

# A Review on Recent Trends in Copper-Catalyzed Organic Synthesis

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**Abstract:** Copper chemistry has great importance owing to its low cost, high functional group tolerance, high abundance, and low toxicity. In addition to natural copper-containing catalysts, significant efforts have been devoted to the development of man-made copper redox catalysts. Apart from these efforts, copper has become one of the most versatile and interesting bio-relevant metals in homogeneous catalysis. The review concentrates on various copper-catalyzed organic transformations covering areas such as heterocyclic synthesis, coupling reactions, asymmetric synthesis, click reactions, multicomponent reactions, C–H activation, trifluoromethylation reactions, and applications in the synthesis of natural products. Copper-catalyzed heterocyclic synthesis and multicomponent reactions were found to be important tools for the synthesis of many biologically active compounds. The review summarizes the developments in copper catalysis in the field of organic chemistry and discusses the future perspectives of copper catalysis for contemporary organic synthesis.

**Keywords:** Copper-catalyzed Reaction, Coupling Reaction, Alkyl Halides, Carbon–heteroatom Bonds

## 1. Introduction

In recent decades, the transition metal-catalyzed reaction has evolved into a formidable instrument in organic synthesis, contributing to the advancement of chemical research and technology through the discovery and creation of novel chemical compounds and novel synthetic techniques [1].

Palladium [2], nickel [3], copper [4], cobalt [5], iron [6], gold [7], manganese [8], rhodium [9], and ruthenium [10] are some of the most common transition metal catalysts. Transition metal catalysts are well known for their use in a variety of bond-breaking and bond-forming processes. Nonetheless, numerous significant and frequently surprising accomplishments continue to emerge.

Apart from the continued development and application of classic noble metals such as palladium [11], rhodium [12], and ruthenium [13], additional low-cost metal catalysts have

recently gotten a lot of interest because of their ease of use and absolute price competitiveness. Copper salts have been used as catalysts for C–N, C–S, C–O, and other bond formation processes for more than a century, ever since the discovery of the Ullmann reaction (Figure 1). [14].

However, with the discovery of palladium-catalyzed cross-coupling processes, copper chemistry was mostly ignored for a long time. Apart from accelerating the processes for the production of arylamines, palladium catalysts have also been used in a variety of other bond forms [2, 11]. Despite its many benefits in chemical synthesis, palladium chemistry has some disadvantages, including its high cost, severe toxicity, and limited scope [11]. As a result, chemists have begun to examine other metal catalysts as a palladium substitute. Copper has regained popularity in recent years as a component of chemical synthesis for the formation of different linkages.

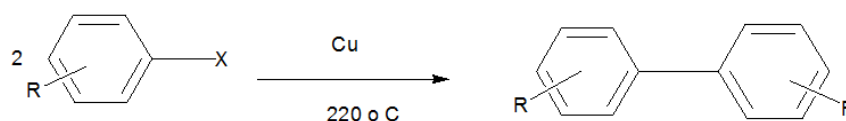


Figure 1. Ullmann reaction.

Copper catalysts fascinate chemists for several reasons. First of all, copper is very cheap compared to palladium and the total amount of copper on earth is vast. Furthermore, copper salts generally present low toxicity. More importantly, copper can take part in cross-coupling chemistry in a way strikingly similar to palladium and possesses unique chemoselectivity and reactivity.

#### General Aspects of Copper Chemistry

As a late transition element, copper exists in a variety of oxidation states (Cu(0), Cu(I), Cu(II), Cu (III), and Cu (IV)), and the ions readily form complexes, resulting in a diversity of coordination compounds. Despite the fact that both Cu(0) and Cu(II) catalysts have been demonstrated to be active, the majority of authors agree that Cu(I) is the active catalyst [15, 16]. However, it should be noted that Cu(I) can be reversibly disproportionate into Cu(0) and Cu (II). For the actual interaction of this complex with the aryl halide, many methods have been proposed:

- Oxidative addition of ArX forming a Cu(III) intermediate followed by reductive elimination.
- Sigma bond metathesis; in this mechanism copper remains in the Cu(II) oxidation state.
- Single electron transfer (SET) in which a radical anion of the aryl halide is formed (Cu(I)/Cu(II)).
- Iodine atom transfer (IAT) to give the aryl radical (Cu(I)/Cu(II)).
- Complexation of the aryl halide with the Cu(I) complex,

which is thought to enable the nucleophilic substitution reaction.

In a recent DFT study, Houk, Buchwald, and coworkers (2010) discovered that the modified Ullmann reaction between aryl iodide and amines or primary alcohols happens via either a SET or an IAT mechanism. Van Koten has shown that adding Cu to halted aminations can bring them back to life (0), which reduces the generated Cu(II) to Cu(I), confirming a Cu(I)/Cu(II) mechanism. Hartwig's DFT calculations appear to support a Cu(I)/Cu(III) type amidation mechanism (Goldberg).

## 2. The Ullmann Reaction

Fritz Ullmann and Irma Goldberg published their groundbreaking work on copper-mediated aromatic nucleophilic substitution processes in the early 1900s [17-18]. The coupling reaction's initial protocol called for stoichiometric quantities of copper salts, as well as high reaction temperatures (200 C) and long reaction times.

