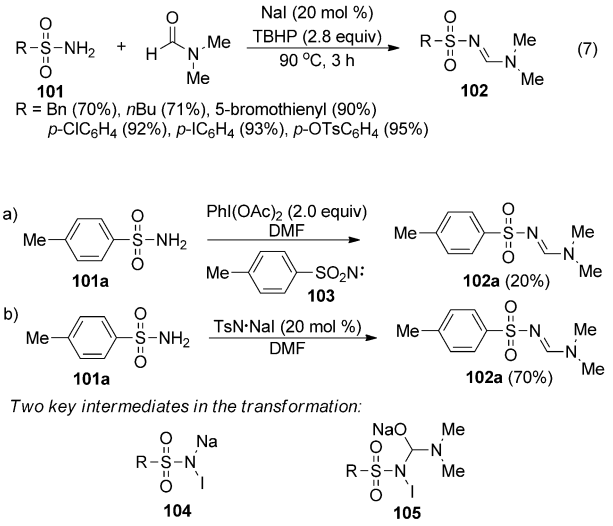
Scheme 18. Synthesis of N,N-dimethylamides from carboxylic acids.

6. Serving as a Precursor of Me_2NCH

As described in Muzart's review, DMF can provide Me_2NCH units for different reactions, such as the synthesis of enamidines (**98**) from silylamines (**97**), and dimethylalkylamines (**100**) from Grignard reagents (**99**) [Eqs. (5) and (6)].[33]

Very recently, Wan and co-workers reported the NaI-catalyzed synthesis of *N*-sulfonylformamidine (**102**) from the direct condensation of sulfonamide and DMF [Eq. (7) in Scheme 19].[34] Some mechanistic studies of this transformation were conducted (Scheme 19a and b), and on the basis of the results, the authors concluded that TsN·NaI, not the free





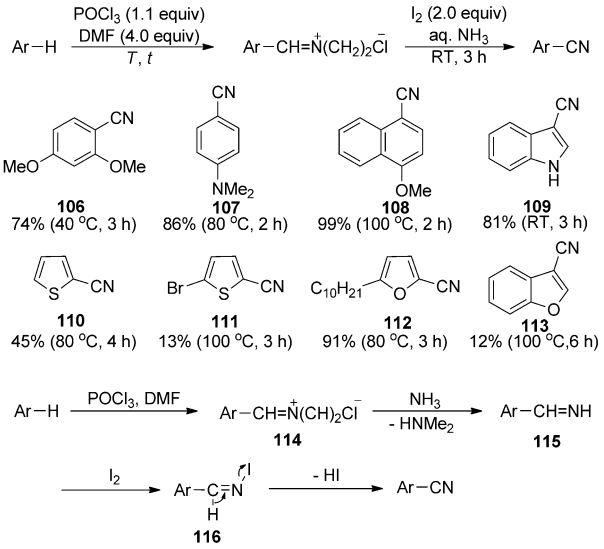
Scheme 19. Mechanistic studies and key intermediates of the direct condensation of sulfonamide with DMF.

nitrene, is the reaction intermediate in this transformation. Hence, two key intermediates, **104** and **105**, were confirmed to be involved in the transformation. As depicted by the authors, under the oxidation of TBHP, the reaction of RSO_2NH_2 with NaI forms **104**, while **105** is formed by the nucleophilic attack of **104** to a formamide.

7. Serving as a Precursor in Cyanation Reactions

Aryl cyanides are versatile building blocks in organic synthesis for natural products, pharmaceuticals, agricultural chemicals, materials, and dyes.[35] Their great importance in chemistry and biology has consistently stimulated the development of novel methods for their preparation.[36]

