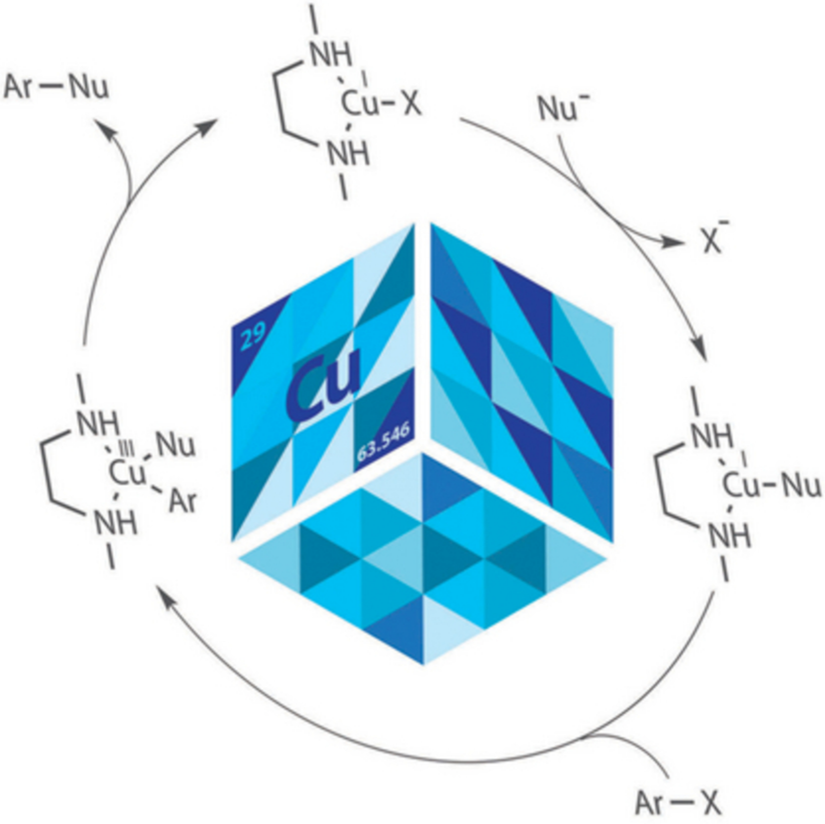
Copper-Mediated Cross-Coupling Reactions



Edited by

Gwilherm Evano and Nicolas Blanchard

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FOREWORD

The development of efficient methods for use in organic synthesis, particularly applicable to polyfunctionalized molecules and heterocycles, remains one of the top challenges in organic chemistry. Oftentimes older reactions are rediscovered and improved, sometimes substantially, in order to solve modern problems. A prime example of this is copper-catalyzed methodology. This topic, studied at the beginning of the twentieth century by Ullmann, Goldberg, and others has experienced a renaissance in the past two decades. A significant reason for this is the development of new and improved ligands to facilitate the transformations of interest.

While the most obvious difference between catalysts based on palladium and copper is the lower cost of the latter, this is only a small part of what makes copper catalysts so attractive. For most chemists in academia or discovery chemistry, the cost is not a major issue. In addition, one must take in to account many factors, such as volumetric productivity (reactor time, labor cost), substrate cost, yield, and substrate scope, which affect the total cost when comparing any two processes. Among the major advantages of using copper catalysts (in addition to cost) are that they tend to show excellent functional group compatibility and, in fact, are often at their best in promoting reactions of substrates that contain coordinating functional groups. A prime example, as delineated in Evano and Blanchard's preface to this book, is seen in Ullmann's seminal work: he was able to accomplish the coupling of aniline with 2-chlorobenzoic acid well before the same transformation could be carried out with palladium catalysts. In fact, the chemistry based on these two metals is really quite complementary. In support of this notion, today these are used interchangeably for many synthetic operations depending on the nature of the substrate combination to be examined.

The chapters in the book cover a range of synthetically and mechanistically important topics. Many aspects of carbon-heteroatom and carbon–carbon, bond-forming reactions are described. These have become an everyday part of the practicing synthetic organic chemist's arsenal. In addition, topics such as the formation of trifluoromethylated organic molecules and the application of copper-catalyzed methods to the total synthesis of natural products and pharmaceuticals are also covered. Taken together, the chapters in this book provide an up-to-date overview of the state of the field, providing the reader with the knowledge of both what has been accomplished and what new areas remain for further investigation.