The 'Ullmann condensation process' is a copper-mediated (stoichiometric or catalytic) reaction in which an aryl halide reacts with an amine, phenol, or thiophenol to produce the corresponding aryl -amine, -ether, or -thioether compounds. The copper-mediated synthesis of biaryls from aryl halides is described with the 'Ullmann reaction' (Figure 2) [19].

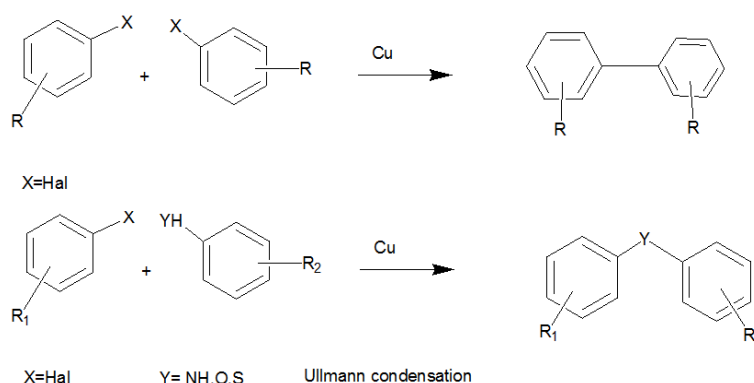


Figure 2. Schematic representation of the Ullmann reaction and Ullmann condensation.

The Goldberg and Hurlley reactions are two types of reactions that are linked. The Goldberg condensation reaction is a copper-mediated process that forms a new C(aryl)-N bond between an aryl halide and an amide.

The ongoing hunt for low-cost, long-lasting reactions has prompted several researchers to revisit copper-mediated cross-coupling reactions. The successful discovery of enhanced catalytic versions of this grand old chemistry has resulted in a true "renaissance" of the "modified Ullmann reaction." Many of the classical reaction's limitations (such as high reaction temperatures, long reaction times, large metal loadings, and limited scope) have been solved, and a wide range of innovative techniques are now accessible for use in a variety of fields [20].

The addition of ligands to the copper catalyst improves the

solubility of the copper precursors, allowing for softer reaction conditions, such as lower reaction temperature and duration, lower catalyst loadings, and a broader range of reactivity.

In general, a copper (pre-)catalyst is made by combining a copper salt with a suitable chelator [20, 21] such as diamines, amino acids 1,10-phenanthroline, diols, and other nitrogen- and oxygen-containing ligands in situ. The modified Ullmann reaction has already found its way into large-scale production as a result of these improvements.

## 3. Copper-Catalyzed Cross-Coupling Reactions

Organometallic reagent-catalyzed asymmetric C-C bond formation is one of the most important organic

transformations [22]. In enantioselective C-C bond formation processes, the asymmetric conjugate addition (ACA, Figure 3a) and asymmetric allylic alkylation (AAA, Figure 3b) are particularly versatile [23].

The intermediate enolate produced (Figure 3c) could be

further functionalized (one-pot transformations) by reacting with other electrophiles, resulting in two vicinal stereocenters. Complex physiologically active compounds are routinely synthesized using these processes [22].

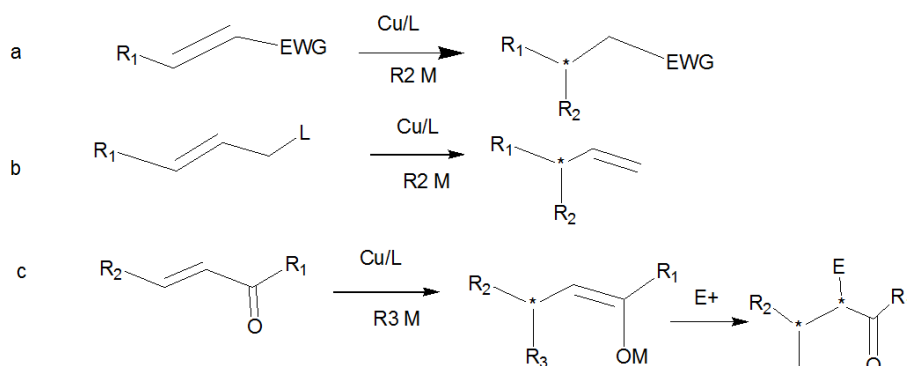


Figure 3. General scheme of ACA and enolate functionalization.

### 3.1. Copper-Catalyzed Asymmetric Conjugate Addition Reactions

In recent decades, copper-catalyzed ACA of organometallics (Grignard reagents, organozinc reagents, organoaluminum compounds, and organosilicon reagents) to Michael acceptors (cyclic enones, acyclic enones, nitroolefins, unsaturated lactones, unsaturated lactams, dehydropiperidinones.

### 3.2. Asymmetric Conjugate Addition with Organozinc

In the realm of ACA, copper-catalyzed ACA of organozinc compounds has been a long-standing goal. Feringa's group made a key breakthrough in 1996 with the invention of a BINOL-derived monodentate phosphoramidate L1 [25].

