Recent Advances in Copper-Catalysed Hydrolysis of Aryl Halides to Phenols

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Abstract. Phenol and its derivatives are indispensable bulk and fine-chemical intermediates, widely used in the synthesis of pharmaceuticals, agrochemicals, polymeric materials, dyes, and a broad range of specialty chemicals [1, 2]. Conventional manufacturing routes to phenols generally suffer from multistep operations, harsh conditions, high energy consumption, substantial environmental burdens, and safety concerns [3, 4]. In recent years, the direct hydrolysis of aryl halides to phenols under transition-metal catalysis has attracted considerable attention owing to its step and atom economy as well as its potential environmental benefits [5, 6]. Among various metals, copper has emerged as a focal point because of its low cost, relatively low toxicity, diverse accessible oxidation states, and flexible catalytic pathways [7, 8]. With the rational design of novel ligands and additives, the growing use of greener media, and breakthroughs in nanocatalysis and single-atom catalysis, copper-catalysed hydrolysis has been realised under increasingly mild conditions, with continuously expanding substrate scope, enhanced functional-group tolerance, and improved catalytic efficiency and selectivity [9, 10]. This review provides a systematic summary of research progress in copper-catalysed hydrolysis of aryl halides to phenols, with emphasis on mechanistic understanding, the key components of catalytic systems, and optimisation of reaction conditions, followed by a perspective on current challenges and future directions.

Keywords: Copper catalysis; hydrolysis; aryl halides; phenols; ligand design.

1. Introduction

Phenol and its derivatives occupy a central position in modern chemical industries. They are key intermediates in medicinal synthesis and foundational building blocks for polymer materials, dyes, and numerous fine chemicals [1, 2]. The ongoing growth of fine chemicals and functional materials has sharpened the demand for efficient and sustainable phenol syntheses, making this topic a long-standing focus in organic synthesis and catalysis [3].

Traditional routes to phenol primarily include direct hydroxylation of benzene and diazotisation protocols. The former often relies on strong oxidants and high temperature/pressure, making it difficult to balance yield and selectivity; the latter, while well established at laboratory scale, involves multiple steps, generates by-products, and raises safety concerns [3, 4]. These drawbacks have limited broader industrial deployment. Consequently, the development of newer, more efficient, and environmentally benign methods is critical [11]. Against this backdrop, direct conversion of aryl halides to phenols has garnered attention [5]. Copper catalysts, which can effectively activate C–X bonds and forge C–O bonds, show particular advantages in these transformations [7]. Relative to palladium and nickel, copper is earth-abundant and inexpensive, thereby better aligned with green and economic imperatives [8]. Moreover, copper can shuttle between Cu(I), Cu (II), and Cu (III) oxidation states, enabling diverse catalytic cycles and paving the way for high-efficiency conversions [12].

In recent years, advances in ligand design, solvent and medium optimisation, and nanocatalyst development have driven marked progress in copper-catalysed hydrolysis of aryl halides [6, 13]. New ligands not only facilitate aryl-halide activation but also lower reaction temperatures and broaden substrate compatibility [14]. Concurrently, the push for greener chemistry has steered these reactions toward aqueous or low-toxicity media, in line with sustainability goals [11, 9]. This review synthesises recent developments with a focus on mechanisms, ligand and condition optimisation, catalyst types, and prospective applications.

2. Mechanistic Overview

At its core, copper-catalysed hydrolysis of aryl halides requires activation of the C–X bond and construction of the C–O bond. Two principal mechanistic manifolds are commonly invoked: (i) a Cu(I)/Cu (III) two-electron redox cycle and (ii) a single-electron transfer (SET) pathway [12, 15].

In the Cu(I)/Cu (III) cycle, a Cu(I) species forms an active complex with a ligand. Oxidative addition of the aryl halide to this complex generates a Cu (III)–aryl intermediate. Nucleophilic attack by hydroxide (or water), displacing the halide, affords a Cu (III)–hydroxy intermediate. Reductive elimination then releases the phenol (Ar–OH) and regenerates Cu(I), closing the catalytic loop [12]. This scenario highlights copper's facility for interconverting oxidation states and rationalises why appropriate ligands can stabilise key intermediates and accelerate turnover.