Massachusetts Institute of Technology STEPHEN L. BUCHWALD

PREFACE

Copper Catalysis from a Historical Perspective: A Legacy from the Past

Gwilherm Evano and Nicolas Blanchard

THE HISTORICAL AND REMARKABLE FIRST DISCOVERIES BY FRITZ ULLMANN AND IRMA GOLDBERG

It all started in 1901 in Geneva when Fritz Ullmann, born in 1875 in Fürth, where his father owned a fabric... of metallic powders,[1] reported, in a remarkable publication that we highly recommend, that "Erhitzt man *o*-Bromnitrobenzol mit fein vertheiltem Kupferpulver, so bemerkt man, dass letzteres seinen Glanz verliert und in eine matte graue Masse verwandelt wird. Bei Aufarbeitung des Reactionsproductes zeigte sich nun, dass das Kupfer zum grössten Theil in Cuprobromid und das Bromnitrobenzol in eine bromfreie Substanz verwandelt worden ist, welche sich bei näherer Untersuchung identisch, mit der von Tauber auf andere Weise dargestellten 2.2′-Dinitrobiphenyl, erwies." (If one heats *o*-bromonitrobenzene with finely divided copper powder, so one recognizes that the last one is losing its shine and turns into a matt grey mass. After purification of the reaction products, it appears that copper has turned into copper bromide and that the bromonitrobenzene has turned into a bromine-free substance, which, on a closer look, turns out to be identical with the 2,2-dinitrobiphenyl synthesized in a different way by Tauber) (Fig. P.1).*,[2] The reaction can also be performed from aryl iodides and, which is just astonishing, even from aryl chlorides (Scheme P.1). Two molecules of aryl

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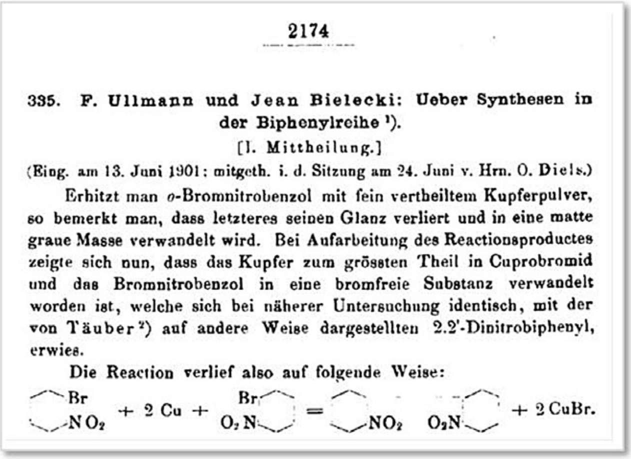
* The editors are truly indebted to Dr. Théophile Tschamber from the University of Mulhouse (France) for his expertise in translating the numerous original German research papers and patents that are cited in the Preface.



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335. **F. Ullmann und Jean Bielecki: Ueber Synthesen in der Biphenylreihe [1]).**

[I. Mittheilung.]

(Eing. am 13. Juni 1901; mitgeth. i. d. Sitzung am 24. Juni v. Hrn. O. Diels.)

Erhitzt man *o*-Bromnitrobenzol mit fein vertheiltem Kupferpulver, so bemerkt man, dass letzteres seinen Glanz verliert und in eine matte graue Masse verwandelt wird. Bei Aufarbeitung des Reactionsproductes zeigte sich nun, dass das Kupfer zum grössten Theil in Cuprobromid und das Bromnitrobenzol in eine bromfreie Substanz verwandelt worden ist, welche sich bei näherer Untersuchung identisch, mit der von Täuber [2]) auf andere Weise dargestellten 2.2'-Dinitrobiphenyl, erwies.

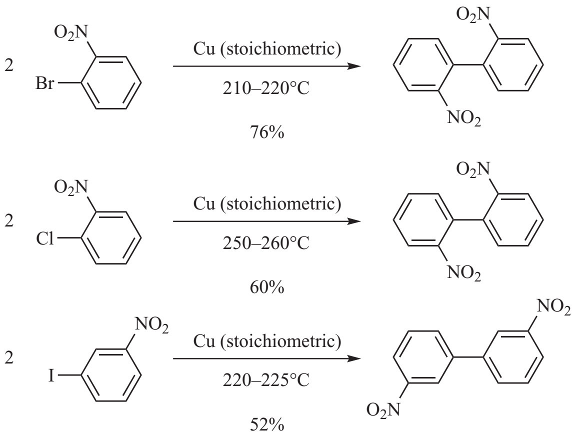
Die Reaction verlief also auf folgende Weise:

Figure P.1 Fritz Ullmann (1875–1939) and an extract from his original publication.

