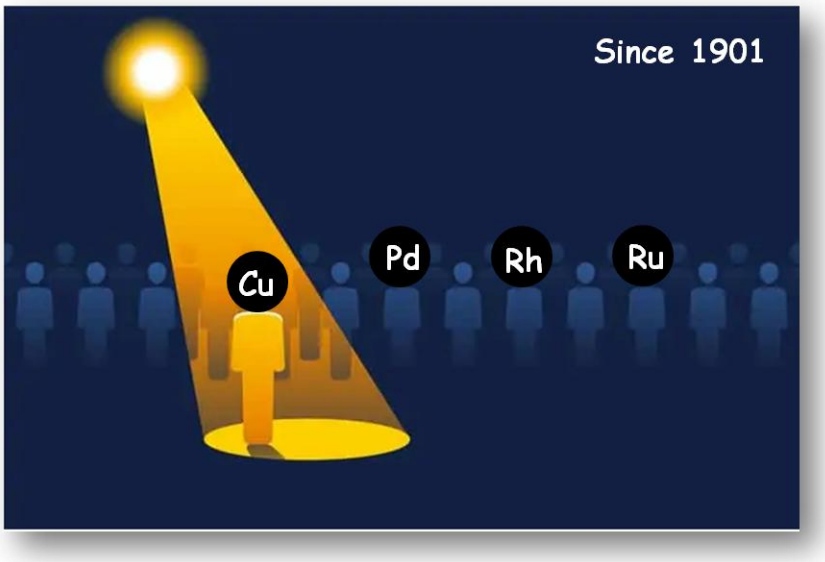
Chapter 1

General Introduction

“Copper Catalysis in Cyanation and Chan–Lam Cross–Coupling Reaction”



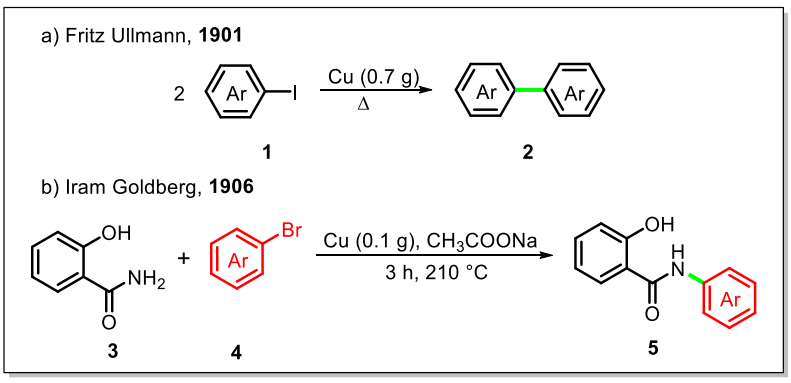
Chapter 1

1. Copper–catalysis

1.1 *Copper as a base-metal*

Copper (Cu) is one of the most abundant and versatile of all transition metals. It is placed in the 11th group and 4th period of the periodic table with an electronic configuration [Ar]3d^{10}4s^{1}. Copper was found on the island of Cyprus and thereafter acquired its symbol 'Cu' from its Latin name "Cuprum". It is most commonly found in the earth's crust as $CuFeS_2$, its chalcopyrite ore. Pure Cu is soft, malleable, highly ductile and thermally and electrically conductive [1]. Cu exhibits interesting chemical properties due to its ability to exist in variable oxidation states i.e. Cu^0, Cu^I, Cu^{II} and Cu^{III}. It is a suitable alternative to complementary precious metals like palladium (Pd), rhodium (Rh) and ruthenium (Ru) and is widely recognized in nanoscience, photovoltaics, optics and electronics [2]. Also, the high boiling point of Cu makes it compatible with flow chemistry, vapour–phase reactions and microwave–assisted transformations under high temperature and pressure reaction conditions. Such unique features have made Cu a very valuable metal and justifies its prominence today and also in the future.

Cu first gained recognition in the chemical industry as catalysts with the independent efforts of Ullmann [3] and Goldberg [4] in biaryl synthesis and *N*–, *O*–arylations respectively (Scheme **1.1**).



Scheme **1.1** Ullmann and Goldberg reaction

The metal was employed in full equivalent (with respect to the substrate) to stitch carbon-carbon (C–C) and carbon-nitrogen (C–N) bonds in the first breakthrough

approach. The economic veil of Cu rationalized its use even in stoichiometric amounts. However, the utilization of Cu metal in cross-couplings took a crucial turn when economic and sustainability factors began to concern modern research. Later improvements by Taillefer [5] Buchwald [6] and Hartwig [7] demonstrated an equivalent efficacy of Cu in catalytic amounts too. Both homogeneous and heterogeneous Cu-catalysis proved to be viable solutions to sustainable organic synthesis. Its inexpensiveness, low-toxicity, high abundance and high functional group tolerance attracted researchers beyond the versatility of Pd and other precious transition metals. Copper-catalysis could achieve various organic transformations that were previously thought to be realized with Pd only. Several robust Cu-based catalytic materials have been designed till date and it is believed that advanced catalytic materials can also be developed by controlling the shape and size of the metal nanoparticles (NPs) and also *via* selection of a suitable support for Cu NPs that can minimize the instability and sensitivity of Cu under atmospheric conditions [8]. Some of the most common organic reactions catalyzed by Cu are the coupling reactions like Chan-Evans-Lam cross-coupling (CEL) and Ullmann coupling, alkyne–azide cycloaddition (CuAAC: Click Chemistry) [9], Glazer coupling [10] and cyanation reactions.

Cu catalyzes reactions both *via* one-electron and two-electron pathways. Cu^{I} is consensually accepted to be the real catalyst; which is prone to oxidative aryl addition, either generated from Cu^{0} or Cu^{II} species in the reaction medium. At the stage of oxidative addition, the organometallic cycle drives the stable Cu^{I} metal into the Cu^{III} state, which is highly unstable and should be effectively stabilized by suitable ligands, unlike the case of Pd^{0} or Ni^{0} where the metal is driven to a more stable Pd^{II} or Ni^{II} state. However, due to its small size and positive charge, it is difficult to control the hard Lewis acidic Cu^{I}–centre through ancillary ligand design. In that case, if bulky ligands are chosen, shorter metal-ligand bonds leads to steric congestion around the Cu-metal centre. Instead, the low nucleophilicity of the Cu^{I} centre requires the “leaving group” to assist in the weakening of the C–X bond to form the C–Cu–X intermediate at the oxidative addition stage. Here, iodides and bromides are highly effective leaving groups in Cu-catalysis, contrary to chlorides and sulfonates. Hence, it can be safely said that the rate of oxidative addition in Cu-catalysis is a function of the properties of the leaving

group, which also acts as a ligand later [11]. Hence, Cu-catalysis is sensitive to the nature of leaving group, contradictory to its complementary competitor Pd, where the nucleophilic metal centre can be easily controlled by bulky electron-rich ligands and is independent of the nature of leaving group. The reductive elimination from the aryl Cu^{III} intermediate, in case of Cu-catalysis is however, fast and spontaneous. The understanding of organometallic chemistry of Cu is still slightly underdeveloped in comparison to that of Pd-chemistry, due to lack of fundamental insights into the reactivity of organo-cuprates in the oxidation states of Cu^{I} or Cu^{III} [12]. A decent share of "ligand-free" Cu-catalyzed syntheses is also known [13]. On the other hand, "synergistic Pd/Cu catalysis" is also being explored as in the case of Sonogashira cross-coupling reaction, where the Cu co-catalyst activates the terminal alkyne through the formation of Cu acetylide complex and Pd participates in the organometallic cycle [14].

The following section discusses two domains of Cu-catalysis. The first domain is that of cyanation reactions for the synthesis of synthetically and pharmaceutically important aryl nitriles. In this regard, Cu is regarded as the most profitable choice of catalyst for scalable syntheses. The second domain is that of the globally acclaimed Chan-Lam cross-coupling reaction where Cu-metal brings about C–N bond formations through an "open-flask reaction chemistry". Details of each are discussed in the following sections.

1.2 *Cyanation Reaction*

1.2.1 *Importance of Cyanation*

The ubiquity of nitrile-containing (CN^-) frameworks and its growing demand in the "clinic" is attributed to the biocompatibility of the nitrile functionality [15]. Around 30 nitrile-containing compounds were suggested in a variety of medications in 2010 and an additional 20 are being considered as leads for clinical development [16] (Figure **1.1**). Benzonitriles and heteroaromatic nitriles also form substructures of various other fine chemicals and agrochemicals [17]. They are commercially utilized in high-performance rubbers, polymers, molecular electronics and can be easily transformed into a plethora of useful functionalities such as aromatic acids, esters, amines, amides, aldehydes and nitrogen heterocycles which accounts for its popularity and applications [18,19] (Figure **1.2**). Hence, the search for sustainable and cost-effective process of nitrile synthesis is always an important area of research.

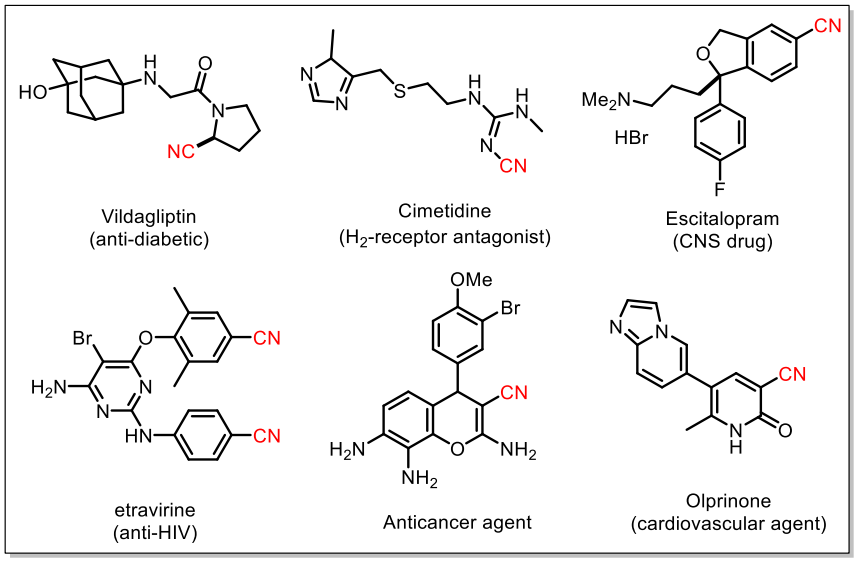


Figure **1.1** Representative nitrile containing drugs

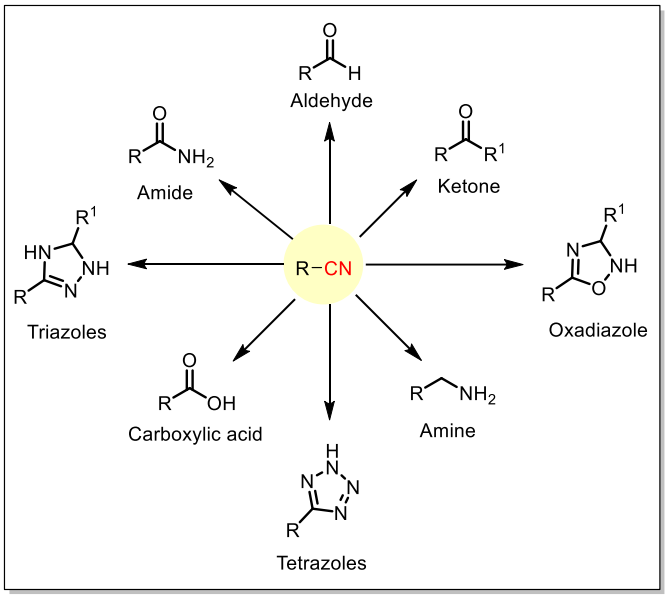


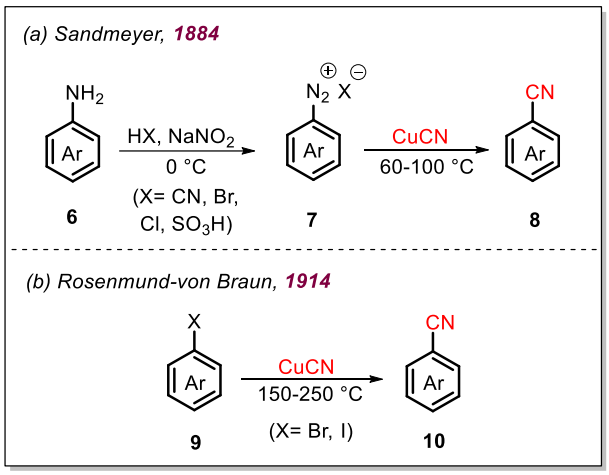
Figure **1.2** Possible transformations of nitriles into other useful functionalities

1.2.2 *The Pioneers of Cyanation reaction*

The first breakthrough protocol for the introduction of a nitrile group into an aromatic framework was reported when Traugott Sandmeyer in 1884, observed that cuprous cyanide (CuCN) in KCN could bring about substitution of a diazo group by a cyanide group [20,21]. The reaction came to be popularly known as “The Sandmeyer Reaction” (Scheme **1.2a**). Improved yields of aryl nitriles were obtained by substituting CuCN with $Ni(CN)_2$ while the cupric analogues were found to accelerate decomposition of the

diazonium compounds. Sandmeyer also obtained aryl bromides and aryl chlorides by reaction of the diazonium salts with the corresponding cuprous bromide and cuprous iodide. The mechanism of the reaction was envisioned to the formation of a complex cation *via* the addition of diazonium salt with CuCN, which subsequently decomposes to the respective aryl nitrile, with the release of nitrogen [22].

