Renaissance of Ullmann and Goldberg Reactions – Progress in Copper Catalyzed C–N-, C–O- and C–S-Coupling

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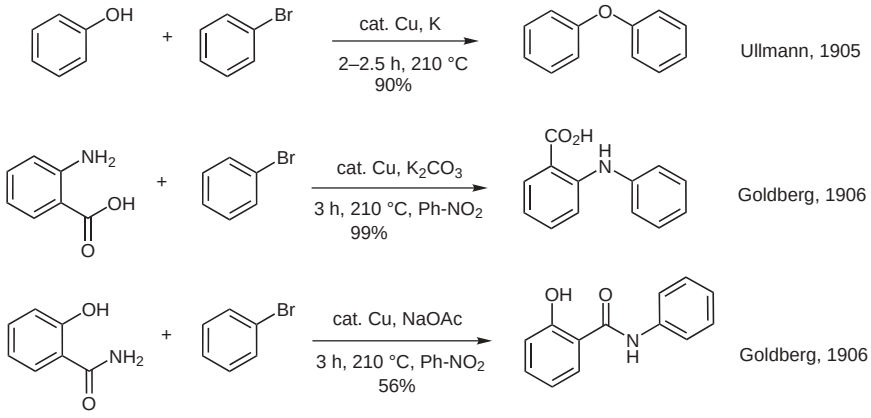
Abstract: Copper-catalyzed C–N-, C–O- and C–S-coupling reactions are powerful tools in organic synthesis and have been extensively reinvestigated in the past five years. The understanding of solubilizing and accelerating effects exhibited by substrates and ligands initiated novel developments originally on N-arylation of amines, amides, and nitrogen heterocycles. Nevertheless practical methods for the syntheses of aryl ethers and aryl thioethers have been established as well. A wide range of arylating reagents was explored, of which the aryl halides will be presented in this overview. Among a growing set of ligands and optimized reaction protocols, the most promising procedures are highlighted, covering the literature published through May 2003.

Key words: catalysis, cross-coupling, copper, arylations, nucleophilic aromatic substitution

1 Introduction

The intense attention palladium catalyzed arylation reactions of amines and alcohols have received since their discovery[1–4] might 'imply' to the contemporary reader that this reaction has been a revolutionary novel concept. Although these processes are advantageous concerning the reaction conditions and scope, in this case however academia went backwards by replacing an already existing copper catalysis methodology by a palladium catalyzed version. At the beginning of the last century Fritz Ullmann and Irma Goldberg started their pioneering work on copper mediated and copper catalyzed coupling reactions. They explored new ways to form aryl-C-, aryl-N- and aryl-O-bonds and thus paved the way to access a wide range of new products. For the first time unactivated aryl halides were used as coupling components while classical nucleophilic aromatic substitution reactions required electron poor aryl halides in combination with strong nucleophiles.[5–7]

It has been mentioned only rarely in the literature that their results represent a general breakthrough in the field of catalysis. A closer look into the original publications reveals that Ullmann and Goldberg already practised modern homogeneous cross-coupling chemistry, achieving respectable yields and selectivities and using (unintentionally) bidendate-coordinating substrates as well. Ullmann explored the copper mediated aryl amination[5b] and copper catalyzed diaryl ether synthesis,[5c] while the first catalytic aryl aminations and aryl amidations were both carried out in the laboratory of Goldberg[6] (Scheme 1). These conceptual papers have to be considered the basis of the current work on the copper catalyzed arylation reactions. The importance of the results described in these publications is underlined by the fact that they found their way into numerous industrial applications, such as synthesis of intermediates in pharmaceutical, agrochemical, fine and polymer chemistry.[7]



Scheme 1 Ullmann ether synthesis, Ullmann–Goldberg amination, and Goldberg amidation

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However, major restrictions of classical Ullmann and Goldberg protocols have always been harsh reaction conditions, in particular high temperatures. In addition with the evolution of green chemistry, the necessity to use stochiometric amounts of the heavy metal copper in order to obtain satisfactory yields, has to be considered as a major drawback.

In the mid of the 90s, palladium based approaches set out to conquer these synthetic problems, mainly pushed by numerous contributions of Buchwald and Hartwig. The combined efforts of these and other groups have led to the development of robust and sustainable laboratory procedures for multiple substrate classes during the past eight years. This area of chemistry has recently been reviewed.[1] Nevertheless, high costs of palladium and some problematic functional group tolerances forced scientists to reconsider other transition metal catalysts, mainly nickel and copper. Copper(II)acetate catalyzed coupling reactions involving organobismuth, -lead, -antimony, -silicon, -tin, and -boron reagents as well as iodonium salts as arylating reagents have been investigated and have been recently reviewed.[8] A major breakthrough was certainly achieved 1998 by Chan, Evans, and Lam, who independently reported a generally applicable protocol for the transformation of arylboronic acids to arylamines under mild conditions.[9] The use of simpler and more accessible aryl sources – such as the corresponding aryl halides – in copper catalyzed cross-coupling reactions will be reviewed in the following.

2 The Copper Catalysis Toolbox

In comparison to the corresponding palladium catalyzed coupling reactions, the copper catalyzed version seems to be less sensitive towards the choice of the metal source. In

Biographical Sketches

Klaus Kunz (born 1972) studied Chemistry in Marburg and Bonn and obtained the diploma degree in Prof. J. Bargon's research group on mechanistic investigations of catalytic imine hydrogenation using in situ NMR spectroscopy. With a Kekulé scholarship he moved to the Institute of Organic Chemistry of the University of Münster and earned his PhD in 2001 under the guidance of Prof. G. Erker on the development of novel contrained geometry Ziegler Natta catalysts. After studies in Bonn and Hagen he received the diploma degree in economics from the University of Hagen at the same time. In 2001 he joined the Central Research Department for organic synthesis at Bayer AG before he recently moved to the chemical research division of Bayer CropScience AG.