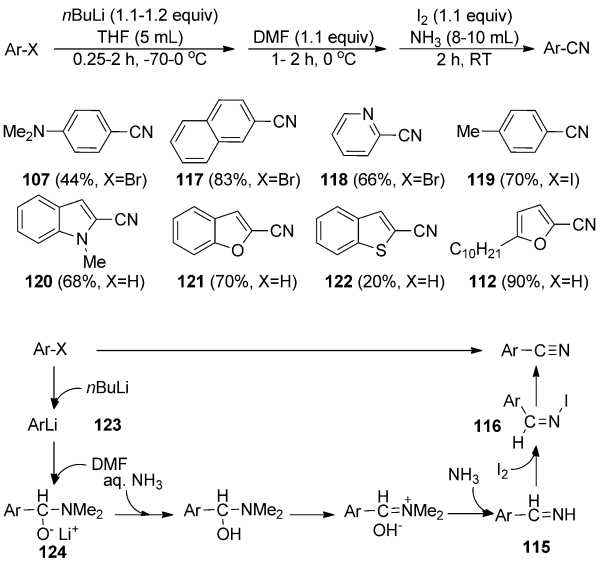
It's well known that during the Vilsmeier–Haack formylation process the iminium salt, formed in the electrophilic aromatic substitution of the electron-rich arene with the Vilsmeier reagent, can be easily transformed into the corresponding aldehyde by hydrolysis. Recently, it was found that the iminium salt could be converted into relevant aromatic nitriles by treatment with molecular iodine in aqueous ammonia. In 2010, Ushijima and Togo reported the synthesis of aromatic nitriles from electron-rich aromatics by treatment with $POCl_3$ and DMF, and subsequent reaction with molecular iodine in aqueous ammonia (Scheme 20).[37] Using this metal-free one-pot conversion, various electron-rich aromatics could be smoothly converted into the corresponding aromatic nitriles in good to moderate yields. A plausible mechanism for this reaction was given as shown in Scheme 20. When treated with ammonia, the iminium salt **114** could be transformed into the aromatic imine **115**. Then molecular iodine serves as an oxidizing agent and reacts with the aromatic imine **115** to provide the corresponding aromatic N-iodoimine **116**, which generates the aromatic nitrile through elimination in aqueous ammonia. A plausible mechanism for this transformation suggests that the carbon



Scheme 20. Conversion of electron-rich aromatics into aromatic nitriles using Vilsmeier reagents.

atom of CN originates from the carbonyl group of DMF, and the nitrogen atom from ammonia.

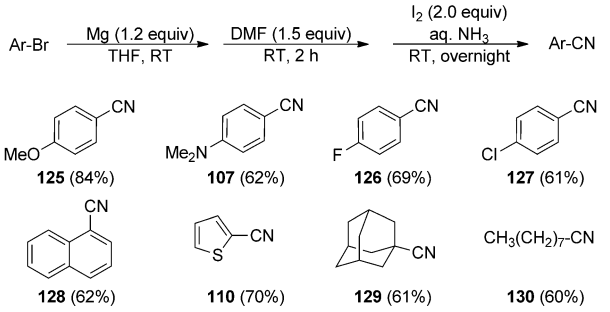
However, the need of highly electron-rich aromatics in the formation of aromatic N,N-dimethyliminium salts limits the scope of this transformation. And this prompted the authors to seek more convenient methods for this conversion. Following this work, they reported a novel one-pot method for the preparation of aromatic nitriles from aryl bromides and arenes through the formation of aryllithiums and their DMF adducts, followed by treatment with molecular iodine in aqueous ammonia (Scheme 21).[38] The scope of this conversion extends to various electron-rich and electron-deficient aromatic bromides, as well as heteroaromatics. This method is not practical for large-scale preparations because of



Scheme 21. Conversion of aryl bromides into aromatic nitriles via organolithium compounds. THF = tetrahydrofuran.

the difficulties in controlling the reaction mixture at low temperature and handling a large amount of *n*BuLi. As shown in Scheme 21, the reaction of aryl bromides or arenes with butyllithium form the aryllithiums **123**, which react with DMF to generate the adduct **124**. In a way similar to that of the previous work,[37] the formation of the aryl imines **115** and N-iodoayl imines **116** are supposed to be involved in this process.