Another breakthrough was obtained when Karl−Wilhelm Rosenmund discovered in 1914 that when aryl halides were treated with KCN and a catalytic amount of CuCN at 200 °C, carboxylic acids were obtained [23]. Later, Julius von Braun investigated the reaction conditions and successfully obtained aryl nitriles from aryl halides by employing CuCN at higher temperature under solvent-free conditions [24]. The transformation came to be known as "The Rosenmund−von Braun Reaction" and could be applied to a variety of aryl halides (Scheme **1.2b**).



Scheme **1.2** Pioneering works on cyanation

These two approaches are regarded as the pioneering protocols of cyanation. However, both the approaches faced some important limitations, such as:

i) Super-stoichiometric amounts of toxic cuprous cyanide (CuCN) were required for the reactions.

ii) The diazonium salts, in case of Sandmeyer reaction, easily decomposed on heating with HCl or HBr, releasing nitrogen.

iii) The reactions required very high temperatures which may hamper sensitive substrates.

iv) Great difficulty was faced during separation and isolation of the products from large amounts of metal wastes (cuprous halides in this case).

v) The reactions gave poor yields with aryl chlorides since the C−Cl bond is more difficult to activate than the C−Br and C−I bonds.

Inspite of the limitations, the pioneering approaches are convenient approaches for obtaining a wide substrate scope and hence, several modifications are still being suggested to meet cost-effectiveness and industrial viability of the methodologies.

1.2.3 *Cyanating sources*

The choice of an appropriate cyanating agent is a crucial factor for a desired transformation. A plethora of cyanating sources has been reported till date [25-28]. In general, these sources can be broadly classified into four categories: Metallic/Metalloid cyanide sources, Non-metallic cyanide sources, Non−CN containing cyanide sources and combined cyanide sources.

A. *Metallic/Metalloid cyanide sources:* These are the most efficient and versatile cyanating sources. HCN, NaCN and KCN were the first known cyanide sources. Later known metallic cyanide sources are CuCN, AgCN, $K_4[Fe(CN)_6]$, $K_3[Fe(CN)_6]$, and $Zn(CN)_2$; while the known metalloid cyanide sources are TMSCN and $^nBu_3SnCN$. Here, TMSCN is very sensitive to moisture and readily releases HCN, while the alkali metal cyanides and $Zn(CN)_2$ creates a lot of metal wastes at the end of reaction, along with the release of toxic HCN. Relatively non-toxic, $K_4[Fe(CN)_6]$ has six CN^- units bonded to the metal atom. If the concentration of CN^-released in the reaction medium is not controlled, they can poison the transition metal-catalyst by binding with the metal atom forming an inactive transition metal−CN complex, thereby inhibiting the reaction. Further, these sources possess serious transportation, handling, storage and disposal issues on account of facile generation of toxic HCN gas.

B. *Non-metallic cyanide sources:* To reduce the environmental impact and the inherent toxicity of metallic cyanide sources, the non-metallic cyanide sources were introduced. In these sources, the −CN unit is linked to a C, N, O or S atom by covalent bonds. Although an additional effort for synthesizing these sources has to be made, these sources produce minimized amount of wastes and causes less frequent deactivation of

transition metal catalysts. The utilized non-metallic cyanide sources are acetone cyanohydrin, TBACN, DDQ, AIBN, benzyl cyanide, malononitrile, acetonitrile, ICN, *N*-cyanobenzimidazole, aryl(cyano)-iodoniumtriflates, ethyl(ethoxymethylene) cyanoacetate and NCTS.

C. *Non–CN containing cyanide sources:* These non–CN containing cyanide sources do not contain a directly linked –CN unit in the molecular skeleton, but they can produce CN^- under some given reaction conditions. DMF, formamide, *tert*-butylisocyanide, NaN_3 and nitromethane are some reported non-CN containing cyanide sources.

D. *Combined Cyanide Sources:* The safest of all cyanide sources are the "combined cyanide sources". In this case, a suitable combination of carbon source (usually, the solvent) and a nitrogen source (usually, an ammonium salt) are chosen. The combination of carbon and nitrogen releases CN^- *in situ* through some parallel reactions under the given reaction conditions, producing aryl nitriles in good yields. The combination of NH_3(aq)–DMF, NH_4I–DMF, NH_4HCO_3–DMSO, NH_4HCO_3–DMF, urea–DMSO, CO_2–NH_3 and $ClCF_2H$–$NaNH_2$ are the combined cyanide sources known so far.

All the above cyanide sources have promising application potentials and should be carefully chosen in accordance to the substrate to be cyanated and the environmental impact they hold. Figure **1.3** gives a schematic representation of the available cyanating sources and their order of toxicity.

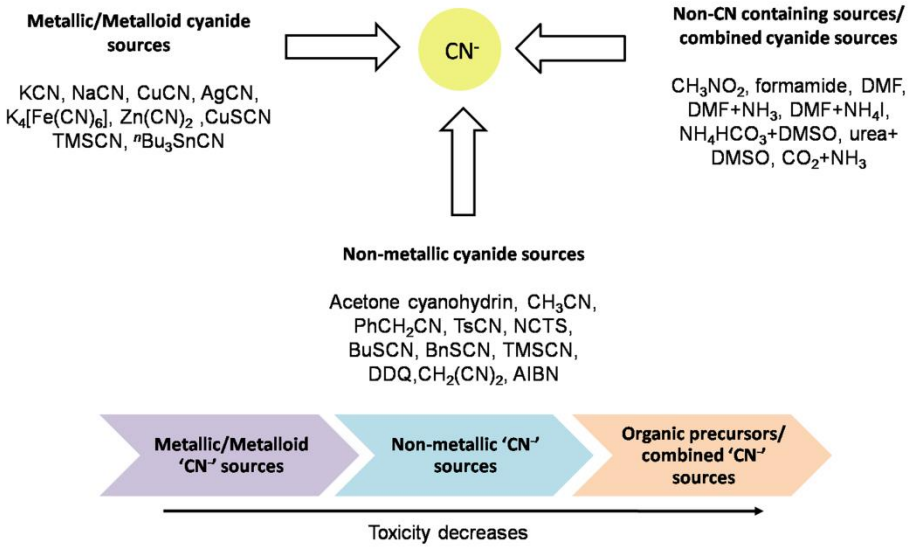


Figure **1.3** Cyanating sources and their order of toxicity

2.4 *Copper–catalysis in Cyanation Reactions*

Cu is the most preferred catalyst of choice for cyanation reactions in terms of scalability, sustainability and economy. Although both Cu and Pd are favourites for cyanation reactions and Pd is considered more active with a wider functional group tolerance, it faces some important challenges:

i) *Economic*: Pd is far more expensive in comparison to Cu. It also requires fancy ligand design for its participation in the organometallic cycle.

ii) *Scalability*: The methodologies designed with Pd may not always be industrially viable because of its expensiveness. Transition metal poisoning is another issue with Pd since it is highly fond of CN^-. Hence, control of CN^- concentration in the reaction medium is important, which is difficult at an industrial level.

iii) *Sustainability*: Disposal of toxic Pd–metal wastes generated at the end of the reaction is another concern.

Hence, Cu has been extensively utilized as a cheap alternative to Pd for cyanation and is reported to be compatible with a variety of cyanating sources. It produces a wide range of aryl nitriles under milder reaction conditions, generally through a two electron pathway.

Cu was first conceived in cyanation by the research group of Anderson [29] when they employed CuI as a "co-catalyst" in the Pd–catalyzed cyanation of aryl halides, vinyl bromides and triflates. Here, **KCN** was the cyanating source. The reaction proceeds through the general organometallic cycle involving oxidative addition, transmetallation and reductive elimination of the desired aryl nitrile (**C**, Figure **1.4**).

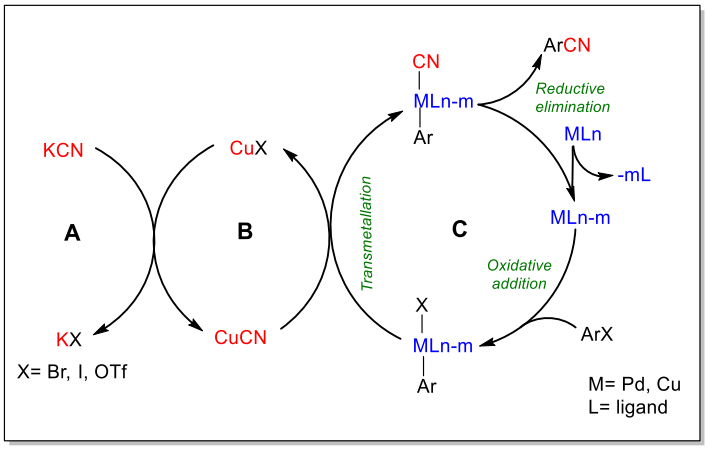
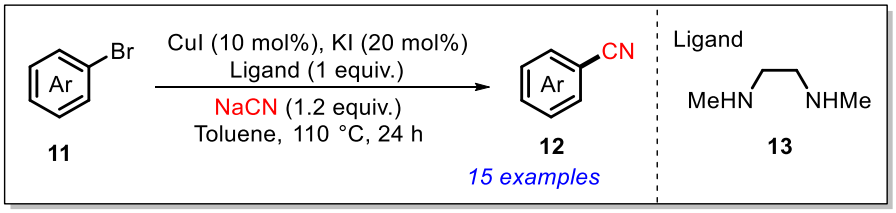


Figure **1.4** General reaction mechanism of cyanation

The additive (CuX) serves to form a more-soluble, covalently bonded CuCN from the poorly soluble and ionic, KCN (or other metallic cyanide sources). CN^- can be delivered more easily from CuCN at the stage of transmetallation. If a more soluble cyanide source like TBACN was used, the additive was not found necessary. It also addresses the issue of catalyst deactivation caused by high concentration of CN^- from KCN. The secondary process (**B**) takes place in a concerted pathway along with the organometallic cycle (**C**).

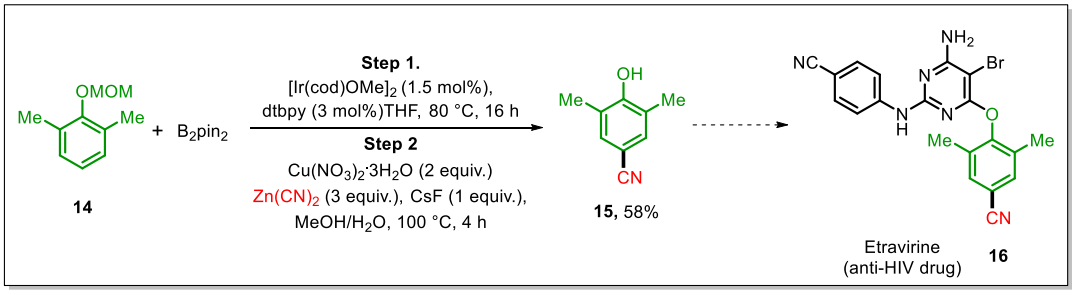
A. Cu-catalyzed cyanation with metal/metalloid cyanide sources: Inspired by the dramatic change in yields of aromatic nitriles with the use of CuI, Buchwald and co-workers [30] designed the first independent Cu-catalyzed synthesis of aryl nitriles from aryl bromides with **NaCN** as the cyanating source (Scheme **1.3**). The reaction was accelerated by the use of 1,2-diammine ligand, **13**. The reaction mechanism proceeded through a domino exchange of $Br^-$with I^- (from KI) to form aryl iodide, and subsequent cyanation of the aryl iodide to yield aromatic nitriles. The methodology was feasible for a range of aryl and heteroaryl bromides containing free N–H and O–H groups including acidic C–H bonds. It was a substantial advancement from the Rosenmund-von Braun reaction as the methodology surpassed the stoichiometric use of metal cyanides or generation of large amount of metal wastes.



