Chapter

# *N*,*N*-Dialkyl Amides as Versatile Synthons for Synthesis of Heterocycles and Acyclic Systems

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## Abstract

*N*,*N*-Dialkyl amides such as *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA), are common polar solvents, finds application as a multipurpose reagent in synthetic organic chemistry. They are cheap, readily available and versatile synthons that can be used in a variety of ways to generate different functional groups. In recent years, many publications showcasing, excellent and useful applications of *N*,*N*-dialkyl amides in amination (R-$NMe_2$), formylation (R-CHO), as a single carbon source (R-C), methylene group (R-$CH_2$), cyanation (R-CN), amidoalkylation (-R), aminocarbonylation (R-$CONMe_2$), carbonylation (R-CO) and heterocycle synthesis appeared. This chapter highlights important developments in the employment of *N*,*N*-dialkyl amides in the synthesis of heterocycles and functionalization of acyclic systems. Although some review articles covered the application of DMF and/or DMA in organic functional group transformations, there is no specialized review on their application in the synthesis of cyclic and acyclic systems.

**Keywords:** amination, amidation, amidoalkylation, aminocarbonylation, cyanation, dialkyl amides, formylation, heterocycles

## 1. Introduction

The great advantage of DMF, DMA and other *N*,*N*-dialkylamides are their versatility as reaction medium, polar and aprotic nature, high boiling point, cheap and ready availability. DMF can react as electrophile or a nucleophile and also act as a source of several key intermediates and take a role in reactions as a dehydrating agent, as a reducing agents [1] or as a catalyst [2–5], stabilizer [6–10]. For the synthesis of metallic compounds DMF can be an effective ligand. *N*,*N*-dialkylamides could be considered as a combination of several functional groups such as alkyl, amide, carbonyl, dialkyl amine, formyl, N-formyl and highly polar C-N, C〓O, and C-H bonds. Due to flexible reactivity of *N*,*N*-dialkylamides, during the past few years, chemists have succeeded in developing reactions, where DMF and DMA could be used to deliver different functional groups such as amino (R-$NMe_2$), formyl (R-CHO), methylene (R-$CH_2$), cyano (R-CN), amidoalkyl ($CH_2N(CH_3)$-C(〓O) $CH_3$-R) aminocarbonyl(R-$CONMe_2$), carbonyl(R-CO), methyl (-Me), a single atoms such as C, O, H etc. (**Figure 1**). Similarly, DMF and DMA could be used in the

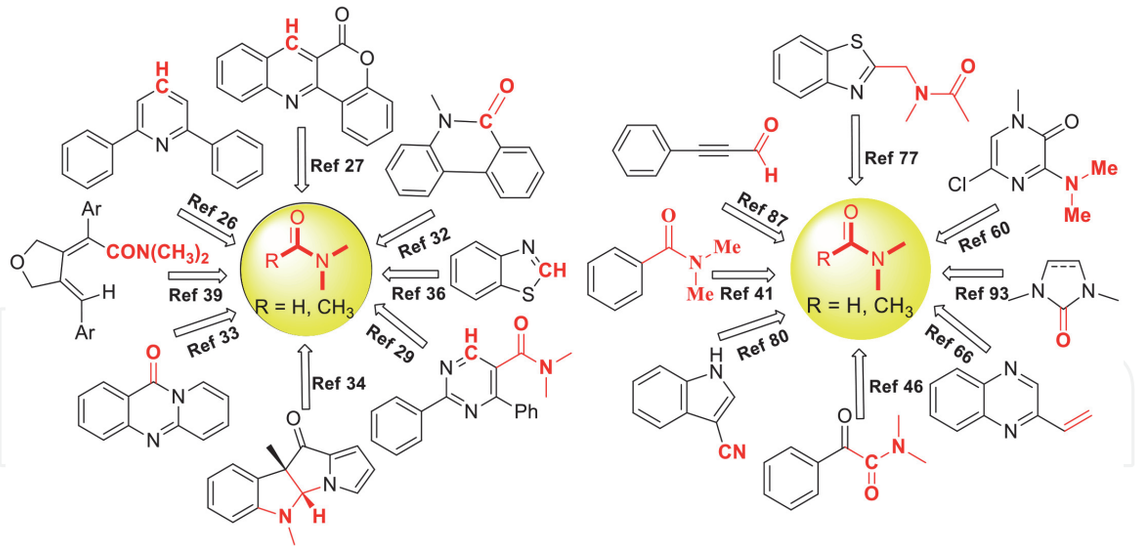


**Figure 1.**
*DMF and DMA as a synthon for the various reactions.*

preparation of heterocyclic compound through formylation of active methylene groups, conversion of methyl groups to enamines, and formylation of amino groups to amidines. Further, it can also be utilized as an intermediate in the modification of heterocyclic compounds [11].

A non-exhaustive seminal review by Muzart [1], highlighted different roles of DMF inorganic synthesis covered literature up to 2009, another comprehensive review by Ding and Jiao appeared in 2012 [12] which covered aspects of DMF as a multipurpose precursor in various reactions. Further, specialized review by Batra et al. [13], and other reviews dealing with recent applications of DMF and DMA as a reagent [14] and triple role of DMF as a catalyst, reagent and stabilizer also appeared [15].

In this book chapter we summarized developments on applications of DMF and DMA in reactions such as amination (R-$NMe_2$) [16], formylation (R-CHO) [17, 18], as a single carbon source (R-C), methylene group (R-$CH_2$) [19], carbonylation (R-CO), as well as newer reactions such as amidoalkylation (-$CH_2N(CH_3)$-C(=O)$CH_3$-R) [20], metal catalyzed aminocarbonylation (R-$CONMe_2$) [21], cyanation (R-CN) [22, 23], and formation heterocycles, took place during the past few decades and up to October 2019. Heterocycles are important compounds finding excellent applications as useful materials and medicinally important compounds. Thus unlike other reviews appeared on this subject [1, 12–15], we provided special emphasis on synthesis of heterocyclic compounds and reactions involving DMF and DMA. Thus, first part of this book chapter will cover synthesis of construction of cyclic system, especially heterocycles, the next part will cover the formation of open chain compounds. Although DMF can serve as a reagent in organic reactions such as Friedel-Crafts [24] and Vilsmeier-Haack [25] reactions the actual reagent is derivative of DMF, hence we did not cover such subjects. We hope this book chapter will stimulate further research interest on the application of DMF and DMA in organic synthesis.

## 2. DMF and DMA as synthon in synthesis of heterocycles

### 2.1 Construction of pyridine ring

Guan and co-workers reported synthesis of symmetrical pyridines from ketoxime carboxylates using DMF as a one carbon source in the presence of

ruthenium catalyst and $NaHSO_3$ as an additive (**Figure 2**). A series of ketoxime acetates **2** reacted smoothly with DMF to give corresponding pyridine derivatives **3**. Replacement $NaHSO_3$ with other oxidants led to decrease in the yield. The reaction condition was optimized by use of various additives and catalysts. The desired product was obtained in good yield, in the presence of $NaHSO_3$, $Ru(cod)Cl_2$ and at 120°C. Both electron withdrawing and electron donating group attached to the aryl rings gave the corresponding symmetrical pyridines. But the yield decreased due to steric effect by the orthosubstituents.

A possible mechanism for the reaction was proposed. Oxidation of DMF by Ru (II) gives an iminium species **A** and Ru(0). Followed by which oxidative addition of ketoxime acetate to Ru(0) generates an imino-Ru(II) complex **B**, undergoes tautomerization to afford enamino-Ru(II) complex **C**. Then, nucleophilic addition of **C** to species **A** produces an imine intermediate **D**. Condensation of imine intermediate **D** with a second ketoxime acetate gives intermediate **E**. Nucleophilic substitution of **E** by $NaHSO_3$ followed by intramolecular cyclization of the intermediate **F** forms a dihydropyridine intermediate **G**. Finally, Ru-catalyzed oxidative aromatization of **G** by oxygen provided the product **H** [26].

Su et al., reported cyclisation of 4-(phenylamino)-2*H*-chromen-2-ones to give novel functionalized 6*H*-chromeno[4,3-b]quinolin-6-ones (**Figure 3**) in the presence of $Cu(OAc)_2.H_2O$/TBPB catalytic system (**Figure 3**). In this reaction, DMF served as the source of methine group.

The reaction proceeded smoothly with electron-donating and electron-withdrawing substituents on the aniline ring and the expected products were obtained in good yields. A plausible mechanism was proposed by the author in. Initially, DMF is converted into iminium ion **A** with the help of Cu/TBPB via radical pathway. Next, reaction of 4-(phenylamino)-2H-chromen-2-ones with active iminium ion **B** gives intermediate **C**. Further, removal of MeNHCHO group afforded **D** which is attacked by $NaHSO_3$ followed by an intramolecular cyclization to afford desired product **5** [27].

In 2015, Deng and co-workers reported the Ru catalyzed multi-component reaction of acetophenones **6**, ammonium acetate (N source) and DMF (one carbon source) to get 2,4-diarylsubstituted-pyridines **7** under $O_2$ atmosphere (**Figure 4**).

In this reaction DMF, in the presence of $Ru/O_2$ catalyst, acted as a single carbon source. For better understanding of reaction mechanism, several control experiments were carried out [28] (**Figure 4**). Acetophenone was converted into a methyl