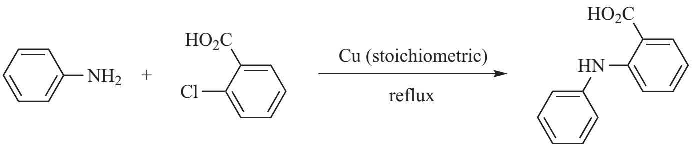
halides can be coupled together in the presence of stoichiometric amounts of metallic copper: The Ullmann reaction had just been discovered.

Obviously fascinated with the power of the metallic copper, Ullmann next reported in 1903 an equally fascinating reaction in a publication entitled "Über eine neue Bildungsweise von Diphenylaminderivaten" (*On a New Method for the Formation of Diphenylamine Derivatives*). By mixing aniline (or other aniline derivatives) and *ortho*-chlorobenzoic acid in the presence of metallic copper at reflux, the aniline was smoothly arylated to the corresponding diarylamine with a remarkable efficiency (Scheme P.2).[3] Two years after his initial discovery of the biaryl synthesis, Ullmann continued to set the foundations of copper-mediated cross-coupling reactions and the arylation of amines that would later on be named after him was invented. Also remarkable is that the aryl halide substrate chosen for this study, *ortho*-chlorobenzoic acid, already possessed a non-innocent chelating group: the *ortho*-effect, which still has a deep impact in copper catalysis today and which was crucial to the success of many copper-mediated transformations including in Nicolaou's synthesis of vancomycin (see further), was already touched upon in 1903.

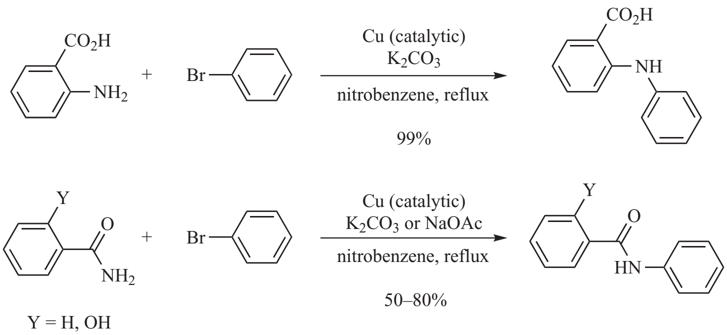
Following these two reports, Ullmann's assistant in Geneva, Irma Goldberg, reported 3 years later that a related reaction could be performed using only catalytic amounts of copper. By reacting anthranilic acid and bromobenzene in the presence of potassium carbonate and catalytic amounts of "Naturkupfer C" in refluxing nitrobenzene for 3 hours, the reaction proceeded with a remarkable efficiency, the corresponding condensation product being isolated in 99% yield (Scheme P.3).[4] The arylation could also be efficiently performed with *para*-nitro-bromobenzene and, even better, the arylation of amides (benzamide in this case), known nowadays as the Goldberg condensation reaction, could also be catalyzed by traces of metallic copper. These three remarkable



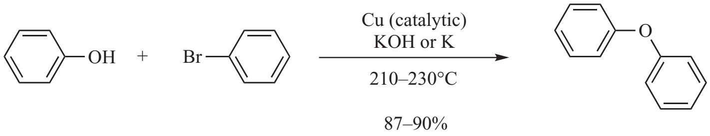
Scheme P.1 1901: the discovery of the Ullmann reaction.



Scheme P.2 1903: the discovery of the Ullmann condensation reaction for the synthesis of diarylamines.



Scheme P.3 1906: the discovery of the copper-catalyzed arylation of anilines and amides by Irma Goldberg.



Scheme P.4 1905: the discovery of the copper-catalyzed arylation of phenols by Fritz Ullmann.

reactions published between 1901 and 1906 mark the beginning of cross-coupling reactions and clearly paved the way for all recent developments.