A more facile and practical transformation of aryl bromides into the corresponding aromatic nitriles was reported recently by the same group (Scheme 22).[39] In this conversion, various aryl bromides were transformed into the



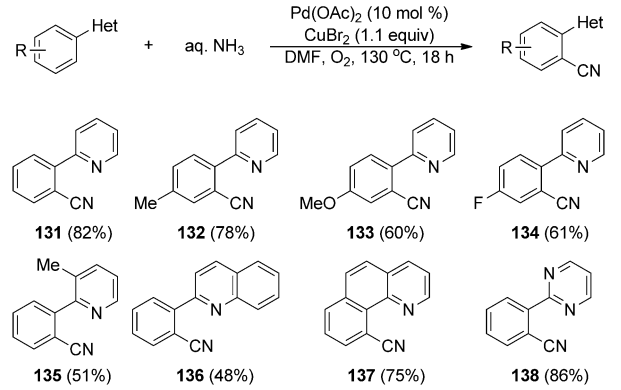
Scheme 22. Conversion of aromatic bromides into aromatic nitriles through the formation of Grignard reagents and their DMF adducts.

corresponding aromatic nitriles in good yields by treatment with Mg and subsequently with DMF, and then treatment with molecular iodine in aqueous ammonia. Additionally, aliphatic bromides could also be transformed into the corresponding alphatic nitriles in good yields.

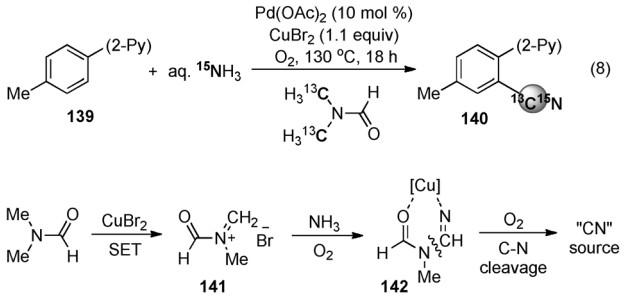
Metal-catalyzed cyanation of aryl halides or cyanation by C–H bond functionalization of arenes has been significantly developed. Generally, CN sources containing the whole CN unit, such as metal cyanide salts (CuCN, KCN, NaCN, ZnCN), TMSCN, $[K_3Fe(CN)_6]$, and acetone cyanohydrin, have been utilized in the above cyanation reactions.[40]

Recently, Kim and Chang disclosed a palladium-catalyzed cyanation of aryl C–H bonds by employing DMF and ammonia as a combined source for the CN unit, and it was applicable to a range of substrates (Scheme 23).[41] Different from Togo's work, isotopic incorporation experiments revealed that the carbon atom of the CN group originates from the N,N-dimethyl moiety rather than the formyl group of DMF [Eq. (8) in Scheme 24]. As reported by the authors, this transformation could be completely inhibited in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). A mechanism was proposed by the author (Scheme 24). The imine species **141** is possibly formed in a single-electron transfer (SET) step, and then attacked by ammonia to afford the amidine intermediate **142**. The CN unit is presumably provided by the C–N bond cleavage in the amidine intermediate **142** under the aerobic conditions.

In 2011, Cheng and co-workers reported a palladium-catalyzed cyanation of indole C–H bonds with the combination of NH_4HCO_3 and DMSO as a safe cyanide source. In this context it was found that the combination of DMF and NH_4HCO_3 delivered the cyano product in low yield [Eq. (9)

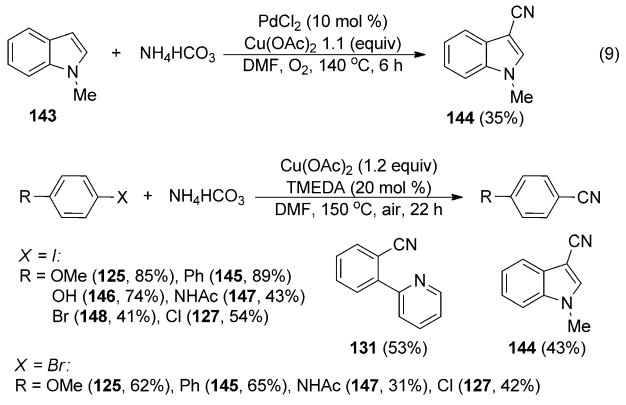


Scheme 23. The combined source of CN from DMF and ammonia.