Ulrich Scholz (born 1970) started his studies in chemistry in 1990 at the University of Hannover, Germany. In 1993, he joined Professor Paul A. Wender's research group at Stanford University, California, USA on a DAAD scholarship. After returning to his home town of Hannover, he finished his basic studies in chemistry and received his diploma degree in Professor E. Winterfeldt's research group in 1996 on the synthesis of unsymmetrical pyrazines. He stayed in Professor Winterfeldt's group and spent the subsequent three years on the elaboration of bile acids as potential building blocks for the synthesis of cephalostatin analogues. After graduation he continued as a teaching assistant at Hannover University to finally join the Central Research Department for homogeneous catalysis of Bayer AG at the end of 1999. He recently moved to the process development department of the newly formed Bayer Chemicals Company and specializes on transition metal catalyzed aromatic aminations.

Dirk Ganzer (born 1968) grew up in Leverkusen. After industrial training as a laboratory assistant at Bayer AG Leverkusen he was promoted to a synthetic technician in 2001. At his time at Bayer he has worked for different category groups in the Central Research Department. In 2002 he joined the chemical research division of Bayer CropScience AG.

many cases, precursors as different as copper powder and air sensitive copper(I) salts proved to be suitable for the conversions of components in high yields. On the other hand, the selection of a ligand, the choice of the solvent and base likewise play an important role as in palladium catalysis. A selection of ligand additives in the copper catalysis toolbox is outlined in Scheme 2.

Neutral bidentate chelators appear to be in the majority of the reaction protocols, the ligands of choice. The variety of donor combinations includes N,N-, O,O- and N,O-chelators as well as phosphines and carbenes. The wide choice of chelators implies the potential for optimization and fine-tuning of a given transformation. Even if the focus is set on mild reaction conditions, the required temperatures range from 80–120 °C, which excludes low boiling solvents. Toluene is commonly used, but unsuitable in certain cases and can be replaced by dioxane or polar solvents such as NMP or DMF. For the selection of the appropiate base, a careful tuning and comparison with literature procedures is essential as well. Potassium carbonate is applied in many procedures, but, for example, efficient C–O-coupling often requires the use of cesium carbonate. Alternatively, preforming the anions using sodium methoxide or potassium *t*-butoxide can be advantageous.

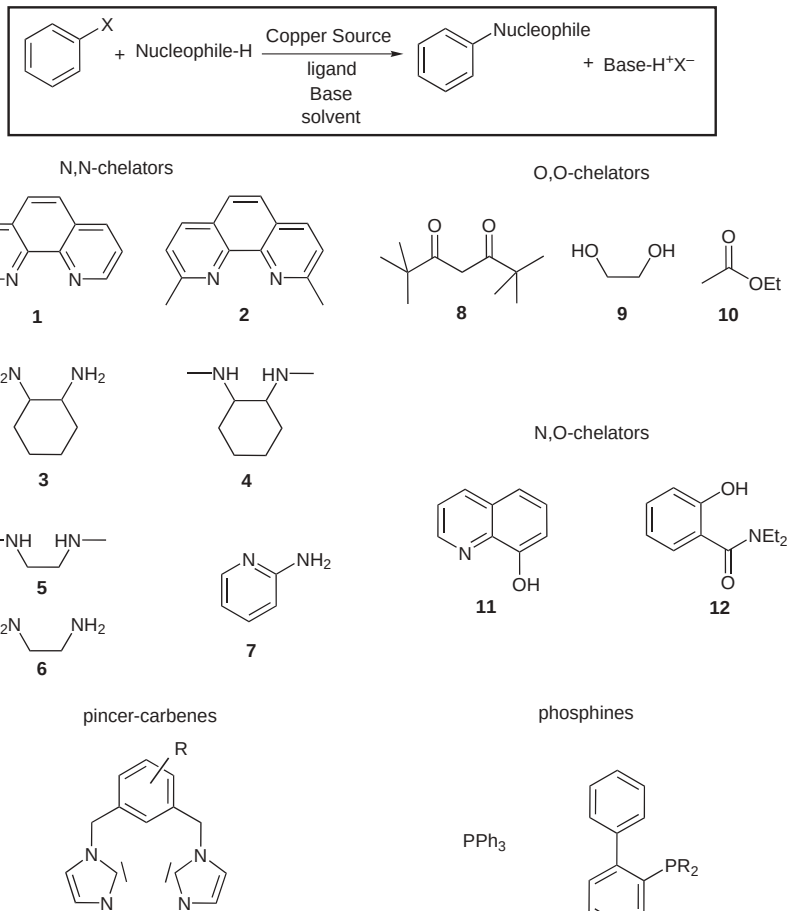
3 Formation of C–N-bonds

Most of the publications on copper catalyzed nucleophilic aromatic substitution deal with N-nucleophiles such as aliphatic and aromatic amines, N-heterocycles and amides. In the subsequent chapters the N-nucleophiles are classified, taking their different reactivities into account.