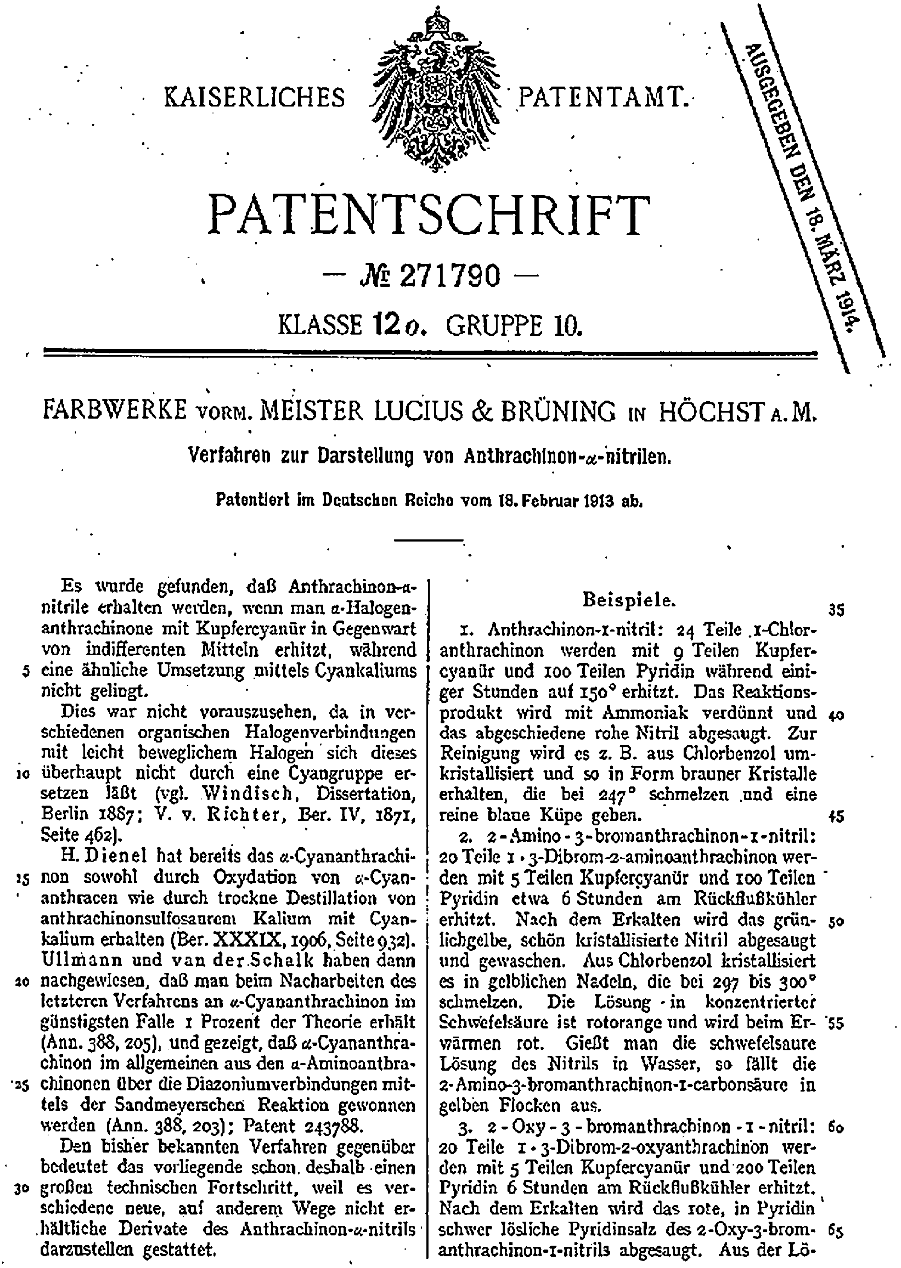
Last but not least, Ullmann also studied the cross coupling involving phenols and reported in 1905 that "if you try to react potassium phenoxide with bromobenzene, the yield of the biphenyl ether is 0.9%. If you however add small quantities of copper to the reaction mixture, the yield goes to 90%" (Scheme P.4).[5] It is therefore possible to catalyze the cross coupling between phenols and aryl bromides with small amounts of copper, which obviously have a dramatic effect on the reaction rate and yields.

FURTHER HISTORICAL DEVELOPMENTS: THE CYANATION OF ARYL HALIDES BY ROSENMUND AND VON BRAUN AND THE ARYLATION OF DIKETONES AND MALONATES BY HURTLEY

In a series of just four publications, Fritz Ullmann and Irma Goldberg, who eventually got married in 1910, clearly set the foundations of modern copper catalysis. This pioneering work was followed by other key reports in the next 30 years or so, which further demonstrated the potential of copper-mediated cross-coupling reactions.

The next major development in this field was stimulated by the interest in the copper-mediated cyanation of aryl halides, which appeared closely after the seminal publications of Ullmann and Goldberg. Although this transformation is known as the "Rosenmund–von Braun" reaction, many academic and industrial research groups contributed to the development of this very useful reaction.[6–8] Indeed, the first report of such a reaction appeared in the patent literature in 1913 by the Meister, Lucius & Brüning Company who found that chloro- and bromoanthraquinones reacted with copper(I) cyanide in pyridine at 150°C to give the corresponding nitriles (Fig. P.2 and Scheme P.5).[8]

Karl W. Rosenmund and his PhD student Erich Struck described next in 1919 that potassium cyanide in combination with copper(I) cyanide converted aryl halides to the corresponding benzoic acids in water at 200°C under pressure. The intermediate nitriles were not isolated, but the central role of the copper(I) species was put forward (Scheme P.6, Eq. 1).[9a] Rosenmund disclosed a year later[9b] that stoichiometric copper(I) thiocyanate in pyridine



KAISERLICHES PATENTAMT.