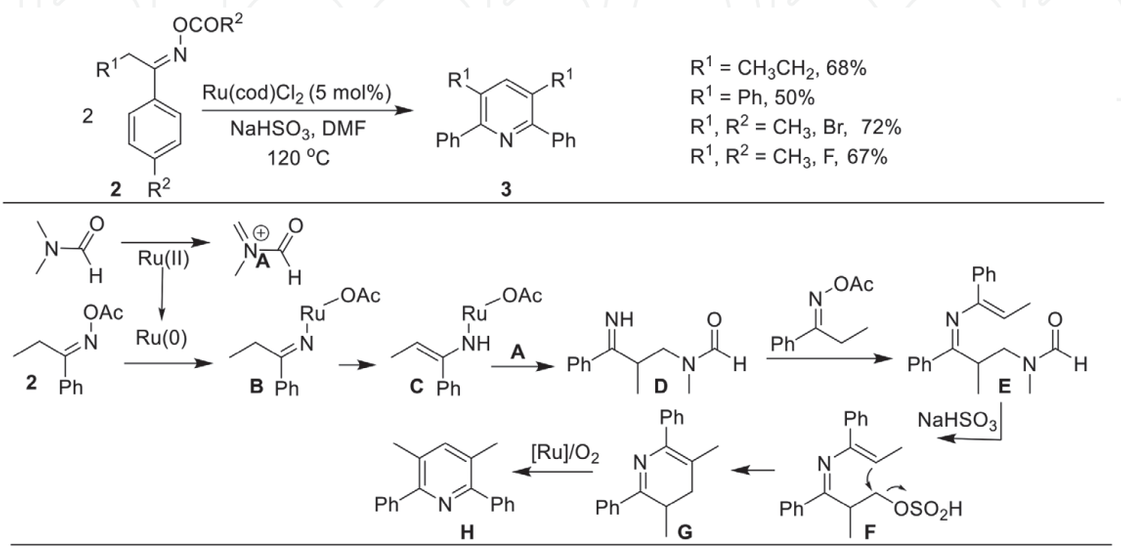


**Figure 2.**
*Pyridine ring formation by DMF using Ru-catalyzed cyclization of aryl ethyl ketoxime acetates.*

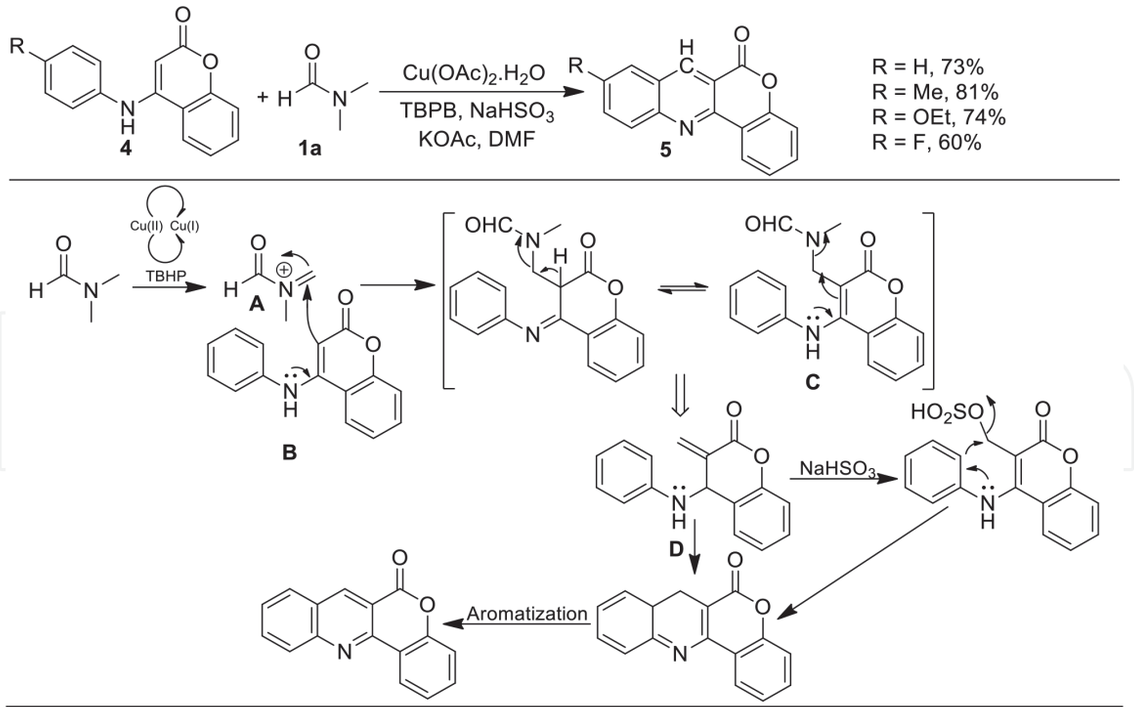


**Figure 3.**
*DMF as a methine source in pyridine ring formation via cyclization of 4-(phenylamino)-2H-chromen-2-ones.*

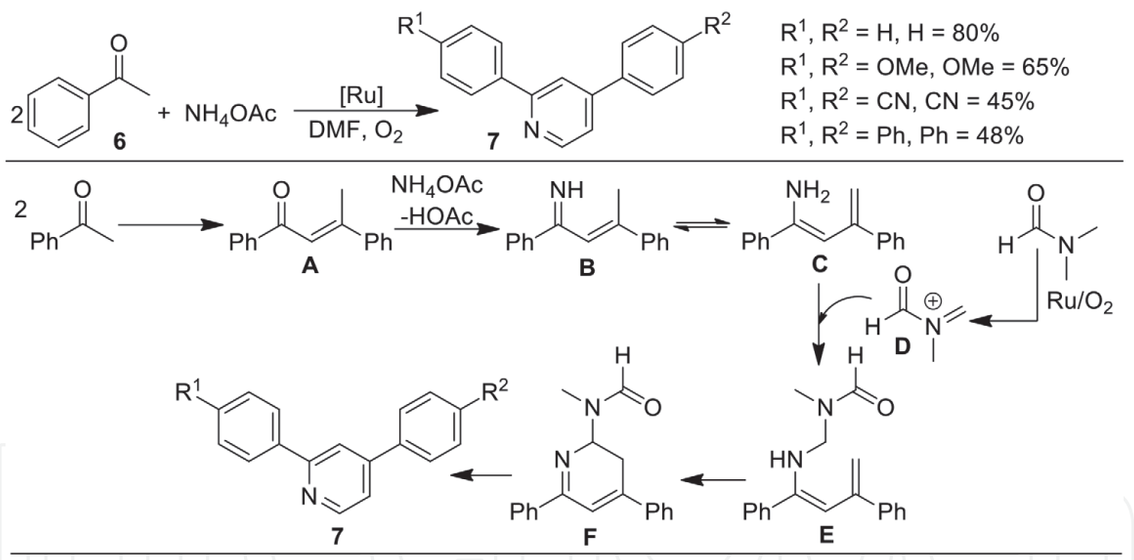


**Figure 4.**
*Ru-catalyzed cyclization of acetophenones with NH4OAc.*

ketene intermediate **A** by homo-condensation, which immediately converts into imine intermediate **B**, with the aid of $NH_4OAc$. Further, tautomerization of imine intermediates lead to the formation of intermediate **C**, which reacted smoothly with iminium species **D** to give intermediate **E** then this can be oxidized by $Ru/O_2$ to afford intermediate **F**, which further undergoes 6π electron cyclization followed by methylamide elimination to give the desired pyridine.

## 2.2 Construction of pyrimidine ring

Jiang and co-workers developed the first example of employing *N*,*N*-dimethylformamide (DMF) as a dual synthon, a one-carbon atom and amide source. A multicomponent reaction between amidines **8**, styrene **9**, and *N*,*N*-dimethylformamide

(DMF) took place in the presence of palladium-catalyst (**Figure 5**) to form pyrimidine carboxamide **10**.

The desired product was obtained in good yield under the optimal reaction condition $Pd(TFA)_2$ (5 mol%), Xantphos (5 mol%) and 70% TBHP (3.0 equiv) in 1.0 mL DMF at 120°C. Benzamidine salts containing electron-releasing or electron-withdrawing group on the benzene ring gave their desired product in moderate to good yield. Addition of radical scavenger, such as TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), BHT (2,6-di-tert-butyl-4-methylphenol), and DPE (1,1-diphenylethylene) led to no desired product formation, which indicates the radical pathway is involved in this transformation [29].

Xiong et al., reported a general and highly selective method for annulation of amidines **15** (**Figure 6**).

This is an efficient copper catalyzed synthesis of quinazolines **12** through C-N bond formation reaction between N-H bonds of amidines and $C(sp^3)$-H bond adjacent to sulfur or nitrogen atoms. In addition to DMF and DMA, DMSO, NMP and TMEDA could be used as solvent and as one carbon synthon [30]. This method avoids pre-functionalization of substrates.

In 2017, Fan et al., reported an efficient method for the synthesis of pyrimidines **13** from amidines **8** and ketones **12** through [3 + 2 + 1] type intermolecular cycloaddition reaction, under metal free condition (**Figure 7**). The reaction condition was optimized with different parameters and the suitable condition for multicomponent synthesis of pyrimidines was found to be, treatment of amidines (0.25 mmol), ketone (0.30 mmol), 70% TBHP (3.0 equiv), $Cs_2CO_3$ (2.0 equiv) in DMF (1.0 mL) at 120°C [31]. Both substituted amidines and substituted ketones worked well under standard condition to give pyrimidines in moderate to good yield. The reaction progressed well with $d_7$-DMF and the desired isotopic labeled product was obtained. This is evidence that the carbon atom comes from the DMF.

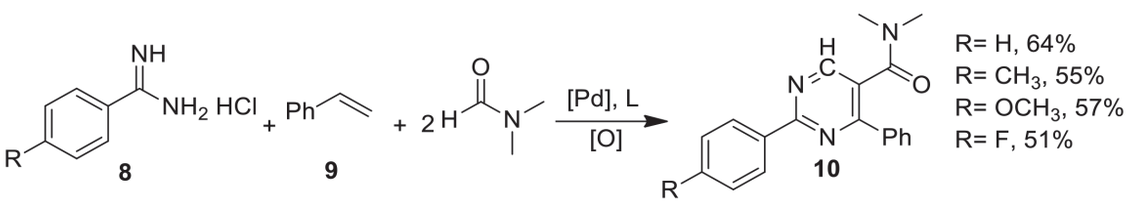


**Figure 5.**
*DMF as a dual synthon in synthesis of pyrimidine carboxamide.*

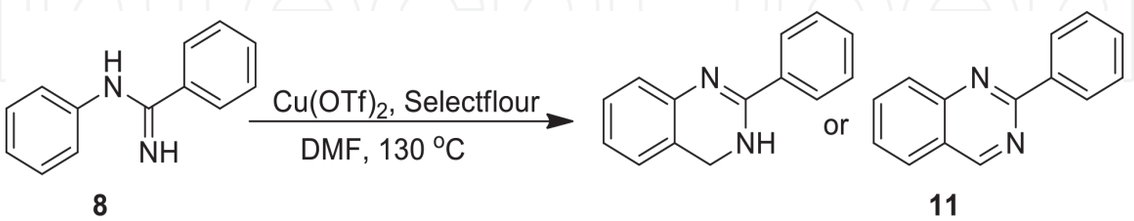


**Figure 6.**
*DMF as a one carbon source in Cu-catalyzed annulations of amidines.*

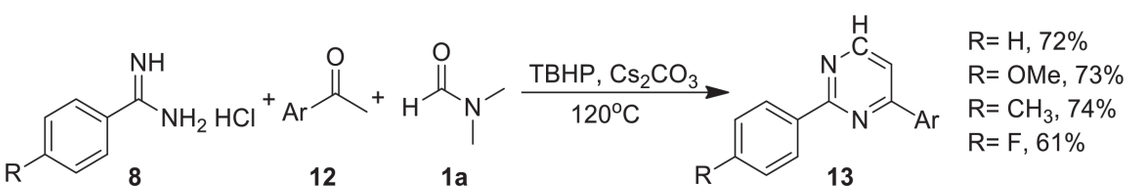


**Figure 7.**
*DMF in multicomponent synthesis of pyrimidines from amidines.*

## 2.3 Construction of quinazolinone ring

In 2016, Das et al., reported Pd/Ag catalyzed direct carbonylation of $sp^2$C-H bonds of **14** and **16** by employing DMF as one carbon source under oxygen for the synthesis of biologically important motifs pyrido-fused quinazolinone **15** and phenanthridinone **17**, respectively (**Figure 8**).

The reaction was examined using different metal catalyst systems such as Pd-Ag, Cu-Ag, Co-Ag, Ni-Ag and finally Pd-Ag catalytic system was found to be suitable for this transformation [32]. When labeled DMF ($CO^{18}$) was used as the solvent it has been found that product found not to contain $O^{18}$. From these results, it can be concluded that incorporated carbonyl group is coming from the methyl group of DMF. Reaction under argon instead of oxygen lead to the poor yield, which indicates "O" atom is coming from oxygen environment.

In 2015, Wu et al., reported C-H bond activation of arenes **14** followed by cyclization wherein DMF was used as the CO synthon, in the presence of $Pd(OAc)_2$-$K_2S_2O_8$ catalytic system under carbon monoxide atmosphere (**Figure 9**). The reaction works at autoclave free condition for the formation of *H*-pyrido[2,1*b*] quinazolin-11-ones **15**.

The reaction was optimized using different oxidant and catalysts under different temperature condition and the desired product was obtained in good yield in the

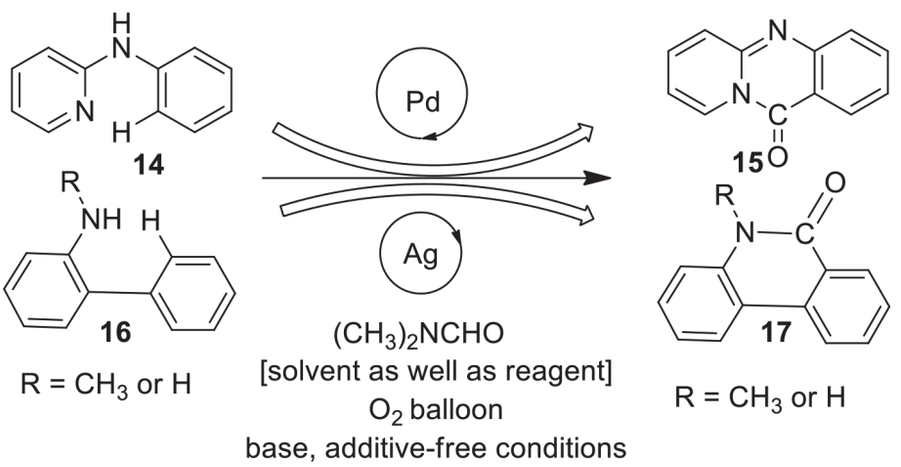


**Figure 8.**
*Pd/Ag catalyzed pyrido carbonylation of* N*-phenylpyridin-2-amine.*

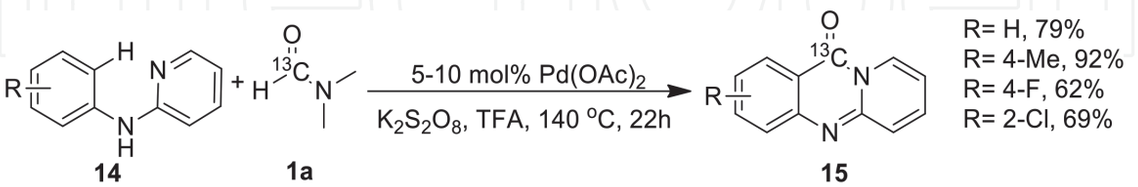


**Figure 9.**
*DMF as CO source in Pd-catalyzed carbonylation.*

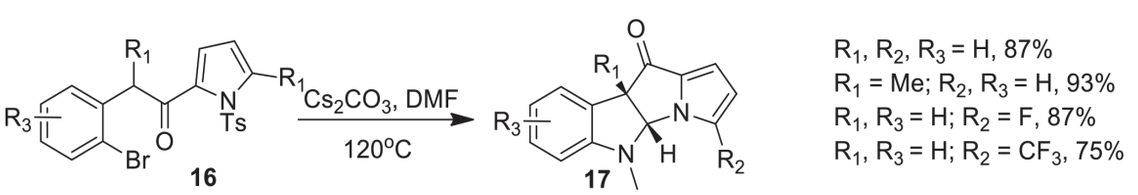


**Figure 10.**
*Synthesis of dihydropyrrolizino[3,2-*b*]indol-10-one.*

presence of $Pd(OAc)_2$-$K_2S_2O_8$ and DMF/TFA solvent system at 140°C under $O_2$ atmosphere. When the reaction was conducted with $^{13}CO$-labeled DMF (**1a**), the formation of $^{13}C$ product was detected using gas chromatography (GC). This indicates CO gas has been generated from the carbonyl of DMF with acid as the promoter. This protocol is simple, has broad substrate scope and the products are obtained in excellent yields [33].