Scheme **1.3** Cu-catalyzed synthesis of aryl nitriles with NaCN

With a similar protocol of sequential iodination and cyanation, Daugulis and his group [31] utilized NaCN to obtain a regioselective direct cyanation of *N*-heterocycles and azulene. Interestingly, the reaction was catalyzed by another metallic cyanide source, **CuCN** along with 1,10–Phenanthroline ligand. Iodine was used as the oxidant. In another report utilizing CuCN in a dual role (as a catalyst as well as cyanating source), Ding's group [32] achieved aryl nitriles from aryl bromides in a Rosenmund-von Braun fashion. The reaction was promoted by the amino acid; L-Proline at lower temperatures (80-120 °C). CuCN was employed in stoichiometric amounts though. With an analogous

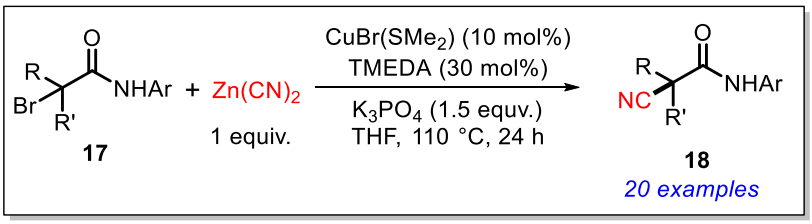
stoichiometric employment of CuCN, Pyne's group [33] synthesized 3−cyanobenzofurans and 3−cyanoindoles from β−hydroxyalkynes and *O*−alkynylphenols through a Cu−mediated one-step sequential cyclization and cyanation approach. The reaction was claimed to be cost-effective in terms of using cheap CuCN compared to its previously engaged costlier alternatives, Iodine and NIS. CuCN was also utilized by Cheng and co-workers [34] to obtain aryl nitriles from easy-to-handle phenylboronic acids. Variously substituted arylboronic acids were endured under the developed protocol with the exception of arylboronic acids bearing strong EWGs and with *o*-substitutions. Likewise, other cyanide sources viz. AgCN, $Zn(CN)_2$ and TMSCN were also tested for their efficiencies under the same reaction conditions. Alternatively, it was found that an additive, CuI (in stoichiometric amount) was necessary to gain decent yields of the desired nitriles. Beletskaya's group [35] obtained aryl nitriles from arene diazonium salts with KCN as the cyanating source. This upgraded version of the Sandmeyer reaction gave very high yields of the corresponding benzonitriles applying $Cu(BF_4)_2$ as a co-catalyst. In a complementary approach to Pd-catalyzed cyanation processes, Hartwig's group [36] conceptualized a unique Ir−catalyzed direct borylation of arenes and a sequential Cu-catalyzed cyanation of the corresponding arylboronate esters. Although cyanating sources like NaCN, TMSCN, $K_4[Fe(CN)_6]$ and CuCN were tested, $Zn(CN)_2$ gave the best results with $Cu(NO_3)_2{\cdot}3H_2O$ as the catalyst. This was a first of its kind example for the synthesis of *m*-substituted benzonitriles. The methodology was further demonstrated in the synthesis of 4-Cyano-2,6-dimethylphenol (**15**), a precursor of the anti-HIV drug, Etravirine (**16**, Scheme **1.4**).



Scheme **1.4** Synthesis of 4-Cyano-2,6-dimethylphenol

$Zn(CN)_2$ was also successfully employed in the cyanation of α-bromocarboxamides and their peptide derivatives under CuBr catalysis [37] (Scheme **1.5**). The previously known

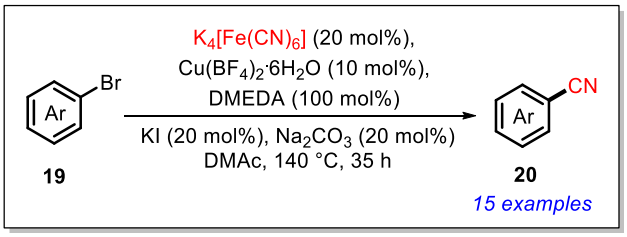
concept of exchange of anion between CuBr and $Zn(CN)_2$ to form covalent CuCN was postulated behind the success of the reaction.



Scheme **1.5** Cyanation of α-bromocarboxamides with $Zn(CN)_2$

Kim et al. [38] developed the first photo-induced Cu-catalyzed methodology for cyanation of aryl halides. The reaction proceeded through a single electron transfer (SET) mechanism, unlike the regular two electron pathway and utilized readily available NaCN as the cyanating source. Bisimine ligands were used along with CuI to improve catalytic performance. The protocol endured a wide range of aryl halides, reactive carboxylic and amine groups and alkyl chlorides.

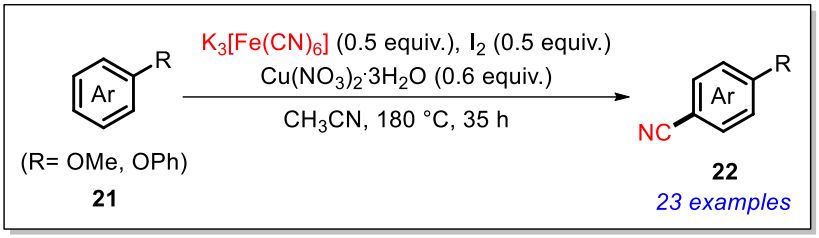
The discovery of Potassium hexacyanoferrate(II); **$K_4[Fe(CN)_6]$** as a cyanating source represents a paradigm shift from toxic metallic cyanides. It is a relatively non-toxic alternative to other metallic cyanide sources. It is readily available and cheaper than KCN. Although the use of $K_4[Fe(CN)_6]$ is generally reported with Pd-catalysis, its first use in Cu-catalysis was reported by Beller's group [39]. They developed a Cu-catalyzed methodology of cyanation of aryl bromides with $K_4[Fe(CN)_6]$ as the cyanating agent. The uniqueness of the protocol was the use of $Cu(BF_4)\cdot 6H_2O$ as the Cu-precursor and DMEDA as the ligand (Scheme **1.6**).



Scheme **1.6** Cu-catalyzed cyanation with $K_4[Fe(CN)_6]$

It was thought that water of crystallization in the Cu–salt helped to solvate the $[Fe(CN)_6]^{4-}$ anion where the metal catalyst and the nucleophile would stay in close contact to each other in the solvent, providing an ideal environment for the cyanation

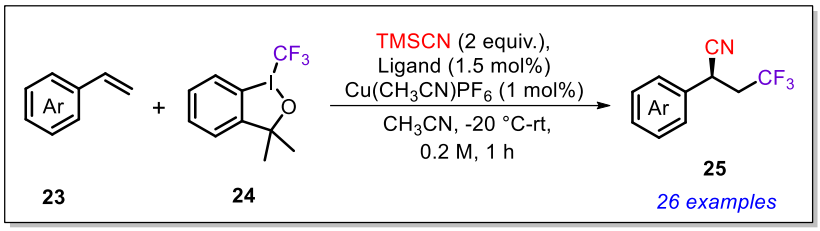
reaction. Later works by the same group [40-42] described a "biomimetic" Cu/1-butylimidazole catalytic system to achieve cyanation of sterically hindered aryl bromides, heterocyclic aryl bromides and amine substituted bromoarenes. The lipophilic and electron-rich 1-butylimidazole was thought to enhance the reactivity of bromoarenes. Ren et al. [43] devised a novel $Cu(OAc)_2 \cdot H_2O$/diamine catalytic system and obtained benzonitriles with just 20 mol% of $K_4[Fe(CN)_6]$. An additive, KI was used to accelerate the reaction and difficult substrates like aryl chlorides were also cyanated in good yields. Ren and co-workers also used the same cyanating agent to cyanate arylacetic acids under Cu-catalysis [44]. In another unique approach, potassium ferricyanide, $K_3[Fe(CN)_6]$ was used to cyanate alkoxy and benzyloxy-substituted arenes [45]. Although the cyanating agent as well as the Cu-salt was employed in equivalence, regioselective *p*-substituted benzonitriles were obtained in good to very good yields (Scheme **1.7**). The methodology involved I_2 as an additive and the reaction mechanism was also thought to proceed *via* sequential iodination and cyanation.



Scheme **1.7** Cyanation of arenes with $K_3[Fe(CN)_6]$

A series of reports utilizing **TMSCN** as the cyanating agent was published by the research groups of Liu [46] and Xu [47-49] (Scheme **1.8**). Enantioselective Cu-catalyzed cyanations of trifluoromethylalkanes, alkyl fluorides and alkyl bromides respectively, were described in a sequential photo-induced trifluoromethylation, fluoroalkylation and bromoalkylation of alkenes and sequential cyanation of the corresponding alkanes. In another recent report by Yang and co-workers [50], a decarbonylative alkylation of aliphatic aldehydes with styrene derivatives followed by cyanation of the corresponding α-substituted aldehydes was described. The reaction was catalyzed by Cu and TMSCN was the nitrile source. Another reductive cyanation of tertiary amides mediated by KO^tBu was developed by Liu et al. [51] using TMSCN as the cyanating agent. A wide range of aminonitriles was obtained in very good yields. Other works by Shi and co-

workers [52] also showed successful utilization of TMSCN as the nitrile source. TMSCN is the more-soluble organometallic cyanide source.



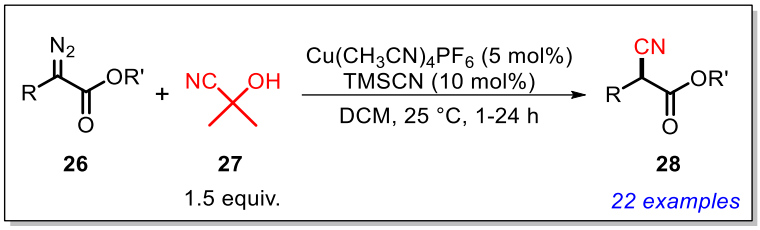
Scheme **1.8** Cyanation of alkenes with TMSCN

As evident from the above discussion, the earlier known metallic cyanides; KCN, NaCN and CuCN were efficiently utilized as cyanating sources and gave excellent yields of the corresponding benzonitriles. However, due to the potential risks associated with handling them, relatively stable $Zn(CN)_2$ was introduced. Least toxic of them all, $K_4[Fe(CN)_6]$ was the most easily available cyanide source that can be handled without precaution. It was believed to release CN^- comparatively slowly in the reaction medium, minimizing the problem of catalyst deactivation.

B. Cu-catalyzed cyanation with non-metallic cyanide sources: To minimize the environmental impact associated with cyanation by metallic sources, the non-metallic cyanide sources were introduced.

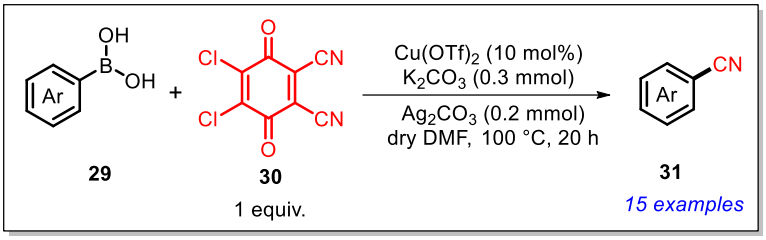
Acetone cyanohydrin was one of the first introduced non-metallic cyanide sources and is still considered to be one of the safest hydrogen cyanide (HCN) surrogate. Although it stays in equilibrium with HCN and acetone at ambient conditions, the equilibrium shifts to the right on successful cyanation. The first Cu-catalyzed cyanation with acetone cyanohydrin (**27**) as the cyanating source was reported by Beller [53]. Various aryl and heteroaryl bromides were cyanated to the corresponding benzonitriles with the help of a CuI/1-Butylimidazole catalytic system previously developed by the same group. The most interesting feature of this protocol was that the concentration of CN^- in the reaction medium was controlled by regulating the addition of acetone cyanohydrin through a syringe pump. Hence, catalyst deactivation was controlled in this protocol. Further, acetone cyanohydrin was also used for the hydrocyanation of α-aryl diazoacetates [54]. The reaction was catalyzed by $Cu(CH_3CN)_4PF_6$ and the combined quantity of CN^- released from TMSCN and acetone cyanohydrin (high concentration of

CN^-) was utilized to drive the equilibrium towards the formation of cyanated products (Scheme **1.9**). Another interesting work by Peters and co-workers [55] utilized acetone cyanohydrin for an asymmetric Strecker synthesis to prepare α-amino acids.



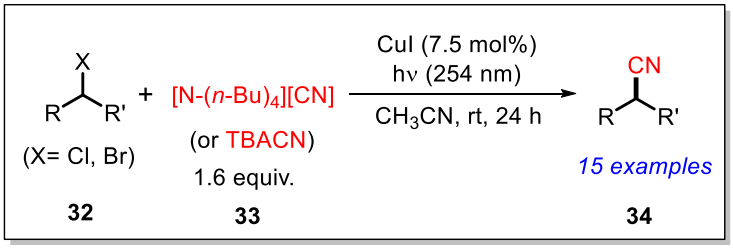
Scheme **1.9** Cyanation of α−aryl diazoacetates with acetone cyanohydrin

DDQ was first introduced as a cyanating agent by the research group of Chen [56]. A well-known dehydrogenative oxidant, DDQ (**30**) was found to release HCN in water or organic solvent. It was conveniently applied in the synthesis of benzonitriles from the parent arylboronic acids with operational simplicity and under Cu-catalysis (Scheme **1.10**).