By contrast, the SET mechanism features radical character. Here, Cu(I) transfers a single electron to the aryl halide, forming an aryl radical (Ar•) and Cu (II). Subsequent capture of the radical by hydroxyl species furnishes the phenol. This pathway is more prominent under particular conditions, such as strong base, light irradiation, or microwave heating [14, 15]. Although the generality of SET remains debated, its possibility accounts for mechanistic diversity. For comparison, palladium-catalysed aryl-halide hydroxylations typically follow a Pd (0)/Pd (II) cycle with efficient oxidative addition and reductive elimination, but Pd's scarcity, cost, and compatibility limitations are notable [5]. While copper systems can be kinetically more intricate, their low cost, sustainability profile, and redox flexibility make them compelling alternatives [7]. Overall, the Cu(I)/Cu (III) two-electron cycle is widely considered dominant, with SET as a conditional auxiliary pathway [12]. Clarifying how these routes compete or cooperate across conditions, ligand environments, and substrates will inform future catalyst design and greener process development.

3. Ligand Design and Selection

Ligand choice is pivotal for reaction efficiency and substrate scope, as ligands stabilise the metal centre and modulate both C–X activation and C–O bond formation through electronic and steric effects [7, 6]. Considerable effort has been devoted to developing ligand platforms that promote high activity under mild conditions [8].

Picolinamide-type ligands. Early studies identified hydroxypicolinamide ligands as markedly beneficial for aryl-halide activation. By forming robust chelates with copper and enhancing electron transfer, these ligands promote oxidative addition and can enable otherwise recalcitrant aryl chlorides [12, 16].

Diamide ligands (e.g., BHMPO). Reported by Xia and co-workers in 2016, BHMPO allows efficient hydroxylation of aryl chlorides at ~130 °C and delivers high conversions for aryl bromides/iodides at comparatively low catalyst loadings [14], underscoring how electronic tuning can lower activation barriers.

8-Hydroxyquinoline-N-oxide ligands. Introduced by Yang et al. [13], these ligands enable hydroxylation under relatively mild conditions and even extend to aryl-ether formation [13]. Strong coordination and favourable donor properties sustain activity in aqueous media [7].

Natural-product-derived ligands. Chiral molecules such as L-(–)-quebrachitol have been used as ligands to achieve efficient reactions in water or ethanol, offering greener, scalable options [17].

Diamine ligands (e.g., DMEDA). Mehmood and Leadbeater demonstrated that CuI/DMEDA in water under microwave irradiation rapidly converts aryl bromides and iodides, combining speed with high yields [9].

Polyhydroxy ligands (e.g., 4,7-dihydroxy-1,10-phenanthroline). Wang and co-workers employed such ligands in neat water, aligning with green-chemistry targets while maintaining commendable functional-group tolerance [18].

Beyond ligands, additives can further enhance performance. For instance, glycolic acid additives have been shown to facilitate C–X activation, suggesting opportunities for cooperative ligand–additive systems [6].

4. Catalyst Forms: Homogeneous, Nanostructured, and Atomically Dispersed

4.1. Homogeneous Copper Catalysts

Early studies commonly used simple copper salts (e.g., CuI, CuBr, $Cu(OAc)_2$) with appropriate ligands to activate C–X bonds [8, 7]. Mehmood and Leadbeater reported that CuI/DMEDA in water under microwave assistance rapidly hydroxylates aryl bromides and iodides under mild conditions with high yields [9]. Homogeneous systems typically offer high activity and straightforward formulation but can suffer from challenging catalyst recovery and metal residues, hindering industrial uptake [4].

4.2. Nanostructured Copper Catalysts

To address recovery and reuse, nanocopper systems have been developed [13]. Yang and co-workers prepared CuI nanoparticles (CuI NPs) that catalyse the conversion of aryl bromides/iodides to phenols efficiently in water, with multiple reuse cycles and only modest loss of activity [13]. Cu_2O nanomaterials have also shown strong performance in alcohol/water mixtures with good functional-group tolerance [19]. High surface area and abundant active sites allow these catalysts to remain effective at lower temperatures—valuable complements to homogeneous systems [10].