AUSGEGEBEN DEN 18. MÄRZ 1914.

PATENTSCHRIFT

— № 271790 —

KLASSE 12*o*. GRUPPE 10.

FARBWERKE VORM. MEISTER LUCIUS & BRÜNING IN HÖCHST A.M.

Verfahren zur Darstellung von Anthrachinon-α-nitrilen.

Patentiert im Deutschen Reiche vom 18. Februar 1913 ab.

Es wurde gefunden, daß Anthrachinon-α-nitrile erhalten werden, wenn man α-Halogenanthrachinone mit Kupfercyanür in Gegenwart von indifferenten Mitteln erhitzt, während eine ähnliche Umsetzung mittels Cyankaliums nicht gelingt.

Dies war nicht vorauszusehen, da in verschiedenen organischen Halogenverbindungen mit leicht beweglichem Halogen sich dieses überhaupt nicht durch eine Cyangruppe ersetzen läßt (vgl. Windisch, Dissertation, Berlin 1887; V. v. Richter, Ber. IV, 1871, Seite 462).

H. Dienel hat bereits das α-Cyananthrachinon sowohl durch Oxydation von α-Cyananthracen wie durch trockne Destillation von anthrachinonsulfosaurem Kalium mit Cyankalium erhalten (Ber. XXXIX, 1906, Seite 932). Ullmann und van der Schalk haben dann nachgewiesen, daß man beim Nacharbeiten des letzteren Verfahrens an α-Cyananthrachinon im günstigsten Falle 1 Prozent der Theorie erhält (Ann. 388, 205), und gezeigt, daß α-Cyananthrachinon im allgemeinen aus den α-Aminoanthrachinonen über die Diazoniumverbindungen mittels der Sandmeyerschen Reaktion gewonnen werden (Ann. 388, 203); Patent 243788.

Den bisher bekannten Verfahren gegenüber bedeutet das vorliegende schon deshalb einen großen technischen Fortschritt, weil es verschiedene neue, auf anderem Wege nicht erhältliche Derivate des Anthrachinon-α-nitrils darzustellen gestattet.

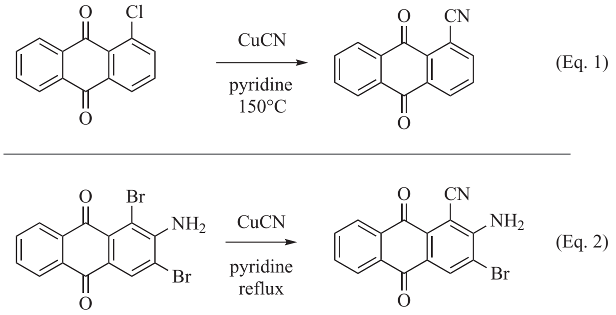
Beispiele.

1. Anthrachinon-1-nitril: 24 Teile 1-Chloranthrachinon werden mit 9 Teilen Kupfercyanür und 100 Teilen Pyridin während einiger Stunden auf 150° erhitzt. Das Reaktionsprodukt wird mit Ammoniak verdünnt und das abgeschiedene rohe Nitril abgesaugt. Zur Reinigung wird es z. B. aus Chlorbenzol umkristallisiert und so in Form brauner Kristalle erhalten, die bei 247° schmelzen und eine reine blaue Küpe geben.