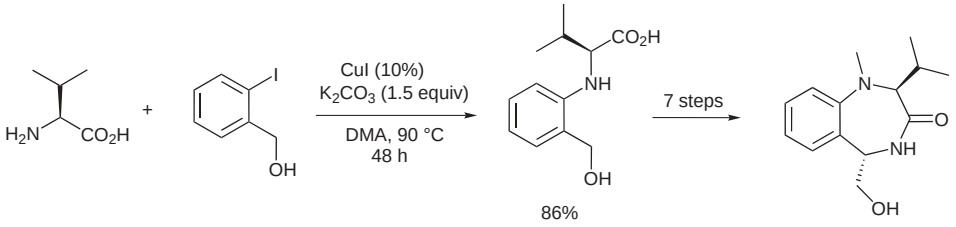
3.1 Aromatic Amination

While the coupling of substituted anilines with arylhalides has been the subject of several contributions during the last 100 years,[37a–c] the more delicate coupling of aliphatic amines with aryl halides was excessively revisited by Ma and co-workers for the synthesis of phosphokinase C activator Benzolactam V8 (Scheme 3).[10]

Ma understood that Goldberg's amination reaction was enabled by the chelating nature of the substrate and devised the first protocol for a mild copper catalyzed coupling of aryl bromides with chelating α-amino acids. In



Scheme 2 Ligand toolbox for copper catalyzed cross couplings



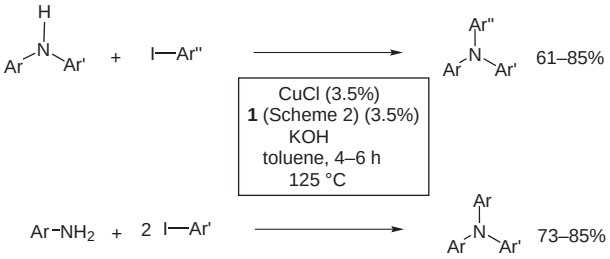
Scheme 3 α-Amino acids as chelating substrates in the synthesis of Benzolactam V8

this publication Ma also shows a structure-catalytic activity relationship for the different amino acids on the coupling step.

Ma extended the methodology of chelating substrates to the coupling of β-amino acid derivatives with aryl halides[11] in the synthesis of the Gl IIb/IIIa receptor antagonist Lotrafiban, a benzodiazepinone. They again recognized a strong dependence of the catalytic turnover on the chelating nature of the starting β-amino acid. In this publication he also gives the first speculations on the mechanism of the reaction, however with no experimental proof.

At the same time Hayes and co-workers from GlaxoSmithKline published the synthesis of Lotrafiban via an alternative approach (Scheme 4).[12] The key step differs only in the nature of the amine nucleophile, L-aspartic acid, showing the substructures of both α- and β-amino acids. This group also found Raney-nickel to be an effective activator for the reaction, which however has the drawback of increased racemization during the coupling step. A further elegant application of coupling a β-amino acid with 1,4-diiodobenzene was recently described by Ma in the total synthesis of alkaloid martinellic acid (Scheme 4).[13] However, both Ma and Hayes never attempted to develop a more general 'activating ligand' for the coupling of non-chelating substrates.

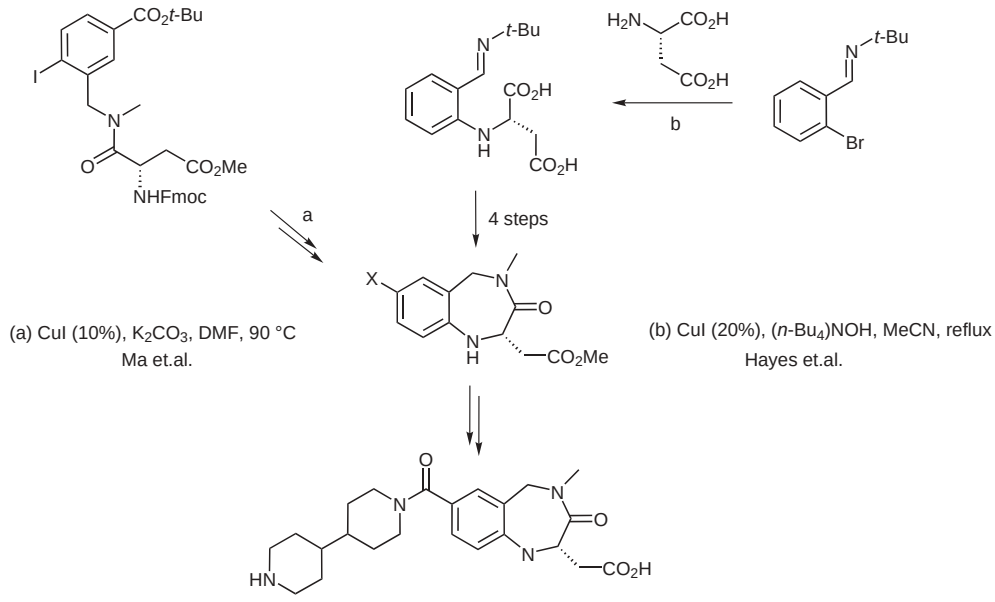
This idea of a 'chelating activator' was further promoted by Goodbrand and co-workers from Xerox[14] in their syntheses of triarylamine based photoreceptors (Scheme 5).



Scheme 5 Triarylamine syntheses by Goodbrand

Goodbrand used aryl iodides and mono- or diarylamines in combination with a catalyst consisting of copper iodide and phenanthroline (**1**) at moderate temperatures to furnish triarylamines in good yields. Venkataraman and coworkers extended Goodbrand's work by optimizing the ligand into a dimethylated phenanthroline (**2**) and a change to a stronger base, potassium *tert*-butoxide.[15]

Phenanthroline (**1**) as a ligand for copper(I) has also found application in amination reactions of bromoarylguanidines to selectively yield 2-aminobenzimidazoles.[16]

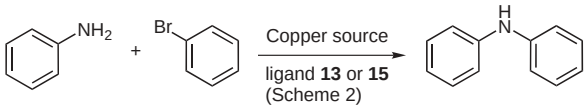


Scheme 4 Lotrafiban syntheses by Ma and Hayes

Interestingly the authors state that copper is superior to palladium in this case.