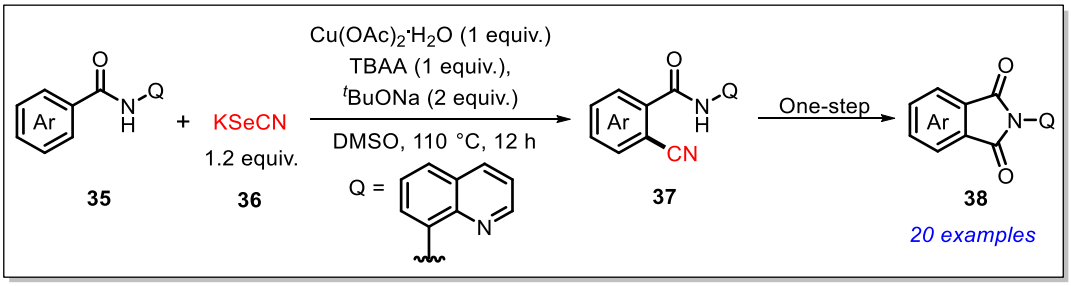
Scheme **1.10** Cyanation of arylboronic acids with DDQ

TBACN (**33**) was reported as another non-metallic cyanating source which was utilized in the cyanating of unactivated secondary alkyl chlorides and bromides [57]. The reaction was catalyzed by an inexpensive Cu-salt, CuI under UV light irradiation (Scheme **1.11**). The reaction was also extended to the cyanation of cyclohexyl chlorides and bromides. The reaction mechanism was postulated to occur *via* the formation of a $[Cu(CN)_2]^-$ species that involves in a single electron transfer (SET) process.



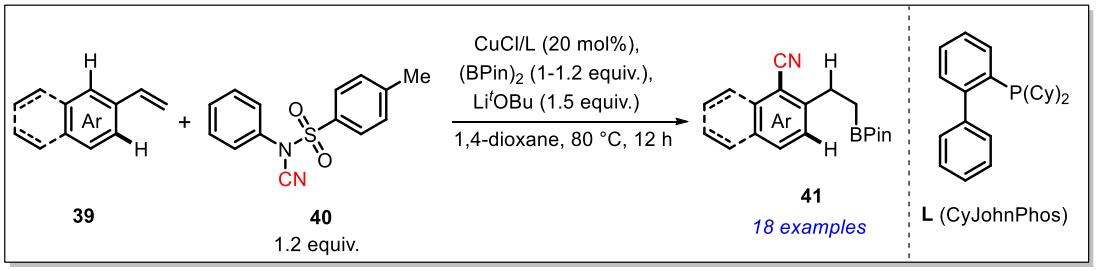
Scheme **1.11** Cyanation of secondary aryl halides with TBACN

KSeCN (**36**) was reported as a new nitrile source for the first time by the research group of Hu [58]. They used KSeCN for the efficient monocyanation of benzamides, through a sequential *ortho* C-H activation and cyanation (Scheme **1.12**). A wide range of *ortho*-cyanated benzamides were obtained under Cu-catalysis and 8-aminoquinoline as the promoter. The obtained cyanated products were further propagated to a one-step synthesis of 3-imino-1-oxoisoindolines (**38**).



Scheme **1.12** Cyanation of benzamides with KSeCN

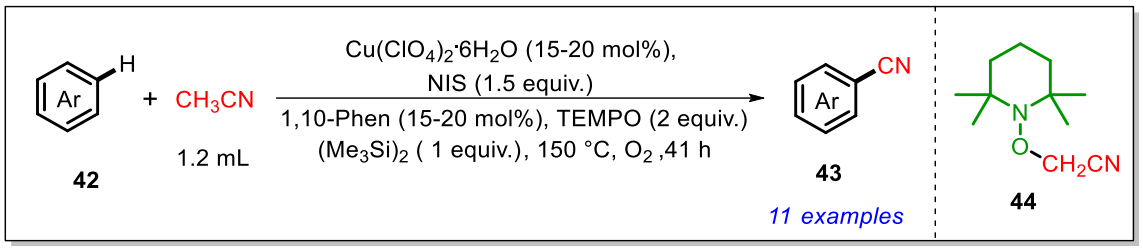
NCTS (**40**) is an electrophilic cyanating agent and was first reported under Cu-catalysis by Buchwald's group [59]. They designed a technique for the regioselective *ortho* C–H cyanation of vinylarenes. 2-Vinylnaphthalenes were cyanated selectively at the C-1 position in excellent yields, including 1-Vinylnaphthalenes and heterocyclic vinyl arenes (Scheme **1.13**). The reaction was proposed to proceed through an electrophilic cyanative dearomatization pathway. Other works on utilization of NCTS was carried out by the research groups of Yang [60], Zhao [61,62] and recently by Proctor [63]. A wide range of cyanated 1-Allyl-2-vinylnaphthalenes, substituted styrenes and boro-cyanated aryl-1,3-butadienes respectively, was obtained with NCTS under Cu-Catalysis [64].



Scheme **1.13** Cyanation of vinylnaphthalenes with NCTS

Acetonitrile (CH_3CN) is a common organic solvent and can be used as a source of CN^-, but is typically inert because of its high CH_3–CN bond dissociation energy. Its high p*K*a

value does not allow it to behave as a pro-nucleophile [65]. A careful design of transition metal-ligand system is necessary to cleave the C–C bond of CH_3CN. Li and co-workers utilized CH_3CN for the oxidative cyanation of aryl iodides under Cu-catalysis. A Ag-salt was used as an oxidant which accelerated the yields of corresponding benzonitriles. In an attractive approach for the direct cyanation of arenes, a Cu/TEMPO system was designed to activate CH_3CN for cyanation. A one-pot tandem iodination followed by cyanation strategy was contemplated by Shen and co-workers [66] (Scheme **1.14**). It was found that the actual cyanating agent formed in the reaction medium was TEMPO–CH_2CN (**44**), detected by GC analysis during the course of the reaction.

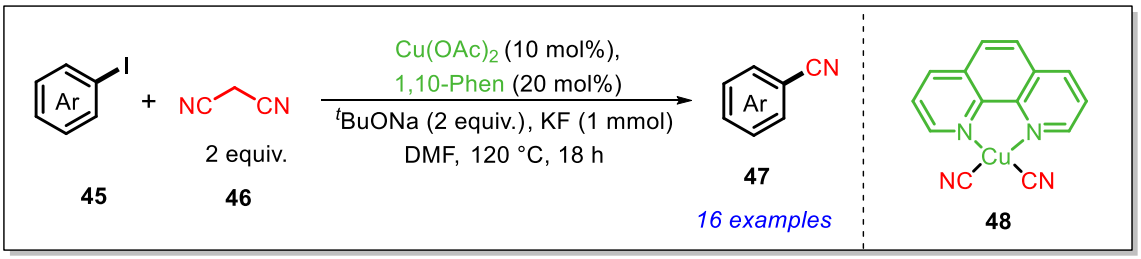


Scheme **1.14** Cyanation of arenes with acetonitrile

The same group had previously reported the cyanation of arenes with CH_3CN with the help of directing groups [67]. Hexamethylsilane, $(Me_3Si)_2$ was used to enhance the yields of the desired *ortho*-cyanated 2-Phenylpyridines. It played a critical role in the cleavage of the CH_3–CN bond by transfer of the silyl group to the nitrogen atom of CH_3–CN, which forms a η^2–coordinated iminoacylcopper(II) complexand weakens the C-C bond of CH_3–CN. Other works by Shen also utilized a combination of the above two systems to bring about cyanation of *N*–protected indoles and arylboronic acids [68,69]. Subsequently, acetonitrile was also used as a cyanating source by the research groups of Zhu [70], Shao [71] and recently by Ahmad [72].

Malononitrile (**46**) is another safe, bench-stable non-metallic cyanating source. Cyanation of aryl iodides with malononitrile would mean CN^- transfer from a sp^3 carbon atom to a sp^2 carbon atom. To achieve this, Jiang et al. [73] designed a $Cu(OAc)_2$–Phenanthroline system to achieve variously substituted benzonitriles in good to very good yields (Scheme **1.15**). An additive, KF was thought to assist in the C–C bond cleavage of malononitrile, where the released CN^- units formed a coordination complex with the Cu-Phen system *in-situ*. To confirm the observation, the coordination complex

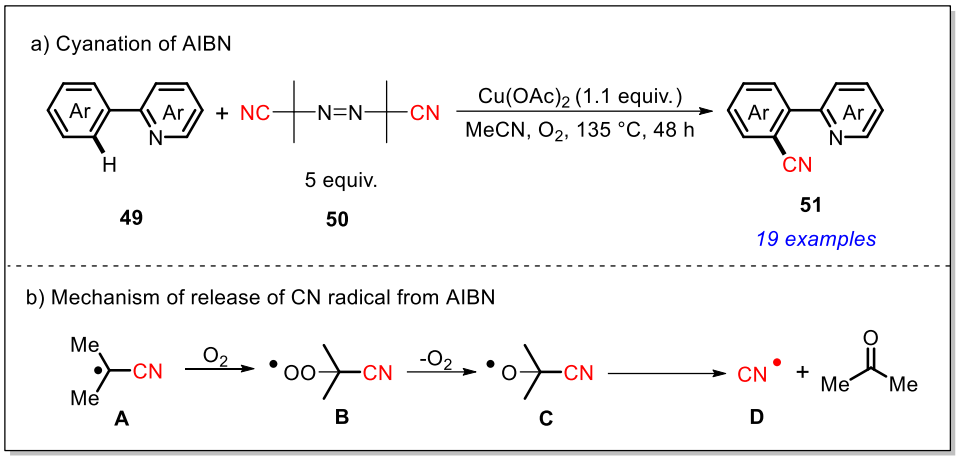
[Cu(phen)$_2$(CN)$_2$] (**48**) was prepared *ex-situ* and then employed with the model substrate to obtain the corresponding benzonitrile. Inspired by the use of malononitrile as a CN^-source, Peng's group designed an unprecedented one-pot C–H activation, iodination and cyanation of 2,4-Diarylquinazolines[74].



Scheme **1.15** Cyanation of aryl iodides with malononitrile

Cyanation of the iodinated intermediate took place under Cu-catalysis to produce the corresponding 2-(2-Cyanoaryl)-4-arylquinazolines or 2-(2,6-Dicyanoaryl)-4-arylquinazolines in superior yields. Another derivative of malononitrile; ***N,N*-dimethyl aminomalononitrile** also serves as a cyanating source for aryl iodides [75]. The reaction was efficiently promoted by cupric phosphate without the use of additional ligands and additives.

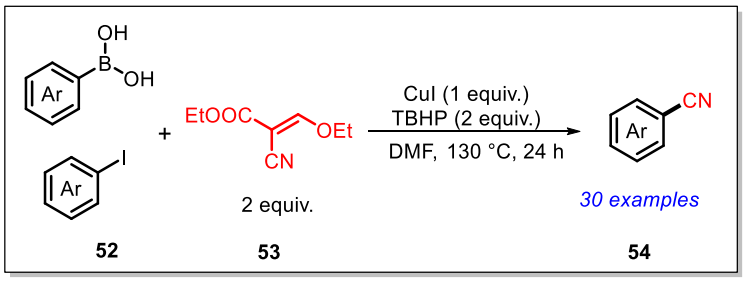
AIBN (**50**) is a cyanide radical generator ($^{\bullet}CN$) and have been used efficiently as a cyanating source by various groups. To circumvent the problem of catalyst deactivation by unmanageable CN^- concentration in the reaction medium, AIBN was first introduced by the research group of Han [76] for a direct C–H cyanation of 2-Phenylpyridines through a free-radical route (Scheme **1.16a**). The properties of the cyanide radical differ from the CN^- anion in terms of its oxidizing ability, which facilitates reductive elimination. GC-MS analysis and other spectroscopic studies proved that AIBN first decomposes to the radical form by elimination of nitrogen (Scheme **1.16b**). The radical is trapped by oxygen to form peroxide radical (**B**), which in turn gives the cyanide radical (**D**) by the release of acetone (acetone was detected in GC-MS analysis). Thus, O_2 was essential for cyanation with AIBN. The cyanation reaction with 2–Phenylpyridines took place only with stoichiometric amounts of $Cu(OAc)_2$ and O_2 to produce *o*-substituted 2-Phenylpyridines in good yields.



Scheme **1.16** Cyanation of 2-Phenylpyridines with AIBN

Another work by Xu and co-workers [77] disclosed a Cu-catalyzed cyanation of terminal alkynes with AIBN and **AMBN** as the nitrile source. Various terminal aryl, alkyl and silyl substituted alkynes and their derivatives were cyanated in good to excellent yields. The methodology was a significant improvement over other cyanation reactions of terminal alkynes in terms of substrate scope.