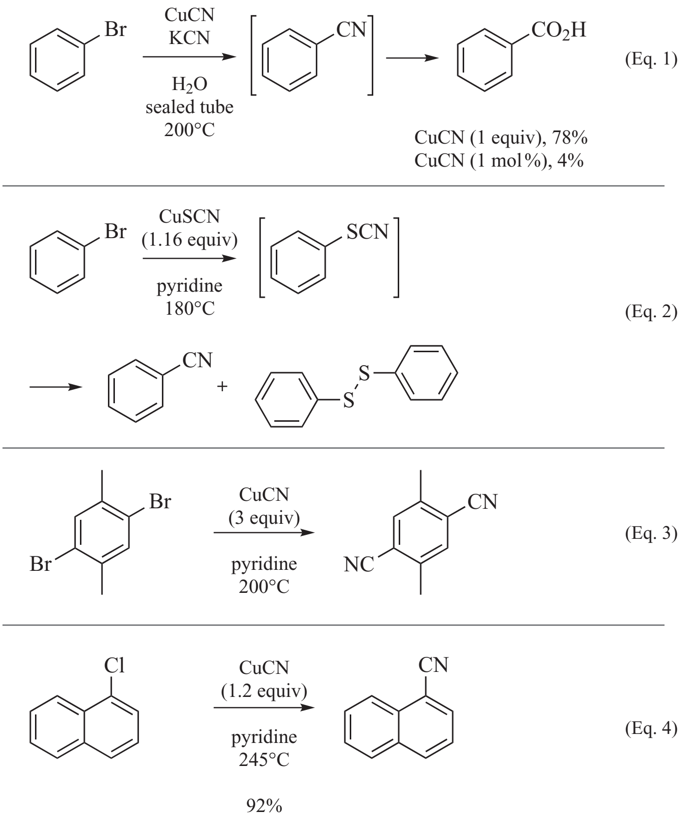
2. 2-Amino-3-bromanthrachinon-1-nitril: 20 Teile 1·3-Dibrom-2-aminoanthrachinon werden mit 5 Teilen Kupfercyanür und 100 Teilen Pyridin etwa 6 Stunden am Rückflußkühler erhitzt. Nach dem Erkalten wird das grünlichgelbe, schön kristallisierte Nitril abgesaugt und gewaschen. Aus Chlorbenzol kristallisiert es in gelblichen Nadeln, die bei 297 bis 300° schmelzen. Die Lösung in konzentrierter Schwefelsäure ist rotorange und wird beim Erwärmen rot. Gießt man die schwefelsaure Lösung des Nitrils in Wasser, so fällt die 2-Amino-3-bromanthrachinon-1-carbonsäure in gelben Flocken aus.

3. 2-Oxy-3-bromanthrachinon-1-nitril: 20 Teile 1·3-Dibrom-2-oxyanthrachinon werden mit 5 Teilen Kupfercyanür und 200 Teilen Pyridin 6 Stunden am Rückflußkühler erhitzt. Nach dem Erkalten wird das rote, in Pyridin schwer lösliche Pyridinsalz des 2-Oxy-3-bromanthrachinon-1-nitrils abgesaugt. Aus der Lö-

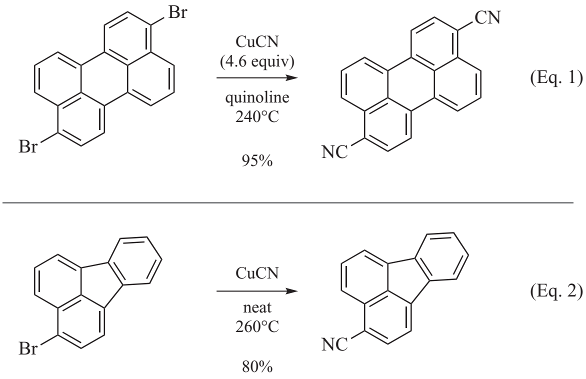
Figure P.2 The 1913 Meister, Lucius & Brüning Company patent.



Scheme P.5 1913: The first copper(I)-mediated cyanations of haloanthraquinones by the Meister, Lucius & Brüning Company.



Scheme P.6 1919–1923: Karl W. Rosenmund and Henri de Diesbach early reports on the cyanation of aryl halides.

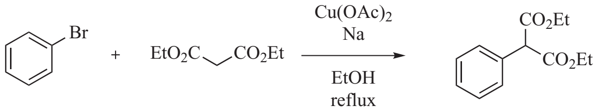


Scheme P.7 1927–1931: Alfred Pongratz and Julius von Braun cyanation of aryl halides.

converted aryl bromides to intermediate aryl thiocyanates, which spontaneously gave the corresponding nitriles at 180°C in the presence of the copper species,[6] the nitriles being characterized as carboxylic acids after aqueous acidic treatment (Scheme P.6, Eq. 2). Shortly after, Henri de Diesbach reported in two back-to-back articles in 1923 that dibromoxylene derivatives could be converted to the corresponding dinitriles in excellent yield using an excess of copper(I) cyanide in pyridine at 200°C (Scheme P.6, Eq. 3),[10] and even aryl chlorides could be transformed to the corresponding nitriles, as seen in Scheme P.6, Eq. 4.[11]

In 1927, Alfred Pongratz described that copper(I) cyanide in refluxing quinoline was efficient for the cyanation of perylene-3,9-dibromide (Scheme P.7, Eq. 1) and that the corresponding chloride could be converted in the absence of solvent at 300°C, although no yield was given in the latter case.[12] Finally, during investigation on the chemistry of fluoranthene derivatives, Julius von Braun, who gave his name to this cyanation reaction, demonstrated that 4-bromo-fluoranthene could be transformed to the corresponding nitrile in 80% yield when reacted with copper(I) cyanide at 260°C (Scheme P.7, Eq. 2).[13]