High yield, chemoselectivity, efficiency, and enantioselectivity were achieved employing this ligand in the

copper-catalyzed ACA of cyclic enones using dialkyl zinc reagents for C-C bond synthesis. Phosphoramidate ligands have the advantage of being easily accessible and, according to their modular structure, can be easily modified for a given application [26].

The copper-catalyzed ACA of dialkylzinc 3 to cyclopentenone 1 was used in the synthesis of PGE1 methyl ester 6 (Figure 4), with trapping with aldehyde 2 being the critical step. 6.

The aldehyde trapping diastereoselectivity was only modest (thre/erythro=83/17), but reduction with  $\text{Zn}(\text{BH}_4)_2$  followed by diastereomer separation yielded advanced intermediate 5 as a single diastereomer with 94 percent ee. PGE1 methyl ester 6 was produced in good yield after further 5 stages. In this approach, PGE1 methyl ester 6 was produced in 7 steps from 1 to 7 with a 7 percent overall yield and 94 percent optical purity.

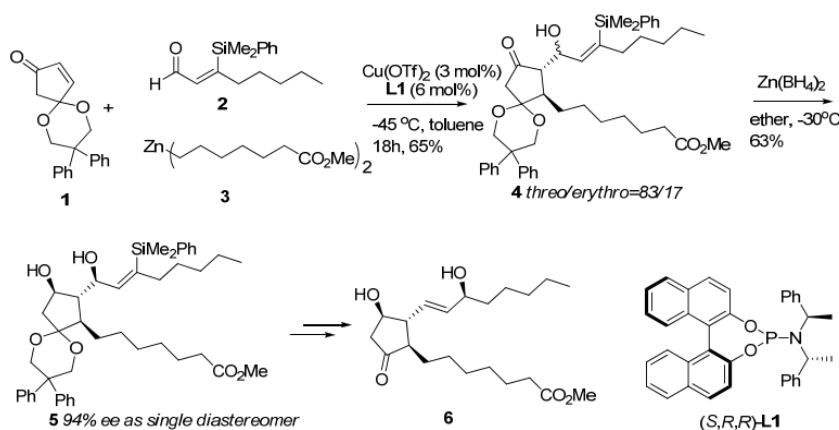


Figure 4. Total synthesis of PGE1 methyl ester (6).

Cordova's group recently published a new catalytic enantioselective  $\alpha$ -alkylation of  $\alpha,\beta$ -unsaturated aldehydes using a mix of transition metal catalysis and aminocatalysis (Figure 5)

[27].

Product 9 was produced in 65 percent yield with high regioselectivity (1,4/1,2=93/7) and ee using copper-PPh<sub>3</sub>

complex and amine 8. (94 percent). Three natural products were synthesized using Intermediate 9. (Curcumene 10,

Dehydrocurcumene 11, and Tumerone 12). Figure 5. Total synthesis of Curcumene, Dehydrocurcumene, and Tumerone.

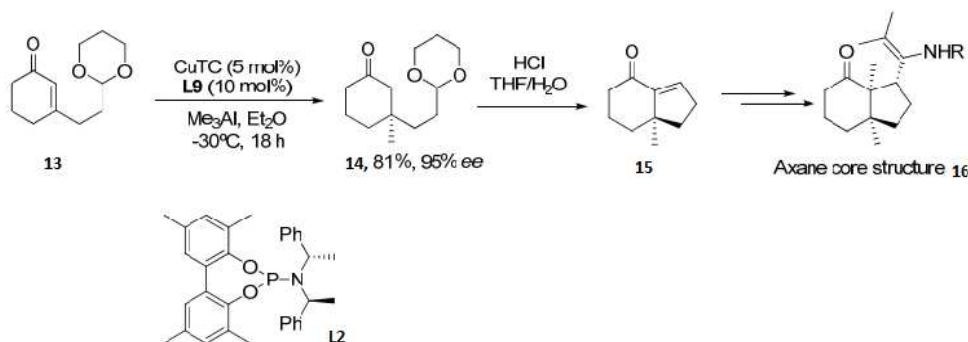


Figure 5. Synthesis of Axane core structure (16).

### 3.3. Asymmetric Conjugate Addition with Organoaluminum

In addition to organozinc reagents, organoaluminum compounds are commonly used in natural product synthesis. Using copper-catalyzed ACA of trialkyl aluminum reagents to cyclic enones, the Alexakis group established an efficient technique for creating a chiral quaternary center in 2007. (Figure 6). [28] When 5 mol% CuTC and 10 mol% ligand L2 are combined, the result is 14 was isolated in 81% yield and 95% ee. HCl-promoted hydrolysis of the acetal and *in situ*

intramolecular cyclization gave 15 which was used for the preparation of Axane core structure 16.

In 2008, Feringa and coworkers reported the complete synthesis of Myrtine (Figure 6) using a copper-catalyzed ACA of N-Boc-2,3-dihydro-4-piperidone (17) with trimethylaluminum and the ligand L3, using a copper-catalyzed ACA of N-Boc-2,3-dihydro-4-piperidone (17) with trimethylaluminum and the [29] Product 18 had a strong yield and yielded 96 percent ee.