### 2.4 Construction of dihydropyrroline indolone ring

In 2017, Chang and coworkers reported metal, ligand free, base promoted cascade reaction of DMF with *N*-tosyl-2-(2-bromophenylacetyl)pyrroles (**17**) for the synthesis of dihydropyrrolizino[3,2-*b*]indol-10-ones **16** (**Figure 10**) [34].

### 2.5 Construction of acyl indole ring

Deng et al., reported a metal free approach for the synthesis of 3-acylindoles **18** through a cascade reaction between 2-alkenylanilines **19** with *N*,*N*-dimethylformamide (DMF) as a one-carbon source (**Figure 11**). This methodology worked with $O_2$ as a terminal oxidant as well as oxygen donor. The 2-alkenylanilines containing different substitution such as, tosyl groups and other sulfonamides gave the desired 3-acylindoles in low to good yields. Unluckily, the substrate with a primary amine group failed to provide the desired product.

To prove the synthetic utility of this transformation gram scale experiment was conducted under optimized condition, wherein the yield of the corresponding product decreased slightly. Control experiments revealed that DMF acts as carbon source and $O_2$ is the source of the oxygen. When deuterium labeled DMF was used as solvent, the labeled product was observed. Meantime, to probe the source oxygen atom in the final product a reaction has implemented with $^{18}O$-DMF and only non-labeled product was obtained. Thus, author justified that $O_2$ is the source of the oxygen atom in the final product [35].

### 2.6 Construction of benzothiazole ring

Liu et al., developed a methodology for the synthesis of *N*-containing heterocycles including benzothiazoles, benzomidazoles, quinazolinone and benzoxazole using combination of $B(C_6F_5)_3$, atmospheric $CO_2$ and $Et_2SiH_2$ (**Figure 12**).

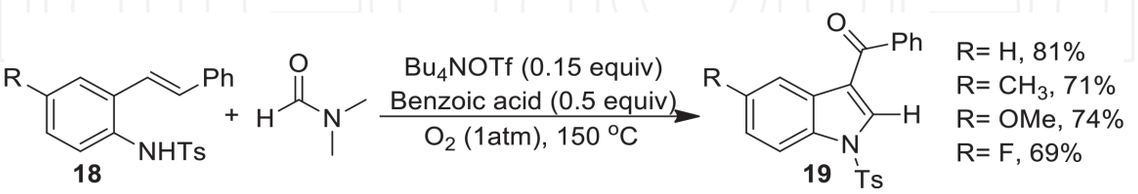


**Figure 11.**
*Formation of 3-acylindoles from 2-alkenylanilines.*

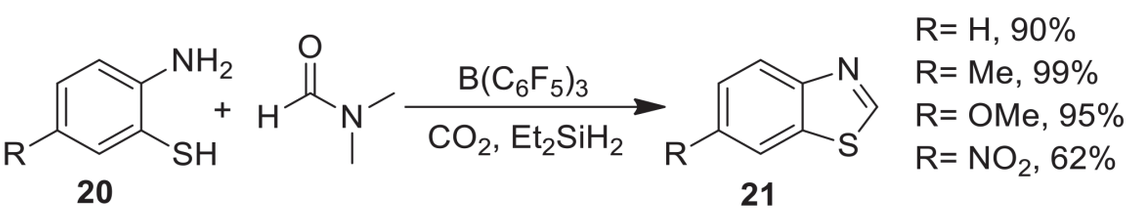


**Figure 12.**
*The cyclization of 2-aminothiophenol with DMF.*

This catalytic system was found to be highly effective for the cyclization of 2-aminobenzenethiol **20** or *o*-phenylenediamine **23** with *N*,*N*-dimethylformamide **1a**, utilizing $CO_2$ in this process. The reaction condition was optimized with different parameters and the corresponding product was obtained in the presence of 2-aminothiophenol (0.5 mmol), $B(C_6F_5)_3$ (5 mol%), $Et_2SiH_2$ (2 mmol), DMF (1 mL), $CO_2$ at 120°C.

To understand the role of $CO_2$ in this reaction, isotopic labeling reaction were carried out using $^{13}CO_2$, the non-labeled benzothiazole was observed in excellent yield [36]. When this cyclization reaction was carried out using $d_7$-DMF instead of DMF, deuterated benzothiazole was obtained. This experiment revealed that DMF served as the formylating reagent $CO_2$ as the promoter.

## 2.7 Construction of benzimidazole ring

Yadav et al. developed a cost effective synthetic protocol with 100% conversion of o-nitroaniline to benzimidazole using DMF as in-situ source of dimethylamine and CO. Herein, DMF undergoes water gas shift reaction in the presence of $CuFe_2O_4$ as catalyst to produce hydrogen (**Figure 13**). It mainly involves two steps the reduction of o-nitroaniline **22** to o-phenylenediamine **24** followed by cyclization. The ratio of DMF:water affects the conversion of o-nitroaniline to benzimdazole **24** hence the optimized ratio is 2:1 for the best conversion and selectivity. Homogeneous catalyst ($CuCl_2$) didn't show any conversion, CuO showed diminished activity and $CuFe_2O_4$ exhibited better activity. Optimum temperature for the reaction condition was 180°C [37].

A possible mechanism was proposed by author. Thermal degradation of DMF in the presence of water provides CO, which undergoes water gas shift reaction in the presence of catalyst to release hydrogen gas. This $H_2$ reduces nitro group to form amine group. The formation of o-phenylenediamine was confirmed with the help of GC-MS and HPLC analysis and compared with standard samples. Further, formylation of one of the amine groups took place in the presence CO, then intramolecular cyclisation takes place to give benzimidazole.

## 2.8 Construction of coumarin ring

Ohshita et al. developed method for the synthesis of coumarins **29** from *ortho*-quinone methide **26** formed *via* [2 + 2] cycloaddition of aryne **25** with DMF. Compound **26** reacted effectively with ester enolates **27** or ketenimine **28** *via* [4 + 2] cycloaddition to provide different coumarins **29** (**Figure 14**) [38].

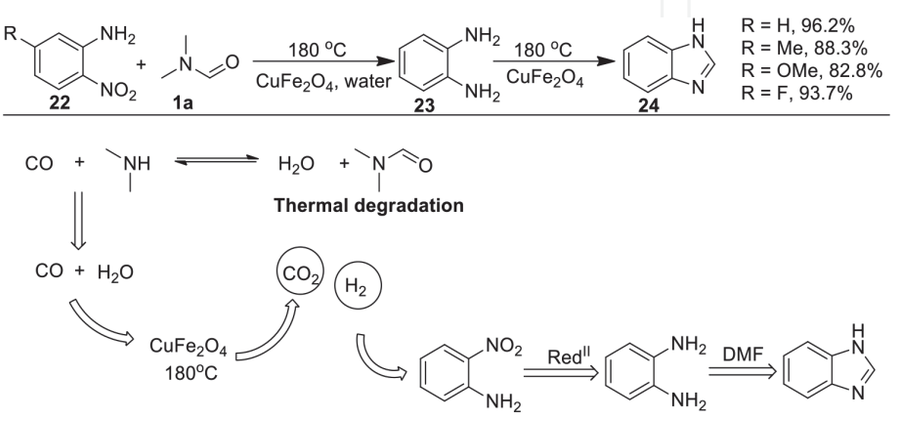


**Figure 13.**
*One-pot synthesis of benzimidazole.*

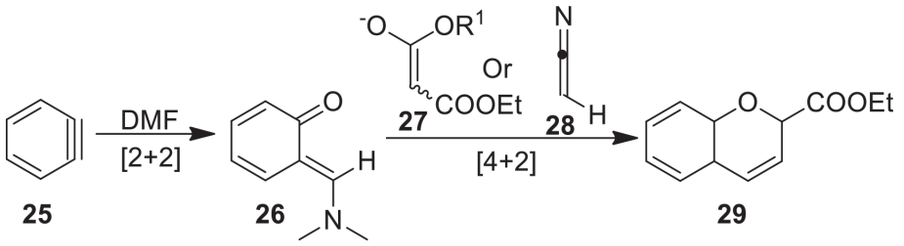


**Figure 14.**
*Synthesis of different coumarin derivatives.*

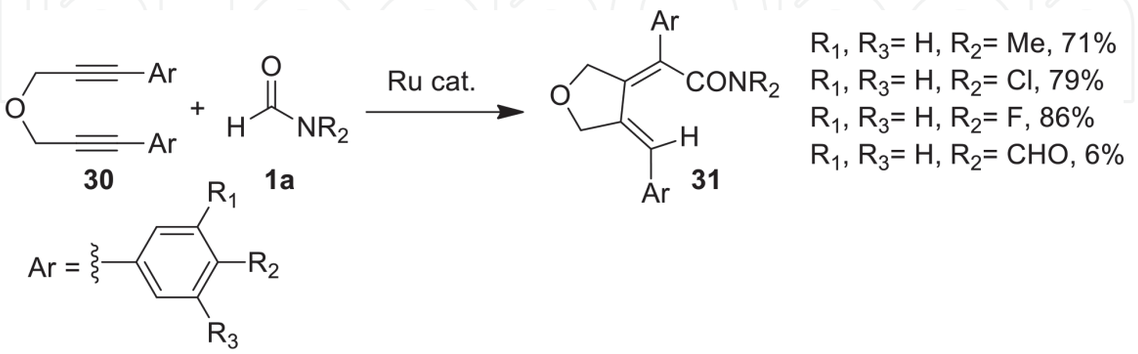


**Figure 15.**
*Hydrocarbamoylative cyclization of 1,6-diynes with DMF.*

### 2.9 Construction of cyclic ether

Yamamoto and coworkers synthesized exocyclicdiene-type α,β,γ,δ-unsaturated amides **31** from hydrocarbamoylative cyclization of 1,6-diynes **30** with formamides under Ru-catalyst with complete stereoselectivity (**Figure 15**) [39].

## 3. Amidation

Having covered literature on construction of cyclic system, especially heterocycles using DMF or DMA as a next part we cover literature on the formation of open chain compounds.

An excellent method to access benzamides **33** *via* aminocarbonylation of aryl and alkenyl iodides **32**, with DMF as amide source, in the presence of Pd/$POCl_3$ catalytic system, was demonstrated by Hiyama et al. (**Figure 16**) [40].

Similarly, Indolese et al. reported aminocarbonylation of aryl halides **32** with Pd catalyst, triphenylphosphine ligand in CO atmosphere under pressure. DMAP is used as base for this reaction and the yield obtained is very high [41]. It is an important synthetic method since it can also be applied to pyridine and thiophene halides (**Figure 16**).

Furthermore, Lee and co-workers demonstrated the same reaction between aryl bromides/iodides **32** and DMF with the help of inexpensive Nickel acetate

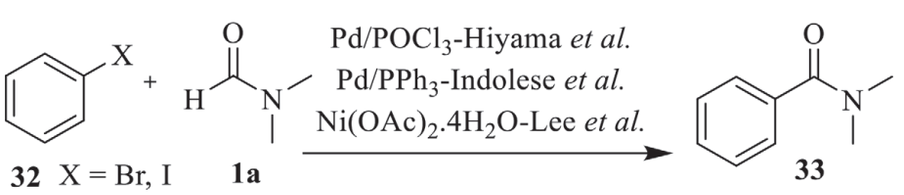


**Figure 16.**
*Metal catalyzed aminocarbonylation of aryl halides using DMF.*

tetrahydrate as catalyst and using phosphite ligand and sodium methoxide as base in dioxane solvent (**Figure 16**) [42].