Scheme 24. Proposed mechanism for the formation of CN.

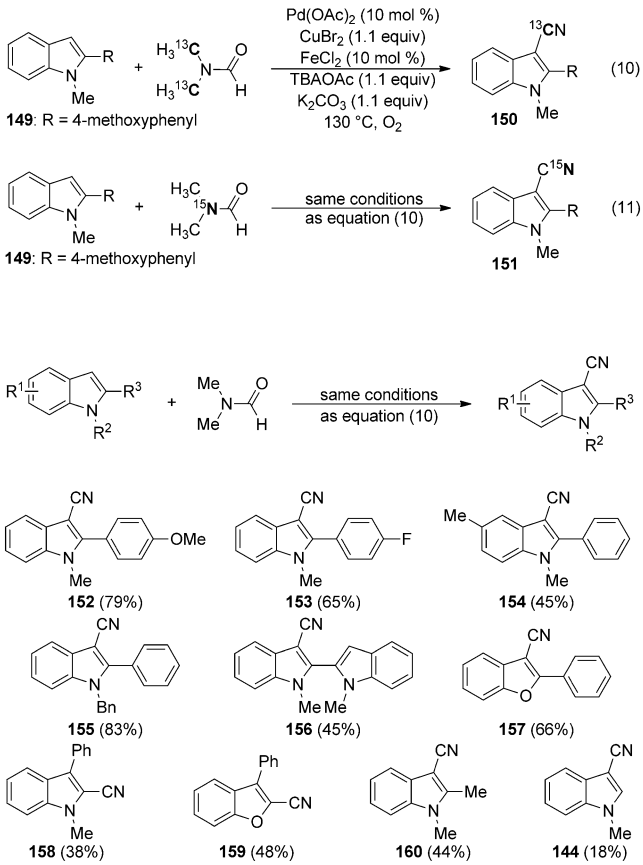
in Scheme 25].[42] Subsequently, they reported the copper-mediated cyanation of aryl halides with the combined cynanide source of DMF and NH_4HCO_3 (Scheme 25).[43] Similar to the work of Chang,[41] the C atom in the CN was proven to be derived from a methyl group in DMF and the N atom in the CN comes from NH_4HCO_3. As reported, CN^- was detected by indicator paper when the combination of DMF, NH_4HCO_3, and $Cu(OAc)_2$ was heated at 150 °C for 2 h, whereas no detectable CN^- was formed in the absence of $Cu(OAc)_2$. According to these results, the authors suggested that copper played an important role in the formation of CN^-



Scheme 25. Copper-mediated cyanation of aryl halides. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

in situ. However, the mechanism of the formation of the CN^- from the combination of DMF and NH_4HCO_3 is still unclear.

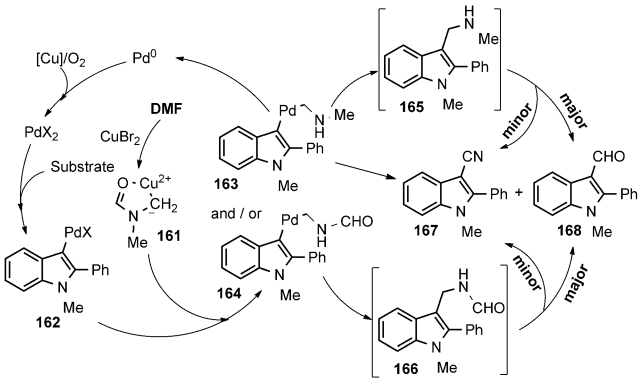
Jiao and Ding disclosed the intriguing direct transformation of DMF into a CN substituent.[44] Isotope-labeling experiments indicated that both the C and N of the cyano group were derived from DMF [Eqs. (10) and (11) in Scheme 26; TBA = tetra-*n*-butylammonium]. This novel transformation offers an alternative method for preparing



Scheme 26. Direct transformation of DMF into a CN group.