The pioneering investigations of Ullmann, Goldberg and Rosenmund[8b] were a source of inspiration for William R. H. Hurtley, who recognized their contributions in his seminal 1929 report, stating that "under the catalytic influence of copper, the halogen in *o*-bromo-benzoic acid is much more reactive than is commonly realized."[14] Hurtley showed that copper bronze or copper acetate can promote the C-arylation of some families of CH-acids in reaction with *o*-bromobenzoic acid in the presence of sodium ethoxide as a base (Scheme P.8). Since then, this transformation, commonly known as the "Hurtley reaction", has triggered mechanistic investigations as well as very elegant applications in organic synthesis. Mild conditions are now available thanks to



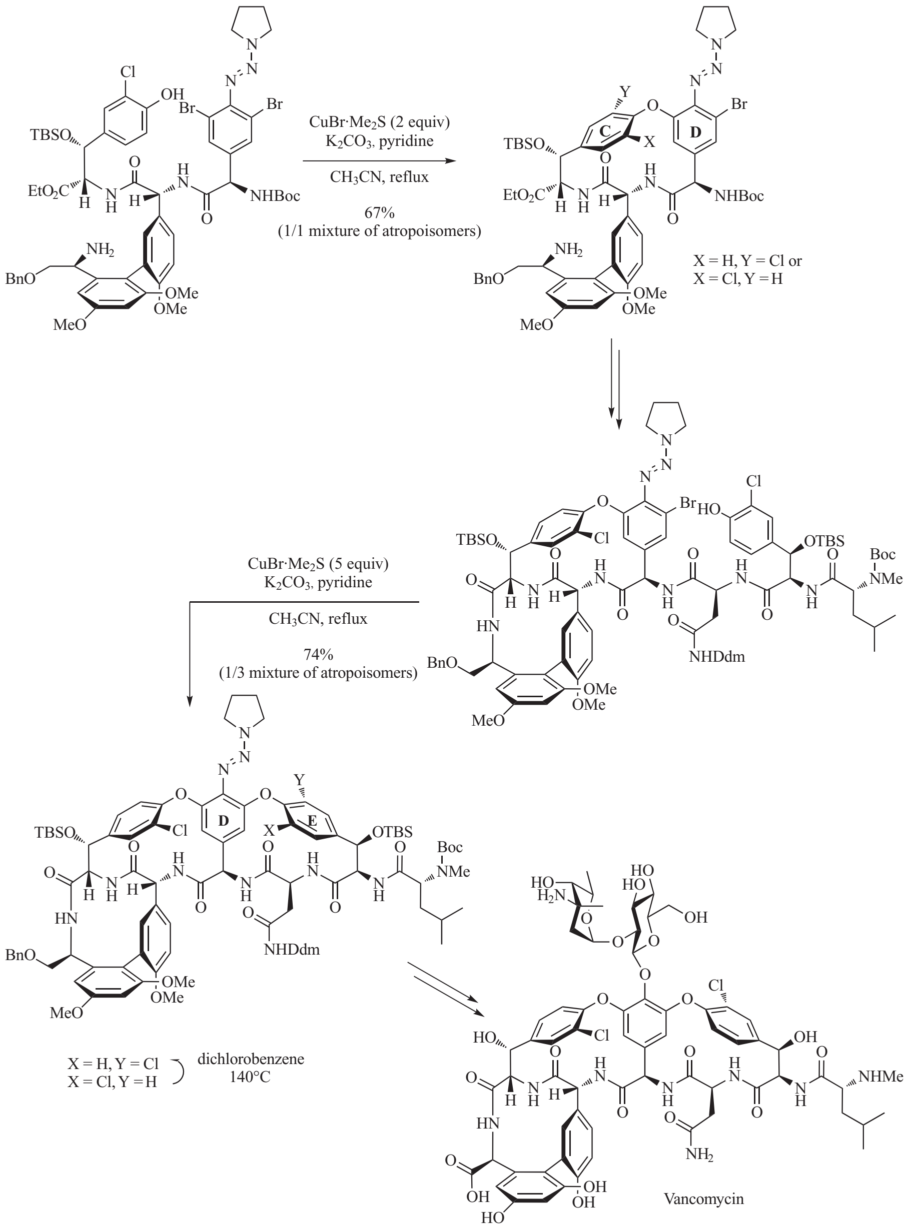
Scheme P.8 1929: the discovery of the copper-mediated arylation of CH-acid derivatives by William R. H. Hurtley.

new classes of ligands that even allowed the development of an asymmetric version of the Hurtley reaction.