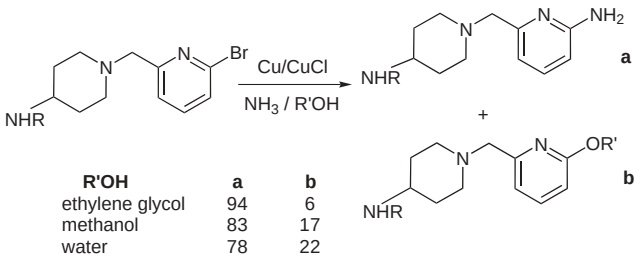
A systematic catalyst screening on a reaction similar to the one reported by Goodbrand, the double arylation of anilines with iodobenzene, has been described by Chaudari and co-workers.[17] The influence of the ligand on the ratio of di- to triarylamine in the mixture of products was clearly demonstrated. However no ligand at all gave the highest yield of the desired triarylamine product.

The opposite selective mono-arylation of anilines with aromatic halides without double arylation was the aim of a recent investigation (Scheme 6).[18,19] It turned out that the use of bulky phosphines or chelating carbene ligands yielded the monoarylated product almost exclusively.



Scheme 6 Aryl amination utilizing special ligands

The search for an alternative means of activating the copper catalyst lead to a protocol applied by Lang and coworkers from Merck in the synthesis of a M3-antagonist (Scheme 7).[20] In ethylene glycol as chelating solvent at mild temperatures, and elevated pressure, ammonia served as both the nucleophile and the base and successfully replaced bromine or iodine on several aromatic and heteroaromatic substrates.



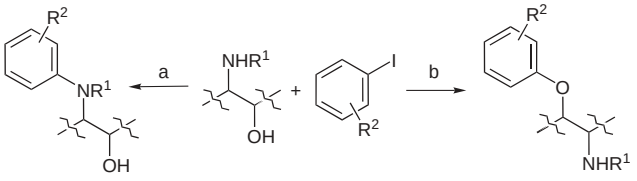
R'OH	a	b
ethylene glycol	94	6
methanol	83	17
water	78	22

Scheme 7 Mild ammonolysis procedure developed by Lang

The role of ethylene glycol in these reactions has lead to a protocol with broader applicability by Buchwald.[21] In a screening of different polyols and phenols as additives a general protocol was elaborated using a mild base and low temperature to induce the coupling of aryl iodides and bromides with anilines, primary, and secondary aliphatic amines in the presence of copper iodide as the catalyst precursor.

The same group changed the mode of the coupling reaction from C–N to C–O in the reactions of aryl iodides and amino alcohols. Depending on catalyst and base, the system effectively distinguished between the two competing pathways (Scheme 8).[22]

To close the cycle, Buchwald just recently published the utilization of a clever 'look-alike' to Goldberg's original chelating substrate as an activating ligand for the reaction.



(a) CuI (2.5%), NaOH, DMSO/H_2O; resp. *i*-PrOH, 90 °C
(b) CuI (5%), Cs_2CO_3, Butyronitrile, 125 °C

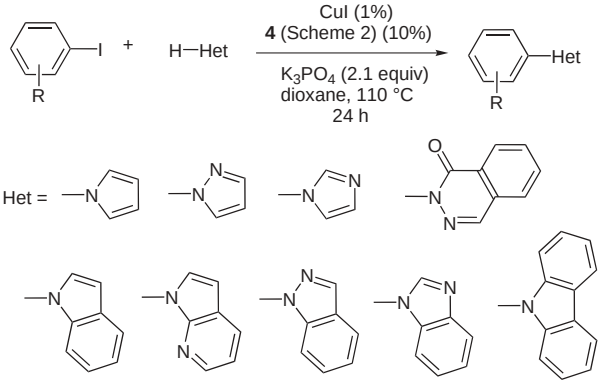
Scheme 8 Buchwald's chemoselective coupling of aminoalcohols

With *N*,*N*-diethylsalicylamide (**12**) as additive, aryl bromides have successfully been coupled with primary amines under mild conditions.[23] The different protocols have been summarized in Table 1.

3.2 *N*-Arylation of Heterocycles

N-Arylation of heterocycles is considered attractive for the synthesis of several valuable substrate classes with high biological activity. Buchwald reported the successful mono-arylation of imidazoles with aryl bromides and iodides using copper triflate and phenanthroline (**1**) or dibenzylidene acetone as ligands.[24]

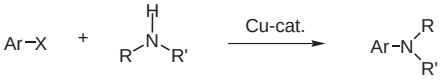
An extension of this methodology has been achieved by the use of cyclohexane diamine (**3**) as ligand to synthesize various arylated heterocycles.[25] Arylated imidazoles, indoles, carbazoles, pyrazoles, and phtalazines were accessible by this copper catalyzed process (Scheme 9).



Scheme 9 Synthesis of arylated heterocyles

Similar coupling reactions of aryl halides with *N*-Boc-hydrazide, a prominent heterocycle precursor, have been performed. Provided the catalyst was chosen appropriately, the two nitrogen atoms could be effectively differentiated.[26] The arylation reaction of indoles with ligand **4** (Scheme 2) and other secondary amines as ligands represent another effective protocol for the copper catalyzed amination of aryl halides.[27] In order to synthesize substituted 5-aminouraciles as antiviral drugs, Arterburn investigated the copper catalyzed amination of 5-iodouracil.[28] Best results were obtained using either equimolar amounts of phenanthroline (**1**) in combination with traces of dibenzylideneacetone (dba) or catalytic amounts of 1,1-

Table 1 Optimized Reaction Conditions for Copper-Catalyzed Coupling of Ar–X and Amines