Wang et al., reported a metal-free radical amidation of thiazoles and oxazoles **34** with a series of formamides and *tert*-butyl perbenzoate (TBPB) as radical initiator. By this method, synthesis of high yields of amidated azoles **35** were easily achieved (**Figure 17**) [43].

Wang et al., demonstrated direct amidation of alcohols **36** with formamides in the presence of an $I_2$/TBHP with sodium hydroxide as a base and DMF as amide source (**Figure 18**) [44]. The same author reported amidation of benzyl amine **38** under the acidic condition [45].

Feng and coworkers proposed green protocol for the synthesis of α-ketoamides **41** through TBAI catalyzed $sp^3$ C-H oxidative radical/radical cross-coupling. This method is applicable for broad range of substrates [46]. The only by product is water and no CO or $CO_2$ emission is observed (**Figure 19**).

Similarly, the synthesis of α-ketoamides **41** was achieved with readily available aryl methyl ketones **42** using inexpensive *N*,*N*-dialkylformamides in the presence of $nBu_4NI$ and aq.TBHP as catalyst and oxidant for radical oxidative coupling process (**Figure 19**). This strategy is a green and metal-free approach developed by Mai et al. [47].

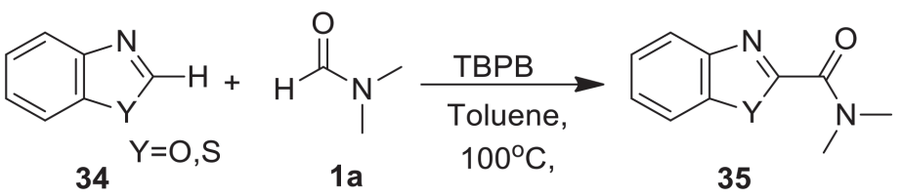


**Figure 17.**
*DMF as a source for aminocarbonylation of azoles.*

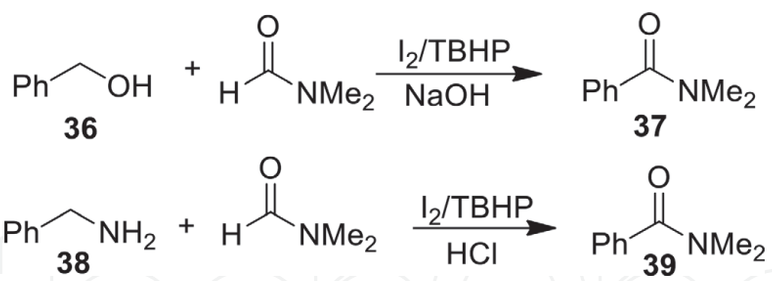


**Figure 18.**
*DMF as a source for aminocarbonylation of alcohol and amines.*

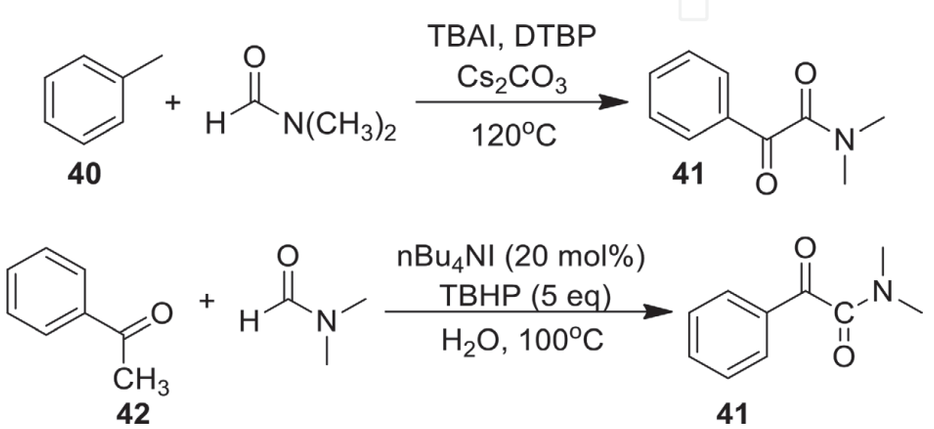


**Figure 19.**
*DMF as aminocarbonylation source in synthesis of α-ketoamides.*

In 2016, Xiao and his team developed a simple and efficient technique for the synthesis of amides **33** by cross coupling of carboxylic acids **43** with *N*-substituted formamides in the presence of Ru catalyst and the desired amide was obtained after the release of $CO_2$ (**Figure 20**). The carbonyl group in the amide product came from benzoic acid and not from N-substituted formamides. This synthetic method is stable, inexpensive, low toxicity and eco-friendly. This method works well with different carboxylic acid derivatives and *N*-substituted formamides [48].

Similarly, Tortoioli and co-workers demonstrated one-pot synthesis of dialkyl amides under metal free condition through the reaction between benzoic acid and DMF in presence of propyl phosphonic anhydride ($T_3P$) with acid additives [49]. This mild method has been applied to the synthesis of dihydrofolate reductase inhibitor, triazinate (**Figure 21**).

Bhat et al. reported direct carbamoylation of heterocycles **44** *via* direct dehydrogenative aminocarbonylation under transition metal-free condition **45** (**Figure 22**). Persulfate which is played the role of an efficient oxidant, good radical initiator, mild and eco-friendly low cost reagent and formamides NMF and DMF acted as reagent to form primary to tertiary carboxamides [50].

Bhisma et al. gave an efficient copper catalyzed synthesis of phenol carbamates **47** from dialkylformamides as aminocarbonyl surrogate and phenols possessing directing groups such as benzothiazoles, quinoline and formyl at ortho-position (**Figure 23**). It's a cheap and eco-friendly reaction with tolerance of wide range of functional groups and phosgene free route to carbamates [51].

Phan and coworkers under oxidative condition synthesized organic carbamates **49** through C-H activation using metal organic framework $Cu_2(BPDC)_2(BPY)$ (BPDC = 4,4′-biphenyldicarboxylative, BPY = 4,4′-bipyridine) as heterogeneous catalyst for cross dehydrogenative coupling of DMF with 2-substituted

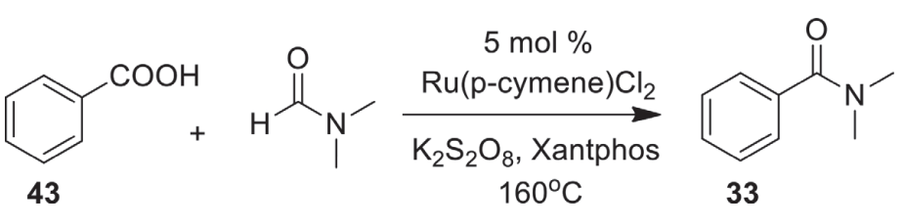


**Figure 20.**
*DMF in Ru-catalyzed amidation of carboxylic acids.*

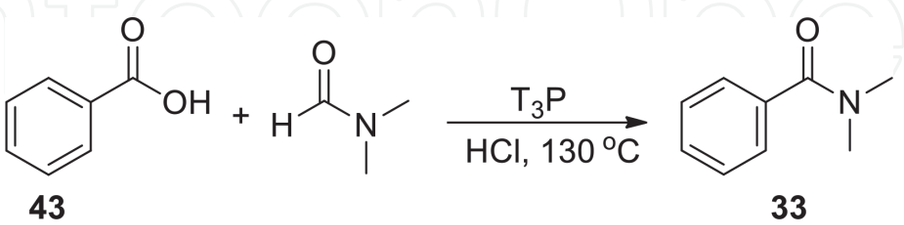


**Figure 21.**
*Amidation of benzoic acid with DMF.*

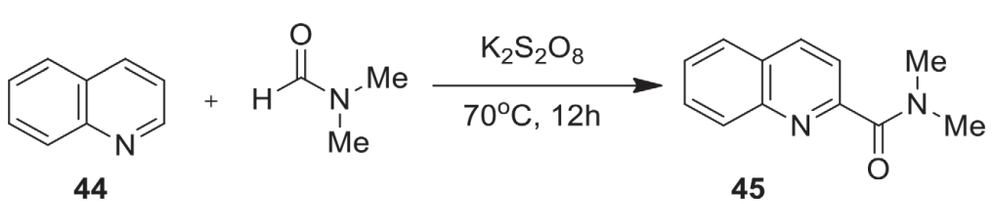


**Figure 22.**
*DMF as source for aminocarbonylation of quinoline.*

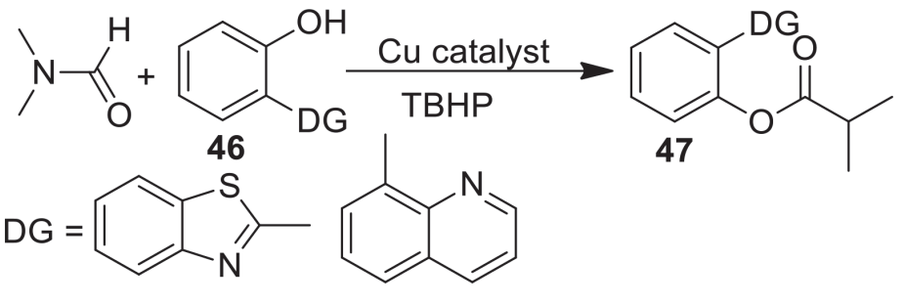


**Figure 23.**
*Carbamate synthesis from phenols and formamides.*

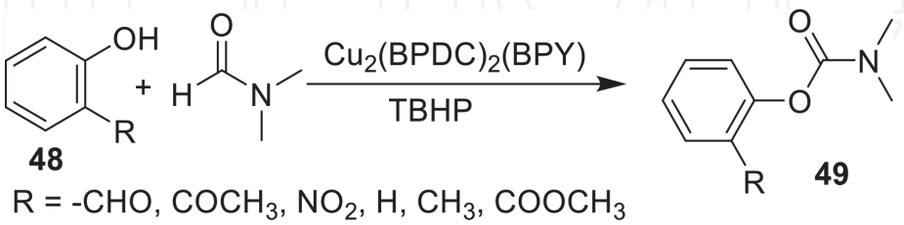


**Figure 24.**
*CDC reaction of phenol with DMF.*

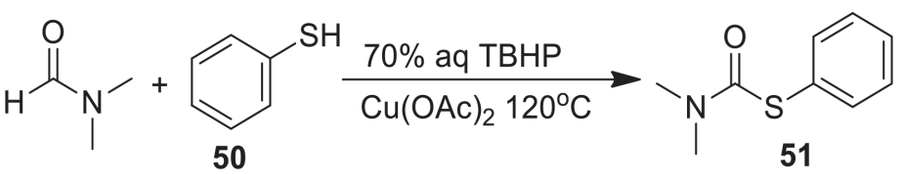


**Figure 25.**
*Synthesis of S-phenyldialkylthiocarbamate.*

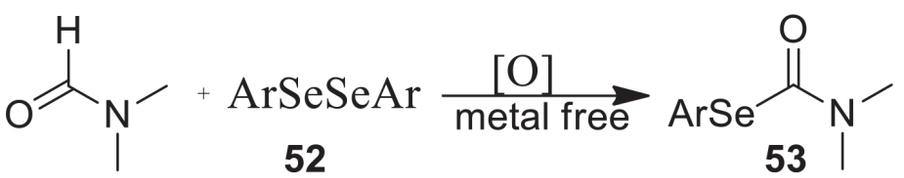


**Figure 26.**
*Oxidative C-Se coupling of formamides and diselenides.*

phenols **48** (**Figure 24**). This catalyst has higher catalytic activity and it is easily recoverable and reusable [52].

Yuan et al., synthesized S-phenyldialkylthiocarbamate **51** compounds under solvent free conditions through TBHP promoted radical pathway, in which direct oxidation of acylC-H bond of formamides took place in the presence of $Cu(OAc)_2$ to form the reaction intermediate for oxidative coupling reaction of formamides with thiols **50** (**Figure 25**) [53]. This protocol is efficient and green.

Kamal and coworkers proposed an efficient and greener methodology for the synthesis of selenocarbamates **53** by oxidative coupling reaction between formamides and diselenides **52** under metal free conditions (**Figure 26**). By using simple reaction condition, a metal-free approach to direct C-Se bond formation occurred at carbonyl carbon by using TBHP and molecular sieves. It uses non-functionalized substrate which is an advantage of this reaction [54].