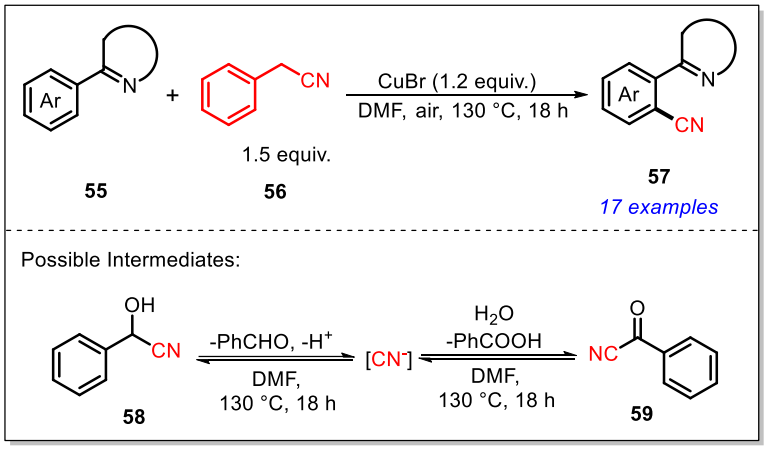
Ethyl(ethoxymethylene)cyanoacetate (**53**) is a versatile building block and was first employed as a cyanating source by the research group of He [78]. The reaction represents an interesting example of C(sp^2)–CN bond cleavage (Scheme **1.17**). They utilized it for the cyanation of arylboronic acids and aryl iodides, mediated by CuI. The metal iodide not only catalyzed the reaction but also brought about *in situ* iodination of the arylboronic acids, facilitating faster cyanation. In a similar example, Jiang's group [79] reported direct C–H cyanation of heteroarenes. The protocol had the advantage of using molecular O_2 as the oxidant, in contrast to TBHP used in the previous case.



Scheme **1.17** Cyanation with ethyl(ethoxymethylene)cyanoacetate

Similarly, Cai's group [80] conducted cyanations of substituted azoles and indoles with ethyl(ethoxymethylene)cyanoacetate as a safe, efficient and non-toxic cyanating agent.

Benzyl cyanide is another safe, non-metallic cyanide source. Under Cu-catalysis, it was first employed by the research group of Wang [81], who described benzyl cyanide (**56**) as a CN^-surrogate in the synthesis of *o*-cyanated arenes (Scheme **1.18**). The reaction was catalyzed by CuBr and good yields of the desired product were obtained, including those of sterically demanding substrates. Spectroscopic studies revealed that in the presence of Cu and O_2, benzyl cyanide could possibly form a cyanohydrin (**58**) through C–H activation, or benzoyl cyanide (**59**). Both these molecules could release CN^- in the reaction medium.

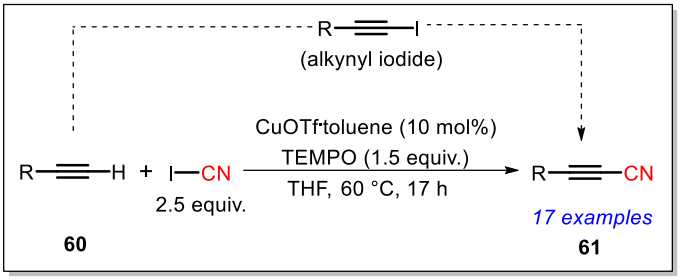


Scheme **1.18** Cyanation of 2-Phenylpyridines with benzyl cyanide

Based on the results and mechanistic study, Wang's group [82] reported the cyanation of aryl bromides and iodides with benzyl cyanide. Both the research groups of Wang [83] and Kwong [84] attempted the cyanation of indoles with benzyl cyanide under Cu-catalysis, however, the latter protocol had the advantage of obtaining regioselective 3-cyanoindoles without the use of oxidant. Another report showcased DFT studies on the mechanism of cyanation of 2–Phenylpyridines by benzyl cyanide [85]. Interestingly, **benzoyl cyanide** (**59**) was also employed as a cyanating agent under Cu-catalysis to obtain direct cyanation of terminal alkynes [86] and C(sp^2)–H cyanation of various naphthalenes [87].

Cyanogen Iodide (**ICN**) is another useful electrophilic cyanide source. It is bench stable and can be easily prepared from the reaction between I_2 and NaCN. It was successfully applied by Okamoto et al. in the cyanation of terminal alkynes under Cu-catalysis [88]. Unlike other Cu-catalyzed mechanisms which expect the formation of Cu-acetylide intermediate, this reaction proposed the formation of alkynyl iodides in the reaction

pathway, as detected by ^{1}H NMR analysis (Scheme **1.19**). Thus, cyanogen iodide played a dual role of being an iodinating agent as well as a cyanating agent. TEMPO was applied as the base and it executed key steps in transferring the −CN unit in the reaction medium. The same group utilized a Cu-bipyridine system to obtain direct cyanation of aryl and alkenylboronic acids with cyanogen iodide [89]. A similar reaction pathway of formation of organoiodides was also proposed in this reaction. **BrCN** is an equivalent electrophilic cyanating agent and is readily obtained from the reaction between Br_2 and NaCN. However, it is extremely toxic and requires many handling precautions. Another useful electrophilic cyanating source, ***N*-cyanobenzimidazole** [90] can be prepared by the reaction between BrCN and imidazole. They are a significant domain in electrophilic cyanation [91].



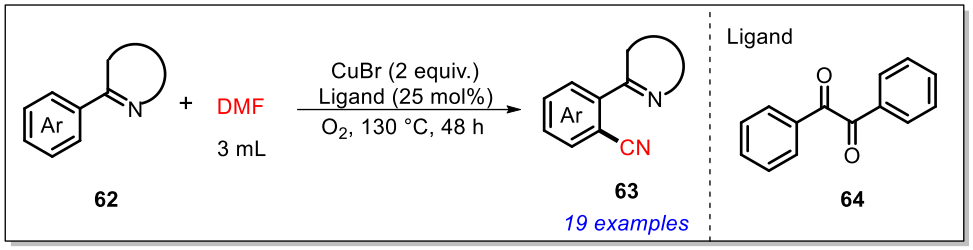
Scheme **1.19** Cyanation of terminal alkynes with cyanogen iodide

Thiocyanates like benzylthiocyanate [92], CuSCN [93], NH_4SCN [94,95], KSCN [96] are other useful non-metallic cyanating agents. However in recent times, they are being employed under transition metal-free conditions. Some examples of cyanation are also reported with hypervalent iodine reagents like aryl(cyano)iodonium triflates under Fe-catalysis [97] and cyanobenziodoxole [98] and α−cyanoacetate under Cu-catalysis [99,100] as the non-metallic CN^- sources.

C. Cu-catalyzed cyanation with non−CN containing cyanide sources: These sources do not contain a directly linked −CN unit, but they can produce CN^- in the reaction medium.

DMF is a multipurpose solvent and a useful precursor of O, −CO, −CHO, $-CONMe_2$, $-NMe_2$, −Me and −CN. Its utility as a CN^- source under Cu-catalysis was first demonstrated by the research group of Jiao [101]. 2-Phenylpyridines were cyanated with operational simplicity and high atom economy under the methodology (Scheme **1.20**). The reaction was catalyzed by CuBr and a lesser explored ligand, benzil (**64**) was

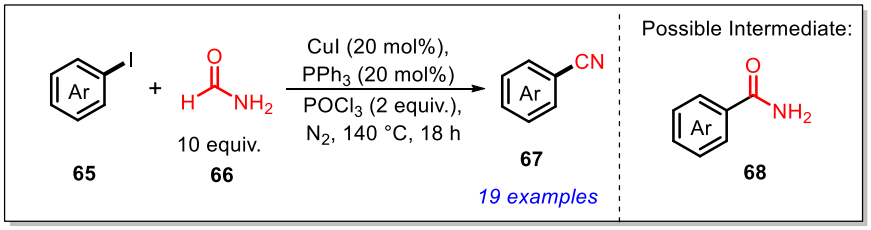
employed to accelerate the cyanation reaction. They proposed that the C−atom and the N−atom of the CN^- unit originated from the *N,N*−dimethylamino moiety of DMF and the usual route of formation of CuCN in the reaction medium was ruled out.



Scheme **1.20** Cyanation of 2−Phenylpyridines with DMF

Soon after, a series of reports by the research groups of Wang [102,103] and Han [104] in 2015 revealed interesting results of cyanation with DMF as the nitrile source. Wang obtained the cyanation of aryl halides and indoles and other electron-rich arenes efficiently under Cu-catalysis. Aryl aldehydes were however, disclosed as the key intermediates in the reaction pathway. On the other hand, Han obtained regioselective C−3 cyanation of indoles through an oxidative Cu-mediated cyanation process with DMF as the cyanating source.

Formamide is another well-known organic nitrile source. Although formamide (**66**) has been efficiently utilized as a CN^- donor in a number of reports [105-108], its use under Cu-catalysis has been limited. The research group of Bhanage utilized a CuI/Ph_3P catalytic system for the cyanide free cyanation of aryl and heteroaryl iodides and bromides (Scheme **1.21**) [109]. The superiority of the protocol was demonstrated in terms of use of non-noble metal-catalyst and inexpensive ligands. Benzamides (**68**) were proposed as intermediates during the course of the reaction, which on dehydration gave the corresponding nitriles.



Scheme **1.21** Cyanation of aryl iodides with formamide

Nitromethane (CH_3NO_2) is another important non−CN containing organic nitrile source. However, the developments of nitromethane as a CN^- source will be discussed in detail in Chapter 2, owing to its relevance with my experimental work described in the next chapter. Other useful non−CN containing sources are 5-methyl-2-phenyl(oxazol-4-yl) boronic acid; a carbon bound cyanide source [110], cyanuric chloride [111] and NaN_3 [112].

D. Cu-catalyzed cyanation with combined cyanide sources: With greater relevance of cyanation with combined sources in my experimental work discussed in Chapter 3, the development in Cu-catalysis with combined cyanide sources will be reviewed in detail in the forthcoming chapter 3.

It is important to mention that the above discussed cyanating sources were also applied successfully under Pd and Ni−catalysis, but that discussion is beyond the scope of this thesis. In brief, the mode of attack of these cyanating sources can be summarized as shown in Table **1.1**.

Table 1.1 Classification of cyanating sources[a]

NaCN, KCN, CuCN, AgCN, $K_4[Fe(CN)_6]$, $K_3[Fe(CN)_6]$, $Zn(CN)_2$, TMSCN, $^nBu_3SnCN$; acetone cyanohydrin, TBACN, DDQ, benzyl cyanide, malononitrile, CH_3CN, aryl(cyano)-iodoniumtriflates, cyanobenziodoxole, ethyl(ethoxymethylene)cyanoacetate; CuSCN, NH_4SCN, KSCN; CH_3NO_2, DMF, Formamide	CN^- (nucleophile)
ICN, BrCN, NCTS, *N*-cyanobenzimidazole, Phenyl cyanate	CN^+ (electrophile)
AIBN, AMBN	$CN^·$ (radical)
NH_3(aq)−DMF, NH_4I−DMF, NH_4HCO_3−DMSO, NH_4HCO_3−DMF, urea−DMSO, CO_2−NH_3 $ClCF_2H$−$NaNH_2$	C + N

[a]Blue colour: Metallic/metalloid cyanating sources; Purple colour: Non−metallic cyanating sources; Green colour: Non−CN containing CN sources; Orange colour: Combined cyanating sources

1.3 The Chan–Lam Cross–Coupling Reaction

The backbone of synthetic organic chemistry is guarded by the strategic placement of carbon−nitrogen bonds [113,114]. In this regard, transition metal-catalyzed fabrication of carbon−nitrogen bonds constitutes an important area of research owing to its diverse applications in academic and industrial research units, particularly in drug discovery and development [115]. This transformation is desirable because aryl ethers, aryl amines and aryl thioethers are prominent moieties in numerous bioactive scaffolds. At present, the three most influential non-amide carbon-nitrogen bond forming strategies that are available to a synthetic chemist are the Buchwald-Hartwig reaction, [116,117] the Ullmann-Goldberg reaction and the Chan-Lam cross-coupling reaction. The Cu-catalyzed Ullmann-Goldberg reaction and Pd-catalyzed Buchwald-Hartwig reaction for C–X bond formation with nucleophiles and electrophilic aryl halides are useful reactions to generate aryl amines and aryl ethers. However, the relatively harsh reaction conditions of classical Ullmann–Goldberg (high temperature and strong base) and Buchwald-Hartwig reactions (elevated reaction temperature and expensive ligands/Pd) limited the extensive application of these transformations. Prior to the discovery of the path-breaking Suzuki-Miyaura cross-coupling for C−C bond formation, the corresponding cross–coupling for aryl carbon–heteroatom (C–X; where X = O, N, S) bond formation involving milder reaction conditions was less established.