4.3. Atomically Dispersed Copper Catalysts

Single-atom catalysts (SACs) have recently come to the fore [10]. Hao et al. reported atomically dispersed Cu–ZnO–ZrO_2 that efficiently hydroxylates aryl iodides and bromides with ultralow Cu loadings, achieving excellent selectivity and stability under mild conditions [10]. SACs maximise atom efficiency and exploit metal–support electronic interactions to boost activity—traits attractive for green chemistry and scale-up [11].

5. Reaction Parameters and Their Influence

Catalytic efficiency depends not only on the metal and ligand but also on reaction conditions:

Substrate reactivity. The general order is I > Br > Cl, reflecting decreasing C–X bond lability [13, 5]. Bromides and iodides therefore react more readily, whereas chlorides often require higher temperature or stronger base. The use of strong donor ligands (e.g., BHMPO, dihydroxy-phenanthroline) has progressively mitigated the challenge of aryl chlorides [14, 18].

Temperature. Many aryl chlorides require ≥ 130 °C for effective conversion, while bromides/iodides frequently afford high yields at 80–100 °C [14]. Microwave assistance or nanocopper catalysts can, in some cases, reduce the effective temperature to 60–80 °C, lowering energy demand [9, 13].

Base. Bases serve both as hydroxide sources and as promoters of C–X cleavage. K_3PO_4, Cs_2CO_3, and TBAOH are common, with Cs_2CO_3 often preferred for aryl chlorides owing to its strength and solubility [18, 6].

Medium. While DMF and DMSO can deliver high activity, their environmental footprints are non-trivial [4]. Green-chemistry principles have motivated the use of water or alcohols [11]. For example, Liang et al. realised high efficiency in water/ethanol with natural-product ligands, reconciling reactivity and sustainability [17].

Functional-group tolerance. Copper systems generally tolerate –NO_2, –CN, –OH and other functionalities, enabling late-stage diversification of complex molecules [10, 14]. However, strong coordinating groups (e.g., pyridyl nitrogen) may compete with the catalyst for binding, diminishing activity—an issue meriting further optimisation [7].

6. Applications and Reaction Extensions

The scope of copper-catalysed aryl-halide hydrolysis is broad, with implications in pharmaceuticals, functional materials, and methodological diversification [6].

Pharmaceuticals**.** Many bioactive compounds or advanced intermediates incorporate phenolic motifs. Copper-catalysed hydroxylation streamlines routes, improves atom economy, and is suitable for late-stage functionalisation, facilitating rapid library expansion [14, 9].

Functional materials. Phenolic monomers are pivotal in liquid-crystal chemistry, dye synthesis, and organic electronics. Copper methods can deliver high-purity phenols under mild conditions, serving the selectivity requirements of materials chemistry, while greener media and recyclable catalysts address sustainability needs [18, 10].

Methodological extensions. Beyond C–O bond formation, copper catalysis extends to C–N and C–S couplings and intramolecular cyclisations (e.g., to benzofurans), offering new avenues for medicinal and natural-product synthesis [13, 7].

7. Conclusion

Copper-catalysed hydrolysis of aryl halides has evolved from a laboratory curiosity into a promising green route to phenols. In-depth mechanistic insight, deliberate ligand design, and a progression of catalyst architectures—from homogeneous to nanostructured and finally to atomically dispersed—have together delivered breakthroughs in activity, selectivity, and sustainability. The development of aqueous media and robust heterogeneous systems has laid groundwork for industrial translation. Challenges remain, notably universal activation of the most inert substrates (aryl chlorides) under truly mild conditions and long-term catalyst stability. Looking ahead, computational design and high-throughput experimentation should accelerate discovery of ligands and additives; water/alcohol media are poised for broader adoption; electrocatalysis, photocatalysis, and multimetal cooperation may elevate efficiency and substrate generality; and catalyst recycling and metal-residue control will be essential for scale-up. With continued progress in mechanistic understanding and system optimisation, copper catalysis is well placed to bridge laboratory innovation and industrial practice, enabling efficient and environmentally responsible syntheses of phenols and their derivatives.

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