Lit.	X	R	Amine	Base	Copper source	Ligand	Reaction conditions	Yields[a]
[13]	I	aryl-I	secondary, chiral, non racemic	K_2CO_3	CuI	none	DMF–H_2O, 100 °C, 24 h	70% (1)
[15]	I, Br, Cl	subst. aryl	diarylamine	KOtBu	Cu (neocup) $(PPh_3)Br$	**2**, **14** (Scheme 2)	toluene, 110 °C	49–88% (6)
[14]	I	aryl	diarylamine	KOH	CuCl	**1** (Scheme 2)	toluene, reflux	61–85% (16)
[10]	Br, I	aryl	α-aminoacids	K_2CO_3	CuI	none	DMA, 90 °C, 48 h	0–92% (38)
[36]	I	aryl	subst. anilines	Cs_2CO_3	Cu $(PPh_3)_3$ Br,	**14** (Scheme 2)	toluene, reflux	70–88% (15)
[11]	Br, I	aryl	β-aminoacids	K_2CO_3	CuI	none	DMF, 90–100 °C	0–69% (11)
[11]	Br, I	aryl	β-aminoacid ester	K_2CO_3	CuI	none	DMF, 100 °C	0–87% (16)
[12]	Br, I	aryl	α-aminoacid	Bu_4NOH (aq. solution)	CuI		MeCN, reflux, 2 h	22–51% (12)
[12]	Br, I	aryl	α-aminoacid	Bu_4NOH (aq. solution)	Raney-copper		MeCN, reflux, 2 h	71–74% (2)
[17]	I	aryl	aniline (double amination)	KOtBu	CuI	none	135 °C, autoclave	72% (38)
[37b]	Br,	trisubst. (activated) aryl	subst. aniline	cat. NMP	Cu/CuCl mixture	solvent	2,3-butanediol, 70 °C, 15 h	78% (1)
[37c]	Cl	trisubst. (activated) aryl	subst. aniline	cat. K_2CO_3	Cu/CuI mixture	none	boiling DMF, ultrasound, 20 min	75% (9)
[21]	I	subst. aryl	1° and 2° alkylamines	K_3PO_4	CuI	1,2-diols	*i*-PrOH, 80 °C	48–95% (65)
[22]	I	subst. aryl	β-aminoalcohols	K_3PO_4 or NaOH	CuI	**9** (Scheme 2)	tunable O-N- selectivity, *i*-PrOH or DMSO–H_2O, sealed tube, 75–90 °C	66–89% (17)
[23]	Br	subst. aryl	1° amines	K_3PO_4	CuI	**12** (Scheme 2)	DMF or solventless 90 °C	71–95% (42)
[20]	Br	pyridine	concd ammonia (excess)	none	Cu/CuCl/Cu_2O	solvent	ethylene glycol, sealed vessel, 100 °C	91% (29)

[a] In parentheses: number of examples reported.

bis(diphenylphosphino) ferrocene (dppf) as catalysts. An overview of the procedures is given in Table 2.

3.3 Aromatic Amidation

The amidation of aromatic halides has been the subject of intense studies during the past five years. The same field was opened again by Goldberg, in the already mentioned publication,[6] by the condensation of benzamide with bromobenzene with a trace of copper in refluxing nitrobenzene.

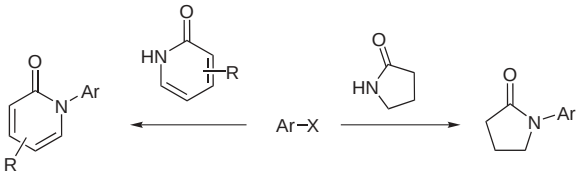
Some 90 years later, Ukita reported the reaction of several bromo- and iodo aromatics with different aromatic amides in DMF as solvent at 120 °C and potassium carbonate as base (Scheme 10).[29]

Table 2 Optimized Reaction Conditions for Copper-Catalyzed Arylation of N-Heterocycles

Ar–X + H–Het^N —Cu-cat.→ Ar–Het^N

Lit.	X	Ar	Heterocycle	Base	Copper source	Ligand	Reaction conditions	Yields[a]
[24]	I	subst. aryl	imidazoles	Cs_2CO_3	$(CuOTf)_2{\cdot}PhH$	dba, **1** (Scheme 2) mixture	xylenes, 110–125 °C	62–99% (10)
[25]	Br, I, Cl	subst. aryl	Pyrazoles, indazoles, 7-azaindoles, phthalazinones, indoles, pyrroles, carbazoles, benzimidazoles, imidazoles	K_3PO_4, K_2CO_3 or Cs_2CO_3	CuI	**3** (Scheme 2)	dioxane, 110 °C, 24 h	62–99% (52)
[31]	I	subst. aryl	pyrroles, indoles	Cs_2CO_3 or K_3PO_4	CuI	**6** (Scheme 2)	dioxane, 110 °C	87–96% (2)
[27]	Br, I	subst. aryl	subst. indoles	K_3PO_4	CuI	**4**, **5** (Scheme 2)	toluene, 110 °C	57–96% (60)

[a] In parentheses: number of examples reported.

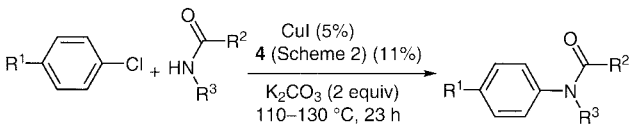


Reaction conditions: 2 equiv aryl bromide or aryl iodide, 1 equiv heterocyclic compound, CuI(1–10%), 1 equiv K_2CO_3, DMF, 150 °C, 6 h

Scheme 10 Goldberg amidation of heterocycles by Ukita

Buchwald's ligand **3** (Scheme 2) was the first reported to assist the copper catalyzed amidation.[25] This catalytic system allowed a wide range of amides to be coupled with bromo and iodo aromatics, including open chain alkylamides under mild conditions and in good yields.

In a subsequent publication,[30] the same methodology was extended to aryl chlorides. In these examples, the already mentioned ligand **4** successfully promoted the transformation of deactivated aryl chlorides into N-aryl amides. Several examples of these conversions indicate that copper catalyzed reactions can be advantageous over palladium-catalyzed protocols due to their wider functional group tolerance and fewer problems of heavy metal contamination in the final product (Scheme 11).