1.3.1 ***The History of Chan-Lam Cross-Coupling***

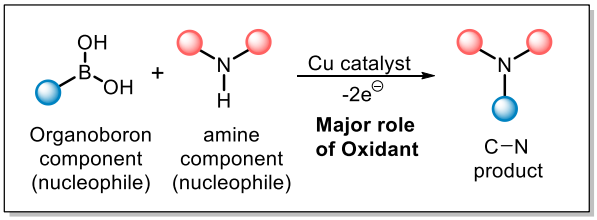
The development of “Cu-catalyzed” C−N cross-coupling reactions sparked with a report by Dodonov’s group [118] of utilization of triphenylbismuth diacetate for the arylation of alcohols, phenols, amines and water. Subsequently, Barton’s group disclosed two reports on utilization of triarylbismuthdiacylates [119] and phenyllead triacetate [120] in *N*-arylations. Subsequent works by the same group [121,122] employed triphenylbismuth and aryllead triacetate for the *N*-arylation of amino acids and heterocyclic amines respectively. Due to similarity in chemical behaviour of organobismuth and organolead reagents, they could bring about efficient C−N cross-couplings. In practice, arybismuth reagents are still utilized to obtain arylated products [123-126]. Although these reagents had attractive prospects, aryllead reagents needed

elevated temperatures for reaction and produced toxic organolead by-products; while arylbismuth reagents were limited to arylation of indole-like heteroarenes only. Moreover, their inadequate accessibility and potential toxicity limited their use in C–N coupling reactions. Later, Chan employed arylboronic acids during his ongoing work on triarylbismuth arylations [127] (Table **1.2**).

Table **1.2** Timeline of arylating agents used in Cu-catalyzed C–N cross-couplings

Year	***Arylating partner***	***Target nucleophile***
Dodonov; 1986	$Ph_3Bi(OAc)_2$	Alcohols, amines, phenols, water
Barton; 1986	$Ph_3Bi(OCOR)_2$	Amines
Barton; 1987	$PhPb(OAc)_3$	Aromatic and aliphatic amines
Barton; 1989	$Ph_3Bi(OAc)_2$	Amino acids
Barton; 1989	$PhPb(OAc)_3$	Aliphatic, heterocyclic and aromatic amines
Barton, 1996	$AlEt_2Cl$	Hydrazine, hydrazone, hydroxylamine
Chan; 1996	Ar_3Bi	Amides, ureas, carbamates, imides, sulfonamides
Chan, Lam, Evans; 1998	Arylboronic acids	*N*-, *O*-, *S*-nucleophiles

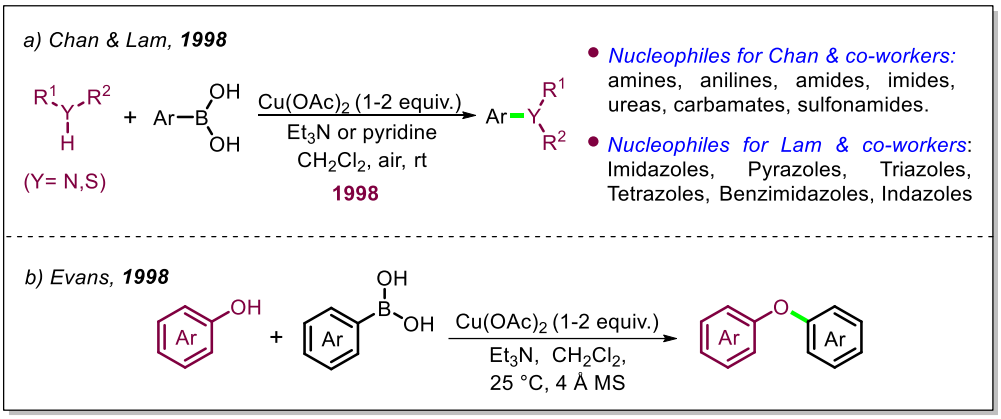
The discovery of a powerful Cu^{II} promoted nucleophile-nucleophile or oxidative Cu-catalyzed cross-coupling of nucleophiles and arylboronic acids, better known as Chan-Evans-Lam (CEL) cross-coupling represented a breakthrough in this respect (Scheme **1.22**).



Scheme **1.22** Representative nucleophile–nucleophile cross-coupling

Prof. Dominic M. T. Chan and his research group reported the first use of arylboronic acids for the arylation of a wide range of substrates with the same reaction conditions as in arylations with triarylbismuth [128]. Working in the same DuPont Merck Pharmaceutical Company, Prof. Patrick Y. S. Lam and co-workers [129] independently reported the utilization of arylboronic acids for the synthesis of biologically active *N*–arylated heterocycles (Scheme **1.23a**). Concurrently, Prof. David Evans and his group

[130] developed a similar Cu-based methodology for the arylation of variously substituted phenols and tyrosine derivatives with arylboronic acids (Scheme **1.23b**). The reaction was then successfully applied to an expedient synthesis of a precursor of L-thyroxine. Here, the term CEL is used synonymously with Chan–Lam cross-coupling.



Scheme **1.23** First discovery of Chan–Lam cross-coupling reaction

Although CEL cross-couplings face challenges of employing stoichiometric amounts of Cu-metal/oxidant and excess of arylboronic acids; it had some distinctive advantages over other "stoichiometric metal catalysis–high temperature" reactions:

i) The reaction employed cheap, readily available Cu-catalyst without elaborate ligand design.

ii) "Open-flask" reaction condition i.e. ambient temperature, mild base and run in air.

iii) The arylating partner i.e. organoboronic acids are easily accessible, insensitive to air, bench-stable and allow reactions in aqueous medium.

iv) The reactions were compatible with a wide range of target nucleophiles and endured substrates with sensitive functional groups.

1.3.2 *The arylating partner*

The arylating partner in Chan-Lam cross-coupling reactions are the arylboronic acids and its derivatives (Figure **1.5**). Arylboronic acids are compounds of boron, having one carbon substituent and two hydroxyl groups oriented in a sp^2 trigonal planar geometry. The remaining low-energy, vacant p–orbital lies orthogonal to the substituents. As mild Lewis acids, aryl boronic acids are non-toxic and moisture-stable (mostly exists as solids). In the context of green chemistry, they can be regarded as "green" compounds

on account of their ultimate degradation to boric acid [131]. The mild Lewis acidity of boron and hydrogen bonding ability of −OH groups in boronic acids make them polar. Arylboronic acids are easily prepared from a two-step oxidation of boranes. In recent times, they have also been shown to be prepared directly from arenes and indoles [132,133].

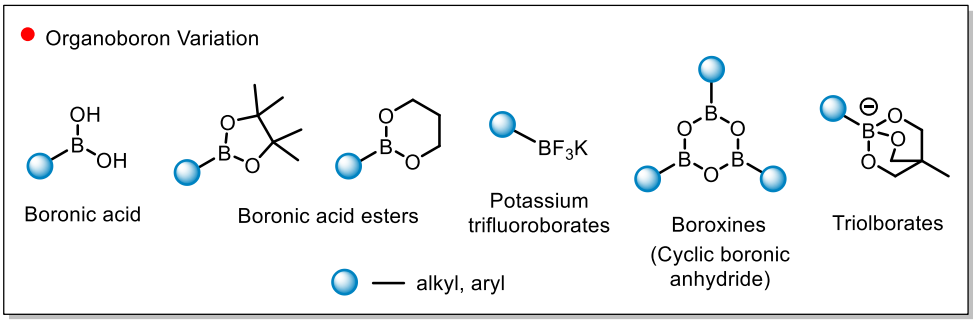


Figure **1.5** Boronic acid counterparts used in Chan-Lam cross-coupling

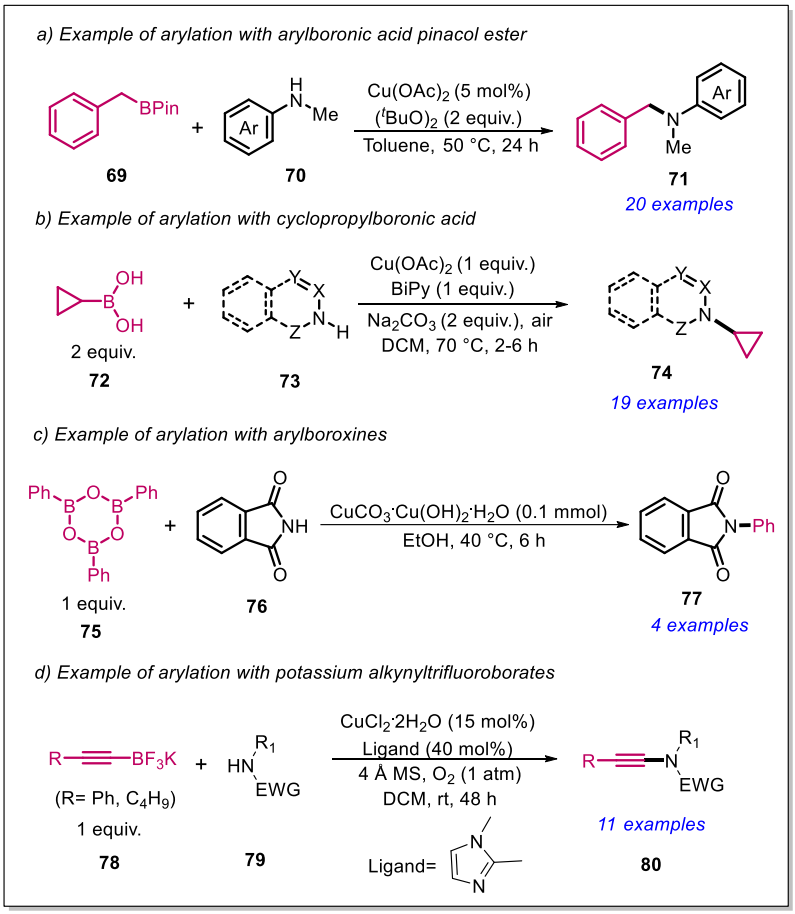
Apart from arylboronic acids, it was found that most of its derivatives are less easily compatible in achieving Chan−Lam arylations.

Arylboronic acid pinacol esters are the alkoxy or aryloxy derivative of arylboronic acids. They are less polar, easier to handle and more preferred in comparison to boronic acids because the latter often tends to exist as mixtures with its cyclic anhydride; which may complicate synthetic procedures. The esters are however, accused of inhibiting the transmetallation process through the formation of a substantially stable Cu^{II}–pinacol complex. However, Kuninobu and his group [134] utilized benzylboronic acid pinacol esters (**69**) to obtain arylation and alkylation of amines with $Cu(OAc)_2$ and di-*tert*-butoxide as the terminal oxidant (Scheme **1.24a**). $Cu(O^tBu)_2$ was considered as the active catalytic species and the corresponding secondary and tertiary amines were obtained in very good yields under mild basic conditions. Other works by Clark [135,136] and Sukach [137] also demonstrated equivalent efficiency of arylboronic acid pinacol esters. Another report by Cruces [138] disclosed an alkylation of anilines by an *in situ* generated alkylborane to obtain unique Phenethyl derivatives through Chan-Lam cross-coupling strategy. The alkylborane was not isolable and hence generated *in situ* from the hydroboration substituted of styrenes.

Alkyl boronic acids, except cyclopropylboronic acids and methylboronic acids, are rarely preferred in arylations due to their poor response towards transmetallation with

transition metals including Cu. In this regard, cyclopropyl boronic acids are easily accessible, possess a certain amount of sp^2 character in its carbon atoms and comparatively stable to air and water. A $Cu(OAc)_2$ mediated *N*-cyclopropylation of a wide range of amines was performed with cyclopropylboronic acid (**72**) by the research group of Zhu (Scheme **1.24b**) [139]. Another report by Tsuritani [140] disclosed Cu-catalyzed *N*-cyclopropylation of cyclic imides and indoles. Larrosa et al. [141] also reported efficient *N*-arylation of anilines with nine structurally diverse alkylboronic acids like 1-Propylboronic acid, 1-Butylboronic acid, Phenethylboronic acid, 2-Propylboronic acid, cyclohexylboronic acid, cyclopropylboronic acid etc. Employing the general conditions of Chan-Lam arylation, a sterospecific *N*/*O*−vinylation of amines and ethers was reported by Lam's group too [142]. Although a handful methodologies of arylation with methylboronic acids are known, very efficient *N*-methylations have been accomplished by the groups of Cruces [143], Gorin [144,145] and Watson [146]. Selective mono-methylated anilines and methylated primary amides were respectively obtained by Cruces and Watson under Cu-catalysis; while application of methylboronic acids was successfully extended to *O*−nucleophiles like carboxylic acids and phenols by Gorin. A unique electrophilic C−N cross-coupling between aryl(alkenyl)boronic acids and *N*-containing hypervalent iodine(III) reagent was also reported by Yuan's group [147] under oxidant-free, base-free reaction conditions.