Reddy and coworkers synthesized chiral symmetrical urea derivatives **54** through copper catalyzed C-H/N-H coupling of formamides (both mono and di) with different amines **53** (primary, secondary and substituted aromatic amines) using TBHP as an oxidant and it involves a radical pathway (**Figure 27**).

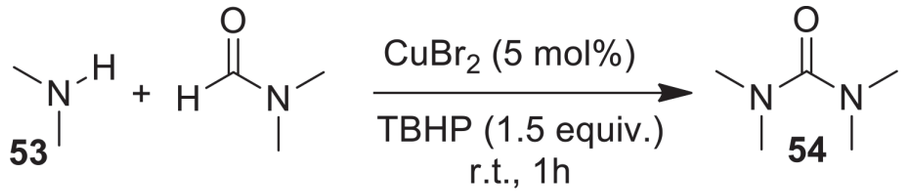


**Figure 27.**
*Synthesis of chiral symmetrical urea derivatives from DMF.*

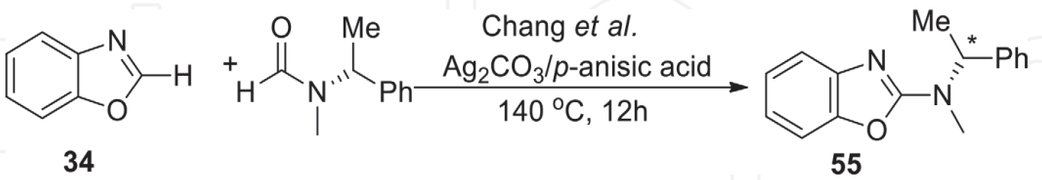


**Figure 28.**
*Amidation of benzoxazole using $Ag_2CO_3$ catalyst.*

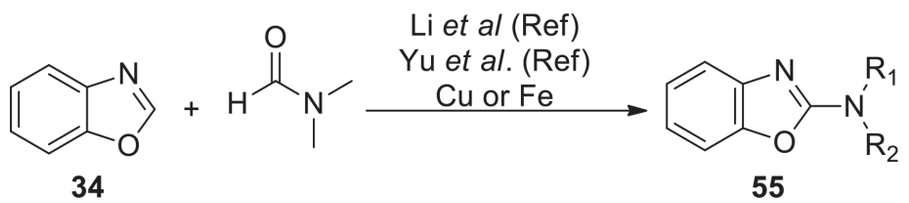


**Figure 29.**
*Amidation of benzoxazole using Cu or Fe catalyst.*

The importance of this green reaction is, it avoids the use of pre-functionalized substrates, atom economical [55].

### 3.1 Amination

Chang et al., reported that benzoxazoles **34** on treatment with *N*,*N*-dimethyl-formamide (DMF) using the $Ag_2CO_3$ as catalyst in the presence of an acid additive, 2-aminated benzoxazole **55** was obtained as a single product in moderate yield (**Figure 28**).

Interestingly, this method is also suitable for the optically active formamide, the desired product was obtained in better yield without racimization [56].

Li et al., gave a method for the synthesis of 2-aminoazole derivatives **58** in which construction of C-N bond of azoles **34** either by decarboxylative coupling with formamides as nitrogen source or by a direct C-H amination with secondary amines as nitrogen source by the use of inexpensive Cu catalyst, $O_2$ or air as oxidant is green and benzoic acid has its main role in the release of amine from amides by decarbonylation other than C-H activation [57].

Similarly, Yu et al., developed a decarbonylative coupling between azoles and formamides. The iron catalyzed direct C-H amination of azoles at $C_2$ took place in the presence of formamides and amines as nitrogen source (**Figure 29**). Easily accessible iron (II) salts acted as Lewis acid which activated the $C_2$ position of benzoxaoles **34** and oxidant and imidazole was used as an additive in the catalyst under air. This direct azole amination was catalyzed by inexpensive and environmentally benign reagents. The reaction was also carried with amines in the presence of acetonitrile [58].

Peng and coworkers developed a facile and efficient route for one pot synthesis of 2-acyl-4-(dimethylamino)-quinazoline **57** through direct amination of 2-aryl quinazoline-4(3*H*)ones **56** with DMF in which 4-toluene sulfonyl chloride acted as

C-OH bond activator (**Figure 30**). KO$^t$Bu was used as base which leads to the formation of tosylate which attacks DMF which in turn undergoes hydrolysis to give aminated product **59**. This reaction is inexpensive and uses easy to handle reagents [59].

Eycken et al. demonstrated a convenient microwave-assisted de-sulfitative dimethylamination of 5-chloro-3-(phenylsulfanyl)-2-pyrazinones **58** using DMF as a dimethylamine source and sodium carbonate as an essential (**Figure 31**). The solvent system used for this reaction is DMF:$H_2O$ in 1:1 ratio and the corresponding de-sulfitative aminated product **59** was obtained in good yield. Finally, the utility of this methodology was also examined on oxazinone in place of pyrazinones under the optimized conditions and the desired products were formed in good yield [60].

Hongting et al. developed an efficient, atom-economic and eco-friendly approach for synthesizing enamines **61** by intermolecular hydroamination of activated alkynes (**Figure 32**). The reaction was carried out under solvent free condition using a catalyst at room temperature. Primary or secondary amines **53** were added to triple bonds **60** without generating any waste products. DMF pretreated

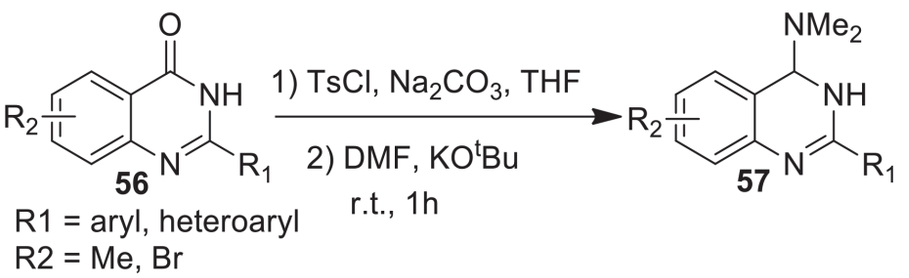


**Figure 30.**
*Direct amination of 2-aryl quinazoline-4(3*H*)ones with DMF.*

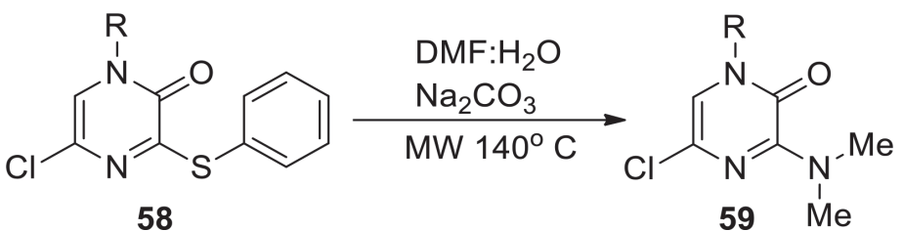


**Figure 31.**
*De-sulfitative amination of 2(1H) pyrazinone.*

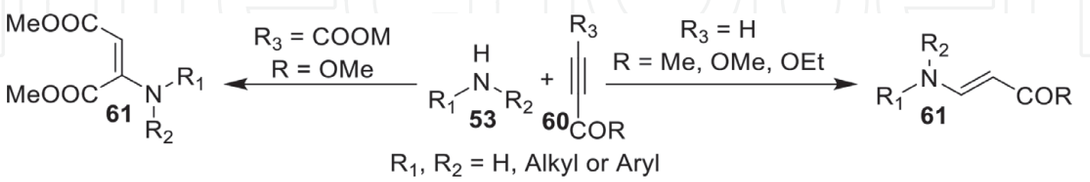


**Figure 32.**
*Intermolecular hydroamination of activated alkynes.*

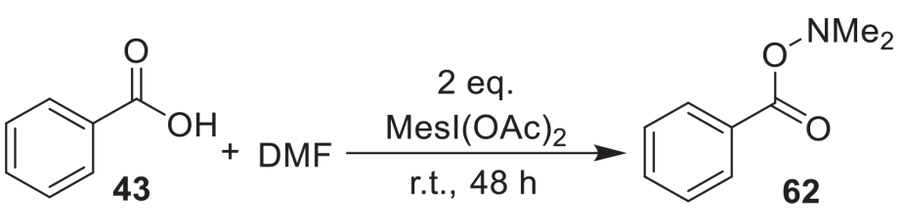


**Figure 33.**
*Synthesis of O-aroyl-*N,N*-dimethyl hydroxyl amines.*

with metal Na was used for synthesis of (E)-ethyl-3-(dimethylamino)acrylate and a new way for synthesis of quinolines was given [61].

Li et al., developed hypervalent iodine mediated reaction between carboxylic acids **43** and *N*,*N*-dimethylformamide which occur under mild conditions at room temperature to provide novel *O*-aroyl-*N*,*N*-dimethyl hydroxyl amines **62** in good yields (**Figure 33**), which are important electrophilic amination reagents. The process shows good functional group compatibility, air and moisture tolerance [62].

Liang and coworkers gave a simple and efficient one-pot multicomponent reaction of chalcones **63**, malononitrile **64** and DMF in the presence of NaOH for the synthesis of functionalized 4-oxobutanamides **65** (γ-ketoamides) from simple α,β-unsaturated enones (**Figure 34**). This reaction has a high atom economy, easily available starting materials, operational simplicity with mild conditions, broad substrate scope and good tolerance with diverse functional groups [63].

Xia and coworkers proposed a simple and green approach for the synthesis of sulfonamides through t-BuOK mediated direct S-N bond formation from sodium sulfinates **66** with formamides (**Figure 35**). This reaction undergoes in a metal-free conditions and formamides are used as amine source. It avoids pre-functionalized starting materials and forms an alternative method for the synthesis of sulfonamids **67** [64].

Gong et al., reported a base-promoted amination of aromatic halides **32** using a limited amount of *N*,*N*-dimethylformamide or amine as an amino source. Various aryl halides, including F, Cl, Br, and I, have been successfully aminated **68** in good to excellent yields (**Figure 36**) [65]. This protocol is valuable for industrial application due to the simplicity of operation, the unrestricted availability of amino sources and aromatic halides.

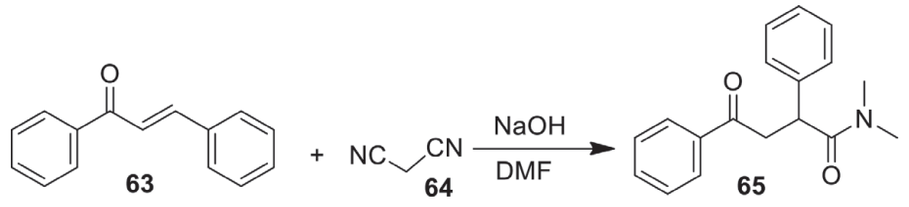


**Figure 34.**
*Synthesis of γ-ketoamide.*

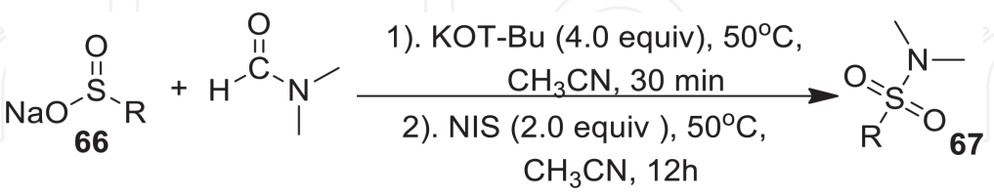


**Figure 35.**
*Synthesis of sulfonamides using DMF as a amine source.*

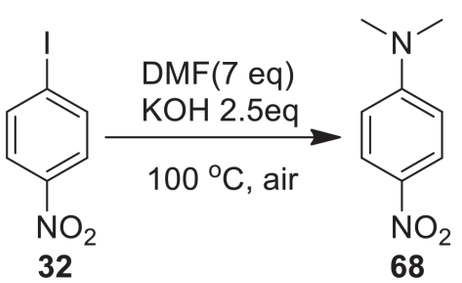


**Figure 36.**
*A base-promoted amination of aromatic halides.*

### 3.2 Methylenation

In recent past several methods were developed for using DMF as a methylene source.