FROM THE HISTORICAL DISCOVERIES TO THE DEVELOPMENT OF MODERN COPPER-MEDIATED CROSS-COUPLING REACTIONS

While remarkable, these reactions, however, have found only a limited number of applications, especially when compared to their impressive potential. Indeed, drawbacks associated with the use of harsh reaction conditions (strong bases, stoichiometric amounts of copper in some cases, and high reaction temperatures) have clearly hampered the development of these copper-mediated cross-coupling reactions. From the first discoveries in the early 1900s up to the beginning of the twenty-first century, no real breakthrough was made to significantly improve the original systems and the strategy was to tailor the substrate, not the catalyst, to obtain systems that would perform under milder conditions. Nicolaou's remarkable total synthesis of vancomycin is one of the most representative example of such a strategy. Capitalizing on the well-known *ortho*-effect in copper-mediated transformations, a mild copper-mediated arylation reaction was designed based on the ingenious incorporation of a triazene unit in the starting material strategically placed *ortho* to the bromine: this internal helper auxiliary served both as a potential "electron sink" and to coordinate the intermediate copper species. The triazene indeed considerably helped the reaction, which enabled the formation of the C–O–D and D–O–E ring systems under remarkably mild conditions since the reaction could be performed in refluxing acetonitrile (Scheme P.9).[15]

Besides these strategies based on substrate modifications, the inherent shortcomings of the original copper-mediated cross-coupling reactions were still not overcome at the end of the twentieth century and palladium was in most cases preferred to copper. Despite remarkable work done with palladium catalysis for the construction of an impressive and ever-increasing number of C–C and C–heteroatom bonds, limitations still exist and the high cost of palladium and ligands has forced chemists to consider alternative metals. This evolution eventually led to the renaissance of copper catalysis, which has been extremely revisited over the past decade. Following extensive and remarkable studies of the Ullmann condensation by Payne,[16] who showed that the active



Scheme P.9 The Ullmann condensation reaction under milder conditions: redesigning the substrate to improve the efficiency (Nicolaou's total synthesis of vancomycin).

catalytic species are soluble cuprous ions and pioneering work by Bryant,[17] Capdevielle,[18] and Goodbrand,[19] who investigated the idea of a "ligated copper catalysis", the key breakthrough was the introduction of chelating ligands for copper.

Remarkable and pioneering studies in this area from, among others, the Buchwald, Ma, and Taillefer groups had a strong impact in the renaissance of copper catalysis, and the Ullmann, Goldberg, Rosenmund–von Braun, Hurtley, and other related copper-mediated processes can now be conducted under much milder conditions together with dramatically enhanced yield. Recent advances in the arylation of N-, O-, and S- as well as P-nucleophiles with aryl halides will be described in Chapters 1, 2, and 3, respectively.

In addition to the development of improved protocols for the arylation of various heteronucleophiles, the introduction of chelating ligands also considerably expanded the scope of the original procedures and allowed for the use of new reaction partners for the introduction of vinyl, alkyne, and allene functional groups. These copper-mediated syntheses of heterosubstituted alkenes, alkynes, and allenes will be overviewed in Chapter 5. Copper-catalyzed aromatic versions of the Finkelstein reaction have also been recently reported: they proceed with remarkable efficiencies and will be covered in Chapter 6.

These recent developments also had a strong impact on the development of new and improved protocols for the formation of C–C bonds, and a variety of robust, mild, and reliable procedures have been designed with the assistance of copper complexes.

The classical Hurtley-type transformation as well as the tremendous progresses that have been reported recently in this central C-arylation reaction of CH-acid derivatives will be presented in Chapter 8, with an emphasis on the importance of the different types of ligands, mechanisms, and synthetic applications. The copper-catalyzed synthesis of nitriles from aryl halides is then covered in Chapter 9, including discussions on the different catalytic systems and sources of cyanide that have been greatly improved in the past two decades.

A central reaction in the realm of copper-catalyzed and copper-mediated transformations is of course the aryl–aryl coupling that has continuously evolved into an efficient and practical tool with multiple applications. Chapter 10 is devoted to this vibrant field of research that has recently witnessed a shift of paradigm with even more direct reactions such as the copper-catalyzed direct C–H arylations. The next three chapters, Chapters 11, 12, and 13, have captured relevant advances in some of the most practical and efficient copper-catalyzed transformations that have clearly modified our conception of carbon–carbon bond disconnections: the alkenylation and alkynylation of aryl, alkynyl, and vinyl derivatives.

To close this section dedicated to the formation of carbon–carbon bonds, the central role of copper catalysts in methods aiming at the introduction of the trifluoromethyl moiety will be exposed. Indeed, the occurrence of the trifluoromethyl motif in pharmaceutical and agrochemical active ingredients