Arylboroxines are the trimeric cyclic anhydride of arylboronic acids and are easily produced from the dehydration of arylboronic acids. They possess some aromatic character and are isoelectronic with benzene. On the synthetic front, they have shown limited progression in Chan-Lam cross-coupling reactions, as it is thought to be the active arylating agent (formed from the corresponding boronic acid) in Chan-Lam reactions that are conducted under anhydrous conditions. Yu's group [148] showed that when arylboroxines (**75**) were employed as arylating agents under Cu-catalysis, *N*-arylation of phthalimides took place under base-free, oxidant-free reaction conditions (Scheme **1.24c**). The methodology could be extended to arylation of amines, imides, amides and sulfonamides. Although reports of arylboroxine arylations under Cu-catalysis are few, they have been effectively used as arylating agents under Rh- and Pd-catalysis [149-151], similar to that of triolborates.



Scheme **1.24** Examples of arylations with boronic acid derivatives

Only example of utilization of *triolborates* with Chan-Lam reaction strategy was demonstrated by Miyaura's group [152]. They utilized potassium aryltriolborate for the *N*-arylation of amines and azoles. An unusual oxidant, trimethylamine–*N*-oxide (Me_3NO) was found to be crucial to obtain high yields of the corresponding *N*-arylated products. *Aryltrifluoroborates* are easily available in crystalline form and are extremely resistant to oxidation on account of the strong B–F bond; in comparison to C–B bond in boronic acids. They are superior to boronic acids in terms of their handling and easy preparation. They are however, poor nucleophiles due to the high electronegativity of the fluorine groups [153]. Batey [154] reported the first arylation of aliphatic amines and anilines with potassium trifluoroborates under Cu-catalysis. In subsequent reports by the same group, potassium alkenyltrifluoroborates were implemented for the synthesis of enamides (from amide arylation) [155] and non-decarboxylative synthesis of (*E*) or (*Z*)–enol esters (from carboxylic acid arylation) [156]. Inspired by these works,

Evans and his co-workers [157] synthesized potassium alkynyltrifluoroborates (**78**) for a room-temperature, base-free synthesis of ynamides with Cu-catalyst (Scheme **1.24d**). Above all, arylboronic acids have proven to be versatile arylating agents and are compatible with a wide range of *N*−, *O*− and *S*−nucleophiles owing to their bench-stability, easy preparation and enabling reactions in open-flasks. Apart from all the above, organostannanes [158,159], organozinc [160,161] and organoaluminium [162] have also been employed as the organometalloid partner in CEL couplings.

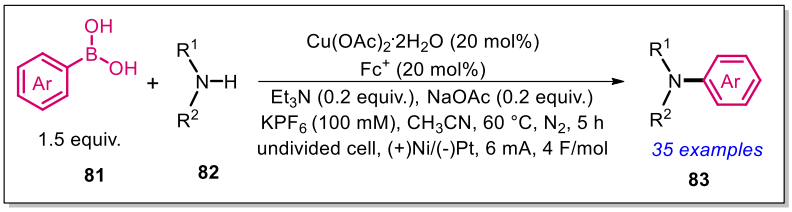
1.3.3 *The nucleophile*

Amines are the primary target nucleophiles in Chan−Lam cross-coupling reactions. However, CEL couplings are expected to enable the formation of about twelve different types of C−heteroatom bonds. The multi-verse of target nucleophiles arylated using Chan−Lam cross-coupling strategy [163-168] is shown in Table **1.3**. Although unique examples of Chan−Evans−Lam type C−O bond formation [169], C−P bond formation [170], C−Se and C-Te bond formation [171,172] and C−C bond formations [173] are also known, the scope of *N*-nucleophiles under Chan−Lam cross−coupling strategy is undeniably most extensive. Therefore, this category of nucleophiles is the most widely studied and discussed. Some recent examples are discussed below:

N-nucleophile:	Aryl and heteroaryl amines, aliphatic amines, Fused azaheterocycles, cyclic primary and secondary amines, primary amides, Lactams, guanidine, hydrazine, carbamates, imides, fluoroalkylamine & fluoroacetamide, hydantoins
O-nucleophile:	Phenols, urea, alcohols, water, carboxylic acids, hydroxylamine
S-nucleophile:	Sulfonamides & *N*-arylsulfonamides, sulfoxines, arylthioureas, thiols, sodium arylsulfinates, sulfoximines, disulfides
P-nucleophile:	H-phosphonate diesters, H-phosphine oxides
Se/Te-nucleophile:	Diselenides, Se, ditellurides
C-nucleophile:	Trifluoromethyltrimethylsilane, malonates, tertiary Malonates and Amido Esters, Benzoic Anhydrides
Biomolecules:	Amino acids (Cysteine, Histidine), Peptides, Alkaloids, purines,pyrimidines

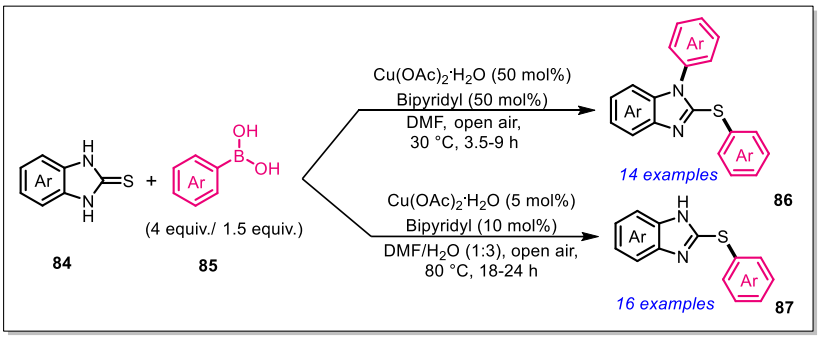
Table **1.3** Target nucleophiles employed in Chan−Lam cross-coupling.

In an alternative to Chan–Lam cross-coupling methodologies that requires stoichiometric amount of a terminal oxidant, the research group of Sevov [174] resorted to electrooxidation for an "air-free" Chan-Lam cross-coupling of aryl, heteroaryl and alkyl amines with arylboronic acids. Ligandless Cu–catalyzed and stoichiometric oxidant-free methodology was described in an undivided electrocatalytic cell (Ni|Pt cell) with ferrocenium hexafluorophosphate (Fc^+) as the redox mediator (Scheme **1.25**). The principle role of the redox mediator was to prevent oxidation of the amine substrates and to maintain a high concentration of Cu^{II} ions in the reaction medium. The methodology endured aryl amines with electron-donating as well as electron-withdrawing groups, electron rich alkyl amines and primary amines; but was sluggish for secondary amines, sterically hindered alkyl amines and heterocyclic amines.



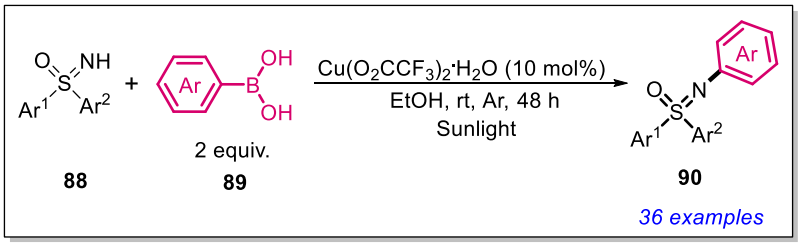
Scheme **1.25** Electrochemical Chan–Lam cross–coupling reaction

Another interesting approach was disclosed by the research group of Dong [175] to attain a Chemoselective arylation of Benzimidazoline-2-thiones (**84**) using Chan-Lam cross-coupling strategy (Scheme **1.26**). Selective S-arylated products (**87**) and bis-arylated products (**86**) were obtained with arylboronic acids by simply varying the Cu-catalyst amount, solvent and temperature. The protocol endured a wide range of functional groups on both the benzimidazole unit and arylboronic acid and defined an easily accessible route to biologically active benzimidazole sulfides.



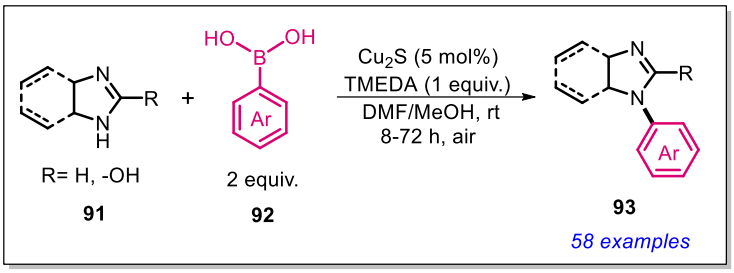
Scheme **1.26** Chemoselective Chan–Lam arylation of Benzimidazoline–2–thione

Jia's group [176] reported a fascinating photo-induced and autocatalytic Chan-Lam arylation of free diarylsulfoximines (Scheme **1.27**). The idea behind the reaction design was to devise an oxidant-free methodology through a photo-induced single electron oxidation of Cu^{I} to Cu^{II}. A range of diarylsulfoximines and arylboronic acids were compatible with the methodology including those with heteroaryl groups. Mechanism study revealed that the *N*-arylsulfoximine species behaved as ligand and bonded to Cu^{I} in the reaction medium, catalyzing the reaction cycle like an efficient photocatalyst. DFT studies hinted at the possible participation of both the substrate sulfoximine and the arylated sulfoximine in the catalytic cycle. The reaction represented another milestone for an oxidant-free Chan-Lam cross-coupling with maximum by-product elimination in the reaction medium formed from the use of stoichiometric amounts of oxidants in Chan-Lam cross-couplings.



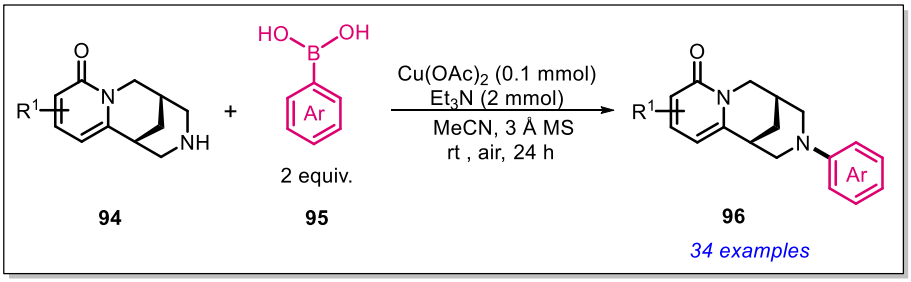
Scheme **1.27** Autocatalytic photo-redox Chan-Lam arylation of free diarylsulfoximines

The research group of Cancar [177] utilized a readily available Cu_2S/TMEDA for the Chan–Lam arylation of azole-based heterocycles like 1*H*-benzo[*d*]imidazol-2(3*H*)-one, 1*H*-benzo[*d*]imidazole, and 1*H*-imidazoles (Scheme **1.28**). Arylation of benzimidazolone produced both the mono– and di–arylated products and those possessing a restricted C–N bond rotation lead to the formation of atropisomers. Interesting, a sequential one–pot Chan–Lam reaction and Suzuki–Miyaura cross–coupling was demonstrated with 4–bromophenylboronic acid and benzimidazole to obtain the Chan–Lam arylation product and then 4–Methylphenylboronic acid was added for the final Suzuki–coupling product. The methodology was scalable upto gram scale.



Scheme **1.28** Chan–Lam *N*–arylation of imidazole-based heterocycles

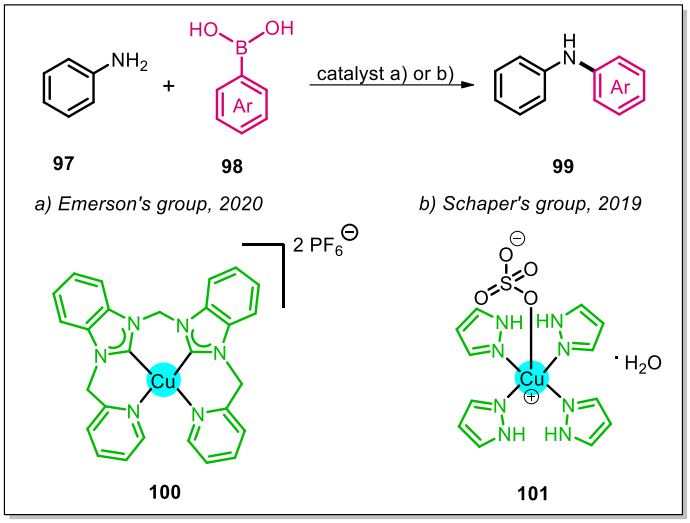
Cytisines are pharmacologically active molecules and a lot of study is being dedicated to the modification of its properties *via* functionalization. The research group of Perez obtained rare *N*–arylcytisine derivatives through the Cu–catalyzed Chan–Lam cross-coupling strategy (Scheme **1.29**). The reaction employed simple phenylboronic acids and successful arylations of cytisine and 3,5-dihalocytisines were conducted at room temperature under air [178]. The *N*–arylated products were further derivatized into the corresponding biaryl (through Pd–catalysis), acid or amide which may be of interest in the biological field.