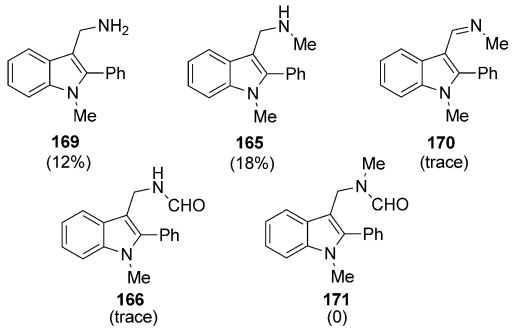
aryl cyanides, though it is currently limited in scope to indoles and benzofurans (Scheme 26). A series of experiments were carried out to probe the mechanism of this conversion. It is noteworthy that the reaction was scarcely influenced by the presence of TEMPO, thus suggesting that a single-electron transfer mechanism is unlikely to operate in this case. The possibilities of generating the isonitrile or CN^- were ruled out as well by a control reaction in the presence of CuCN.

As reported by the authors, the mechanism of this transformation is not completely clear yet. A plausible mechanism for this transformation was proposed and is illustrated in Scheme 27. It was observed that none of the desired product was detected when 1,1-dimethoxy-*N*,*N*-dimethylmethanamine was employed instead of DMF, whereas a low yield of the product could be obtained when the reaction was carried out in DMA. Hence, the copper complex **161**, which was easily formed as reported,[45] could be an intermediate involved in this conversion. Though several



Scheme 27. Proposed mechanism for the direct transformation of DMF into a CN group.

possible intermediates, which might be generated through an electrophilic reaction ofthe complex **161** with the Pd intermediate **162**, were investigated under the standard reaction conditions, no conclusive result was obtained (Scheme 28). More studies are needed to more accurately elucidate this mechanism.

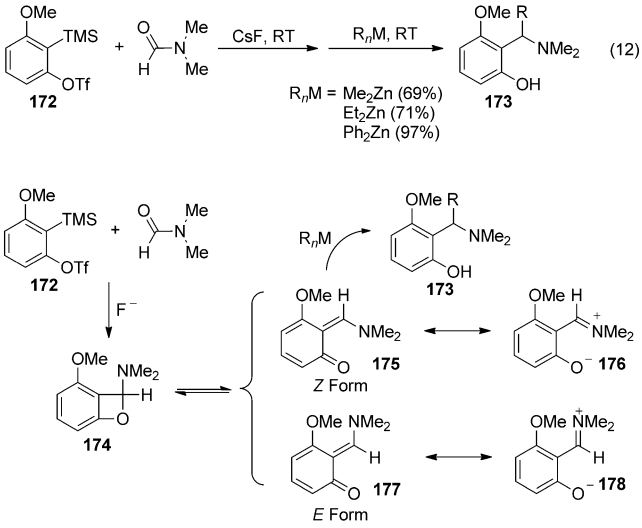


Scheme 28. Possible intermediates in the transformation shown in Scheme 27. The yield of the cyano product in parentheses was obtained when the reactions of these substrates were carried out under standard reaction conditions.

8. Reactions with Arynes

In 2010, Miyabe and co-workers reported on the insertion of arynes into the C=O π bond of DMF and subsequent trapping of the intermediate with dialkylzinc reagents [Eq. (12) in Scheme 29].[46] To enhance the reactivity and regioselectivity toward the C=O bond, 3-methoxy-2-(trimethylsilyl)phenyl triflate (**172**) was employed as an aryne precursor. The formal [2+2] cycloadduct **174** and the quinone methide *E* and *Z* forms were thought to be involved in the trapping process (Scheme 29). Furthermore, investigations indicate that dialkyzincs did not add to the four-membered ring intermediate but rather to the quinone methide intermediates.