Wang et al., developed a new method for the synthesis of vinylquinolines **70** from methyl quinolines **69** (**Figure 37**) using DMF as a methylene source. The synthesis was carried out *via* an iron-catalyzed $sp^3$ C-H functionalization and a subsequent C-N cleavage using TBHP as a radical initiator. This method is simple and effective for synthesis of large number of vinyl substituted quinoline derivatives in excellent yield. It also avoids the usage of organometallic compounds as reagents [66].

Qian Xu and coworkers developed an eco-friendly iron-catalyzed benzylic vinylation which transfers the carbon atom in *N*,*N*-dimethyl group from DMA or DMF to 2-methyl azaarenes **71** to generate 2-vinyl azaarenes **72** (**Figure 38**). The reaction of *N*,*N*-dimethyl amides as one carbon source proceeded *via* radical mechanism [67].

Miura et al., demonstrated an effective way for α-methylenation of benzyl pyridines **73** using copper catalyst. In the methylenation, *N*-methyl group of DMA was incorporated as the one-carbon source to produce α-styrylpyridine **74** derivatives (**Figure 39**), which are famous for their unique biological properties [68].

Li et al., developed an iron-catalyzed α-methylenation of aryl ketones **75** by using *N*,*N*-dimethylacetamides as a one-carbon source to form α, β-unsaturated carbonyl compounds (**Figure 40**). Potassium persulfate is used as oxidant and this method acts as an excellent synthetic method for synthesis of α, β-unsaturated carbonyl compounds **76** [69].

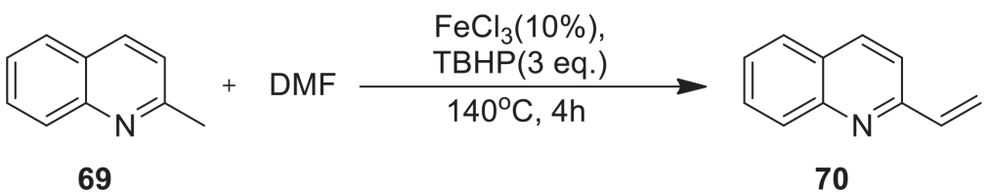


**Figure 37.**
*Synthesis of vinyl quinolones using DMF with iron catalyst.*

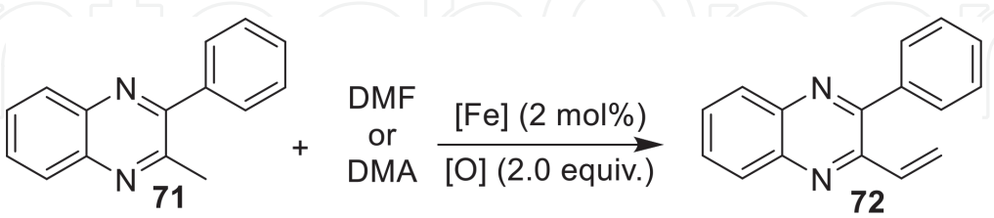


**Figure 38.**
*DMA or DMF Synthesis of vinyl 2-vinylazaarenes.*

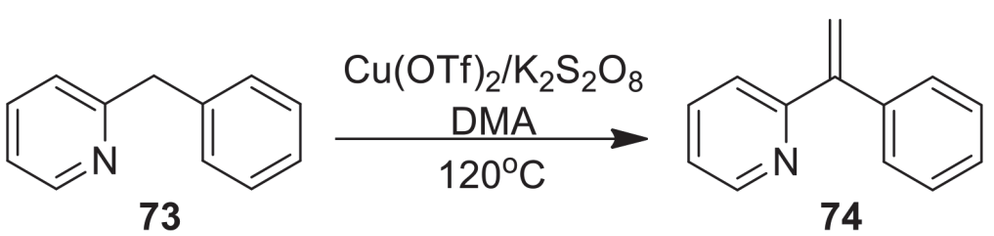


**Figure 39.**
*α-methylenation of benzylpyridines using DMA.*

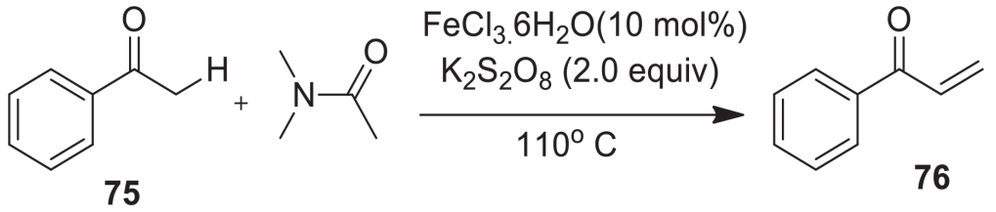


**Figure 40.**
*α-methylenation of acetophenones.*

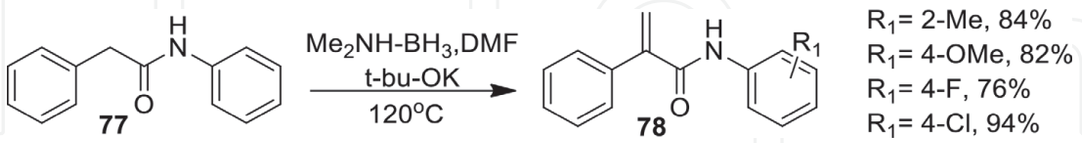


**Figure 41.**
*α-methylenation of 2-arylacetamides with DMF.*

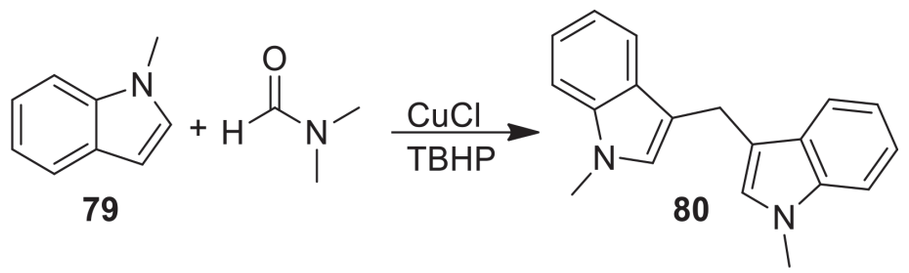


**Figure 42.**
*Cu-catalyzed synthesis of diindolylmethane.*

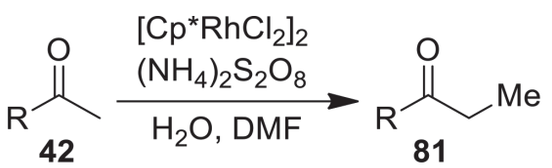


**Figure 43.**
*Rh-catalyzed direct methylation and hydrogenation of ketones using DMF.*

In 2019, Wang et al., reported a one-pot procedure for the synthesis of 3-indolyl-3-methyl oxindoles **78** *via* C($sp^3$)-H methylenation of 2-arylacetamides **77** using DMF/$Me_2NH$-$BH_3$ as the methylene source (**Figure 41**) [70].

Liu and coworkers reported a method for the synthesis of diindolylmethane **80** and its derivatives which is done through copper catalyzed C-H activation of indole **79** where in DMF was used as a methylenating reagent. CuCl was mainly used as a catalyst which affords high regioselectivity and TBHP as oxidant. The reaction utilizes readily available copper catalyst and inexpensive DMF as carbon source and it has a broad scope of substrates with relatively mild reaction conditions (**Figure 42**) [71].

In 2014, Xue and co-workers developed methylation of ketones **42** with DMF, control experiment studies indicate that DMF plays dual functions as the source of carbon for methylation and source of hydrogen in the rhodium-catalyzed reduction of the methylene into a methyl group (**Figure 43**) [72].

A possible mechanism was proposed as shown in **Figure 44**. Initially, persulfate oxidizes DMF to give a reactive iminium intermediate. The intermediate **A** generated by attack of enolate is converted to intermediate **B** followed by C-N bond cleavage to generate unsaturated ketone intermediate **C**. Afterwards, the

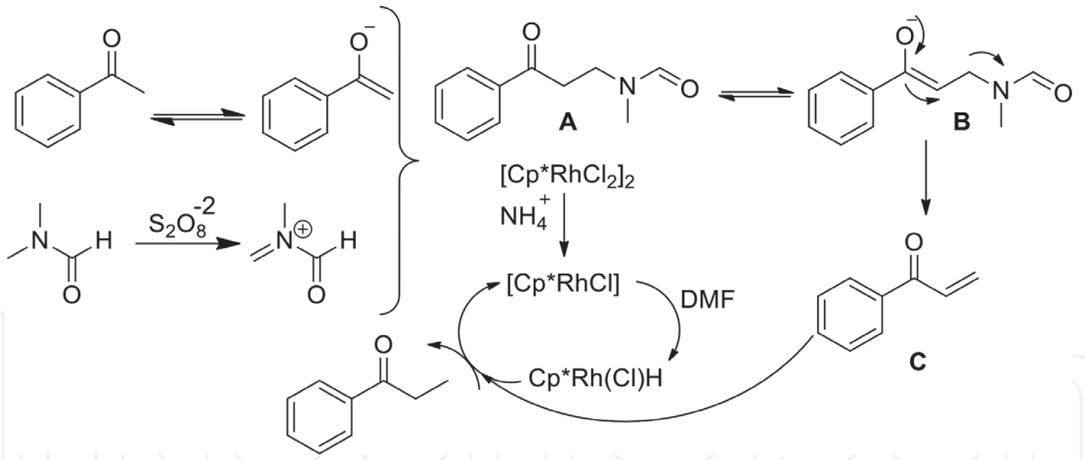


**Figure 44.**
*A possible mechanism for methylation and hydrogenation of ketone.*

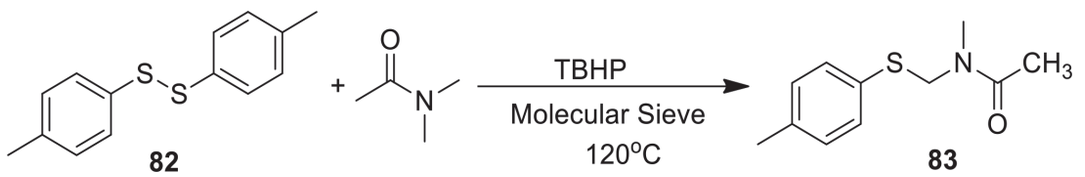


**Figure 45.**
*Thiolation of $sp^3$ C-H bond next to a nitrogen atom.*

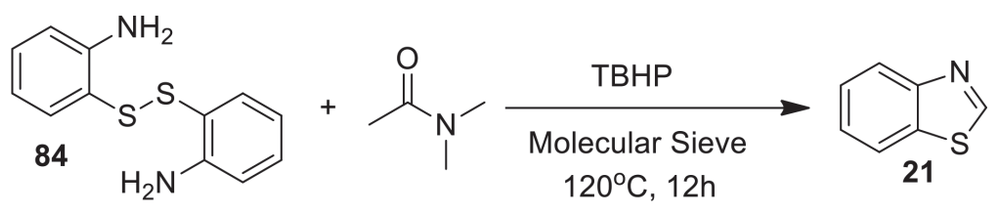


**Figure 46.**
*TBHP-mediated synthesis of benzothiazoles.*

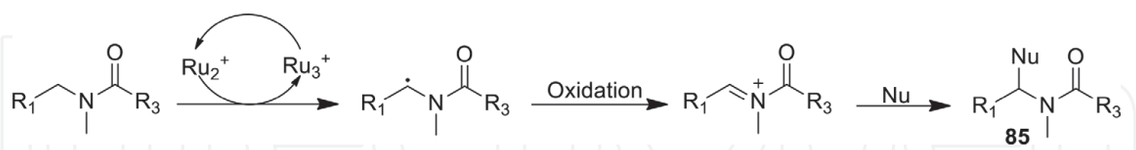


**Figure 47.**
*FC amidoalkylation using alkyl amides.*

intermediate **C** is reduced, which is probably generated by using DMF *via* dehydrogenation with the aid of $[Cp^*RhCl_2]_2$, which results in the formation of methylated product.

### 3.3 Amidoalkylation

Li et al., reported direct oxidative thiolation of $sp^3$ C-H bond next to a nitrogen atom **83** with disulfides **82** under metal free condition for the synthesis of several N, S containing compounds (**Figure 45**).

In this oxidative thiolation reaction, thiol group was successfully coupled with $sp^3$ C-H bond of *N*,*N*-dialkyl amides in the presence of TBHP/Molecular sieves through the formation of radical intermediate.