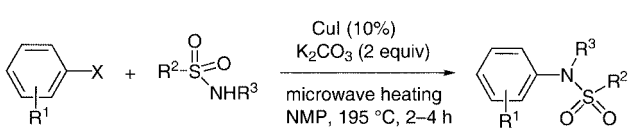
Scheme 11 Coupling of aryl chlorides and amides

In this publication the role of the catalyst is discussed in terms of the improved solubility of the catalytic species caused by the chelating nature of the additive. On the other hand the catalyst seems to be deactivated by complexation with several of the nucleophillic amides. Therefore, bulky and strongly chelating ligands should prevent this complexation and exhibit higher catalytic activity.

The accelerating effect of chelating diamines was also exploited by Kang and Padwa who reported protocols for effective amidation reactions of thiophenes and furans.[31,32] A ligand free coupling of amides and aryl bromides was significantly promoted by the use of microwave heating in NMP.[33] The elegant total syntheses of potential antibiotics, Linezolid and Toloxatone, by Trehan illustrate the synthetic potential of modern Goldberg-reactions.[35]

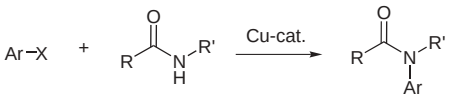
A step forward in the related copper catalyzed syntheses of aryl sulfonamides was recently achieved by He, who utilized a microwave oven to furnish sulfonamide formation within 2 hours (Scheme 12). However, reaction temperatures of 195 °C in overheated solvents impose severe limits on these applications at the moment. The development of reactions under mild conditions remain a demand for further improvement.[34]

An overview of the procedures is presented in Table 3.



Scheme 12 Synthesis of sulfonamides by He

Table 3 Optimized Reaction Conditions for Copper-Catalyzed Coupling of Ar–X and Amides[a]



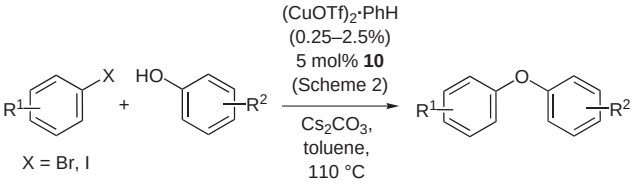
Lit	X	Ar	Amide	Base	Copper source	Ligand	Reaction conditions	Yields[a]
[31]	I	thiophenes, subst. aryls	lactames, arylamides,	K_3PO_4, Cs_2CO_3	CuI	**6** (Scheme 2) TMEDA	polar aprotic and unpolar solvents, reflux, 24 h	41–95% (22)
[30,25]	Br, Cl, I	subst. aryl, thiophenes	lactames, carbamates, arylamides, amides, formamides	K_3PO_4, Cs_2CO_3, K_2CO_3	CuI	**4**, **5** (Scheme 2)	dioxane, toluene	51–97% (72 + 52)
[26]	I	subst. aryl	hydrazides	Cs_2CO_3	CuI	**1** (Scheme 2) or none	tunable N-selectivity, DMF, 80 °C	43–97% (9)
[29]	I, Br	subst. aryl, thiophenes, pyridines, quinolines	phtalazinones, pyrrolidones, isoquinolones, benzotriazinones, hydroxypyridines, quinolines	K_2CO_3	CuI	none	DMF, DMSO, NMP, 150 °C, 6 h	14–91% (35)

[a] In parentheses: number of examples reported.

4 Formation of C–O-Bonds

The Ullmann ether synthesis was extensively applied for the formation of diaryl ethers, but in contrast to the original procedure[5c] usually stochiometric amounts of copper salts were compulsory to obtain satisfying conversions.[7,38] A first step towards homogeneous coupling reactions was achieved by Comdom who described the copper powder catalyzed reaction of *ortho*-chlorobenzoic acid with phenols in aqueous media.[39] Pyridine as an additive was crucial to obtain good yields, even in an improved protocol using ultrasound,[40] but only *ortho*-activated aryl chlorides were employed. Thus, Buchwald published an alternative approach to copper-catalyzed C–O-formation (Scheme 13). However, the solubilizing and accelerating effect in reactions promoted by ligands was not explicitely pointed out at that time.[41] The reaction protocol employing only 0.25–2.5% of catalyst, ethyl acetate as the ligand and cesium carbonate as the base is one of the most efficient methods for diarylether synthesis to date. It is applicable to a wide range of activated and deactivated aryl bromides and iodides. Even *ortho*-substitution on both aryl units is tolerated. The only restriction, which applies to almost all following procedures as well, is the need for electron rich or at least electron neutral phenols. In the case of less soluble phenols, addition of 1-naphthoic acid leads to a significant increase in yields.

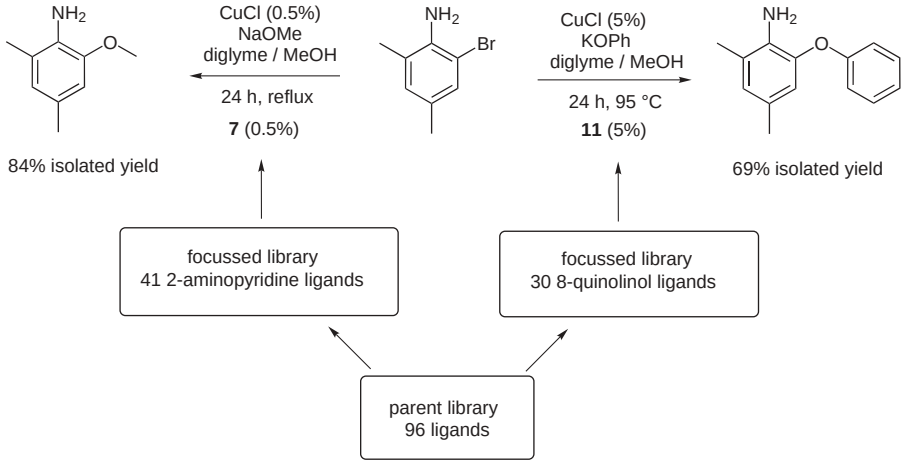
Cesium carbonate proved to be the base of choice in most of the following protocols (see Table 4), whereas a particular selection of the copper source was usually not essential for the success of the reaction. In accordance with