Scheme **1.29** Chan–Lam *N*–arylation of cytisines

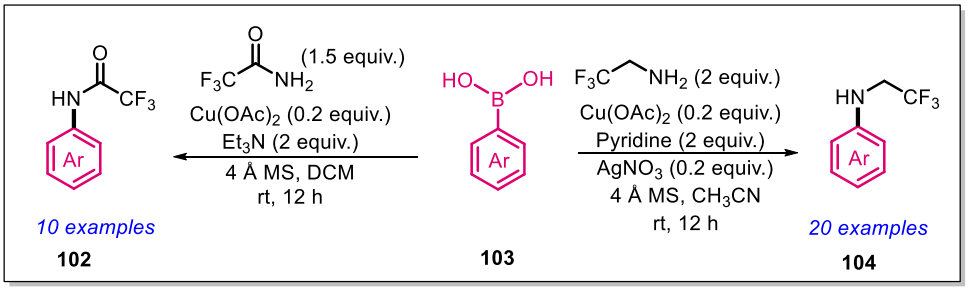
Heterogeneous Cu–based catalysts have gained immense attention on account of its proven robustness in Chan–Lam cross–coupling reaction. The research group of Emerson [179] synthesized a unique tunable Cu^{II}–NHC complex which was expected to provide easy access to all the three oxidation states of Cu under atmospheric conditions (Scheme **1.30a**). The Cu–complex (**100**) exhibited a distorted four-coordinated geometry. Its synthetic utilized was illustrated in the CEL coupling of anilines and phenylboronic acids. Although the metal complex displayed a decent reactivity with most anilines and phenylboronic acids; it exhibited poor reactivity towards amines with bulky groups. The properties of the supporting ligand in the NHC complex was thought to play a significant role in its reactivity towards CEL coupling. Another heterogeneous

system was synthesized by Schaper's group [180] that allowed CEL couplings in aqueous medium. Unlike the previous example, the synthesized "Tetrapyrazole copper sulfate monohydrate" system (**101**) exhibited decent reactivity towards sterically hindered substrates (Scheme **1.30b**).



Scheme **1.30** Chan–Lam *N*–arylation of anilines under heterogeneous catalysis

N-arylation of fluoroalkylamines and trifluoroacetamides was easily achieved by the research group of Leng [181] through a simple Cu–catalyzed Chan–Lam protocol (Scheme **1.31**). Two methodologies were developed for the arylation of amines and amides containing a β–CF_3 group. The protocol tolerated both electron–donating and electron–withdrawing substituents on the substrates and furnished good to excellent yields of the corresponding products at room temperature.



Scheme **1.31** *N*-arylation of fluoroalkylamines and trifluoroacetamides

When a $Cu(OAc)_2$–Et_3N system was employed with phenylboronic acids, *N*-arylated trifluoroacetamides were obtained; while employing a $Cu(OAc)_2$–pyridine–$AgNO_3$ system yielded *N*-arylated fluoroalkylamines. A similar strategy was demonstrated by

the research group of Das [182], where a $Cu(OAc)_2$/AgOAc system was designed to obtain *N*-arylation of 3-aminophenols while a $Cu(OAc)_2/Cs_2CO_3$ combination gave *N*-arylated 4-Aminophenols.

1.3.4 *Important applications of Chan–Lam cross–coupling*

As already discussed, the CEL cross-coupling is one of the most utilized C–N bond forming strategies on account of its mild reaction conditions and substrate tolerance. Several novel drug molecules have been designed by utilizing CEL cross-coupling methodologies in the synthetic route. Some of them are shown in Figure **1.6**.

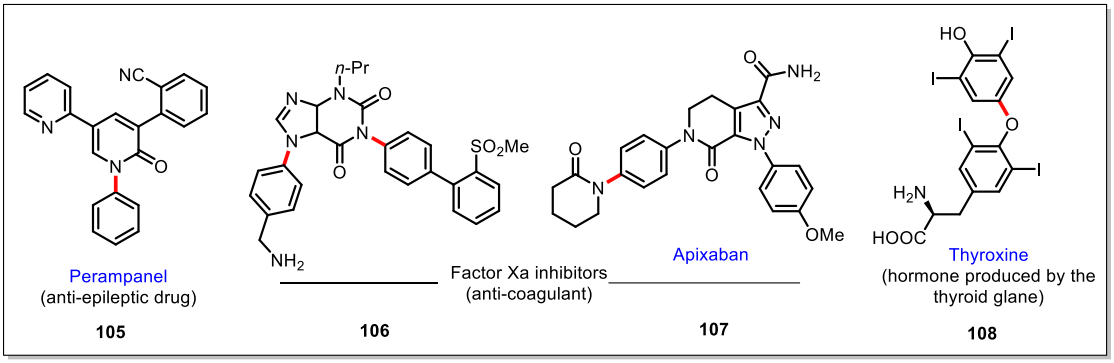


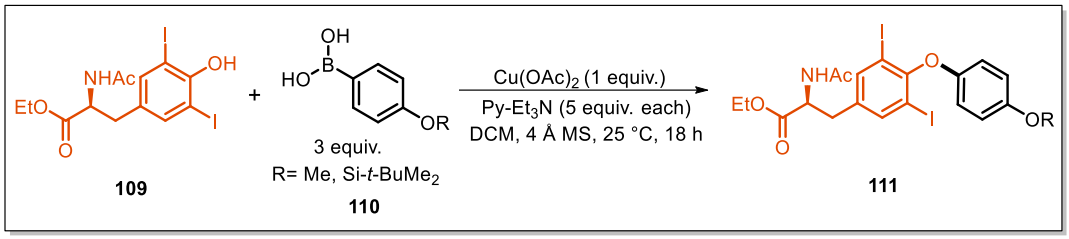
Figure **1.6** Drug molecules achieved through CEL cross-coupling

The synthesis of Perampanel (**105**), an epileptic drug (Brand name: Fycompa) was first reported by the research group of Yonaga [183]. It is a pyridin-2-one derivative, where the C–N bond (indicated in red, Figure **1.6**) was formed through a Chan-Lam cross-coupling strategy involving phenylboronic acid.

While working on pyrazole-based factor Xa inhibitors, Lam's group founded the blockbuster drug, Apixaban (Brand name: Eliquis) [184]. Interestingly, the C–N bond (indicated in red, **107**) was constructed applying Ullmann's C–N bond formation approach. However, Chan-Lam cross-coupling strategies were applied to synthesize similar factor Xa inhibitors (**106**). The two C–N bonds (in red) were formed through Chan-Lam cross-coupling employing arylboronic acids and Cu.

In another important discovery, Evan's group defined an expedient route to the synthesis of hormone, L-thyroxine (**108**) by applying the CEL strategy in the synthesis of one of its intermediates (Scheme **1.32**) [130]. Compound **111**, a very important intermediate in the Hem's synthesis of L-thyroxine [185] was formerly obtained in a

multi-step synthetic process. This intermediate could be obtained in a single step through CEL coupling for formation of diarylethers.



Scheme **1.32** Synthesis of intermediate in L-thyroxine synthesis

1.3.5 *General mechanism of Chan–Lam cross-coupling*

The current understanding of the mechanism of Chan-Lam cross-coupling reaction by Cu^{II} is comprehended through the extensive studies by the research groups of Stahl and Watson [186-188]. Based on spectroscopic evaluations, Watson's group propounded the general mechanism of Chan–Lam cross-coupling reaction (Figure **1.7**). The mechanism was explained considering the classical conditions of Chan–Lam coupling i.e. $Cu(OAc)_2 \cdot H_2O$ as the Cu-source, aerial O_2 as the terminal oxidant and Et_3N as base in acetonitrile at room temperature. However, change in these variables (Cu-salt, base, oxidant, solvent) may bring about change in kinetics of the individual steps or an alternative pathway.

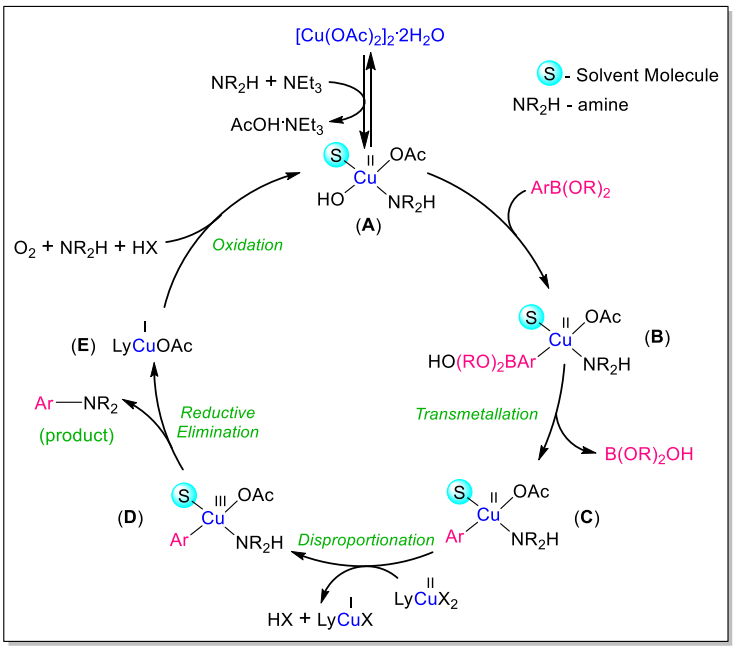


Figure **1.7** General mechanism of Chan–Lam cross–coupling reaction (Watson's model)

i) $Cu(OAc)_2 \cdot H_2O$ exists in dimeric form in the solvent. This dimeric form, $[Cu(OAc)_2 \cdot H_2O]_2$, is considered as the pre-catalyst. The first step of Chan–Lam amination is the de-nucleation of the pre-catalyst (also known as the paddlewheel species) to the "active" catalytic form (**A**), which is triggered in the presence of an amine. DFT studies have shown that gradual attachment of the amine to the dimeric species decreases the intra metal-metal interactions and facilitates de-nucleation. This step may or may not be necessary depending on the Cu-source.

ii) In the next step, ligation of the arylboronic acid to the active catalyst complex (**A**) brings about transmetallation leading to the formation of complex (**C**). The transmetallation step is expected to occur *via* a four-member transition state with the concurrent removal of $B(OH)_3$.

iii) The presence of Cu^{II} in different electronic environments after transmetallation(**C**) promotes disproportionation of the Cu^{II} centre. Subsequently, another molecule of Cu^{II} interacts with complex (**C**) to undergo spontaneous disproportionation to Cu^{III} complex (**D**). Disproportionation is believed to be the rate-determining step.

iv) Facile reductive elimination takes place from the Cu^{III} complex (**D**) to release the product and a Cu^{I} complex (**E**).

v) The catalytic Cu^{II} complex is regenerated from (**E**) by the merger of two different Cu^{II} catalytic centres brought about by O_2 and HX. Electrocatalysis and photocatalysis have been shown to assist this oxidative turnover, without the need of terminal oxidants.

It is very important to consider that efficient Chan–Lam reactions usually require boronic acids in excess, which foster undesirable side pathways. The side-products in Chan–Lam reactions are undeniably derived from the boron partner (Figure **1.8**). While the formation of phenol and its corresponding oxidative homocoupling product; ether, can be minimized by using anhydrous reaction conditions and equipments [189], the origin of formation of protodeboronated product and reductive homocoupling of boronic acids are slightly underdeveloped. Several homogeneous and heterogeneous Cu-catalytic systems have also been shown to reduce these side-products.

Mechanistically, a slower disproportionation step may lead to accumulation of the Cu^{II}–aryl species and result in the formation of unwanted side-products. Proper analysis of these by-products leads to better development of reaction conditions.

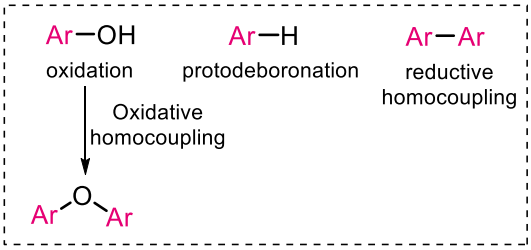


Figure **1.8** Common side-products of CEL cross-coupling reactions

1.4 *Thesis Overview and Objectives*

Cu–catalyzed cyanation reactions and Chan-Lam cross-couplings have been a major research goal and are among the ongoing studies across laboratories. With emphasis on milder Cu-catalysis and the necessity for designing profitable Cu–mediated processes, we have set our objectives to integrate the effectiveness of "Cu" with cyanation reactions and Chan-Lam cross-coupling reactions. Keeping this in mind, the objectives of my proposed investigation are:

i) Development of Cu–catalyzed methodologies for the cyanation of aryl halides. Although reports of aryl nitrile synthesis are many, development of safer and alternative non-toxic cyanation sources is always beneficial, considering the broad synthetic utility of aryl nitriles.

ii) Design of Cu–based catalytic system for Chan-Lam cross-coupling reaction and their characterization. A plethora of C–N bond formation reactions have been efficiently catalyzed by Cu in its various homogeneous and heterogeneous modifications.

iii) Development of methodologies for Chan–Lam cross-coupling reaction with the synthesized catalysts**.** Among the various C–N bond formation reactions, Chan-Lam cross-coupling strategy is the most sought after process on account of its versatility and wide tolerance of functional groups.

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