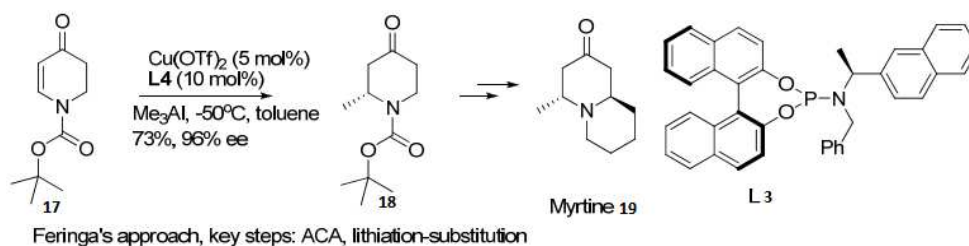


Figure 6. Total synthesis of Myrtine (19).

### 3.4. Asymmetric Conjugate Addition with Grignard Reagent

In 2008, Feringa and coworkers reported the complete synthesis of Myrtine (Figure 7) using a copper-catalyzed ACA of N-Boc-2,3-dihydro-4-piperidone (17) with trimethylaluminum and the ligand L3, using a copper-catalyzed ACA of N-Boc-2,3-dihydro-4-piperidone (17) with

trimethylaluminum and the [29] Product 18 had a strong yield and yielded 96 percent ee.

Copper-catalyzed ACA of ester 20 with methylmagnesium bromide and ligand L4 generated magnesium enolate (21) that was trapped by hexanal to give 22 in high yield with excellent dr and ee in the whole synthesis of Phaseolinic acid (23) (Figure 7) [31]. In just two steps, phaseolinic acid (23) might be produced from 22.

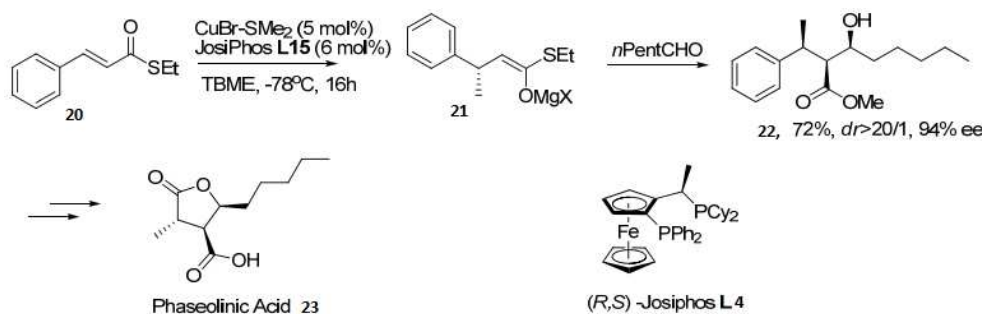


Figure 7. Total synthesis of Phaseolinic Acid (23).

## 4. Copper-Catalyzed Cross-Coupling Reactions for the Formation of C–N Bonds

The recent rebirth of copper catalysis has had a significant impact on how one thinks about the production of a C–N bond. All forms of C(sp<sup>2</sup>)–N, C(sp)<sup>3</sup>–N, and even C(sp<sup>3</sup>)–N bonds can now be formed with surprising efficiency using a variety of catalytic systems based on simple copper salts and easily available ligands [32, 33].

These efficient and robust reactions, which provide new bond disconnections in natural product synthesis, have been elegantly used in various total syntheses [34]. Anilines, anilides, enamides, and many other functional groups that are

at the core structure of various natural products can now be formed by arylation or vinylation of amines, amides, or synthetic equivalents.

### 4.1. Intermolecular Copper-Catalyzed Arylation of Amine

Aniline is a structural motif that can be found in a variety of natural compounds that have different biological functions. The Ma group detailed the entire synthesis of martinelllic acid in 2001, which was an early example of using a copper-catalyzed arylation of an amine in the context of natural product synthesis [35, 36]. Ma and colleagues employed a copper-catalyzed arylation of *b*-amino ester (25) with 1,4-diiodobenzene (24) [37] to build the aniline core of martinelllic acid (27) in their synthesis.

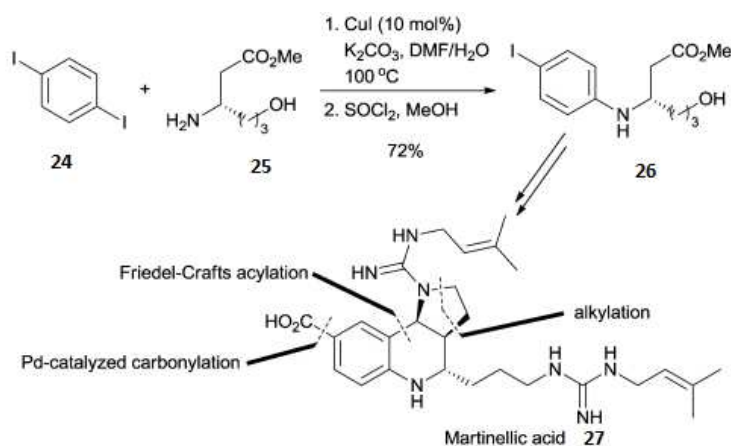


Figure 8. Total synthesis of martinelllic acid (27) featuring a copper-catalyzed amine arylation.