Scheme 13 Buchwald's early protocol for diarylether synthesis

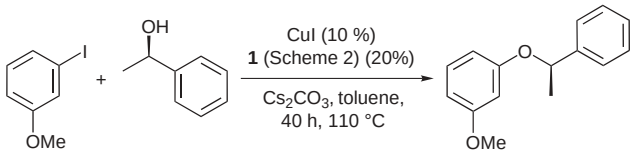
these observations are the results of Snieckus who introduced $CuPF_6(MeCN)_4$ as a more air stable catalyst, whereas the use of cesium carbonate again was crucial for considerable reaction rates.[42] Interestingly, the coupling of electron poor *ortho*-hydroxybenzodiethylamide proceeded with 49% yield and secondary *ortho*-iodobenzamides were tolerated. Nevertheless it should be noted that only activated aryl halides were employed. Fagan et al. systematically investigated the accelerating effect of ligands by screening a broad range of mono-, bi- and tridendate ligands (96 in the parent library; 23, 30 and 40 in 3 focussed libraries, Scheme 14) in the copper-catalyzed coupling of 2-bromo-4,6-dimethylaniline with methanol and phenol.[43] It turned out that the use of bidentate chelators with small 'bite-angles', especially 2-aminopyridine (**7**) and 8-hydroxyquinoline (**11**), was most successful. On the other hand, similarly constructed ligands did not work well, which was explained as an evidence for the complexity of the reaction mechanism.

Many other ligands like phosphines (**14**, **15**)[18,44], TMHD (**8**)[45] and the 1,2-diaminoethane-substructures (**3**–**6**)[46] were investigated in later work. Venkataraman's air stable



Scheme 14 Combinatorial approach to copper-catalyzed C–O-coupling

homogeneous copper catalyst $Cu(PPh_3)_3Br$ showed good activity, even in the coupling of *ortho*-bromotoluene with *ortho*-cresole.[44] A mixed ligand system with neocuproine (**2**) and triphenylphosphine was less efficient in the case of sterically hindered substrates.[15] A significant rate enhancement for diaryl ether formation was observed, when 2,2,6,6-tetramethylheptan-3,5-dione (TMHD) (**8**) was introduced as ligand, leading also to respectable results when isopropyl-4-hydroxybenzoate as an electron poor phenol was employed.[45] However, stronger electron withdrawing functionalities in the substrates like nitriles or aldehydes were not tolerated. A mild method for the coupling of aryl iodides with aliphatic primary and secondary alcohols was presented by Buchwald.[46] The reaction was carried out in the presence of phenanthroline (**1**) in toluene or in the reacting alcohol as the solvent. Noteworthy, optically active alcohols react with complete retention of their configuration (Scheme 15).

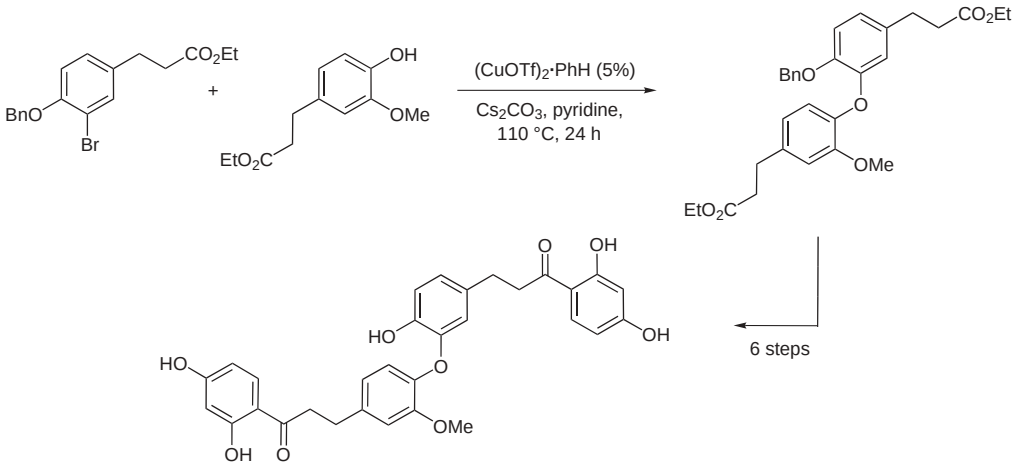


89% yield, 98% ee

Scheme 15 Copper-catalyzed C–O-formation of optically active alcohols

Nicolaou's copper bromide dimethylsulfide mediated double diaryl ether formation in the course of the total synthesis of the vancomycin aglycon is one of the most remarkable examples of the 'classical' Ullmann reaction in the construction of complex molecules and natural products.[47] An elegant catalytic application was reported by Cuny in context of the synthesis of verbenachalcone, which has been reported to stimulate nerve growth factors. The key aryl ether formation was performed using catalytic amounts (5%) of $(CuOTf)_2$. PhH and Cs_2CO_3 (1 equiv) as the base in pyridine (24 h, 110 °C) (Scheme 16).[48]

It can be concluded from these results that copper-catalyzed coupling reactions offer access to a broad range of diaryl and arylalkyl ethers. Various copper salts proved to be useful catalyst precursors. However, the choice of cesium carbonate as the base is crucial if the alcoholate is not preformed (Table 4).