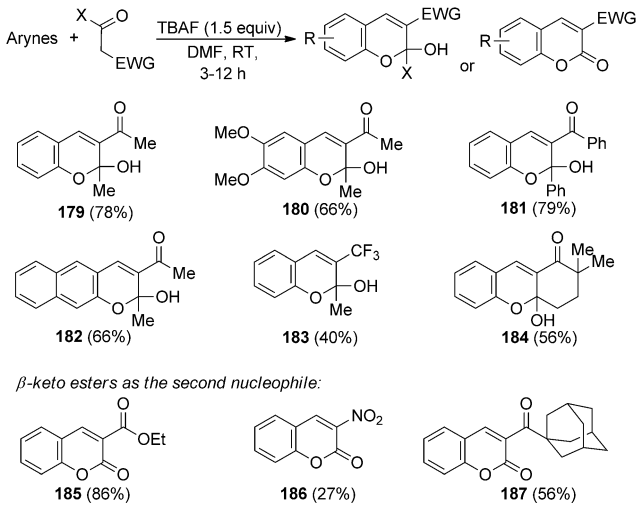
Recently, active methylene compounds were employed as a second nucleophile for trapping the unstable intermediates, thus completing the three-component coupling reaction and



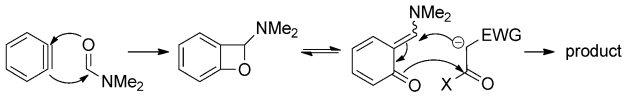
Scheme 29. Proposed mechanism for this reaction. TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl

leading to cyclic products (Scheme 30).[47] Since the active methylene compounds have excellent reactivity towards arynes, the control of two competitive insertions between DMF and the active methylene compounds toward the intermediates is the key requirement for this reaction. The addition of an enolate anion to the unstable intermediates and subsequent elimination of dimethylamine is proposed to be the major pathway in this reaction (Scheme 31). While β-keto esters were utilized as a second nuclephile to trap the unstable intermediates, coumarin derivatives were obtained by the elimination of an ethoxide and dimethylamine.

Simultaneously, Yoshida et al. reported a similar three-component coupling reaction of arynes and DMF to deliver coumarins.[48] Arylacetonitriles were found to be suitable as

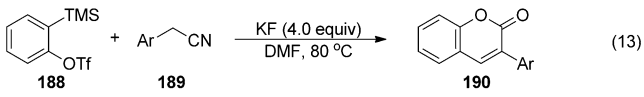


Scheme 30. A multicomponent coupling reaction induced by insertion of arynes into the C=O bond of DMF. EWG = electron-withdrawing group, TBAF = tetra-*n*-butylammonium fluoride.



Scheme 31. Major reaction pathway for this multicomponent coupling reaction.

a second nucleophile and provide good yields of the coumarins as well [Eq. (13)].



(13)

Ar = Ph (60%), *o*-$OMeC_6H_4$ (39%), *o*-ClC_6H_4 (31%), 2-naphthyl (66%) 2-benzo[*d*]thiazoyl (31%), 3-benzo[*d*]dioxolyl (40%)

9. Conclusion

This Minireview highlights recent progress in utilizing DMF as a multipurpose precursor in various reactions such as formylation, amination, aminocarbonylation, amidation, and cyanation, as well as its reaction with arynes. In particualar, the utilization of DMF as a precursor in cyanation has seen significant development. It is noteworthy that in some reactions other amides can be used as precursors as well. With the development of green and sustainable chemistry, it can be predicted that utilization of DMF as a precursor will continue to develop in organic synthesis. The development of new catalytic systems with increased reactivity will have important implications for the practical application of DMF as a reagent. Moreover, mechanistic investigations in both the reported reactions and future developments of novel reactions will have to be conducted.

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