### 4.2. Intermolecular Copper-Catalyzed Arylation of Amide

An innovative alternative to aniline acylation. Anilides are structural motifs that can be found in a wide variety of natural goods. Ansamycins were found to trigger apoptosis in human acute promyelocytic leukemia HL-60 cells with an

ED50 value of 7.7 nM after being recovered from the fermentation broth of *Streptomyces* sp. RK95-74 [38, 39].

The Buchwald technique [41] was employed in this synthesis [40] to prepare the anilide fragment 30 by copper-mediated arylation of amide 29 with bromide 28. (Figure 9).

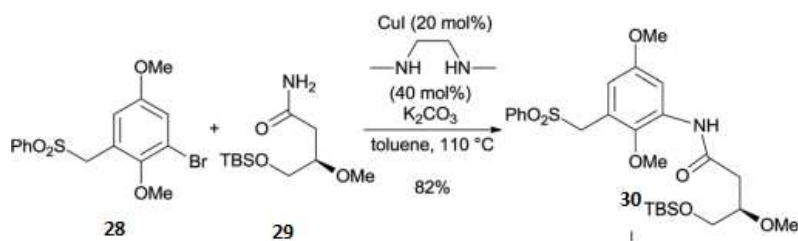


Figure 9. Synthesis of the macrocyclic core.

### 4.3. Intermolecular Copper-Catalyzed Vinylation

Enamide is included in the structure of a number of natural compounds. Poor yields and/or lack of selectivity have long impeded the regio- and stereoselective synthesis of enamides, which has been hampered by low yields and/or lack of selectivity.

Copper-catalyzed cross-coupling between vinyl iodide 32

and dienamide 31 was envisioned by the Furstner group (Figure 10). [42] They really employed the Porco group's one, 40, which is based on the utilization of the Liebeskind catalyst CuTC in combination with rubidium carbonate in DMA at 90 °C, which was one of the only processes disclosed at the time of this whole synthesis.

The coupling went relatively smoothly, allowing the introduction of the salicylihalamides A and B 70 side chains



in 57 percent yield. While this method, which was first described in 2001, is very efficient and easy, the main

disadvantage is that the vinyl iodide is isomerized during the process.

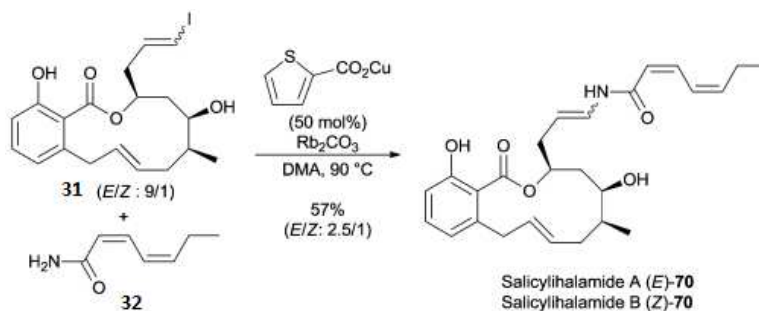


Figure 10. Copper-catalyzed cross-coupling for the formation of the enamide side chain of salicylhalamide A.

## 5. Copper-Catalyzed Cross-Coupling Reactions for the Formation of C–O Bond

Jiang and colleagues [43] discovered a copper-catalyzed intermolecular oxidative [3+2] cycloaddition using oxygen as the only oxidant between alkenes 33 and anhydrides 34 in 2010. (Figure 11). In good to outstanding yields, the reaction gave a new synthetic method to  $\gamma$ -lactones 35.

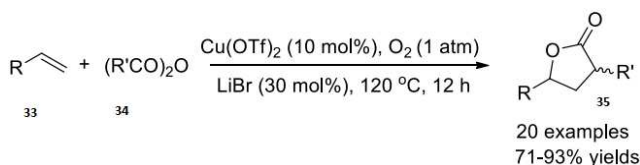


Figure 11. Copper-catalyzed intermolecular oxidative [3+2] cycloaddition between alkenes and anhydrides. [43].

Wang and co-workers [44] discovered a copper-catalyzed tandem oxidative cyclization between 36 and 37 for the synthesis of polysubstituted oxazoles 38. (Figure 12). Various oxazole derivatives 38 were produced under moderate circumstances using widely available starting materials..

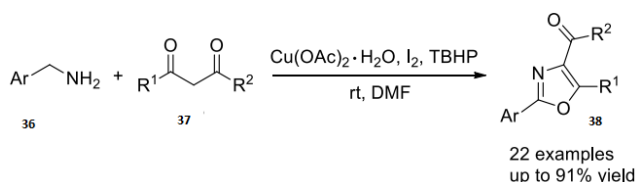


Figure 12. Synthesis of polysubstituted oxazoles through copper-catalyzed tandem oxidative cyclization. [44].