Scheme 16 Synthesis of verbenachalcone by Cuny

Table 4 Optimized Reaction Conditions for Copper-Catalyzed Coupling of Ar–X and R–OH

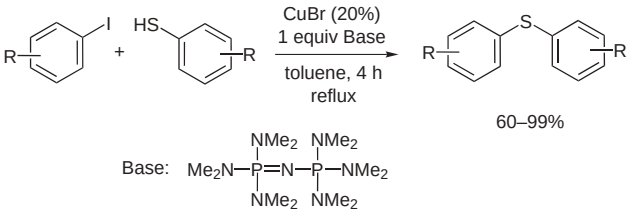
Lit.	X	R	Base	Copper source	Ligand	Reaction conditions	Yields[a]
[41]	Br, I	aryl	Cs_2CO_3	$(CuOTf)_2$·PhH	**10** (Scheme 2)	toluene, reflux, 16–26 h	76–93% (20)
[42]	Cl, Br, I	aryl	Cs_2CO_3	$CuPF_6$ $(MeCN)_4$	–	toluene, reflux	77–98% (13)
[43]	Br	Me	NaOMe (reagent)	CuCl	**7** (Scheme 2)	diglyme–MeOH, 85 °C, 24 h	92% (1)[b]
[43]	Br	Ph	KOPh (reagent)	CuCl	**11** (Scheme 2)	diglyme, 95 °C, 16 h	69% (1)[b]
[44]	Br	aryl	Cs_2CO_3	$Cu(PPh_3)Br$	**14** (Scheme 2)	NMP, 100 °C, 20 h	55–75% (10)
[15]	Br	aryl	Cs_2CO_3	Cu(neocup) $(PPh_3)Br$	**2** (Scheme 2)	toluene, reflux, 36 h	31–99% (7)
[46]	I	alkyl	Cs_2CO_3	CuI	**1** (Scheme 2)	toluene or no solvent, 110 °C, 18–38h	54–93% (24)
[45]	Br, I	aryl	Cs_2CO_3	CuCl	**8** (Scheme 2)	NMP, 120 °C, 4–47 h	51–85% (13)

[a] In parentheses: number of examples reported.
[b] Focus on optimization of ligands.

5 Formation of C–S-Bonds

In contrast to the carefully investigated arylation reactions of amines, amides, and alcohols, copper-catalyzed thioether formation has received only little attention, probably due to the limited use of these products. Although thiols are generally stronger nucleophiles than alcohols and amines, the sensitivity of sulfides towards oxidation holds some difficulties. Nevertheless, the suppression of disulfide formation remains the main challenge of this reaction type.

In Snieckus' work on intramolecular diarylether synthesis, two examples of diaryl thioethers have been described.[42] However, only activated aryl halides were used. The first systematic investigation of thiol arylation was carried out by Palomo et. al., who used a phosphazene base and catalytic amounts of copper(I) bromide in the absence of additional ligands.[49] The applicability of the reaction is limited to aryl iodides but a wide range of substituents is tolerated. Hydroxy thiophenols reacted with aryl iodides chemoselectively to yield the corresponding hydroxy bisarylthioethers. Interestingly the use of DBU as the base afforded similar results while attempts carried out in the presence of Cs_2CO_3, DMAP, or diisopropylamine failed.



Scheme 17 Diarylthioether coupling catalyzed by a CuBr/ phosphazene system

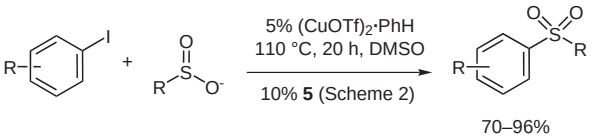
In quick succession Venkataraman[50] and Buchwald[51] published improved methods for the synthesis of bisaryl- and arylalkyl thioethers. In addition to the synthetic progress the use of cheap bases (*t*-BuONa and K_2CO_3) and ligands (mainly ethylene glycol) do extend the economic potential of copper-catalyzed C-S-coupling reactions. A survey of the published methods is given in Table 5.

Table 5 Optimized Reaction Conditions for Copper-Catalyzed Coupling of Ar–I and R–SH

Lit	R	Base	Copper source	Ligand	Reaction conditions	Yields[a]
[49]	aryl	P_2-Et (Scheme 17)	CuBr	–	toluene, reflux, 6h	60–99% (17)
[50]	aryl, alkyl	*t*-BuONa	CuI	**2** (Scheme 2)	toluene, reflux	77–98% (28)
[51]	aryl, alkyl	K_2CO_3	CuI	**9** (Scheme 2)	*i*-PrOH, 80 °C, 22h	71–95% (27)

[a] In parentheses: number of examples reported.

A new copper-catalyzed reaction was reported by Wang,[52] the coupling of sulfinic salts with aryl iodides provides a unique approach to arylsulfones (Scheme 18). The method is applicable to aryl and alkyl sulfinic salts and *ortho*-substituted aryl iodides whereas the corresponding bromides show only low conversions.



Scheme 18 Arylsulfone synthesis by Wang

6 Conclusion

Copper catalyzed C–N-, C–O- and C–S-coupling reactions constitute a powerful tool in organic synthesis complementing the more extensively investigated palladium-catalyzed processes. Chemists can take advantage of a growing set of optimized protocols including mild reaction conditions and readily accessible ligands.

High stability of the catalysts even under air and low costs should be pointed out as general advantages of the copper-catalysis. The synthetic potential includes the arylation of primary and secondary amides, which are largely incompatible with palladium chemistry. In the case of N-arylation of heterocycles the use of copper proved superior in many cases as well. On the other hand there is still demand for improvements: only in a few examples aryl chlorides can be converted sufficiently. For successful C–S-coupling, even aryl bromides were not reactive enough. The mechanistic understanding of the catalytic process remains unsatisfying to date. Hopefully future efforts will fill these gaps and might lead to an even more effective and more general set of parameters for this interesting and growingly powerful toolbox of copper catalyzed nucleophilic aromatic substitutions.

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