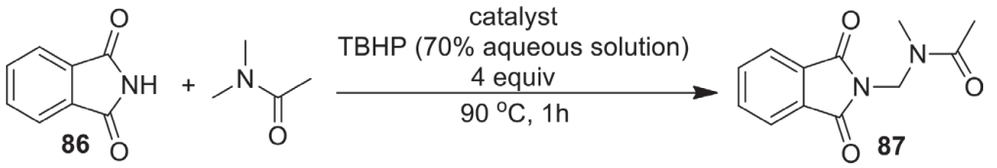


**Figure 48.**
*Amidoalkylation under metal free condition using DMA.*

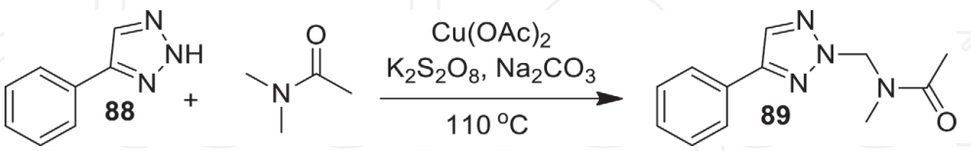


**Figure 49.**
*Copper-catalyzed C-N bond formation of triazoles.*

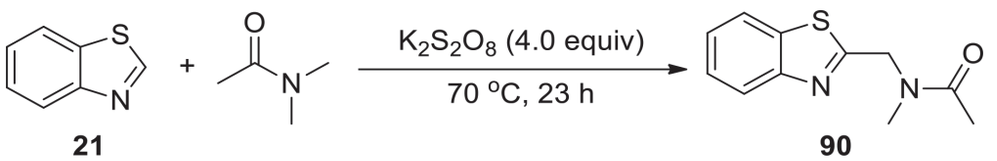


**Figure 50.**
*Amidoalkylation of benzothiazoles with DMA.*

It is noteworthy that various benzothiazole and a fipronil analogs could also be synthesized through this methodology (**Figure 46**) [73].

Stephenson et al., developed Friedel-Craft amidoalkylation of alcohols and electron rich arenes as potent nucleophile with alkyl amides **1b** *via* thermolysis and oxidative photocatalysis (**Figure 47**). The FC amidoalkylated product **85** was obtained by oxidation of *N*,*N*-dialkyl amides with the aid of persulfate and photocatalyst. On the other hand, persulfate at 55°C also afford amidoalkylated product.

In this method inexpensive and efficient persulfate was used as oxidant for the construction of C-O and C-C bonds. Most of the time, photo catalysis provided better selectivity and good yields for the Friedel-Crafts reactions as compared with the thermolytic reaction conditions [74].

Li et al., gave a transition metal-free method for amidation of $sp^3$ C-H bond in amides through cross dehydrogenative coupling process by using iodide anion as catalyst and TBHP as oxidant (**Figure 48**). It proceeds through free radical intermediate which is confirmed by TEMPO and the products has an potential bioactivity **87**. This is an efficient method for direct C-N bond formation because of its mild conditions and readily available reagents [75].

In 2017, Chen and coworkers demonstrated copper-catalyzed C-N bond formation of triazoles *via* cross dehydrogenative coupling (CDC) of *NH*-1,2,3-triazoles **88** with *N*,*N*-dialkylamides to construct *N*-amidoalkylated triazoles **89** (**Figure 49**). When the reaction was performed with 4-aryl-substituted *NH*-1,2,3-triazoles the desired $N^2$-substituted 1,2,3-triazoles was obtained and small amount of $N^1$ products were also observed. This method is useful for the synthesis of $N^2$-substituted 1,2,3-triazolesselectively [76].

Zhu and Co-Workers discovered a new methodology for the synthesis of 2-amidoalkylated benzothiazole and 3-amidoalkyl substituted indolinone derivatives using *N*,*N*-dialkylamides and potassium persulfate as an oxidant under metal free

condition (**Figure 50**). The corresponding amidoalkylation products were formed selectively using simple *N*,*N*-dialkyl amides including formamides [77].

### 3.4 Cyanation

It is interesting to note that dialkylamides could undergo reaction to generate cycano group. In 2011 Ding et al., reported a novel and another kind of pathway to produce the aryl nitriles *through* the Pd-catalyzed cyanation of indoles **79** and benzofurans by functionalization of C-H bond using DMF as a source of CN and control experiments revealed that N and C of the cyano group are generated from DMF [78].

Similarly, in 2015, Chen and co-workers developed a selective copper-catalyzed $C_3$-cyanation of indole under an oxygen atmosphere with DMF as a safe CN source and as a solvent (**Figure 51**) [79].

Wang et al., demonstrated a copper catalyzed cyanation of indoles **82** using DMF as a single surrogate of CN (**Figure 52**). Electron rich arenes and aryl aldehydes can be transformed to acyl nitriles. Acyl aldehydes is the key intermediate for this transformation. The mechanism of this reaction involved C-H activation with

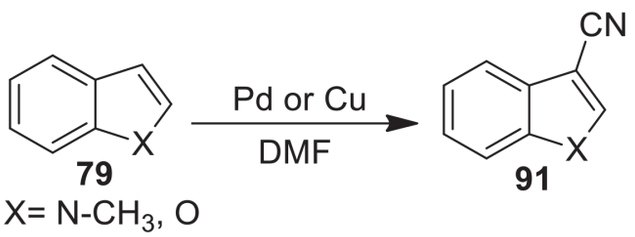


**Figure 51.**
*Cyanation of indole and benzofuran.*

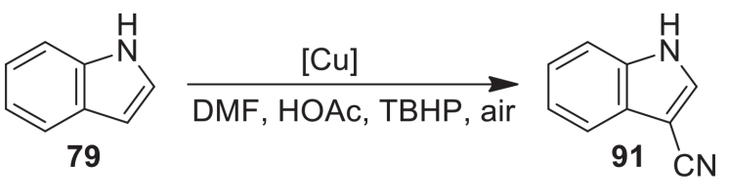


**Figure 52.**
*Cyanation of indole with DMF.*

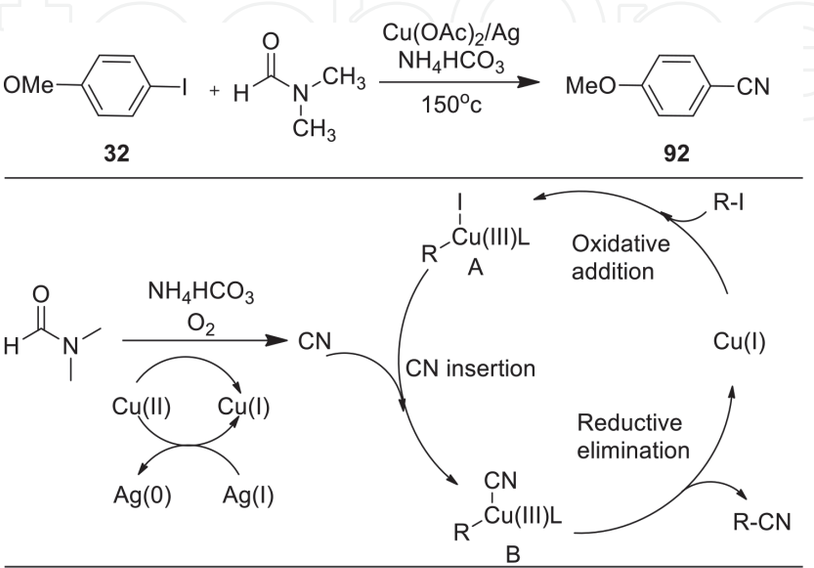


**Figure 53.**
*Cyanation of arylhalides and plausible mechanism.*

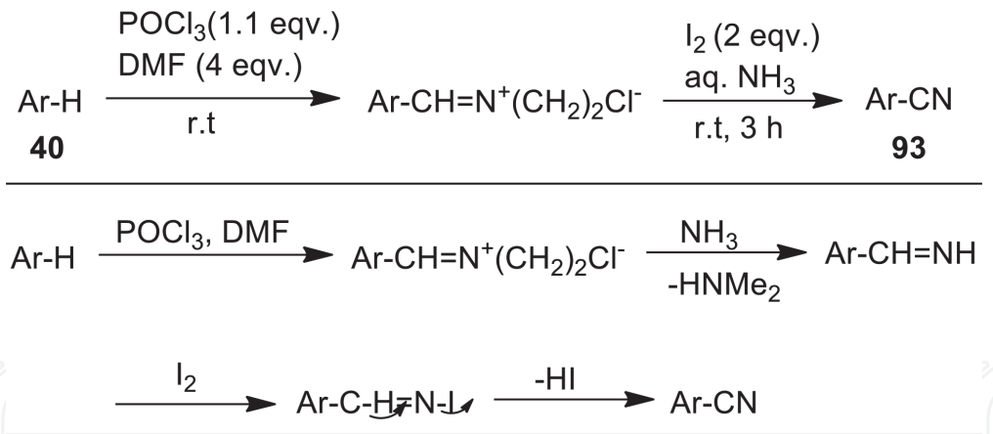


**Figure 54.**
*Conversion of electron-rich aromatics into aromatic nitriles.*

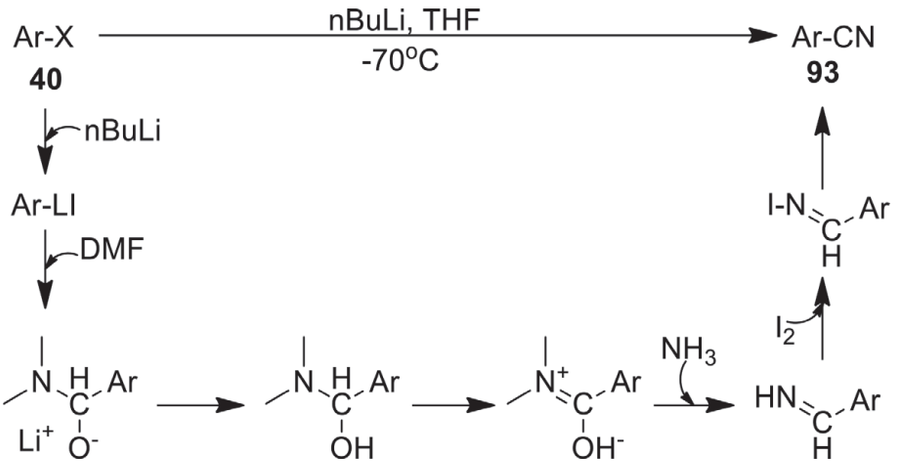


**Figure 55.**
*Conversion of electron-rich aromatics into aromatic nitriles and plausible mechanism.*

the help of copper catalyst then followed by carbonylation. 3-cyanoindoles have attracted much great extend owing to their importance in medicinal field especially in the preparation of therapeutic estrogen receptor ligand [80].

Chang et al., reported a new approach for the synthesis of Aryl nitriles **93**. Cyanation of aryl halides **32** catalyzed with copper acetate and Ag as an oxidant, in combination of ammonium bicarbonate as N source and DMF as a C source for cyanide functional group (**Figure 53**). With respect to the key roles of Cu(II) species in the *in-situ* formation of CN units and followed by cyanation of aryl halides, $Ag_2CO_3$ re-oxidizes the resultant Cu(I) species under copper-catalyzed oxidative conditions. This strategy is a practical and safe method and capable of providing nitriles in moderate to good yields [81].

Ushijima et al., reported the synthesis of aromatic nitriles **93** from electron-rich aromatics **40** under metal free one pot reaction condition. When the combination of molecular iodine in aqueous ammonia, with $POCl_3$ and DMF (**Figure 54**).

A possible mechanism for this reaction was given in **Figure 54**. When treated with ammonia, the iminium salt can be transformed into the aromatic imine. Then molecular iodine serves as an oxidizing agent and reacts with the aromatic imine to provide the corresponding aromatic *N*-iodoimine, which generates the aromatic nitrile through elimination in aqueous ammonia [82].

However, the need of highly electron-rich aromatics in the formation of aromatic *N*,*N*-dimethyl iminium salts limits the scope of this transformation. So, the authors should develop more convenient methods for this transformation.

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 aryl lithium and their DMF adducts (**Figure 55**) [83].

Followed by the treatment with molecular iodine in aqueous ammonia. Similarly, the same author reported synthesis of aryl nitriles from aryl bromides in the presence of Mg [84].

### 3.5 Formylation

Further, dialkylamides were also used as a formylation source. Wang et al., transformylated different amines, primary or secondary, aromatic or alkyl cyclic or linear, mono- or di-amine with DMF as formylation reagent to obtain corresponding formamides **95** with $CeO_2$ catalyst and the reaction does not require any homogeneous acidic or basic additives and it is tolerant to water.

The best part about the $CeO_2$ catalyst is the strong basicity and medium water-tolerant acidity (**Figure 56**) [85].