### 5.1. Copper-Catalyzed Oxidation of Alcohols

The creation of a highly active catalyst for the selective oxidation of alcohols with air in an aqueous medium is a hot subject in chemistry right now. Various hurdles remain in the progress of natural product synthesis as transition metal-catalyzed aerobic alcohol oxidations improve. Low  $O_2$  pressure, especially inflammable organic solvents, low

catalyst loading, and the avoidance of costly or dangerous auxiliary compounds are some of these.

### 5.2. Ligand-Assisted Copper-Catalyzed Alcohol Oxidation

In 1977, a ligand-assisted Cu system for oxidation of alcohols into their carbonyl compounds was reported for the first time. The selective oxidation of alcohols to aldehydes utilizing  $O_2$  as an end-oxidant is catalyzed by a Cu complex of pyridine (py) and 1,10-phenanthroline (phen). [45] (Figure 13) (Figure 13) (Figure 13).

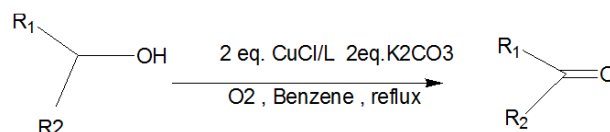


Figure 13. The oxidation of selected alcohols is catalyzed by Cu-py and Cu-phen [45].

### 5.3. TEMPO-mediated Copper-Catalyzed Alcohol Oxidation

In 1966, the TEMPO-mediated Cu method for aerobic MeOH to formaldehyde oxidation was first demonstrated. [46] For the aerobic oxidation of alcohols, the ligand-free TEMPO mediated Cu system was introduced (Figure 15).

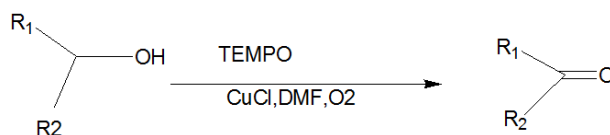


Figure 14. Aerobic oxidation of alcohols catalyzed by CuCl-TEMPO. [46].

The TEMPO mediated Cu-bipy systems, a method for the selective oxidation of alcohols to carbonyl compounds by Cu and the perfluoroalkylated bipy ligand in the presence of the catalytic amount of TEMPO has been developed [48].

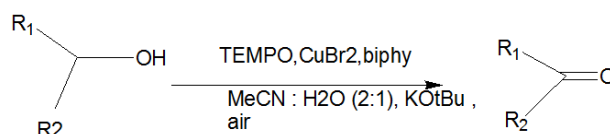


Figure 15. Aerobic oxidation of alcohols catalyzed by TEMPO/Cu-bipy. [47].

## 6. Copper-Catalyzed Cross-Coupling Reactions for the Formation of C–S Bond

Because of the frequency of these bonds in many compounds of pharmacological and material relevance [49–51], the creation of the C(aryl)–S bond is critical. Biaryl sulfides have been identified as a common structural theme in numerous medication candidates and have been utilized to treat disorders such as Alzheimer's and Parkinson's disease, [52, 53], human immunodeficiency virus infections, [54], and cancer [50].

Traditionally, C(aryl)–S bonds have been produced in hazardous, high boiling polar solvents like HMPA under

difficult reaction conditions such as higher temperature (200°C). These sulfides can also be made by reducing aryl sulfones and sulfoxides with strong acids. reducing agents like DIBAL-H or  $\text{LiAlH}_4$ . For different C–S bond-forming processes, transition metal catalysts are used to overcome the aforementioned constraints [57, 58].

Cu/ethylene glycol was created by Buchwald et al. [59] for the S-arylation of thiol derivatives at a lower temperature (80°C), despite the use of excess ethylene glycol (Figure 16 a). Later, they used the aforesaid catalytic systems to cross-couple six halogenoimidazo-[1,2]pyridines with aryl thiols (Figure 16b). [60].

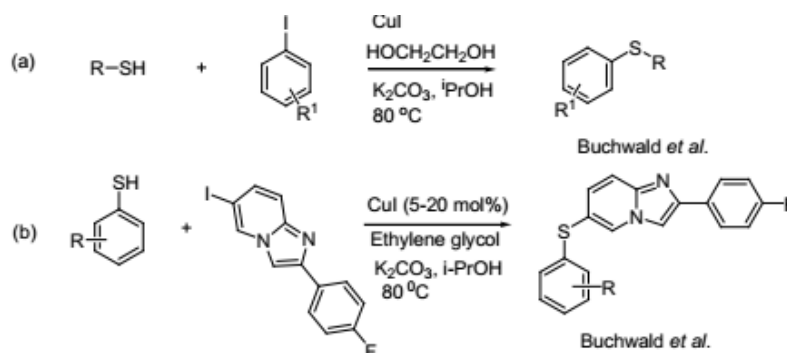


Figure 16. Cu-catalyzed C–S cross-coupling.

Verma et al. (2007) reported CuI/benzotriazole catalytic systems for coupling the thiols with less reactive aryl bromides (Figure 17) [61]. Subsequently, various amines including *trans*-1,2- diaminocyclohexane [62].

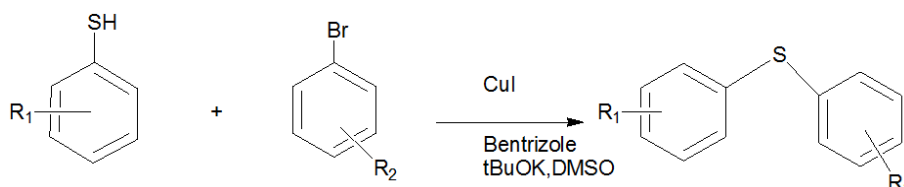


Figure 17. Ligand-assisted Cu-catalyzed C–S cross-coupling.

## 7. C–H Bond Halogenation Catalyzed Copper

Carbon–halogen (C–X) bonds are one of the most basic groups in organic synthesis, and they are used in the synthesis of a wide range of organic compounds. Because of their widespread use in the synthesis of organic goods, organo halides are the most valuable compounds. C–X bonds were utilized as precursors in the development of natural products, pharmaceuticals, functional materials, and agricultural compounds due to their flexible reactivity [63]. In organic synthesis, the catalytic production of C–X bonds is a major problem.

### 7.1. Copper-Catalyzed Halogenation of the C(sp<sup>2</sup>)–H Bond

In the synthesis of aryl halides employing the

conventional electrophilic halogenation of arenes. i Han and co-workers [64] reported aryl C–H halogenations via a CuX-mediated with the assistance of NXS (*N*-halosuccinimide, X = Cl or Br) and different acid (Figure 18) product 2 and 7 obtained..

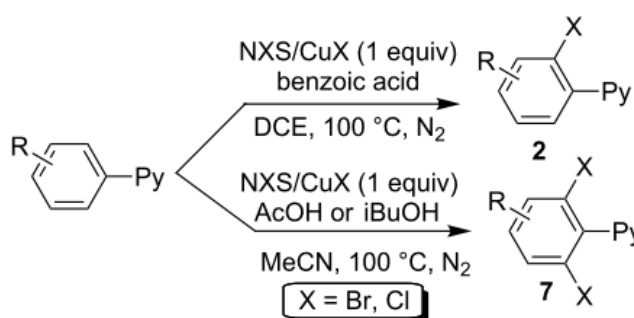


Figure 18. Copper-mediated selective C–H halogenations of 2-arylpyridine.

### 7.2. Copper-Catalyzed Halogenation of the Alkene C(sp<sup>2</sup>)-H Bond

Another typical C(sp<sup>2</sup>)-H bond is the alkene C-H, which tends to undergo functionalization via cleavage of the  $\pi$ -bond in the presence of a halogen source. Yu and coworkers [65] reported the dual C-H functionalization of  $\alpha$ -alkenylketene N, Sacetals in a cascade synthesis of functionalized pyrrolones (40) in 2014. (39). Using LiX as the halogen source, the products were made by oxidative alkene C-H amination and alkene C-H chlorination in the presence of Cu(II) halide. (Figure 19).

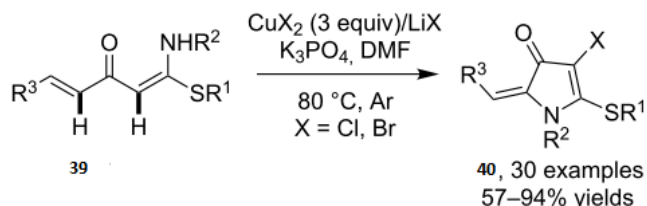


Figure 19. Copper-mediated cascade synthesis of halogenated pyrrolones.

### 7.3. Copper-Catalyzed Halogenation of the C(sp<sup>3</sup>)-H Bond

Ball and Kundu [66] established a copper catalysis procedure for distant C-H chlorination of alkyl hydroperoxides in 2010. (Figure 20) In the presence of CuI and N, N, N', N'', N''-pentamethyldiethylenetriamine (PMDTA), the alkyl hydroperoxides 41 and suitable chlorine source (NH<sub>4</sub>Cl or iPr<sub>2</sub>NHCl) might couple to produce  $\alpha$ -chlorinated alcohols 42 via an intramolecular redox process.

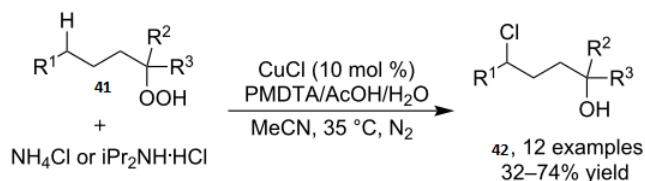


Figure 20. Copper-catalyzed remote C-H chlorination of alkyl hydroperoxides.

## 8. Copper-Catalyzed C-H Bond Amidation

In nature, the amide functional group is a basic component. The amides have sparked a lot of interest in the chemical, pharmacological, biological, and material sciences because of their natural significance to biological processes [67]. Copper catalysts are particularly favorable for catalyzing C-H amidation reactions because of their inexpensive cost, low toxicity, and broad tolerance. Kuninobu and Kanai et al. published Kuninobu and Kanai et al. in 2014.