In 2017, Jagtap and coworkers reported highly efficient Ni(II) metal complex catalyzing *N*-formylation **96** and *N*-acyltion **97** of amines using *N*,*N*-dimethylformamide and *N*,*N*-dimethylacetamide as acyl source (CHO) in the presence of imidazole at a temperature of 150°C in a homogeneous medium (**Figure 57**). It has a broad substrate scope to aliphatic, aromatic and heterocyclic compounds.

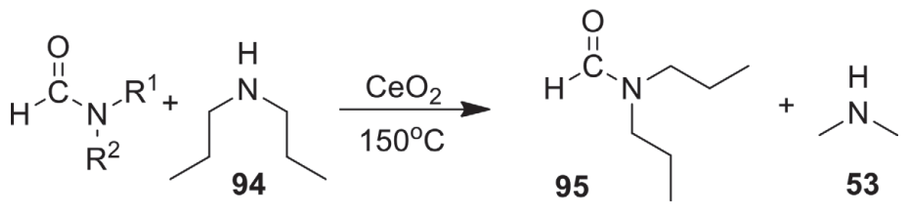


**Figure 56.**
*Transformylation of amines with DMF.*

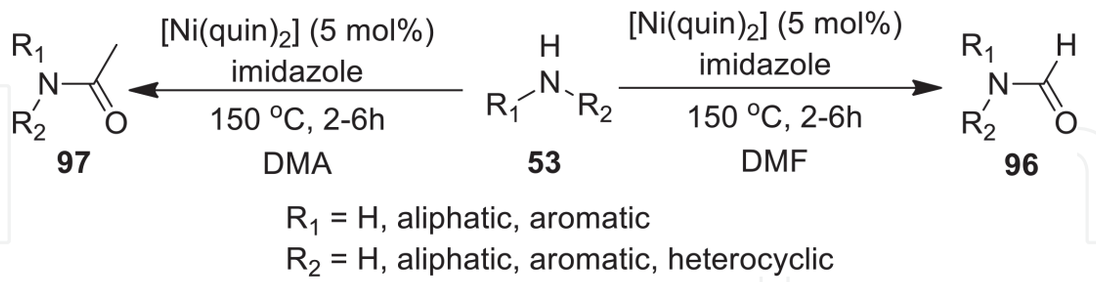


**Figure 57.**
*Formylation and acylation of amines using* N,N*-dialkylamides.*

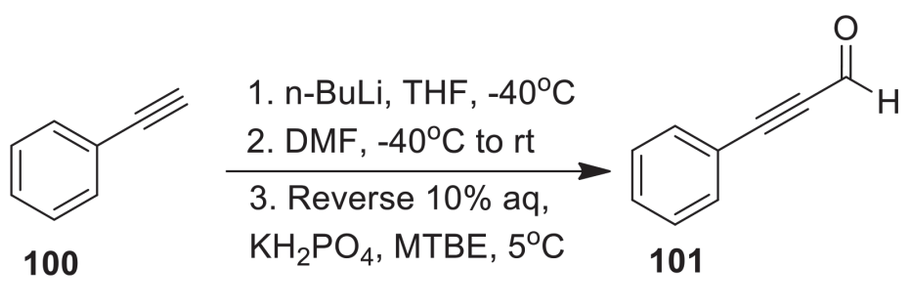


**Figure 58.**
*Synthesis of α,β-acetylenic aldehydes.*

The importance of this reactions are cost-effective, easily available starting material, high reactivity and inertness toward air and water [86].

Larsen et al., developed a convenient method for the synthesis of α,β-acetylenic aldehydes **101**, acetylides that are initially transformed to lithium acetylides with the aid of *n*-BuLi (**Figure 58**). The formylation of lithium acetylides was accomplished in the presence of DMF and followed by α-aminoalkoxide with 10% aqueous $KH_2PO_4$ to provide desired product with good yield [87].

Jeon and co-workers reported methyl benzoate **102** promoted *N*-formylation of different primary and secondary amines **38** employing DMF as a formylating agent under microwave irradiation (**Figure 59**). Key advantage of this methodology is selective *N*-formylation in the presence of a hydroxyl group [88].

### 3.6 Hydrogenation

Dialkylamides have ability to acts as hydrogen source and it has been used in several functional group transformations. It is advantageous to use hydrogen gas *in situ* generated from dialkylamides rather than handling easily flammable hydrogen gas.

Hua et al. reported triruthenium dodecacarbonyl [$Ru_3(CO)_{12}$] catalyzed stereo divergent semi-hydrogenation of diaryl alkynes **104** with *N*,*N*-dimethylformamide/water as hydrogen source for the synthesis of cis-**105** and trans **106**-stilbenes (**Figure 60**). When the HOAc was used excellent stereoslectivity was observed in favor of formation of *cis*-product. Surprisingly, the stereochemical preference changed to *trans*-isomer, with TFA as additive. This strategy is useful for the

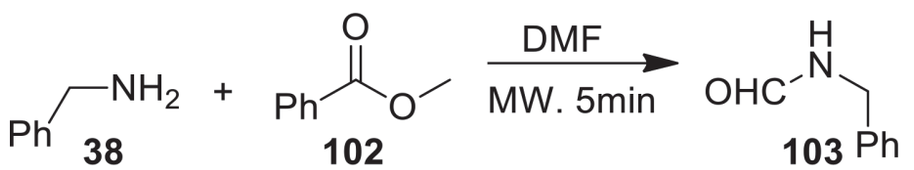


**Figure 59.**
N-*formylation of various 1° and 2°.*

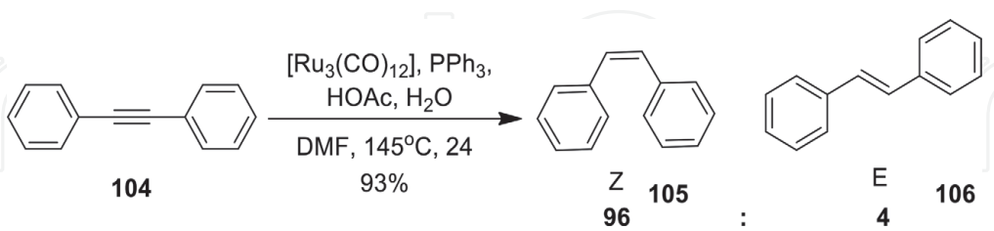


**Figure 60.**
*Stereodivergent [$Ru_3(CO)_{12}$] catalyzed semihydrogenation of diaryl alkynes.*

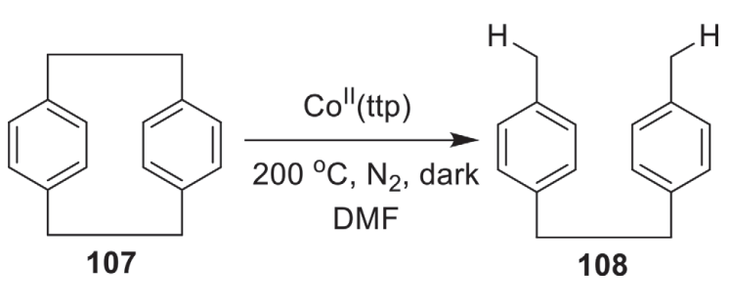


**Figure 61.**
*DMF as hydrogenating reagent for benzylic positions.*

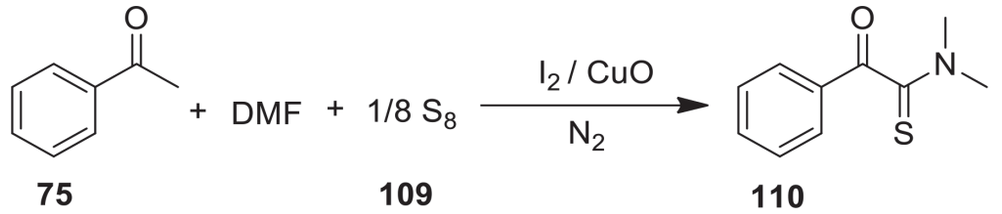


**Figure 62.**
*Synthesis of α-arylketothioamides.*

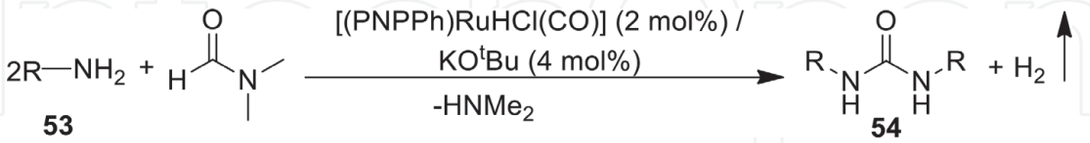


**Figure 63.**
*Carbonylation of amines with DMF.*

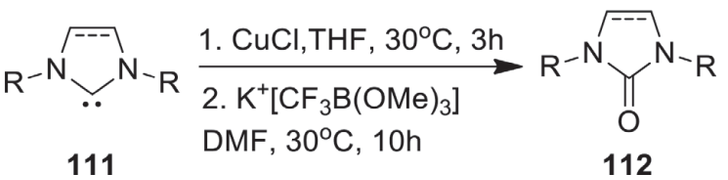


**Figure 64.**
*Formation of complicated imidazolinones with DMF.*

synthesis of analogs of natural products such as cis-combretastatin A-4 and trans-resveratrol [89].

Chan et al., reported a hydrogenation reaction catalyzed by cobalt porphyrins which hydrogenated C-C bond of [2.2] paracyclophane **107** (PCP) with DMF as solvent as well as hydrogen atom transfer agent (**Figure 61**). Metalloradical Co(II) porphyrins attacks the C-C sigma bond of PCP and the resultant benzyl radical abstracts a hydrogen atom from DMF to afford the hydrogenated product **108**. Results obtained from various control experiment revealed that the presence of benzyl radical intermediates in undergoing hydrogen atom transfer from DMF [90].

In 2017, Liu and coworkers synthesized α-arylketothioamides **110** *via* copper oxide and iodine mediated direct redox reaction from acetophenones **78**, elemental sulfur **109** and DMF under the nitrogen atmosphere (**Figure 62**). The elemental sulfur acts as a nucleophilic building block while DMF act as solvent and as the source of amino group (dimethylamine). This reaction tolerates a wide range of functional groups and proceeded in a redox efficient manner [91].

### 3.7 Carbonylation

Carbonylation is another important reaction in which the poisonous "CO" gas is generated from dialkylamides in the presence of suitable catalysts. Thus carbonylation reaction using dialkylamides is highly advantageous.

Gunanathan and coworkers developed a new mode of bond activation which is used effectively for the synthesis of simple and functionalized symmetrical and unsymmetrical urea derivatives from amines using DMF as CO source (**Figure 63**). Activation of N-H bond of amines by Ruthenium pincer complex and after that CO insertion from DMF with the liberation of hydrogen. Nucleophilicity of amines is

essential for urea formation. The significance of this reaction occurs in an open condition, it avoids side products, doesn't require any pressure setup [92].

Furthermore, Chen and co-workers reported a unique and highly effective method for the formation of imidazolinones **112** from carbene complexes **111** through oxygen atom insertion reaction of NHC copper complexes in the presence of DMF as the source of oxygen (**Figure 64**) [93].

## 4. Conclusion

It is noteworthy that, the utilization of DMF as a precursor in heterocyclic synthesis was important development in the field of synthetic organic chemistry. With advent of new reagents, catalytic systems and need for development of efficient synthetic protocols it could be predicted that dialkyl amides will continue to find new applications in organic synthesis. So far dialkyl amides have been mainly utilized as a synthon through mono functionalization of one of the groups. Further, there is a lot of scope for its utilization as a difuctionalization, for example, alkyl group attached to carbonyl and nitrogen in DMA could be functionalized at both the ends simultaneously. Dialkyl amides due to low cost, ready availability and flexibility in reactivity, will continue to gain attention of synthetic chemists as a synthon, ligand, dehydrating agent and solvent. We appreciate all of the authors cited herein for their tremendous contributions that have developed this field. We hope that it is sufficiently impressive and thorough that it will increase the interest on organic chemistry and will initiate further developments in the applications of DMF/DMA beyond being just a polar solvent, because it can be used as substrates in several reactions such as formylation, amination, amidoalkylation, aminocarbonylation, amidation, and cyanation and it has been achieved under both metal-catalyzed and metal-free conditions. We believe this book chapter will make it easy for the synthetic chemists and invoke an idea about utility of dialkyl amides for some novel functional group transformations.

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## Conflict of interest

The authors declare no conflict of interest.

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