S. Girault, P et al [68] reported an unprecedented intramolecular C(sp<sup>3</sup>)-H bond amidation for the synthesis of a lactam via chelatinggroup assisted copper catalysis. Figure 21, the N-quinolinen-8-yl substituted amides 43 could be smoothly transformed into lactams 44 and/or 44' via C-H amidation by using Cu(OAc)<sub>2</sub> as catalyst and Ag<sub>2</sub>CO<sub>3</sub> as a base. the C-H bond transformation was the presence of the quinoline auxiliary which acted as a bidentate fragment to incorporate the copper catalyst and facilitate the bond cleavage and formation via intermediates A and B.

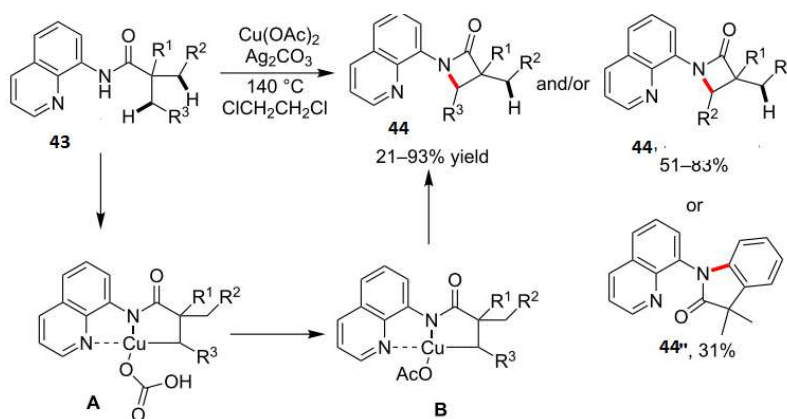


Figure 21. Copper-catalyzed intramolecular C-H amidation for lactam synthesis.

## 9. Goldberg Reaction with Copper Catalyst for Fenamic Acid, Mefenamic Acid Derivatives, and Fenamates Synthesis

N-Aryl anthranilic acids, such as flufenamic and mefenamic acid, are important nonsteroidal anti-inflammatory drugs (NSAIDs) and promising candidates for the therapy of neurodegenerative and amyloid diseases (Figure 22) [69] They are also important precursors for the

synthesis of substituted acridines which have been used as antimalarial and anticancer drugs. [70].

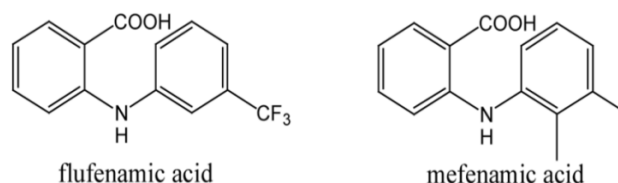


Figure 22. Structures of anthranilic acid derivatives used as NSAIDs and for the treatment of amyloidogenic diseases.



In 2006 Mei et al. reported a copper-catalyzed amination protocol for the synthesis of substituted *N*-aryl anthranilic acids, which were further utilized as precursors for ring construction of 9-chloro- and 9-bromoacridines. *N*-aryl anthranilic acid derivatives are usually prepared through the Ullmann-Jourdan reaction. they also reported Cu-catalyzed amination of *ortho*-chlorobenzene acids high yield *N*-aryl anthranilic acids product is formed.

Mei et al reported anthranilic acid (47) was formed in 90% and 82% through Cu/ Cu<sub>2</sub>O-catalyzed amination of (45) with (46) using K<sub>2</sub>CO<sub>3</sub> or Na<sub>2</sub>CO<sub>3</sub> in diethylene glycol (Figure 23).

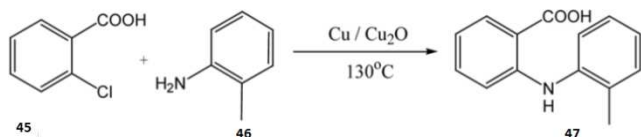


Figure 23. Arylation of aryl chlorides with aryl amines.

## 10. Summary

Copper-catalyzed cross-coupling reactions experienced a revival, which had a significant impact on natural product synthesis. Ullmann–Goldberg reactions have been plagued by severe reaction conditions and limited substrate scope for over a century, but the development of copper chelating ligands has allowed these reactions to be done under considerably more benign conditions.

They've been used in an increasing number of complete syntheses, even as end-game strategies. Clearly, no one should be scared to employ these reactions anymore, and the new-bond disconnections that these reactions provide have already demonstrated their utility.

Recently developed catalytic systems based on copper (I) and bidentate ligands present new prospects in natural product synthesis, in addition to their low cost, availability, and excellent functional group tolerance. They enable innovative and efficient retrosynthetic disconnections, and they are expected to find various uses in the near future for the synthesis of complicated natural and/or biologically relevant compounds.

It is also expected to have a significant impact on the development of enantioselective reactions. These considerations, as well as the ongoing development of copper-catalyzed oxidative coupling processes, are important.

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